Esomeprazole Magnesium Delayed-release Capsules

エソメプラゾールマグネシウム腸溶カプセル

Esomeprazole Magnesium Delayed-release Capsules contain not less than 90.0% and not more than105.0% of the labeled amount of Esomeprazole ($C_{17}H_{19}N_3O_3S$: 345.42).

Method of preparation Prepare as directed under Capsules, with Esomeprazole Magnesium Hydrate.

Identification Take out the contents of Esomeprazole Magnesium Delayed-release Capsules, equivalent to 20 mg of esomeprazole ($C_{17}H_{19}N_3O_3S$), add about 120 mL of the dissolving solution, and shake for 20 minutes. Then, add 40 mL of ethanol (95) and sonicate to dissolve. To this solution add the dissolving solution to make 200 mL. Filter this solution through a membrane filter with a pore size not exceeding 1 μm, to 5 mL of the filtrate add water to make 50 mL, and use this solution as the sample solution. Separately, dissolve 20 mg of Omeprazole RS in 20 mL of ethanol (95), and add the dissolving solution to make 100 mL. To 5 mL of this solution add water to make 50 mL, and use this solution as the standard solution. Perform the test with 20 μL of the sample solution and standard solution as directed under Liquid Chromatography <*2.01*> according to the following conditions: the retention times of the principal peak obtained from the sample solution and the peak that elutes late of the two principal peaks from the standard solution are the same.

Dissolving solution: Dissolve 5.24 g trisodium phosphate dodecahydrate in 110 mL of 0.5 mol/L disodium hydrogen phosphate TS and water to make 1000 mL. If necessary, adjust to pH 11.0 ± 0.2 with sodium hydroxide TS or a solution of phosphoric acid (17 in 250).

Operating conditions—

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

Column: A stainless steel column 4 mm in inside diameter and 10 cm in length, packed with α1-acid glycoprotein binding silica gel for liquid chromatography (5 μm in particle diameter).

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

Mobile phase: Dissolve 21.2 g of anhydrous disodium hydrogen phosphate and 62.4 g of sodium dihydrogen phosphate dihydrate in water to make 1000 mL, and, if necessary, adjust to pH 6.0 with sodium hydroxide TS or a solution of phosphoric acid (17 in 250). To 85 mL of this solution add 150 mL of acetonitrile and water to make 1000 mL.

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

System suitability—

System performance: When the procedure is run with 20 μL of the standard solution under the above operating conditions, the resolution between the two principal peaks is not less than 1.5.

Purity Related substances—Conduct this procedure without exposure to light within 2 hours after preparation of the sample solution, using a light-resistant vessels. Take out the contents of Esomeprazole Magnesium Delayed-release Capsules, and powder. To a portion of the powder, equivalent to 20 mg of esomeprazole ($C_{17}H_{19}N_3O_3S$), add 20 mL of methanol, shake for 30 seconds, add 40 mL of the dissolving solution, shake for 30 seconds, then sonicate to dissolve, and add water to make 200 mL. Filter this solution through a membrane filter with a pore size not exceeding 0.45 μm, discard the first 3 mL of the filtrate and use the subsequent filtrate 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 amounts of the peaks of related substance D having the relative retention time of about 0.9 to esomeprazole, related substance G having the retention time of about 0.2 and related substance H having the retention time of about 0.3 are not more than 0.5%, respectively, and the amount of the peak other than esomeprazole and the peaks mentioned above is not more than 0.2%. Furthermore, the total amount of the peaks other than esomeprazole is not more than 2%.

Dissolving solution: Dissolve 5.24 g of trisodium phosphate dodecahydrate in 110 mL of 0.5 mol/L disodium hydrogen phosphate TS and water to make 1000 mL. If necessary, adjust to pH 11.0 ± 0.2 with sodium hydroxide TS or a solution of phosphoric acid (17 in 250) .

Operating conditions—

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

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

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

Mobile phase A: 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, and, if necessary, adjust to pH 7.6 with sodium hydroxide TS or a solution of phosphoric acid (17 in 250). To 100 mL of this solution and 100 mL of acetonitrile add water to make 1000 mL.

Mobile phase B: 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, and, if necessary, adjust to pH 7.6 with sodium hydroxide TS or a solution of phosphoric acid (17 in 250). To 10 mL of this solution and 800 mL of acetonitrile add water to make 1000 mL.

Flowing of mobile phase: Control the gradient by mixing the mobile phases A and B as directed in the following table.

Time after injection of sample (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 — 10	100 → 80	0 → 20
10 — 30	80 → 0	20 → 100

Flow rate: 1.0 mL per minute.

Time span of measurement: About 2 times as long as the retention time of omeprazole, beginning after the solvent peak.

System suitability—

Test for required detectability: Dissolve 5 mg of Omeprazole RS in 5 mL of methanol, and add 10 mL of the dissolving solution and water to make 50 mL. To 2 mL of this solution, add a mixture of water, the dissolving solution and methanol (7:2:1) to make 100 mL. To 2.5 mL of this solution, add a mixture of water, the dissolving solution and methanol (7:2:1) to make 100 mL. When the procedure is run with 20 μL of this solution under the above operating conditions, the SN ratio of the peak of omeprazole is not less than 10.

System performance: Dissolve 5 mg each of Omeprazole RS and omeprazole sulfone in 5 mL each of methanol, add 10 mL of the dissolving solution and water to make 50 mL. To 1 mL each of these solutions add 20 mL of the dissolving solution and water to make 100 mL. When the procedure is run with 20 μL of this solution under the above operating conditions, omeprazole sulfone and omeprazole are eluted in this order with the resolution between these peaks being not less than 2.5.

Uniformity of dosage units *<6.02>* Perform the Mass variation test, or the Content uniformity test according to the following method: it meets the requirement.

Take out the content of 1 capsule of Esomeprazole Magnesium Delayed-release Capsules, add 60 mL of the dissolving solution, shake for 20 minutes, if necessary, sonicate to disintegrate, then add 20 mL of ethanol (95), sonicate to dissolve, and add the dissolving solution to make exactly 100 mL. Filter this solution through a membrane filter with a pore size not exceeding 1 μm, discard the first 3 mL of the filtrate, pipet 10 mL of the subsequent filtrate, add water to make exactly V mL so that each mL contains about 40 μg of esomeprazole ($C_{17}H_{19}N_3O_3S$), and use this solution as the sample solution. Then, proceed as directed in the Assay.

Amount (mg) of esomeprazole ($C_{17}H_{19}N_3O_3S$)
$= M_S \times A_T / A_S \times V / 50$

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

Dissolving solution: Dissolve 5.24 g of trisodium phosphate dodecahydrate in 110 mL of 0.5 mol/L disodium hydrogen phosphate TS and water to make 1000 mL. If necessary, adjust to pH 11.0 ± 0.2 with sodium hydroxide TS or a solution of phosphoric acid (17 in 250).

Dissolution *<6.10>* After stirring at 100 revolutions per minute according to the Paddle method for 2 hours, using 300 mL of 0.1 mol/L hydrochloric acid TS as the dissolution medium, subsequently add 700 mL of a solution prepared by dissolving 12.21 g of anhydrous disodium hydrogen phosphate in water to make 1000 mL, and then the test is performed at 100 revolutions per minute according to the Paddle method, the values Q in 30 minutes of a 10-mg capsule and a 20-mg capsule are 75%.

Start the test with 1 capsule of Esomeprazole Magnesium Delayed-release Capsules, withdraw not less than 10 mL of the medium at the specified minute after starting the test, and filter through a membrane filter with a pore size not exceeding 1 μm. Discard not less than 2 mL of the first filtrate, pipet 5 mL of the subsequent filtrate, add exactly 1 mL of 0.25 mol/L sodium hydroxide TS, and use this solution as the sample solution. Separately, weigh accurately about 20 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 ethanol (95), and add the dissolving solution to make exactly 100 mL. Dilute this solution as follows.

10-mg capsule: pipet 5 mL of this solution, and immediately add the dissolving solution to make exactly 100 mL.

20-mg capsules: pipet 5 mL of this solution, and immediately add the dissolving solution to make exactly 50 mL.

Immediately pipet 5 mL of this solution, immediately add exactly 1 mL of 0.25 mol/L sodium hydroxide TS, and use this solution as the standard solution. Perform the test with exactly 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 in the sample solution and the peak area, A_S, of omeprazole in the standard solution.

Dissolution rate (%) with respect to the labeled amount of esomeprazole ($C_{17}H_{19}N_3O_3S$)
$= M_S \times A_T / A_S \times 1 / V \times 1 / C \times 5000$

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

C: Labeled amount (mg) of esomeprazole ($C_{17}H_{19}N_3O_3S$) in 1 capsule

V: 100 for a 10-mg capsule and 50 for a 20-mg capsule

Dissolving solution: Dissolve 12.21 g of anhydrous disodium hydrogen phosphate in water to make 1000 mL. To 700 mL of this solution add 300 mL of 0.1 mol/L hydrochloric acid TS.

Operating conditions—

Proceed as directed in the operating conditions in the Assay.

System suitability—

Proceed as directed in the system suitability in the Assay.

Assay Take out the contents of not less than 20 Esomeprazole Magnesium Delayed-release Capsules, weigh accurately the mass of the contents, and mix uniformly. Weigh accurately an amount, equivalent to about 20 mg of esomeprazole ($C_{17}H_{19}N_3O_3S$), add 60 mL of the dissolving solution, shake for 20 minutes, and, if necessary, sonicate to disintegrate. Then, add 20 mL of ethanol (95), sonicate to dissolve, and add the dissolving solution to make exactly 100 mL. Filter this solution through a membrane filter with a pore size not exceeding 1 μm, discard the first 3 mL of the filtrate, pipet 5 mL of the subsequent filtrate, add water to make exactly 25 mL, and use this solution as the sample solution. Separately, weigh accurately about 20 mg of Omeprazole RS (separately determine the Loss on drying <*2.41*> in vacuum at 50℃ for 2 hours using phosphorous (V) oxide as a desiccant, using 1 g of Omeprazole RS), dissolve in 20 mL of ethanol (95), and add the dissolving solution to make exactly 100 mL. Pipet 5 mL of this solution, add water to make exactly 25 mL, and use this solution as the standard solution. Perform the test with exactly 20 μL 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 in the sample solution and the peak area, A_S, of omeprazole in the standard solution.

$$\text{Amount (mg) of esomeprazole } (C_{17}H_{19}N_3O_3S) = M_S \times A_T / A_S$$

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

Dissolving solution: Dissolve 5.24 g of trisodium phosphate dodecahydrate in 110 mL of 0.5 mol/L disodium hydrogen phosphate TS and water to make 1000 mL. If necessary, adjust to pH 11.0 ± 0.2 with sodium hydroxide TS or a solution of phosphoric acid (17 in 250).

Operating conditions—

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

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

Column temperature: A constant temperature of about 22℃.

Mobile phase: To 10.5 mL of a solution of sodium dihydrogen phosphate dihydrate (39 in 250) add 60 mL of 0.5mol/L disodium hydrogen phosphate TS and water to make 1000 mL, and, if necessary, adjust to pH 7.3 with sodium hydroxide TS or a solution of phosphoric acid (17 in 250). To 500 mL of this solution add 350 mL of acetonitrile and water to make 1000 mL.

Flow rate: 1.0 mL per minute.

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%.

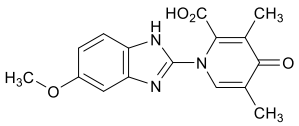
Containers and storage Containers—Tight containers.

Others

Related substances D: Refer to it described in Esomeprazole Magnesium Hydrate.

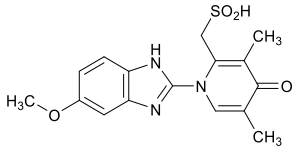
Related substances G:

1-(5-Methoxy-1*H*-benzimidazol-2-yl)-3,5-dimethyl-4-oxo-1,4-dihydropyridine-2-carboxylic acid



Related substances H:

[1-(5-Methoxy-1*H*-benzimidazol-2-yl)-3,5-dimethyl-4-oxo-1,4-dihydropyridin-2-yl]methanesulfinic acid



9.01 Add the following to Reference Standards (1) section.

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 ^{1}H 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).

0.25 mol/L Sodium hydroxide TS To 50 mL of 0.5 mol/L sodium hydroxide TS add water to make 100 mL.