Omeprazole Delayed-Release Capsules

Type of Posting: Notice of Intent to Revise
Posting Date: 27–Dec–2019
Targeted Official Date: To Be Determined, Revision Bulletin
Expert Committee: Chemical Medicines Monographs 3

In accordance with section 7.04 (c) of the 2015–2020 Rules and Procedures of the Council of Experts and the Pending Monograph Guideline, this is to provide notice that the Chemical Medicines Monographs 3 Expert Committee intends to revise the Omeprazole Delayed-Release Capsules monograph.

Based on the supporting data received from a manufacturer awaiting FDA approval, the Expert Committee proposes to add Dissolution Test 3 to accommodate different dissolution conditions and tolerances than the existing dissolution tests.

- The Acid stage of Dissolution Test 3 was validated using a Kromasil KR100-5-C18 brand of 4.6-mm x 25-cm column with 5-µm L1 packing. The typical retention time for omeprazole is about 14 min.
- The Buffer stage of Dissolution Test 3 was validated using an Xterra RP8 brand of 4.6-mm x 15-cm column with 5-µm L7 packing. The typical retention time for omeprazole is about 7 min.

The revision also necessitates a change in the table numbering in the test for Organic Impurities.

The proposed revision is contingent on FDA approval of a product that meets the proposed monograph specifications. The proposed revision will be published as a Revision Bulletin and an official date will be assigned to coincide as closely as possible with the FDA approval of the associated product.

See below for additional information about the proposed text.¹

Should you have any questions, please contact Andrea F. Carney, Scientific Liaison to the Chemical Medicines Monographs 3 Expert Committee (301-816-8155 or afc@usp.org).

¹ This text is not the official version of a USP–NF monograph and may not reflect the full and accurate contents of the currently official monograph. Please refer to the current edition of the USP–NF for official text.

USP provides this text to indicate changes that we anticipate will be made official once the product subject to this proposed revision under the Pending Monograph Program receives FDA approval. Once FDA approval is granted for the associated revision request, a Revision Bulletin will be posted that will include the changes indicated herein, as well as any changes indicated in the product’s final approval, combined with the text of the monograph as effective on the date of approval. Any revisions made to a monograph under the Pending Monograph Program that are posted without prior publication for comment in the Pharmacopeial Forum must also meet the requirements outlined in the USP Guideline on Use of Accelerated Processes for Revisions to the USP–NF.
Omeprazole Delayed-Release Capsules

**Definition**
Omeprazole Delayed-Release Capsules contain NLT 90.0% and NMT 110.0% of the labeled amount of omeprazole (C₁₇H₂₀N₃O₅S).

**Identification**
- A. The retention time of the major peak in the Sample solution corresponds to that of the Standard solution, as obtained in the Assay.

**Assay**

**Procedure**
- **Solution A**: Dissolve 6.0 g of glycine in 1500 mL of water, adjust with 50% sodium hydroxide solution to a pH of 9.0, and dilute with water to 2000 mL.
- **Solution B**: Acetonitrile and methanol (85:15)
- **Mobile phase**: See Table 1.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Solution A (%)</th>
<th>Solution B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>88</td>
<td>12</td>
</tr>
<tr>
<td>20</td>
<td>40</td>
<td>60</td>
</tr>
<tr>
<td>21</td>
<td>88</td>
<td>12</td>
</tr>
<tr>
<td>25</td>
<td>88</td>
<td>12</td>
</tr>
</tbody>
</table>

Diluent: Dissolve 7.6 g of sodium borate decahydrate 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**: 0.2 mg/mL of USP Omeprazole RS in Diluent, using sonication as necessary.

**Sample solution**: Weigh and mix the contents of NLT 20 Capsules. Transfer an accurately weighed portion of the Capsule content, equivalent to 20 mg of omeprazole, to a 100-mL volumetric flask, add about 50 mL of Diluent, and sonicate for 15 min. Cool, dilute with Diluent to volume, mix, and pass through a membrane filter of 0.45-µm or finer pore size. [Note—Bubbles may form just before diluting the sample through the three levels unless the results conform to volume.

**Chromatographic system**

<table>
<thead>
<tr>
<th>Buffer stage</th>
<th>Time (min)</th>
<th>Solution A (%)</th>
<th>Solution B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acid resistance</td>
<td>2</td>
<td>88</td>
<td>12</td>
</tr>
<tr>
<td>Medium</td>
<td>100 rpm</td>
<td>88</td>
<td>12</td>
</tr>
<tr>
<td>Buffer C, Mobile phase, Chromatographic system, and System suitability</td>
<td>2 h</td>
<td>88</td>
<td>12</td>
</tr>
</tbody>
</table>

**Analysis**

**Samples**: Standard solution and Sample solution

Calculate the quantity of the labeled amount of omeprazole in a specified volume of Medium, in mg:

Result = T × C₁ / C₂ × D × (r₁ / r₂)

- T = labeled quantity of omeprazole in the capsule (mg)
- C₁ = concentration of USP Omeprazole RS in the Standard solution (mg/mL)
- D = dilution factor used in preparing the Sample solution
- r₁ = peak response from the Sample solution
- r₂ = peak response from the Standard solution

**Acceptance criteria**: 90.0%–110.0%

**Performance tests**

**Change to read:**

- **Dissolution (711)**
  - **Test 1**
    - **Acid resistance stage**
      - **Medium**: 0.1 N hydrochloric acid; 500 mL
      - **Apparatus 2**: 100 rpm
      - **Time**: 2 h
      - **Buffer C, Mobile phase, Chromatographic system, and System suitability**: Proceed as directed for Buffer stage.
      - **Standard solution**: Transfer 50 mg of USP Omeprazole RS to a 250-mL volumetric flask, dissolve in 50 mL of alcohol, and dilute with 0.01 M sodium borate solution to volume. Transfer 10.0 mL of this solution into a 100-mL volumetric flask, add 20 mL of alcohol, dilute with 0.01 M sodium borate solution to volume, and mix.
      - **Sample solution**: After 2 h, filter the Medium containing the pellets through a sieve with an aperture of NMT 0.2 mm. Collect the pellets on the sieve, and rinse them with water. Using approximately 60 mL of 0.01 M sodium borate solution, carefully transfer the pellets quantitatively to a 100-mL volumetric flask. Sonicate for about 20 min until the pellets are broken up. Add 20 mL of alcohol to the flask, dilute with 0.01 M sodium borate solution to volume, and mix. Dilute an appropriate amount of this solution with 0.01 M sodium borate solution to obtain a solution containing 0.02 mg/mL. At level L₁, test 6 units. Test 6 additional units at level L₂, and at level L₃, test an additional 12 units. Continue testing through the three levels unless the results conform to either L₁ or L₂.

- **Analysis**

  **Samples**: Standard solution and Sample solution

  Calculate the percentage of the labeled amount of omeprazole (C₁₇H₂₀N₃O₅S) dissolved in Medium, in mg:

  \[
  \text{Result} = T \times C₁ / D \times (r₁ / r₂)
  \]

  - T = labeled quantity of omeprazole in the capsule (mg)
  - C₁ = concentration of USP Omeprazole RS in the Standard solution (mg/mL)
  - D = dilution factor used in preparing the Sample solution
  - r₁ = peak response from the Sample solution
  - r₂ = peak response from the Standard solution

**Tolerances**

- **Level L₁**: No individual value exceeds 15% of the omeprazole dissolved.
- **Level L₂**: The average of 12 units is NMT 20% of omeprazole dissolved, and no individual unit is greater than 35% of omeprazole dissolved.
- **Level L₃**: The average of 24 units is NMT 20% of omeprazole dissolved, NMT 2 units are greater than 35% of omeprazole dissolved, and no individual unit is greater than 45% of omeprazole dissolved.
Buffer stage

Medium: pH 6.8 phosphate buffer, 900 mL

Proce...
continue the test for 45 more min. Determine the amount of omeprazole \((C_{17}H_{11}N_{3}O_{5})\) dissolved from UV absorbances at the wavelength of maximum absorbance at about 305 nm on portions of the solutions under test passed through a nylon filter of 0.2-μm pore size, in comparison with a Standard solution having a known concentration of omeprazole in the same Medium.

**Tolerances:** NLT 75% (Q) is dissolved.

The percentage of the labeled amount of omeprazole \((C_{17}H_{11}N_{3}O_{5})\) dissolved at the time specified conforms to Dissolution (711), Acceptance Table 1.

**Test 3:** If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 3.

**Acid stage**

**Acid stage medium:** 0.1 N hydrochloric acid; 300 mL

**Apparatus 2:** 100 rpm

**Solution A:** 0.77 g/L of ammonium acetate in water

**Solution B:** Acetonitrile

**Mobile phase:** See Table 3.

<table>
<thead>
<tr>
<th>Table 3</th>
<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>
<td></td>
</tr>
<tr>
<td>3</td>
<td>80</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>65</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>55</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>55</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>80</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>80</td>
<td>20</td>
<td></td>
</tr>
</tbody>
</table>

**Sodium hydroxide solution:** 500 g/L of sodium hydroxide in water

**Diluent:** 3.8 g/L sodium borate and 0.5 g/L of edetate disodium in water as follows. Transfer 3.8 g of sodium borate to suitable volumetric flask containing 80% volume of water. To this solution add 0.5 g of edetate disodium and adjust with Sodium hydroxide solution to a pH of 11.0. Add 400 mL of alcohol and dilute with water to volume.

**Standard solution:** 0.2 mg/mL of USP Omeprazole RS in Diluent. Sonicate as needed.

**Sample solution:** After 2 h, drain the Acid stage medium from each vessel and carefully transfer the pellets to a 100-mL volumetric flask containing 75 mL of Diluent. Sonicate in a water bath maintained at 20°–25° with intermittent shaking until the pellets are dispersed. Allow the solution to equilibrate to room temperature and dilute with Diluent to volume. Centrifuge and pass the clear supernatant through a suitable filter of 0.45-μm pore size.

[NOTE—A centrifuge speed of about 5000 rpm for about 5 min may be suitable.]

**Chromatographic system**

(See Chromatography (621), System Suitability.)

**Mode:** LC

**Detector:** UV 305 nm

**Column:** 4.6-mm × 25-cm; 5-μm packing L1

**Flow rate:** 1.2 mL/min

**Injection volume:** 10 μL

**System suitability**

**Sample:** Standard solution

**Suitability requirements**

**Tailing factor:** 0.8–2.0

**Relative standard deviation:** NMT 2.0%

**Analysis**

**Samples:** Standard solution and Sample solution

Calculate the percentage \(T\) of the labeled amount of omeprazole \((C_{17}H_{11}N_{3}O_{5})\) dissolved:

\[
\text{Result} = \frac{(r_s/r_0) \times C_s \times (1/L) \times V}{100}
\]

\(r_0\) = peak response of omeprazole 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)

\(L\) = label claim (mg/Capsule)

\(V\) = volume of Sample solution, 100 mL

Calculate the percentage of the labeled amount of omeprazole \((C_{17}H_{11}N_{3}O_{5})\) dissolved:

\[
\text{Result} = A - T
\]

\(A\) = labeled amount of omeprazole, as determined by Assay (%)

\(T\) = labeled amount of omeprazole retained, as determined previously (%)

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

**Tolerances:** NMT 10% of the labeled amount of omeprazole \((C_{17}H_{11}N_{3}O_{5})\) is dissolved.

**Buffer stage**

**Buffer:** 12.2 g/L of dibasic sodium phosphate in water

**Buffer stage medium:** Acid stage medium and Buffer (30:70). Adjust with 2 N hydrochloric acid or 2 N sodium hydroxide to a pH of 6.8, if necessary; 1000 mL

**Apparatus 2:** 100 rpm

**Time:** 30 min

**Solution A:** 3.9 g/L of ammonium acetate in water. Adjust with ammonia TS to a pH of 7.6.

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

**Standard stock solution:** 0.4 mg/mL of USP Omeprazole RS as follows. Transfer a suitable amount of USP Omeprazole RS to suitable volumetric flask containing 10% volume of alcohol, sonicate in a water bath maintained at 20°–25° until completely dissolved, and dilute with Buffer stage medium to volume.

**Standard solution:** 0.02 mg/mL of USP Omeprazole RS from Standard stock solution in Buffer stage medium. Immediately transfer 10 mL of this solution to a test tube containing 2 mL of 0.25 M sodium hydroxide and mix.

**Sample stock solution:** Proceed as directed in Acid stage with a new set of Capsules. After 2 h add 700 mL of Buffer to each vessel and adjust with 2 N hydrochloric acid or 2 N sodium hydroxide to a pH of 6.8, if necessary, and continue this test for 30 min more. Withdraw a suitable amount of solution from each vessel and pass through a suitable prefiter with a 70-μm pore size.

**Sample solution:** Immediately transfer 5 mL of the filtrate to a test tube containing 1 mL of 0.25 M sodium hydroxide and mix. Pass this solution through a suitable filter with a 0.45-μm pore size.

**Chromatographic system**

(See Chromatography (621), System Suitability.)

**Mode:** LC

**Detector:** UV 305 nm

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

**Flow rate:** 1 mL/min

© The United States Pharmacopeial Convention All Rights Reserved.

C243656-M58645-CHM32015, rev. 00 20191227
Injection volume: 20 µL

System suitability
Sample: Standard solution
Tailing factor: NLT 0.8 and NMT 2.0
Relative standard deviation: NMT 2.0%

Analysis
Samples: Standard solution and Sample solution
Calculate the percentage of the labeled of omeprazole (C_{17}H_{19}N_{3}O_{3}S) dissolved:

\[ \text{Result} = \left( \frac{r_U}{r_S} \right) \times C_S \times \left( \frac{1}{L} \right) \times V \times 100 \]

\( r_U \) = peak response of omeprazole 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)
\( L \) = label claim (mg/Capsule)
\( V \) = volume of the Buffer stage medium, 1000 mL

Acceptance criteria: See Table 4.

### Table 4

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Relative Response Factor</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole related compounds F and G*</td>
<td>0.33</td>
<td>1.6</td>
<td>0.5</td>
</tr>
<tr>
<td>5-Methoxy-1H-benzimidazole-2-thiol</td>
<td>0.64</td>
<td>3.1</td>
<td>0.5</td>
</tr>
<tr>
<td>Any other individual impurity</td>
<td>—</td>
<td>1.0</td>
<td>0.5</td>
</tr>
<tr>
<td>Total impurities</td>
<td>—</td>
<td>—</td>
<td>2.0</td>
</tr>
</tbody>
</table>

*These impurities undergo transformation in the solution to form a conversion product, which elutes at the relative retention time of 0.33.

Additional requirements

- **Packaging and Storage:** Preserve in tight, light-resistant containers. Store between 15° and 30°.
- **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 F and G Mixture RS
  - 1,3-Dimethyl-8-methoxy-12-thioxopyrido[1',2':3,4]imidazo[1,2-albenzimidazol-2(12H)-one and 1,3-dimethyl-9-methoxy-12-thioxopyrido[1',2':3,4]imidazo[1,2-albenzimidazol-2(12H)-one.

Chromatograph the Peak identification solution, and identify the components on the basis of their relative retention times, given in the Table 4.

Calculate the percentage of each impurity in the portion of Capsules taken:

\[ \text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_S}{C_U} \right) \times \left( \frac{1}{F} \right) \times 100 \]

\( r_U \) = peak response for each impurity from the Sample solution
\( r_S \) = peak response for omeprazole from the Standard solution
\( C_S \) = concentration of USP Omeprazole RS in the Standard solution (mg/mL)
\( C_U \) = nominal concentration of omeprazole in the Sample solution (mg/mL)
\( F \) = relative response factor (see Table 4).

Change to read:

**Uniformity of Dosage Units** (905): Meet the requirements.