

Esomeprazole Magnesium

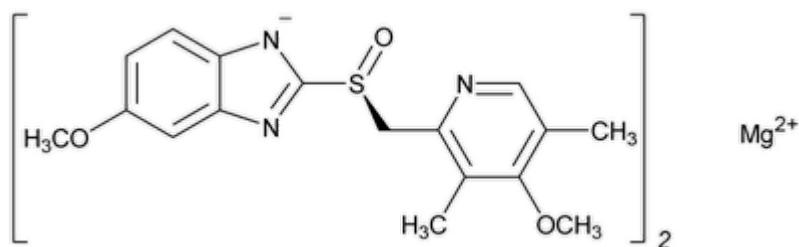
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Expert Committee	Small Molecules 3

In accordance with the Rules and Procedures of the Council of Experts, the Small Molecules 3 Expert Committee has revised the Esomeprazole Magnesium monograph. The purpose of this revision is to widen the *Acceptance criteria* for the *Content of Magnesium* test from 3.30%–3.55% on the anhydrous basis to 3.30%–3.70% on the anhydrous basis.

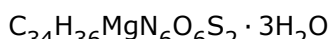
The Esomeprazole Magnesium Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Claire Chisolm, Senior Scientist II (301-230-3215 or cnc@usp.org).

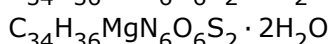
Esomeprazole Magnesium



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Trihydrate: 767.17



Dihydrate: 749.15



Anhydrous: 713.12

1*H*-Benzimidazole,5-methoxy-2-[(*S*)-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-, magnesium salt (2:1)

5-Methoxy-2-[(*S*)-[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]benzimidazole, magnesium salt (2:1)

Trihydrate: CAS RN[®]: 217087-09-7; UNII: R6DXU4WAY9.

Dihydrate: CAS RN[®]: 217087-10-0; UNII: 36H71644EQ.

DEFINITION

Esomeprazole Magnesium contains NLT 98.0% and NMT 102.0% of esomeprazole magnesium

($C_{34}H_{36}MgN_6O_6S_2$), calculated on the anhydrous basis.

IDENTIFICATION

- **A. SPECTROSCOPIC IDENTIFICATION TESTS** (197), *Infrared Spectroscopy*: 197K. [NOTE—If a difference appears in the IR spectra of the analyte and the Standard, separately dissolve equal portions of the sample specimen and [USP Esomeprazole Magnesium RS](#) in equal volumes of methanol, evaporate the solution to dryness in similar containers under identical conditions, and repeat the test on the residues.]
- **B.** The *Sample solution*, prepared and tested as directed in the test for *Content of Magnesium*, exhibits a significant absorption at 285.2 nm.
- **C.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

PROCEDURE

Solution A: 0.181 g/L of [sodium phosphate monobasic](#) and 1.118 g/L of [sodium phosphate dibasic anhydrous](#) in [water](#). If necessary, adjust with [phosphoric acid](#) to a pH of 7.6.

Solution B: Mix 11 mL of 0.25 M [sodium phosphate tribasic](#) with 22 mL of 0.5 M [sodium phosphate dibasic](#), and dilute with [water](#) to 100 mL.

Mobile phase: [Acetonitrile](#) and *Solution A* (35:65)

Standard solution: 0.05 mg/mL of [USP Omeprazole RS](#) prepared as follows. Transfer 10 mg of [USP Omeprazole RS](#) to a 200-mL volumetric flask, and dissolve in about 10 mL of [methanol](#). Add 10 mL of

Solution B, and dilute with [water](#) to volume.

Sample solution: 0.05 mg/mL of Esomeprazole Magnesium prepared as follows. Transfer 10 mg of Esomeprazole Magnesium to a 200-mL volumetric flask, and dissolve in about 10 mL of [methanol](#). Add 10 mL of *Solution B*, and dilute with [water](#) to volume.

Chromatographic system

(See [Chromatography \(621\)](#), [System Suitability](#).)

Mode: LC

Detector: UV 280 nm

Column: 4.0-mm × 12.5-cm or 4.6-mm × 15-cm; 5-μm packing [L7](#). [NOTE—Alternatively, a 3.9-mm × 15-cm column; 4-μm packing [L1](#) may be used.]

Flow rate: 1.0 mL/min

Injection volume: 20 μL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.5

Relative standard deviation: NMT 1.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of esomeprazole magnesium ($C_{34}H_{36}MgN_6O_6S_2$) in the portion of Esomeprazole Magnesium taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times [M_{r1}/(2 \times M_{r2})] \times 100$$

r_U = peak response of esomeprazole from the *Sample solution*

r_S = peak response of omeprazole from the *Standard solution*

C_S = concentration of [USP Omeprazole RS](#) in the *Standard solution* (mg/mL)

C_U = concentration of Esomeprazole Magnesium in the *Sample solution* (mg/mL)

M_{r1} = molecular weight of esomeprazole magnesium, 713.12

M_{r2} = molecular weight of omeprazole, 345.42

Acceptance criteria: 98.0%–102.0% on the anhydrous basis

OTHER COMPONENTS

Change to read:

● CONTENT OF MAGNESIUM

Lanthanum solution: Transfer 58.7 g of lanthanum oxide to a 1000-mL volumetric flask, wet the substance with some water, and dissolve by cautious addition of 250 mL of hydrochloric acid in 20- to 30-mL portions, cooling between the additions. Add water while stirring, cool to room temperature, and dilute with water to volume. [NOTE—Store the solution in a plastic bottle.]

Standard stock solution: 1000 μg/mL of magnesium in water, from a commercially prepared atomic absorption standard solution. [NOTE—Store the solution in a plastic bottle.]

Standard solution A: Transfer 10.0 mL of *Standard stock solution* to a 500-mL volumetric flask, add 50 mL of 1 N hydrochloric acid, and dilute with water to volume. Transfer 20.0 mL of this solution to a

200-mL volumetric flask, and dilute with water to volume. [NOTE—This solution contains 2 µg/mL of magnesium.]

Standard solution B: Combine 5.0 mL of *Standard solution A* and 4.0 mL of *Lanthanum solution*, and dilute with water to 100.0 mL (0.1 µg/mL).

Standard solution C: Combine 10.0 mL of *Standard solution A* and 4.0 mL of *Lanthanum solution*, and dilute with water to 100.0 mL (0.2 µg/mL).

Standard solution D: Combine 15.0 mL of *Standard solution A* and 4.0 mL of *Lanthanum solution*, and dilute with water to 100.0 mL (0.3 µg/mL).

Standard solution E: Combine 20.0 mL of *Standard solution A* and 4.0 mL of *Lanthanum solution*, and dilute with water to 100.0 mL (0.4 µg/mL).

Standard solution F: Combine 25.0 mL of *Standard solution A* and 4.0 mL of *Lanthanum solution*, and dilute with water to 100.0 mL (0.5 µg/mL). [NOTE—Concentrations of the *Standard solutions* and the *Sample solution* may be modified to fit the linear or working range of the instrument. When using instruments with a linear calibration graph, the number of *Standard solutions* can be reduced.]

Sample solution: Transfer 250 mg of Esomeprazole Magnesium to a 100-mL volumetric flask, add 20 mL of 1 N hydrochloric acid, swirl until dissolved, and dilute with water to volume. Allow to stand for 30 min. Transfer 10.0 mL of this solution to a 200-mL volumetric flask, and dilute with water to volume. Transfer 10.0 mL of the solution to another 100-mL volumetric flask, add 4.0 mL of *Lanthanum solution*, and dilute with water to volume.

Blank: Transfer 4.0 mL of *Lanthanum solution* to a 100-mL volumetric flask, and dilute with water to volume.

Instrumental conditions

(See [Atomic Absorption Spectroscopy \(852\)](#).)

Mode: Atomic absorption spectrophotometry

Flame: Air–acetylene

Analytical wavelength: 285.2 nm

Analysis

Samples: *Standard solution B*, *Standard solution C*, *Standard solution D*, *Standard solution E*, *Standard solution F*, *Sample solution*, and *Blank*

Determine the concentration, C_S , in µg/mL, of magnesium in the *Sample solution* using the calibration graph.

Calculate the percentage of magnesium in the portion of Esomeprazole Magnesium taken:

$$\text{Result} = (C_S/C_U) \times [100/(100 - F)] \times 100$$

C_S = concentration of magnesium in the *Sample solution* as calculated above (µg/mL)

C_U = concentration of Esomeprazole Magnesium in the *Sample solution* (µg/mL)

F = content of water in Esomeprazole Magnesium, as determined in *Specific Tests, Water Determination (%)*

Acceptance criteria: ▲ 3.30%–3.70% ▲ (RB 20-Dec-2022) on the anhydrous basis

IMPURITIES

● ORGANIC IMPURITIES

Solution A: Prepare as directed in the *Assay*.

Mobile phase: [Acetonitrile](#) and *Solution A* (11:29). [NOTE—To improve the resolution, the composition may be changed to 1:3, if necessary.]

System suitability solution: 0.04 mg/mL each of [USP Omeprazole RS](#) and [USP Omeprazole Related Compound A RS](#) in *Mobile phase*.

Sample solution: 0.16 mg/mL of Esomeprazole Magnesium in *Mobile phase*. [NOTE—Prepare this solution fresh.]

Chromatographic system

(See [Chromatography](#) (621), [System Suitability](#).)

Mode: LC

Detector: UV 280 nm

Column: 4.0-mm × 12.5-cm or 4.6-mm × 15-cm; 5-μm packing [L7](#). [NOTE—Alternatively, a 3.9-mm × 15-cm column; 4-μm packing [L1](#) may be used.]

Flow rate: 0.8–1.0 mL/min

Injection volume: 50 μL

Run time: NLT 4.5 times the retention time of omeprazole

System suitability

Sample: *System suitability solution*

Suitability requirements

Resolution: NLT 3 between omeprazole related compound A and omeprazole

Analysis

Sample: *Sample solution*

Calculate the percentage of any individual impurity in the portion of Esomeprazole Magnesium taken:

$$\text{Result} = (r_U/r_T) \times 100$$

r_U = peak response of any individual impurity from the *Sample solution*

r_T = sum of all the peak responses from the *Sample solution*

Acceptance criteria: See [Table 1](#).

Table 1

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Omeprazole <i>N</i> -oxide ^a	0.45	0.1
Omeprazole related compound A	0.8	0.2
Esomeprazole	1.0	—
Any other individual impurity	—	0.1
Total impurities	—	0.5

^a 4-Methoxy-2-[[*(RS)*-(5-methoxy-1*H*-benzimidazol-2-yl)sulfinyl]methyl]-3,5-dimethylpyridine 1-oxide.

● ENANTIOMERIC PURITY

Solution A: Mix 70 mL of 1 M [sodium phosphate monobasic](#) with 20 mL of 0.5 M [sodium phosphate dibasic](#), and dilute with [water](#) to 1000 mL. Dilute 250 mL of this solution with [water](#) to 1000 mL.

Mobile phase: [Acetonitrile](#) and *Solution A* (15:85)

Diluent: Mix 11 mL of 0.25 M [sodium phosphate tribasic](#) with 22 mL of 0.5 M [sodium phosphate dibasic](#), and dilute with [water](#) to 1000 mL.

System suitability solution: 0.004 mg/mL of [USP Omeprazole RS](#) in *Diluent*

Sample solution: 0.03 mg/mL of Esomeprazole Magnesium prepared as follows. Dissolve 40 mg of Esomeprazole Magnesium in 5 mL of [methanol](#), and dilute with *Diluent* to 25 mL. Dilute 1 mL of this solution with *Diluent* to 50 mL.

Chromatographic system

(See [Chromatography](#) (621), [System Suitability](#).)

Mode: LC

Detector: UV 302 nm

Column: 4.0-mm × 10-cm; 5-µm packing [L41](#)

Flow rate: 0.6 mL/min

Injection volume: 20 µL

System suitability

Sample: *System suitability solution*

Suitability requirements

Resolution: NLT 3 between the enantiomer peaks. [NOTE—The elution order is the *R*-enantiomer, followed by the esomeprazole peak, which is the *S*-enantiomer.]

Analysis

Sample: *Sample solution*

Calculate the percentage of the *R*-enantiomer in the portion of Esomeprazole Magnesium taken:

$$\text{Result} = (r_U/r_T) \times 100$$

r_U = peak response of the *R*-enantiomer from the *Sample solution*

r_T = sum of the peak responses for esomeprazole and *R*-enantiomer from the *Sample solution*

Acceptance criteria: NMT 0.2% of the *R*-enantiomer

SPECIFIC TESTS

- **WATER DETERMINATION** (921), *Method I*

If labeled as trihydrate: 6.0%–8.0%

If labeled as dihydrate: 4.5%–7.0%

If labeled as amorphous: 7.0%–10.0%

- **CRYSTALLINITY** (695)(if it is labeled as amorphous): Most of the particles do not exhibit birefringence and extinction positions.

- **COLOR OF SOLUTION**

Sample solution: 20 mg/mL of Esomeprazole Magnesium in [methanol](#), filtered

Analysis: Determine the absorbance of this solution at 440 nm, in 1-cm cells, using methanol as the blank.

Acceptance criteria: NMT 0.2

ADDITIONAL REQUIREMENTS

● **PACKAGING AND STORAGE:** Preserve in tight containers, protected from light. Store at room temperature. If it is labeled as amorphous, store at 2°–8° under nitrogen atmosphere.

● **LABELING:** Where it is a dihydrate form, the label so indicates. Where it is an amorphous form, the label so indicates.

● **USP REFERENCE STANDARDS** (11)

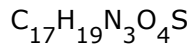
[USP Esomeprazole Magnesium RS](#)

[USP Omeprazole RS](#)

[USP Omeprazole Related Compound A RS](#)

Omeprazole sulfone;

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



361.42

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