Esomeprazole Magnesium Delayed-Release Capsules

Type of Posting: Revision Bulletin
Posting Date: 23–Feb–2018
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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 (C₁₇H₁₉N₃O₃S).

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 100-mL volumetric flask, and dilute with water to volume.
  Sample solution: Transfer 150 mL of acetonitrile and protected from light. Mix 350 mL of acetonitrile and 500 mL of the Buffer. Dilute with water to 1000 mL.

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
[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:

\[
\text{Result} = \left( \frac{t_0}{t_s} \right) \times \left( \frac{C_S}{C_U} \right) \times 100
\]

\( t_0 \) = peak response from the Sample solution
\( t_s \) = 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.]
Esomeprazole

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$_3$O$_3$S) dissolved):

$$\text{Result} = \left(\frac{r_U}{r_S}\right) \times \left(\frac{C_s}{L}\right) \times V \times 100$$

$r_U$ = 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$_3$O$_3$S) 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>
<thead>
<tr>
<th>Time (min)</th>
<th>Solution A (%)</th>
<th>Solution B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>80</td>
<td>20</td>
</tr>
<tr>
<td>5</td>
<td>77</td>
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<td>8</td>
<td>77</td>
<td>23</td>
</tr>
<tr>
<td>10</td>
<td>50</td>
<td>50</td>
</tr>
</tbody>
</table>

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 x 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$_3$O$_3$S) retained:

$$\text{Result} = \left(\frac{r_U}{r_S}\right) \times C_s \times D \times (1/L) \times 100$$

$r_U$ = 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$_3$O$_3$S) 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

Tolerances: NMT 10% of the labeled amount of esomeprazole (C$_{17}$H$_{19}$N$_3$O$_3$S) 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 (C₁₇H₁₉N₃O₃S) dissolved:

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_i}{L} \right) \times D \times V \times 100
\]

- \( r_U = \) peak response from the Sample solution
- \( r_S = \) peak response from the Standard solution
- \( C_i = \) 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:** NMT 2.0% of the label claim

**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>
<thead>
<tr>
<th>Time (min)</th>
<th>Solution A (%)</th>
<th>Solution B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>85</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td>65</td>
<td>35</td>
</tr>
<tr>
<td>4</td>
<td>65</td>
<td>35</td>
</tr>
<tr>
<td>4.5</td>
<td>65</td>
<td>35</td>
</tr>
<tr>
<td>5.5</td>
<td>20</td>
<td>80</td>
</tr>
<tr>
<td>6</td>
<td>85</td>
<td>15</td>
</tr>
<tr>
<td>8</td>
<td>85</td>
<td>15</td>
</tr>
</tbody>
</table>

**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:** Prepare 0.4 mg/mL of USP Omeprazole RS 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 x 20-mm; 5-µm packing L1

[NOTE—A suitable L1 guard column may be used.]

**Column temperature:** 30°C

**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 (C₁₇H₁₉N₃O₃S) dissolved:

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_i}{L} \right) \times V \times 100
\]

- \( r_U = \) peak response of esomeprazole from the Sample solution
- \( r_S = \) peak response of esomeprazole from the Standard solution
- \( C_i = \) concentration of USP Omeprazole RS in the Sample solution (mg/mL)
- \( L = \) dilution factor used to prepare the Sample solution
- \( V = \) volume of 0.25 N sodium hydroxide, 250 mL

Calculate the percentage of the labeled amount of esomeprazole (C₁₇H₁₉N₃O₃S) dissolved:

\[
A = \text{esomeprazole content as a percentage of the labeled amount, as determined in the Assay}
\]

\[
T = \text{percentage of the labeled amount of esomeprazole retained, as determined above}
\]

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

**Tolerances:** NMT 10% of the labeled amount of esomeprazole (C₁₇H₁₉N₃O₃S) 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 \((C_{17}H_{19}N_{3}O_{3}S)\) dissolved:
    \[
    \text{Result} = \frac{r_U}{r_S} \times \frac{C_i \times D \times (1/L) \times V \times 100}{L \times V}
    \]
  - \(r_U\) = peak response of esomeprazole from the Sample solution
  - \(r_S\) = peak response of omeprazole from the Standard solution
  - \(C_i\) = 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 \((C_{17}H_{19}N_{3}O_{3}S)\) is dissolved.

- **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 10 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 34. (RB 1-Mar-2018)

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Solution A (%)</th>
<th>Solution B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>80</td>
<td>20</td>
</tr>
<tr>
<td>30</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>31</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>45</td>
<td>100</td>
<td>0</td>
</tr>
</tbody>
</table>

**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 34. (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:

\[
\text{Result} = \frac{r_U}{r_T} \times 100
\]

- \(r_U\) = peak response for each impurity
- \(r_T\) = sum of all peak responses

**Acceptance criteria:** See Table 34. (RB 1-Mar-2018)

**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**

- **USP Omeprazole RS**
- **USP Omeprazole Related Compound A RS**

- **Omeprazole sulfone**: S-Methoxy-2-[4-methoxy-3,5-dimethyl-2-pyridinyl]methylsulfonyl]-1H-benimidazole. \(C_{17}H_{19}N_{3}O_{3}S\) 361.42