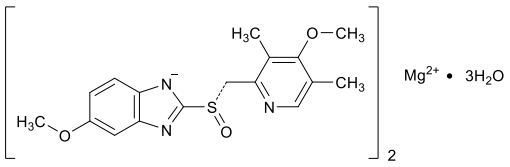
Esomeprazole Magnesium Hydrate

エソメプラゾールマグネシウム水和物



$C_{34}H_{36}MgN_6O_6S_2.3H_2O$: 767.17

Monomagnesium bis[(*S*)-5-methoxy-2-{[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]sulfinyl}-1*H*-benzimidazol-1-ide] trihydrate

[*217087-09-7*]

Esomeprazole Magnesium Hydrate contains not less than 98.0% and not more than 102.0% of esomeprazole magnesium ($C_{34}H_{36}M_gN_6O_6S_2$: 713.12), calculated on the anhydrous basis.

Description Esomeprazole Magnesium Hydrate occurs as a white or slightly colored powder.

It is sparingly soluble in methanol, and slightly soluble in ethanol (99.5) and in water.

Optical rotation <*2.49*> $[\alpha]_D^{20}$: +137 – +142° (0.25 g, methanol, 25 mL, 100 mm).

Identification **(1)** Determine the absorption spectrum of a solution of Esomeprazole Magnesium Hydrate in methanol (1 in 50000) as directed under Ultraviolet-visible Spectrophotometry <*2.24*>, 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 Esomeprazole Magnesium Hydrate as directed in the potassium bromide disk method under Infrared Spectrophotometry <*2.25*>, and compare the spectrum with the Reference Spectrum: both spectra exhibit similar intensities of absorption at the same wave numbers.

(3) Ignite 0.5 g of Esomeprazole Magnesium Hydrate as directed under Residue on Ignition <*2.44*>, cool, and dissolve the residue in 10 mL of water: the solution responds to Qualitative Tests <*1.09*> (1) for magnesium salt.

Purity **(1)** Clarity and color of solution (color)—Conduct this procedure within 1 hour after preparation of the sample solution. Dissolve 0.20 g of Esomeprazole Magnesium Hydrate in 10 mL of methanol, filter this solution through a membrane filter with a pore size not exceeding 0.5 μm, and use the filtrate as the sample solution. Determine the absorbance of the sample solution at 440 nm as directed under Ultraviolet-visible Spectrophotometry <*2.24*>: the absorbance is not more than 0.2.

(2) Clarity and color of solution (Turbidity)—Being specified separately when the drug is granted approval based on the Law.

(3) Related substances—Conduct this procedure within 10 minutes after preparation of the sample solution. To 5 mg of Esomeprazole Magnesium Hydrate add 20 mL of the mobile phase, sonicate to dissolve in a water bath with occasional shaking, add the mobile phase to make 25 mL and use this solution as the sample solution. Perform the test with 50 μL of the sample solution as directed under Liquid Chromatography <*2.01*> according to the following conditions. Determine each peak area by the automatic integration method, and calculate their amounts by the area percentage method: the amount of the peak of related substance D having the relative retention time of about 0.8 to esomeprazole is not more than 0.2%, the amount of the peak of related substance E having the relative retention time of about 0.4 is not more than 0.1%, and the amount of the peak other than esomeprazole and the peaks mentioned above is not more than 0.10%. Furthermore, the total amount of the peaks other than esomeprazole is not more than 0.5%.

Operating conditions—

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

Column: A stainless steel column 3.9 mm in inside diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (4 μm in particle diameter).

Column temperature: A constant temperature of about 22°C.

Mobile phase: To 5.2 mL of a solution of sodium dihydrogen phosphate dihydrate (39 in 250) and 63 mL of 0.5 mol/L disodium hydrogen phosphate TS add water to make 1000 mL. To 250 mL of this solution add water to make 1000 mL. To 760 mL of this solution add 240 mL of acetonitrile.

Flow rate: Adjust so that the retention time of esomeprazole is about 9 minutes.

Time span of measurement: About 4.5 times as long as the retention time of esomeprazole.

System suitability—

Test for required detectability: Dissolve 1 mg each of Omeprazole RS and omeprazole sulfone in the mobile phase to make 25 mL, and use this solution as the solution for system suitability test. Pipet 2.5 mL of the solution for system suitability test, and add the mobile phase to make exactly 100 mL. Pipet 1 mL of this solution, add the mobile phase to make exactly 10 mL. When the procedure is run with 50 μL of this solution under the above operating conditions, the SN ratio of the peak of omeprazole is not less than 10.

System performance: When the procedure is run with 50 μL of the solution for system suitability test under the above operating conditions, omeprazole sulfone and omeprazole

are eluted in this order with the resolution between these peaks being not less than 3.

Enantiomer Conduct this procedure within 1 hour after preparation of the sample solution. Dissolve 40 mg of Esomeprazole Magnesium Hydrate in 5 mL of methanol, and add the diluting solution to make 25 mL. To 0.2 mL of this solution add the diluting solution to make 10 mL, and use this solution as the sample solution. Perform the test with 20 μL of the sample solution as directed under Liquid Chromatography *<2.01>* according to the following conditions. Determine each peak area by the automatic integration method, and calculate their amounts by the area percentage method: the amount of the peak of related substance F (enantiomer) having the relative retention time of about 0.7 to esomeprazole is not more than 0.2%.

Diluting solution: To 11 mL of a solution of trisodium phosphate dodecahydrate (19 in 200) and 22 mL of 0.5 mol/L disodium hydrogen phosphate TS add water to make 1000 mL.

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 302 nm).

Column: A stainless steel column 4.0 mm in inside diameter and 10 cm in length, packed with α_1-acid glycoprotein binding silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 22°C.

Mobile phase: To 70 mL of a solution of sodium dihydrogen phosphate dihydrate (39 in 250) and 20 mL of 0.5 mol/L disodium hydrogen phosphate TS add water to make 1000 mL. To 250 mL of this solution add water to make 1000 mL. To 850 mL of this solution add 150 mL of acetonitrile.

Flow rate: Adjust so that the retention time of esomeprazole is about 5 minutes.

System suitability—

System performance: Dissolve 2 mg of Omeprazole RS in the diluting solution to make 10 mL. To 0.2 mL of this solution add the diluting solution to make 10 mL. When the procedure is run with 20 μL of this solution under the above operating conditions, the resolution between the peaks of related substance F (enantiomer) having the relative retention time of about 0.7 to esomeprazole and esomeprazole is not less than 3.

Water *<2.48>* 6.0 – 8.0% (0.2 g, volumetric titration, direct titration).

Magnesium Weigh accurately about 0.4 g of Esomeprazole Magnesium Hydrate, add 25 mL of methanol, and sonicate to dissolve. To this solution add 25 mL of water, 10 mL of ammonia solution (28) and 20 mL of 0.05 mol/L disodium dihydrogen ethylenediamine tetraacetate VS, and titrate *<2.50>* the excess disodium dihydrogen ethylenediamine tetraacetate with 0.05 mol/L zinc sulfate VS (indicator: 50 mg of eriochrome black T-sodium chloride indicator) until the color of the solution changes from blue to purple. Perform a blank determination in the same manner: Esomeprazole Magnesium Hydrate contains 3.30 – 3.55% of magnesium (Mg: 24.31) calculated on the anhydrous basis.

Each mL of 0.05 mol/L disodium dihydrogen ethylenediamine tetraacetate VS
$= 1.215$ mg of Mg

Assay Weigh accurately about 10 mg of Esomeprazole Magnesium Hydrate, dissolve in 10 mL of methanol, add 10 mL of the diluting solution, add water to make exactly 200 mL, and use this solution as the sample solution. Separately, weigh accurately about 10 mg of Omeprazole RS (separately determine the loss on drying *<2.41>* in vacuum at 50°C for 2 hours using phosphorous (V) oxide as a desiccant, using 1 g of Omeprazole RS), dissolve in 10 mL of methanol, add 10 mL of the diluting solution, add water to make exactly 200 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the sample solution and standard solution as directed under Liquid Chromatography *<2.01>* according to the following conditions, and determine the peak area, A_T, of esomeprazole obtained from the sample solution and the peak area, A_S, of omeprazole from the standard solution.

Amount (mg) of esomeprazole magnesium ($C_{34}H_{36}M_gN_6O_6S_2$)
$= M_S \times A_T / A_S \times 713.12 / (345.42 \times 2)$

713.12: Molecular mass of esomeprazole magnesium
345.42: Molecular mass of omeprazole

M_S: Amount (mg) of Omeprazole RS taken, calculated on the dried basis

Diluting solution: To 110 mL of a solution of trisodium phosphate dodecahydrate (19 in 200) and 220 mL of 0.5 mol/L disodium hydrogen phosphate TS add water to make 1000 mL.

Operating conditions—

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

Column: A stainless steel column 4.0 mm in inside diameter and 125 mm in length, packed with octylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 22°C.

Mobile phase: To 5.2 mL of a solution of sodium dihydrogen phosphate dihydrate (39 in 250) and 63 mL of 0.5 mol/L disodium hydrogen phosphate TS add water to make 1000

mL. To 163 mL of this solution and 487 mL of water add 350 mL of acetonitrile.

Flow rate: Adjust so that the retention time of esomeprazole is about 4 minutes.

System suitability—

System performance: When the procedure is run with 20 μL of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of omeprazole are not less than 2000 and not more than 1.5, respectively.

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 area of omeprazole is not more than 1.0%.

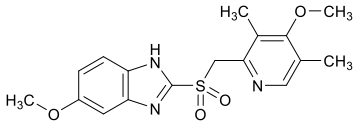
Containers and storage Containers—Tight containers.

Storage—Light-resistant.

Others

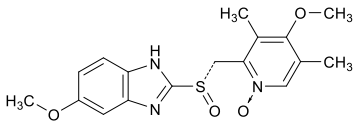
Related substances D (omeprazole sulfone):

5-Methoxy-2-{[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]sulfonyl}-1*H*-benzimidazole



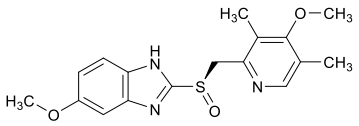
Related substances E:

4-Methoxy-2-{[(*S*)-(5-methoxy-1*H*-benzimidazol-2-yl)sulfinyl]methyl}-3,5-dimethylpyridine 1-oxide



Related substances F (enantiomer):

(*R*)-5-Methoxy-2-{[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]sulfinyl}-1*H*-benzimidazole



Add the following to 9.01 Reference Standards (1).

Omeprazole RS

Add the following to 9.41 Reagents, Test Solutions.

Omeprazole sulfone $C_{17}H_{19}N_3O_4S$: 361.42

Description It occurs as a white to brown powder.

Identification Determine the ^1H spectrum of a solution of Omeprazole sulfone in deuterated dimethyl sulfoxide for nuclear magnetic resonance spectroscopy (1 in 100) as directed under Nuclear Magnetic Resonance Spectroscopy *<2.21>*, using tetramethylsilane for nuclear magnetic resonance spectroscopy as an internal reference compound: it exhibits a singlet signal A at around δ 2.17 ppm, a singlet signal B at around δ 2.20 ppm, a singlet signal C at around δ 3.68 ppm, a singlet signal D at around δ 3.82 ppm, a singlet signal E at around δ 5.01 ppm, a broad singlet signal F at around δ 7.61 ppm, and a singlet signal G at around δ 8.04 ppm. The ratio of the integrated intensity of each signal, A:B:C:D:E:F:G is about 3:3:3:3:2:1:1 (When the frequency is 500 MHz).