Internal standard solution—A solution of etilefrine hydrochloride (1 in 500).

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 285 nm).

Column: A stainless steel column about 4 mm in inside diameter and 15 to 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (about 5 μm in particle diameter).

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

Mobile phase: Dissolve 1.0 g of sodium lauryl sulfate in 500 mL of diluted phosphoric acid (1 in 1000), and adjust the pH to 3.0 with sodium hydroxide TS. To 240 mL of this solution add 70 mL of tetrahydrofuran, and mix.

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

Selection of column: Proceed with 20 μL of the standard solution under the above operating conditions, and calculate the resolution. Use a column giving elution of morphine and the internal standard in this order with the resolution between these peaks being not less than 3.

Containers and storage Containers—Hermetic containers, and colored containers may be used.

Storage—Light-resistant.

Morphine Hydrochloride Tablets

塩酸モルヒネ錠

Morphine Hydrochloride Tablets contain not less than 93% and not more than 107% of the labeled amount of morphine hydrochloride ($C_{17}H_{19}NO_3$. $HCl.3H_2O$: 375.84).

Method of preparation Prepare as directed under Tablets, with Morphine Hydrochloride.

Identification Weigh a quantity of powdered Morphine Hydrochloride Tablets equivalent to 0.01 g of Morphine Hydrochloride, add 100 mL of water, shake for 10 minutes, and filter. Determine the absorption spectrum of the filtrate as directed under the Ultraviolet-visible Spectrophotometry: it exhibits a maximum between 283 nm and 287 nm. And weigh a quantity of powdered Morphine Hydrochloride Tablets equivalent to 0.01 g of Morphine Hydrochloride, add 100 mL of dilute sodium hydroxide TS, shake for 10 minutes, and filter. Determine the absorption spectrum of the filtrate: it exhibits a maximum between 296 nm and 300 nm.

Assay Take not less than 20 Morphine Hydrochloride Tablets, weigh accurately, and powder. Weigh accurately a quantity of the powder, equivalent to about 0.02 g of morphine hydrochloride ($C_{17}H_{19}$ $NO_3.HCl.3H_2O$), add exactly 10 mL of the internal standard solution, extract the mixture with ultrasonic waves for 10 minutes, and add water to make 50 mL. Filter this solution, and use the filtrate as the sample solution. Separately, weigh accurately about 0.025 g of morphine hydrochloride for assay, dissolve in exactly 10 mL of the internal standard solution, add water to make 50 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the sample solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions, and calculate the ratios, Q_T and Q_S, of the peak area of morphine to that of the internal standard.

> Amount (mg) of morphine hydrochloride
> ($C_{17}H_{19}NO_3.HCl.3H_2O$)
> = amount (mg) of morphine hydrochloride
> for assay, calculated on the anhydrous basis
> $$\times\ 1.1680 \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of etilefrine hydrochloride (1 in 500).

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 285 nm).

Column: A stainless steel column about 4 mm in inside diameter and 15 to 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (about 5 μm in particle diameter).

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

Mobile phase: Dissolve 1.0 g of sodium lauryl sulfate in 500 mL of diluted phosphoric acid (1 in 1000), and adjust the pH to 3.0 with sodium hydroxide TS. To 240 mL of this solution add 70 mL of tetrahydrofuran, and mix.

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

Selection of column: Proceed with 20 μL of the standard solution under the above operating conditions, and calculate the resolution. Use a column giving elution of morphine and the internal standard in this order with the resolution between these peaks being not less than 3.

Containers and storage Containers—Tight containers.

Storage—Light-resistant.

Mupirocin Calcium Hydrate

ムピロシンカルシウム 水和物
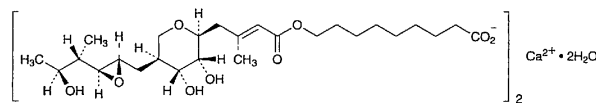
$C_{52}H_{86}CaO_{18}.2H_2O$: 1075.34
Monocalcium bis[9-((2*E*)-4-{(2*S*,3*R*,4*R*,5*S*)-5-[(2*S*,3*S*,4*S*,5*S*)-2,3-epoxy-5-hydroxy-4-methylhexyl]-3,4-dihydroxy-3,4,5,6-tetrahydro-2*H*-pyran-2-yl}-3-methylbut-2-enoyloxy)nonanoate] dihydrate [115074-43-6]

Mupirocin Calcium Hydrate contains not less than 855 μg (potency) per mg, calculated on the anhydrous basis. The potency of Mupirocin Calcium Hydrate is expressed as mass (potency) of mupirocin ($C_{26}H_{44}O_9$: 500.62).

Description Mupirocin Calcium Hydrate occurs as a white powder and has a bitter taste.

It is freely soluble in methanol and slightly soluble in

water and in ethanol (95).

Identification (1) To 1 mL of a solution of Mupirocin Calcium Hydrate in methanol (1 in 200) add 4 mL of hydroxylamine perchlorate-ethanol TS and 1 mL of *N,N'*-dicyclohexylcarbodiimide-ethanol TS, shake well, and allow to stand in lukewarm water for 20 minutes. After cooling, add 1 mL of iron (III) perchorate hexahydrate-ethanol TS to the solution, and shake: a dark purple color develops.

(2) Determine the absorption spectrum of a solution of Mupirocin Calcium Hydrate (1 in 50,000) as directed under the Ultraviolet-visible Spectrophotometry: it exhibits a maximum between 219 nm and 224 nm.

(3) Determine the infrared absorption spectrum of Mupirocin Calcium Hydrate as directed in the paste method under the Infrared Spectrophotometry: it exhibits absorption at the wave numbers of about 1708 cm^{-1}, 1648 cm^{-1}, 1558 cm^{-1}, 1231 cm^{-1}, 1151cm^{-1} and 894 cm^{-1}.

(4) A solution of Mupirocin Calcium Hydrate (3 in 1000) responds to the Qualitative Test (3) for calcium salt.

Optical rotation $[\alpha]_D^{20}$: $-16 - -20°$ (1 g calculated on the anhydrous basis, methanol, 20 mL, 100 mm).

Purity (1) Related substances—Dissolve 0.05 g of Mupirocin Calcium Hydrate in a mixture of 0.1 mol/L acetic acid-sodium acetate buffer solution, pH 4.0, and a solution of tetrahydrofuran (3 in 4) (1:1) to make 10 mL, and use this solution as the sample solution (1). Pipet 2 mL of this solution, add a mixture of 0.1 mol/L acetic acid-sodium acetate buffer solution, pH 4.0, and a solution of tetrahydrofuran (3 in 4) (1:1) to make exactly 100 mL, and use this solution as the sample solution (2). Preserve these sample solutions at a temperature between 4°C and 8°C. Perform the test with exactly 20 μL of the sample solution (1) and the sample solution (2) as directed under the Liquid Chromatography according to the following conditions, and determine the areas of each peak of the sample solution (1) and the sample solution (2) by the automatic integration method. Calculate the amount of the related substances by the following formula: the amount of principal related substance (appeared at about 0.7 of the relative retention time to mupirocin) is not more than 4%, and the total amount of related substances (the total area of the peaks other than of the solvent and mupirocin) is not more than 6%.

Amount (%) of principal related substance

$$= \frac{A_i}{A + A_m} \times 100 \times \frac{P \times 100}{100 - \dfrac{A \times 100}{A + A_m}}$$

Total amount (%) of related substances

$$= \frac{A}{A + A_m} \times 100 \times \frac{P \times 100}{100 - \dfrac{A \times 100}{A + A_m}}$$

A: Total peak areas other than of the solvent and mupirocin from the sample solution (1).

A_i: Peak area of the relative retention time of about 0.7 to mupirocin from the sample solution (1).

A_m: A value of 50 times of peak area of mupirocin from the sample solution (2).

P: Potency per mg obtained from the assay.

Operating conditions—

Detector, column, column temperature, mobile phase, and flow rate: Proceed as directed in the operating condi-

tions in the Assay.

Time span of measurement: About 3 times as long as the retention time of mupirocin after the solvent peak.

System suitability—

Test for required detection: Pipet 1 mL of the sample solution (2), and add a mixture of 0.1 mol/L acetic acid-sodium acetate buffer solution, pH 4.0, and a solution of tetrahydrofuran (3 in 4) (1:1) to make exactly 20 mL. Confirm that the peak area of mupirocin obtained from 20 μL of this solution is equivalent to 4 to 6% of that obtained from 20 μL of the sample solution (2).

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

System repeatability: When the test is repeated 6 times with 20 μL of the sample solution (2) under the above operating conditions, the relative standard deviation of the peak areas of mupirocin is not more than 2.0%.

(2) Inorganic salt from manufacturing process—Being specified separately.

Water Not less than 3.0% and not more than 4.5% (0.5 g, volumetric titration, direct titration).

Assay Weigh accurately an amount of Mupirocin Calcium Hydrate and Mupirocin Lithium Reference Standard, equivalent to about 0.02 g (potency), dissolve in a mixture of 0.1 mol/L acetic acid-sodium acetate buffer solution, pH 4.0 and a solution of tetrahydrofuran (3 in 4) (1:1) to make exactly 200 mL, and use these solutions as the sample solution and the standard solution. Preserve these solutions at a temperature between 4°C and 8°C. Perform the test with 20 μL of the sample solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the peak areas, A_T and A_S, of mupirocin of each solution.

Amount [μg (potency)] of mupirocin (C$_{26}$H$_{44}$O$_9$)
= amount [mg (potency)] of Mupirocin Lithium

$$\text{Reference Standard} \times \frac{A_T}{A_S} \times 1000$$

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 240 nm).

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

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

Mobile phase: Dissolve 7.71 g of ammonium acetate in 750 mL of water, adjust the pH to 5.7 with acetic acid (100), and add water to make 1000 mL. To 300 mL of this solution add 100 mL of tetrahydrofuran.

Flow rate: Adjust the flow rate so that the retention time of mupirocin is about 12.5 minutes.

System suitability—

System performance: Dissolve about 0.02 g of Mupirocin Lithium Reference Standard and about 5 mg of ethyl parahydroxybenzoate in a mixture of 0.1 mol/L acetic acid-sodium acetate buffer solution, pH 4.0 and a solution of tetrahydrofuran (3 in 4) (1:1) to make 200 mL. When the procedure is run with 20 μL of this solution under the above operating conditions, mupirocin and ethyl parahydroxybenzoate are eluted in this order with the resolution between these
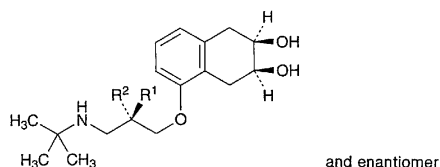
peaks being not less than 12.

System repeatability: When the test is repeated 6 times with 20 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak areas of mupirocin is not more than 1.0%.

Containers and storage   Containers—Tight containers.

Nadolol

ナドロール

and enantiomer

$C_{17}H_{27}NO_4$: 309.40

$R^1 = OH, R^2 = H$

$(2RS,3SR)$-5-[3-$(tert$-Butylamino)-(RS)-2-hydroxy-propyloxy]-1,2,3,4-tetrahydronaphthalene-2,3-diol

$R^1 = H, R^2 = OH$

$(2RS,3SR)$-5-[3-$(tert$-Butylamino)-(SR)-2-hydroxy-propyloxy]-1,2,3,4-tetrahydronaphthalene-2,3-diol

[42200-33-9]

Nadolol, when dried, contains not less than 98.0% of $C_{17}H_{27}NO_4$.

Description   Nadolol occurs as a white to yellow-brownish white crystalline powder.

It is freely soluble in methanol and in acetic acid (100), soluble in ethanol (95), and slightly soluble in water and in chloroform.

A solution of Nadolol in methanol (1 in 100) shows no optical rotation.

Melting point: about 137°C

Identification   (1) Determine the absorption spectrum of a solution of Nadolol in methanol (1 in 5000) as directed under the Ultraviolet-visible Spectrophotometry, and compare the spectrum with the Reference Spectrum: both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared absorption spectrum of Nadolol, previously dried, as directed in the potassium bromide disk method under the Infrared Spectrophotometry: it exhibits absorption at the wave numbers of about 1585 cm^{-1}, 1460 cm^{-1}, 1092 cm^{-1}, 935 cm^{-1} and 770 cm^{-1}.

Purity   (1) Heavy metals—Proceed with 1.0 g of Nadolol according to Method 2, and perform the test. Prepare the control solution with 2.0 mL of Standard Lead Solution (not more than 20 ppm).

(2) Related substances—Dissolve 0.5 g of Nadolol in 10 mL of a mixture of methanol and chloroform (1:1), and use this solution as the sample solution. Perform the test with the sample solution as directed under the Thin-layer Chromatography. Spot 100 μL each of the sample solution and a mixture of methanol and chloroform (1:1) as a control solution with 25 mm each of width at an interval of about 10

mm on the starting line of a plate 0.25 mm in thickness of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of acetone, chloroform and diluted ammonia TS (1 in 3) (8:1:1) to a distance of about 15 cm, and air-dry the plate. Examine under ultraviolet light (main wavelength: 254 nm), and confirm the positions of the principal spot and the spots other than the principal spot from the sample solution. Scratch and collect the silica gel of the positions of the plate corresponding to the principal spot and the spots other than the principal spot. To the silica gel collected from the principal spot add exactly 30 mL of ethanol (95), and to the silica gel from the spots other than the principal spot add exactly 10 mL of ethanol (95). After shaking them for 60 minutes, centrifuge, and determine the absorbances of these supernatant liquids at 278 nm as directed under the Ultraviolet-visible Spectrophotometry. Separately, proceed in the same manner with each position of the silica gel from the control solution corresponding to the principal spot and the spots other than the principal spot of the sample solution, and perform a blank determination to make correction. Amount of the related substances calculated by the following equation is not more than 2.0%.

$$\text{Amount (\%) of related substances} = \frac{A_b}{A_b + 3A_a} \times 100$$

A_a: Corrected absorbance of the principle spot.
A_b: Corrected absorbance of the spots other than the principle spot.

Loss on drying   Not more than 1.0% (1 g, in vacuum, 60°C, 3 hours).

Residue on ignition   Not more than 0.10% (1 g).

Isomer ratio   Prepare a paste with 0.01 g of Nadolol as directed in the paste method under Infrared Spectrophotometry so that its transmittance at an absorption band at a wave number of about 1585 cm^{-1} is 25 to 30%, and determine the infrared absorption spectrum between 1600 cm^{-1} and 1100 cm^{-1}. Obtain the absorbances, A_{1265} and A_{1250}, from the transmittances, T_{1265} and T_{1250}, at wave numbers of about 1265 cm^{-1} (racemic substance A) and 1250 cm^{-1} (racemic substance B), respectively: the ratio A_{1265}/A_{1250} is between 0.72 and 1.08.

Assay   Weigh accurately about 0.28 g of Nadolol, previously dried, dissolve in 50 mL of acetic acid (100), and titrate with 0.1 mol/L perchloric acid VS until the color of the solution changes from purple through blue to green-blue (indicator: 3 drops of crystal violet TS). Perform a blank determination, and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 30.941 mg of $C_{17}H_{27}NO_4$

Containers and storage   Containers—Tight containers. Storage—Light-resistant.