Edition: BP 2025 (Ph. Eur. 11.6 update)

Esomeprazole Gastro-resistant Granules

General Notices

Action and use

Proton pump inhibitor; treatment of peptic ulcer disease.

DEFINITION

Esomeprazole Granules contain Esomeprazole Magnesium Trihydrate in a suitable basis. The granules are covered with a gastro-resistant coating.

The granules comply with the requirements stated under Granules and with the following requirements.

Content of esomeprazole, $C_{17}H_{19}N_3O_3S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Record the UV spectrum of the principal peak in the chromatograms obtained with solutions (1) and (2) with a diode array detector in the range of 210 to 400 nm.

Solution A 11 volumes of 0.25M *trisodium orthophosphate*, 22 volumes of 0.5M *disodium hydrogen orthophosphate* and 67 volumes of *water*. Adjust to pH 11.0 with *orthophosphoric acid* or 10M *sodium hydroxide*.

(1) Shake a quantity of the granules containing the equivalent of 50 mg of esomeprazole in 100 mL of *water* and filter (a 0.2-mm mesh sieve is suitable). Rinse the granules on the sieve with 0.1mM *hydrochloric acid*. Disperse the granules in 100 mL of solution A, add 100 mL of *water* and dilute with *ethanol* to produce 250 mL and mix. To 1 volume, add 1 volume of *water*, dilute to 20 volumes with solution A and filter (a 0.45-µm PVDF filter is suitable).
(2) 0.001% w/v of *omeprazole BPCRS* in solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.0 mm) packed with *α_1-acid-glycoprotein silica gel for chiral separation* (5 µm) (Chiralpak AGP is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 0.6 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 302 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

13 volumes of *acetonitrile* and 87 volumes of a solution containing 0.0025M *disodium hydrogen orthophosphate* and 0.005 M *sodium dihydrogen orthophosphate*.

When the chromatograms are recorded under the prescribed conditions, the relative retention with reference to esomeprazole (retention time about 5 minutes) is: *(R)*-omeprazole (impurity F), about 0.7.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *resolution* between the peaks due to *(R)*-omeprazole and esomeprazole is at least 3.0.

CONFIRMATION

The UV spectrum of the principal peak in the chromatogram obtained with solution (1) is concordant with that of the peak due to esomeprazole in the chromatogram obtained with solution (2);

the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak due to esomeprazole in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

Solution A 11 volumes of 0.25M *trisodium orthophosphate*, 22 volumes of 0.5M *disodium hydrogen orthophosphate* and 67 volumes of *water*. Adjust to pH 11.0 with *orthophosphoric acid* or 10M *sodium hydroxide*.

Solution B 0.1 volumes of 10M *sodium hydroxide* and 10 volumes of *0.05M phosphate buffer solution pH 4.5*.

Solution C 5.2 volumes of 1M *anhydrous sodium dihydrogen orthophosphate* and 63.2 volumes of 0.5M *anhydrous disodium hydrogen orthophosphate* and dilute to 1000 volumes with *water*. Adjust to pH 7.6 with *orthophosphoric acid* or 10M *sodium hydroxide*.

First stage (pH 4.5)

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 100 revolutions per minute.
(b) Use 700 mL of *0.05M phosphate buffer solution pH 4.5*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 60 minutes withdraw 5 mL of the medium and filter (a 0.45-µm nylon filter is suitable). Dilute 1 volume of the filtrate to 5 volumes with solution A and retain the samples for analysis. Proceed immediately to the final stage.
(2) 0.0002% w/v of *omeprazole BPCRS* in a mixture of 1 volume of solution A and 9 volumes of *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 2 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable). Use a suitable guard column.
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 0.25 mL per minute.
(d) Use a column temperature of 30°.
(e) Use a detection wavelength of 302 nm.
(f) Inject 10 µL of each solution.

MOBILE PHASE

25 volumes of solution C, 35 volumes of *water* and 40 volumes of *acetonitrile*, adjusted to pH 7.6 with *orthophosphoric acid* or 10M *sodium hydroxide*.

When the chromatograms are recorded under the prescribed conditions, the retention time of omeprazole is about 4 minutes.

SYSTEM SUITABILITY

The *symmetry factor* of the peak due to omeprazole is between 0.8 and 2.0.

DETERMINATION OF CONTENT

Calculate the total content of $C_{17}H_{19}N_3O_3S$ in the medium using the declared content of $C_{17}H_{19}N_3O_3S$ in *omeprazole BPCRS*.

LIMITS

The amount of esomeprazole released is not more than 10% of the stated amount.

Final stage (pH 6.8)

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 100 revolutions per minute.
(b) Within 1 minute of withdrawing the medium at completion of the first stage, add 200 mL of solution B, at a temperature of 37°, to the vessel.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes withdraw a sample of the medium and filter (a 0.45-µm nylon filter is suitable). To a volume of the filtrate expected to contain the equivalent of 0.05 mg of esomeprazole, add 1 volume of 0.25M *sodium hydroxide* and dilute to 25 volumes with solution A.
(2) 0.001% w/v of *omeprazole BPCRS* in a mixture of 1 volume of solution A and 9 volumes of *water*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under the first stage may be used.

SYSTEM SUITABILITY

The *symmetry factor* of the peak due to omeprazole is between 0.8 and 2.0.

DETERMINATION OF CONTENT

Calculate the total content of $C_{17}H_{19}N_3O_3S$, in the medium using the declared content of $C_{17}H_{19}N_3O_3S$, in *omeprazole BPCRS*.

LIMITS

The amount of esomeprazole released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution A 11 volumes of 0.25M *trisodium orthophosphate*, 22 volumes of 0.5M *disodium hydrogen orthophosphate* and 67 volumes of *water*. Adjust to pH 11.0 with *orthophosphoric acid* or 10M *sodium hydroxide*.

(1) Shake a quantity of the granules containing the equivalent of 50 mg of esomeprazole in 100 mL of *water* and filter (a 0.2 mm mesh sieve is suitable). Rinse the granules on the sieve with 0.1mM *hydrochloric acid*. Disperse the granules in 100 mL of solution A, add 100 mL of *water* and dilute with *ethanol* to produce 250 mL and mix. Dilute 1 volume to 2 volumes with *water* and filter (a 0.45-µm PVDF filter is suitable).
(2) Dilute 1 volume of solution (1) to 20 volumes with solution A. Dilute 1 volume of this solution to 10 volumes with *water*.
(3) 0.0001% w/v each of *omeprazole BPCRS* and *omeprazole impurity D EPCRS*, prepared by dissolving the reference materials in 1 volume of *ethanol*, adding 2 volumes of solution A and diluting to 10 volumes with *water*.
(4) Dilute 1 volume of solution (2) to 5 volumes with *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *octylsilyl silica gel for chromatography* (5 µm) (Microspher C8 is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 302 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

Solution D 5.2 volumes of 1.0M *sodium dihydrogen orthophosphate monohydrate*, 63 volumes of 0.5M *disodium hydrogen orthophosphate dihydrate* and dilute to 1000 volumes with *water*. Adjust to pH 7.6 with *orthophosphoric acid* or 10M *sodium hydroxide*.

Mobile phase A 100 volumes of *acetonitrile*, 100 volumes of solution D and dilute to 1000 volumes with *water*.

Mobile phase B 10 volumes of solution A, 800 volumes of *acetonitrile* and dilute to 1000 volumes with *water*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-1	100	0	isocratic
1-11	100→80	0→20	linear gradient
11-31	80→0	20→100	linear gradient
31-32	0→100	100→0	linear gradient
32-46	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to esomeprazole (retention time about 18 minutes) are: impurity 3, about 0.25; impurity 4, about 0.42; impurity 1, about 0.43; impurity A, about 0.5; impurity E, about 0.8; impurity D, about 0.95; impurity 2, about 1.1; impurity C, about 1.2, and impurity G, about 1.4 (2 peaks may be seen).

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *resolution* between the peaks due to impurity D and omeprazole is at least 2.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity D is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peak* is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all *secondary peaks* is not greater than 4 times the area of the principal peak in the chromatogram obtained with solution (2) (2%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Weigh and powder the contents of 20 sachets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution A 11 volumes of 0.25M *trisodium orthophosphate*, 22 volumes of 0.5M *disodium hydrogen orthophosphate* and 67 volumes of *water*. Adjust to pH 11.0 with *orthophosphoric acid* or 10M *sodium hydroxide*.

(1) Shake a quantity of powdered granules containing the equivalent of 50 mg of esomeprazole with 200 mL of solution A, add 50 mL of *ethanol* and dilute to produce 500 mL with solution A. Dilute 1 volume to 25 volumes with a solution

containing 1 volume of *ethanol*, 4 volumes of *water* and 20 volumes of solution A and filter (a 1-µm glass fibre filter is suitable).
(2) 0.002% w/v of *omeprazole BPCRS* in a mixture of 1 volume of *ethanol* and 4 volumes of solution A. Dilute 1 volume to 5 volumes with *water*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used.

DETERMINATION OF CONTENT

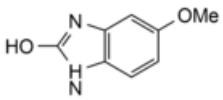
Calculate the content of $C_{17}H_{19}N_3O_3S$ in the granules using the declared content of $C_{17}H_{19}N_3O_3S$ in *omeprazole BPCRS*.

LABELLING

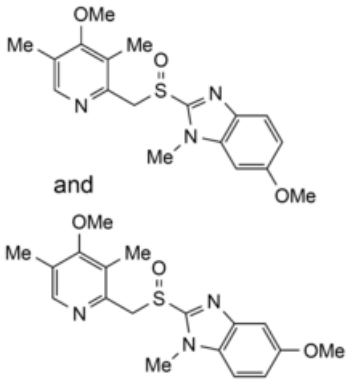
The quantity of active ingredient is stated in terms of the equivalent amount of esomeprazole.

IMPURITIES

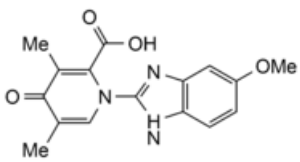
The impurities limited by the requirements of this monograph include impurities A, C, D and E listed under Esomeprazole Magnesium Dihydrate and Esomeprazole Magnesium Trihydrate, impurity G listed under Esomeprazole Sodium and:



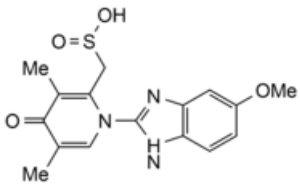
1. 2-hydroxy-5-methoxybenzimidazole (5-methoxy-2-benzimidazolinone),



2. 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1-methyl-1*H*-benzimidazole and 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1-methyl-1*H*-benzimidazole, regioisomers,



3. 1,4-dihydro-1-(5-methoxy-1*H*-benzimidazol-2-yl)-3,5-dimethyl-4-oxo-2-pyridinecarboxylic acid,



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