Esomeprazole Magnesium Delayed-Release Capsules

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Expert Committee	Chemical Medicines Monographs 3
Reason for Revision	Compliance

In accordance with the Rules and Procedures of the 2015-2020 Council of Experts, the Chemical Medicines Monographs 3 Expert Committee has revised the Esomeprazole Magnesium Delayed-Release Capsules monograph. The purpose for the revision is to add *Dissolution Test* 2 for a drug product approved by the FDA. The analytical procedures for the Acid Resistance stage and the Buffer stage, although different, were validated using an XTerra RP8 brand of L7 column. The typical retention time for esomeprazole is about 9 minutse for the Acid Resistance stage and about 8 min for the Buffer stage.

The Esomeprazole Magnesium Delayed-Release Capsules Revision Bulletin supersedes the currently official monograph. The Revision Bulletin will be incorporated in the *First Supplement* to *USP 40–NF 35*.

Should you have any questions, please contact Elena Gonikberg, Ph.D., Principal Scientific Liaison, (301-816-8251 or eg@usp.org).

Esomeprazole Magnesium Delayed-Release Capsules

DEFINITION

Esomeprazole Magnesium Delayed-Release Capsules contain an amount of Esomeprazole Magnesium equivalent to NLT 90.0% and NMT 110.0% of the labeled amount of esomeprazole ($C_{17}H_{19}N_3O_3S$).

IDENTIFICATION

• **A.**

Buffer: Prepare a pH 6.0 phosphate buffer containing 26.6 g/L of dibasic sodium phosphate dihydrate and 55.2 g/L of monobasic sodium phosphate monohydrate in water.

Diluent: Prepare a pH 11.0 diluent as follows. Dissolve 5.24 g of tribasic sodium phosphate dodecahydrate in water. Add 110 mL of 0.5 M dibasic sodium phosphate solution, and dilute with water to 1000 mL.

Mobile phase: Transfer 150 mL of acetonitrile and 85 mL of the *Buffer* to a 1000-mL volumetric flask, and dilute with water to volume.

Standard stock solution: Prepare a solution containing 0.2 mg/mL of USP Omeprazole RS by dissolving a suitable amount first in alcohol, using 20% of the final volume, and then diluting with *Diluent* to volume.

Standard solution: 0.02 mg/mL of USP Omeprazole RS from the *Standard stock solution* in water

Sample stock solution: Transfer a portion of the Capsule content, equivalent to 20 mg of esomeprazole, to a 200-mL volumetric flask, add 120 mL of *Diluent*, and shake for 20 min to dissolve the pellets. Sonicate for a few min, if needed, to completely dissolve. Add 40 mL of alcohol, and sonicate for a few min. Cool, and dilute with *Diluent* to volume. Pass a portion of the solution through a filter of 1-µm pore size.

Sample solution: 0.01 mg/mL of esomeprazole from the *Sample stock solution* in water

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: 1 mL/min
Injection size: 20 µL

System suitability
Sample: *Standard solution*
[NOTE—The elution order is the *R*-enantiomer, followed by the esomeprazole peak, which is the *S*-enantiomer.]
Suitability requirements
Resolution: NLT 1.0 between the enantiomer peaks

Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the ratio of the retention times of the esomeprazole peak in the *Standard solution* and the *Sample solution*:

$$\text{Result} = (t_U/t_S)$$

t_U = retention time of esomeprazole from the *Sample solution*
t_S = retention time of esomeprazole from the *Standard solution*

Acceptance criteria: 0.98–1.02

ASSAY

• **PROCEDURE**

Buffer: Prepare a pH 7.3 phosphate buffer by mixing 10.5 mL of 1.0 M monobasic sodium phosphate buffer and 60 mL of 0.5 M dibasic sodium phosphate buffer, and diluting with water to 1000 mL.

Diluent: Prepare as directed in *Identification* test *A*.

Mobile phase: Mix 350 mL of acetonitrile and 500 mL of the *Buffer*. Dilute with water to 1000 mL.

Standard solution: Transfer 10 mg of USP Omeprazole RS to a 250-mL volumetric flask, and dissolve in about 10 mL of alcohol. Add 40 mL of *Diluent*, and dilute with water to volume. This solution contains 0.04 mg/mL of USP Omeprazole RS.

Sample stock solution: Mix the contents of NLT 20 Capsules. Transfer a portion of the Capsule content, equivalent to 20 mg of esomeprazole, to a 100-mL volumetric flask, add 60 mL of *Diluent*, and shake for 20 min to dissolve the pellets. Sonicate for a few min, if needed, to completely dissolve. Add 20 mL of alcohol, and sonicate for a few min. Cool, and dilute with *Diluent* to volume. Pass a portion of the solution through a filter of 1-µm pore size.

Sample solution: 0.04 mg/mL of esomeprazole from the *Sample stock solution* in water. Store this solution protected from light.

Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 302 nm
Column: 4.6-mm × 15-cm; 5-µm packing L1
Flow rate: 1 mL/min
Injection size: 20 µL

System suitability
Sample: *Standard solution*
Suitability requirements
Relative standard deviation: NMT 2.0%

Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of esomeprazole ($C_{17}H_{19}N_3O_3S$) in the portion of the Capsules taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Omeprazole RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of esomeprazole in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

• **DISSOLUTION** ⟨711⟩

•**Test 1**• (RB 1-Oct-2016)

Medium: 0.1 N hydrochloric acid; 300 mL. After 2 h, continue with a pH 6.8 phosphate buffer as follows. To the vessel, add 700 mL of 0.086 M dibasic sodium phosphate, and adjust with 2 N hydrochloric acid or 2 N sodium hydroxide, if necessary, to a pH of 6.8 ± 0.05.

Apparatus 2: 100 rpm
Time: 30 min in a pH 6.8 phosphate buffer

Standard solution: Prepare a solution containing 2 mg/mL of USP Omeprazole RS in alcohol. Dilute this solution with pH 6.8 phosphate buffer to obtain a solution containing (*L*/1000) mg/mL, where *L* is the label claim, in mg/Capsule. Immediately add 2.0 mL of 0.25 M sodium hydroxide to 10.0 mL of this solution, and mix. [NOTE—Do not allow the solution to stand before adding the sodium hydroxide solution.]

Sample solution: After 30 min in pH 6.8 phosphate buffer, pass a portion of the solution under test through a suitable filter. Transfer 5.0 mL of the filtrate to a suitable glassware containing 1.0 mL of 0.25 M sodium hydroxide. Mix well. Protect from light.

Buffer, Mobile phase, System suitability, and **Chromatographic system:** Proceed as directed in the *Assay*.

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of esomeprazole ($C_{17}H_{19}N_3O_3S$) dissolved:

$$\text{Result} = (r_U/r_S) \times (C_S/L) \times V \times 100$$

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of the *Standard solution* (mg/mL)
L = label claim (mg/Capsule)
V = volume of *Medium*, 1000 mL

Tolerances: NLT 75% (Q) of the labeled amount of esomeprazole ($C_{17}H_{19}N_3O_3S$) is dissolved.

•**Test 2:** If the product complies with this test, the labeling indicates that the product meets USP *Dissolution Test 2*.

Acid resistance stage

Acid stage medium: 0.1 N hydrochloric acid; 300 mL

Apparatus 2: 100 rpm

Time: 2 h

Solution A: Prepare a 0.05 M ammonium acetate buffer pH 7.6 as follows. Dissolve 3.85 g of ammonium acetate in 1000 mL of water, and adjust with a diluted ammonia solution to a pH of 7.6.

Solution B: Use acetonitrile.

Mobile phase: See *Table 1*. Return to original conditions and re-equilibrate the system for 5 min.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	80	20
5	77	23
8	77	23
10	50	50

Diluent: Dissolve 7.6 g of sodium borate in about 800 mL of water. Add 1.0 g of edetate disodium, and adjust with 50% sodium hydroxide solution to a pH of 11.0 ± 0.1. Transfer the solution to a 2000-mL volumetric flask, add 400 mL of dehydrated alcohol, and dilute with water to volume.

Standard solution: 0.12 mg/mL of USP Omeprazole RS in *Diluent*, using sonication at a temperature between 10° and 15° to dissolve. Protect this solution from light.

Sample solution: After 2 h, drain the *Acid stage medium* from each vessel and carefully transfer the pellets into a suitable volumetric flask (use a 100-mL flask for 20-mg Capsules and a 200-mL flask for 40-mg Capsules). Add *Diluent* to about 70% of the final volume, and sonicate at a temperature between 10° and 15° for about 20 min with intermittent shaking. Allow to cool, dilute with *Diluent* to volume, mix, and pass through a PVDF or other suitable filter of 0.45-µm or finer pore size. Further dilute 5 mL of this solution with *Diluent* to 10 mL. Protect this solution from light.

Chromatographic system

(See *Chromatography* ⟨621⟩, *System Suitability*.)

Mode: LC

Detector: UV 302 nm

Column: 4.6-mm × 15-cm; 5-µm packing L7

Column temperature: 30°

Flow rate: 1.5 mL/min

Injection volume: 20 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage, T, of the labeled amount of esomeprazole ($C_{17}H_{19}N_3O_3S$) retained:

$$\text{Result} = (r_U/r_S) \times C_S \times D \times (1/L) \times 100$$

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)
D = dilution factor used in preparing the *Sample solution*
L = label claim (mg/Capsule)

Calculate the percentage of the labeled amount of esomeprazole ($C_{17}H_{19}N_3O_3S$) dissolved:

$$\text{Result} = A - T$$

A = esomeprazole content as a percentage of the labeled amount, as determined in the *Assay*
T = percentage of the labeled amount of esomeprazole retained, as determined above

[NOTE—If T is greater than A, then consider the result to be zero.]

Tolerances: NMT 10% of the labeled amount of esomeprazole ($C_{17}H_{19}N_3O_3S$) is dissolved.

Buffer stage

Buffer stage medium: pH 6.8 phosphate buffer. Proceed as directed in *Acid resistance stage* with a new set of Capsules. After 2 h with *Acid stage medium*, continue with a pH 6.8 phosphate buffer as follows. To the vessel, add 700 mL of 0.086 M dibasic sodium phosphate, and adjust with 2 N hydrochloric acid or 2 N sodium hydroxide, if necessary, to a pH of 6.8 ± 0.05.

Apparatus 2: 100 rpm

Time: 30 min

Solution A: Prepare a 0.05 M ammonium acetate buffer pH 7.6 as follows. Dissolve 3.85 g of ammonium acetate in 1000 mL of water, and adjust with a diluted ammonia solution to a pH of 7.6 ± 0.05.

Mobile phase: Acetonitrile and *Solution A* (27:73)

Diluent: 0.086 M dibasic sodium phosphate buffer and 0.1 N hydrochloric acid (70:30). Adjust with 2 N hydrochloric acid or 2 N sodium hydroxide, if necessary, to a pH of 6.8 ± 0.05.

Standard stock solution: Prepare a solution containing 0.4 mg/mL of USP Omeprazole RS as follows. Dissolve first in alcohol, using 10% of the final volume, and then dilute with *Diluent* to volume. Protect this solution from light.

Standard solution: Dilute the *Standard stock solution* with *Diluent* to obtain a solution containing (L/1000) mg/mL, where L is the label claim, in mg/Capsule. Immediately transfer 10 mL of this solution to a test

tube containing 2.0 mL of 0.25 M sodium hydroxide, and mix. Protect this solution from light.
Sample solution: After 30 min, pass a portion of the solution under test through a PVDF or other suitable filter of 0.45-µm pore size. Immediately transfer 5.0 mL of the filtrate to a test tube containing 1.0 mL of 0.25 M sodium hydroxide. Mix well. Protect this solution from light.
Chromatographic system: Proceed as directed in *Acid resistance stage*, except use a flow rate of 1.0 mL/min.
System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 2.0
Relative standard deviation: NMT 2.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of esomeprazole ($C_{17}H_{19}N_3O_3S$) dissolved:

$$\text{Result} = (r_U/r_S) \times (C_S/L) \times D \times V \times 100$$

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of the *Standard solution* (mg/mL)
L = label claim (mg/Capsule)
D = dilution factor used to prepare the *Sample solution*
V = volume of *Medium*, 1000 mL
Tolerances: NLT 80% (Q) of the labeled amount of esomeprazole ($C_{17}H_{19}N_3O_3S$) is dissolved. ● (RB 1-Oct-2016)

- **UNIFORMITY OF DOSAGE UNITS ⟨905⟩:** Meet the requirements

IMPURITIES

- **ORGANIC IMPURITIES**

Buffer: Prepare a pH 7.6 phosphate buffer by mixing 5.2 mL of 1.0 M monobasic sodium phosphate buffer and 63 mL of 0.5 M dibasic sodium phosphate buffer, and diluting with water to 1000 mL.
Solution A: Mix 100 mL of acetonitrile and 100 mL of the *Buffer*. Dilute with water to 1000 mL.
Solution B: Mix 800 mL of acetonitrile and 10 mL of the *Buffer*. Dilute with water to 1000 mL.
Mobile phase: See *Table 2*.

Table 2

Time (min)	Solution A (%)	Solution B (%)
0	100	0
10	80	20
30	0	100
31	100	0
45	100	0

Diluent: Prepare as directed in *Identification* test *A*.
System suitability stock solution: 1 mg/mL each of USP Omeprazole RS and USP Omeprazole Related Compound A RS in methanol
System suitability solution: 1 µg/mL each of USP Omeprazole RS and USP Omeprazole Related Compound A RS from *System suitability stock solution*, in a mixture of *Diluent* and water (1:4)
Sample solution: Transfer a portion of the powdered pellets (about 80–90 mg), from the Capsule content, to a 200-mL volumetric flask, add 20 mL of methanol, and shake for 30 s. Add 40 mL of *Diluent*, shake for 30 s by hand, and sonicate for a few min. Cool, and dilute with water to volume. Pass a portion of the solution through a filter of 0.45-µm pore size. [NOTE—The solution is stable for 3 h if stored protected from light.]
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 302 nm
Column: 4.6-mm × 10-cm; 3-µm packing L1
Flow rate: 1 mL/min
Injection size: 20 µL
System suitability
Sample: *System suitability solution*
[NOTE—See *Table 3* for the relative retention times.]
Suitability requirements
Resolution: NLT 2.5 between omeprazole related compound A and omeprazole
Analysis
Sample: *Sample solution*
Calculate the percentage of any individual impurity in the portion of the Capsules taken:

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

r_U = peak response for each impurity
r_T = sum of all peak responses
Acceptance criteria: See *Table 3*.

Table 3

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Omeprazole sulfone[a]	0.93	0.5
Omeprazole	1.00	—
Any other individual impurity	—	0.2
Total impurities	—	2

[a] Omeprazole related compound A.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers. Store at room temperature.

Add the following:

●● **LABELING:** When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used. ● (RB 1-Oct-2016)

- **USP REFERENCE STANDARDS ⟨11⟩**

USP Omeprazole RS
USP Omeprazole Related Compound A RS
Omeprazole sulfone; 5-Methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfonyl]-1*H*-benzimidazole.
$C_{17}H_{19}N_3O_4S$ 361.42