Esomeprazole Magnesium Delayed-Release Capsules

Type of Posting	Revision Bulletin
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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 of the revision is to add *Dissolution Test 3* for a drug product approved by the FDA.

Dissolution Test 3 was validated using a Thermo Fisher Hypersil BDS C18 brand, 4.6 mm x 10 mm, L1 guard column and a Waters XBridge BEH C18 brand L1 column. The typical retention time for esomeprazole is about 3.5 min.

The Esomeprazole Magnesium Delayed-Release Capsules Revision Bulletin supersedes the currently official monograph. The Revision Bulletin will be incorporated in *USP 42–NF 37*.

Should you have any questions, please contact Andrea F. Carney, Associate Scientific Liaison, (301-816-8155 or afc@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
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.

•**Test 3:** If the product complies with this test, the labeling indicates that the product meets USP *Dissolution Test 3*.
[NOTE—Use only glass bowls.]
Acid resistance stage
Acid stage medium: 0.1 N hydrochloric acid; 300 mL
Apparatus 2: 100 rpm (*Acid stage medium*)
Time: 2 h
Buffer: Prepare a 25 mM potassium phosphate buffer pH 8.0 as follows. Dissolve 3.4 g of monobasic potassium phosphate in 1000 mL of water, add 8.0 mL of triethylamine, and adjust with phosphoric acid to a pH of 8.0.
Solution A: *Buffer* and methanol (90:10)
Solution B: Acetonitrile and methanol (50:50)
Mobile phase: See *Table 2*.

Table 2

Time (min)	Solution A (%)	Solution B (%)
0	85	15
3	65	35
4	65	35
4.5	20	80
5.5	20	80
6	85	15
8	85	15

Diluent 1: 0.3 N sodium hydroxide and methanol (10:90)
Diluent 2: 0.1 N sodium hydroxide and methanol (75:25)
[NOTE—Protect the *Standard stock solution*, *Standard solution*, and *Sample solution* from light.]
Standard stock solution: 0.4 mg/mL of USP Omeprazole RS prepared as follows. Dissolve a suitable amount of USP Omeprazole RS in a suitable volumetric flask containing 30% volume of 0.3 N sodium hydroxide, sonicate as needed to dissolve, and dilute to volume with *Diluent 1*.
Standard solution: Dilute the *Standard stock solution* with *Diluent 2* to obtain a solution containing (L/500) mg/mL, where L is the label claim, in mg/Capsule.
Sample solution: After 2 h, drain the *Acid stage medium* from each vessel carefully without losing any pellets. Add 250 mL of 0.25 N sodium hydroxide to each vessel and run the dissolution apparatus at 200 rpm for 30 min or until the pellets are completely dissolved. Centrifuge a portion of this solution at 3000 rpm for 10 min. Transfer 5.0 mL of this solution to a 10-mL volumetric flask, and dilute with *Diluent 2* to volume.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 305 nm
Column: 4.6-mm × 20-mm; 5-µm packing L1
[NOTE—A suitable L1 guard column may be used.]
Column temperature: 30°
Flow rate: 1.2 mL/min
Injection volume: 10 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:

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

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 to prepare the *Sample solution*
L = label claim (mg/Capsule)
V = volume of 0.25 N sodium hydroxide, 250 mL
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 stock solution: Prepare a 76-g/L solution of tribasic sodium phosphate in water.
Buffer stage medium: 0.1 N hydrochloric acid and *Buffer stock solution* (3:1). Adjust with 1 N hydrochloric acid or 1 N sodium hydroxide, if necessary, to pH 6.8.
Apparatus 2: 100 rpm
Time: 30 min
Standard solution: Dilute the *Standard stock solution* from *Acid resistance stage* with *Buffer stage medium* to

obtain a solution containing (*L*/1000) mg/mL, where *L* is the label claim, in mg/Capsule. Immediately transfer 5 mL of this solution to a test tube containing 1.0 mL of 0.25 M sodium hydroxide, and mix.

Sample solution: Proceed as directed in *Acid resistance stage* with a new set of Capsules. After 2 h with *Acid stage medium*, continue with *Buffer stage medium* as follows. Completely drain the vessel of *Acid stage medium* carefully without losing any pellets. Add 1000 mL of preheated *Buffer stage medium* to each vessel. After 30 min, pass a portion of the solution under test through a full flow or other suitable filter of 10-µm pore size. Immediately transfer 5 mL of the filtrate to a test tube containing 1 mL of 0.25 N sodium hydroxide, and mix.

Chromatographic system: Proceed as directed in *Acid resistance stage*, except for *Injection volume*.
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 of the labeled amount of esomeprazole ($C_{17}H_{19}N_3O_3S$) dissolved:

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

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 to prepare the *Sample solution*
L = label claim (mg/Capsule)
V = volume of *Buffer stage medium*, 1000 mL

Tolerances: NLT 75% (*Q*) of the labeled amount of esomeprazole ($C_{17}H_{19}N_3O_3S$) is dissolved.● (RB 1-Mar-2018)

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

IMPURITIES

Change to read:

- **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* ●3.● (RB 1-Mar-2018)

Table ●3● (RB 1-Mar-2018)

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* ●4● (RB 1-Mar-2018) 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* ●4.● (RB 1-Mar-2018)

Table ●4● (RB 1-Mar-2018)

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.
- **LABELING:** When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.
- **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