Omeprazole Delayed-Release Capsules

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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 ($C_{17}H_{19}N_3O_3S$).

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 1

Time (min)	Solution A (%)	Solution B (%)
0	88	12
20	40	60
21	88	12
25	88	12

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 bringing the solution to volume. Add a few drops of dehydrated alcohol to dissipate the bubbles if they persist for more than a few minutes.]

Chromatographic system

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

Mode: LC

Detector: UV 305 nm

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

Flow rate: 1.2 mL/min

Injection size: 10 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Column efficiency: NLT 20,000 theoretical plates

Tailing factor: 0.8–2

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of omeprazole ($C_{17}H_{19}N_3O_3S$) in the portion of 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 omeprazole in the *Sample solution* (mg/mL)

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 L_1, test 6 units. Test 6 additional units at level L_2, and at level L_3, test an additional 12 units. Continue testing through the three levels unless the results conform at either L_1 or L_2.

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the quantity of the labeled amount of omeprazole ($C_{17}H_{19}N_3O_3S$) dissolved in *Medium*, in mg:

$$\text{Result} = T - C_S \times D \times (r_U/r_S)$$

T = labeled quantity of omeprazole in the capsule (mg)
C_S = concentration of USP Omeprazole RS in the *Standard solution* (mg/mL)
D = dilution factor used in preparing the *Sample solution*
r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*

Tolerances

Level L_1: No individual value exceeds 15% of the omeprazole dissolved.

Level L_2: The average of 12 units is NMT 20% of omeprazole dissolved, and no individual unit is greater than 35% of omeprazole dissolved.

Level L_3: 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.

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Buffer stage
Medium: pH 6.8 phosphate buffer, 900 mL
Proceed as directed in *Acid resistance stage* with a new set of Capsules from the same batch. After 2 h, add 400 mL of 0.235 M dibasic sodium phosphate to the 500 mL of 0.1 N hydrochloric acid medium in the vessel. Adjust, if necessary, with 2 N hydrochloric acid or 2 N sodium hydroxide to a pH of 6.8 ± 0.05.
Apparatus 2: 100 rpm
At the end of 30 min, determine the amount of omeprazole ($C_{17}H_{19}N_3O_3S$) dissolved in the pH 6.8 phosphate buffer by using the following method.
Buffer A (0.235 M dibasic phosphate buffer, pH 10.4)**:** 33.36 g/L of anhydrous dibasic sodium phosphate, adjusted with 2 N sodium hydroxide to a pH of 10.4 ± 0.1
Buffer B (phosphate buffer, pH 6.8)**:** 0.1 N hydrochloric acid and *Buffer A* (5:4), adjusted with 2 N hydrochloric acid or 2 N sodium hydroxide, if necessary, to a pH of 6.8 ± 0.05.
Buffer C (phosphate buffer, pH 7.6)**:** 0.718 g/L of monobasic sodium phosphate and 4.49 g/L of dibasic sodium phosphate, adjusted with 2 N hydrochloric acid or 2 N sodium hydroxide, if necessary, to a pH of 7.6 ± 0.1. Dilute 250 mL of this solution with water to 1000 mL.
Mobile phase: Transfer 340 mL of acetonitrile to a 1000-mL volumetric flask, dilute with *Buffer C* to volume, and pass through a membrane filter of 0.5-µm or finer pore size.
Standard solution A (for Capsules labeled to contain 10 mg)**:** Prepare a solution containing 2 mg/mL of USP Omeprazole RS in alcohol. Dilute with *Buffer B* to obtain a solution containing 0.01 mg/mL. Immediately add 2 mL of 0.25 M sodium hydroxide to 10 mL of this solution, and mix. [NOTE—Do not allow the solution to stand before adding the sodium hydroxide solution.]
Standard solution B (for Capsules labeled to contain 20 or 40 mg)**:** Proceed as directed for *Standard solution A*, except to obtain a solution containing 0.02 mg/mL before mixing with 2 mL of 0.25 M sodium hydroxide.
Sample solution A (for Capsules containing 10 or 20 mg)**:** Immediately transfer 5.0 mL of the solution under test to a test tube containing 1.0 mL of 0.25 M sodium hydroxide. Mix well, and pass through a membrane filter of 1.2-µm or finer pore size. Protect from light.
Sample solution B (for Capsules labeled 40 mg)**:** Immediately transfer 5.0 mL of the solution under test to a test tube containing 2.0 mL of 0.25 M sodium hydroxide and 5 mL of *Buffer B*. Mix well, and pass through a membrane filter of 1.2-µm or finer pore size. Protect from light.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 280 nm
Column: 4.0-mm × 12.5-cm; 5-µm packing L7
Flow rate: 1.0 mL/min
Injection volume: 20 µL
System suitability
Sample: *Standard solution A* or *B*, as appropriate
Suitability requirements
Column efficiency: NLT 2000 theoretical plates
Relative standard deviation: NMT 2.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of omeprazole ($C_{17}H_{19}N_3O_3S$) dissolved:

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

r_U = peak response from the appropriate *Sample solution*
r_S = peak response from the appropriate *Standard solution*
C_S = concentration of the appropriate *Standard solution* (mg/mL)
L = label claim (mg/Capsule)
V = volume of *Medium*, 900 mL
D = dilution factor used in preparing the appropriate *Sample solution*

Tolerances
For Capsules labeled to contain 10 and 20 mg: NLT 75% (Q) is dissolved.
For Capsules labeled to contain 40 mg: NLT 70% (Q) is dissolved.
The percentages of the labeled amount of omeprazole ($C_{17}H_{19}N_3O_3S$) dissolved at the time specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 1*.
Test 2: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.
Acid resistance stage
Medium: 0.1 N hydrochloric acid; 900 mL
Apparatus 1: 100 rpm
Time: 2 h
Sample solution: After 2 h, remove each sample from the basket, and quantitatively transfer into separate volumetric flasks to obtain a solution having a final concentration of about 0.2 mg/mL. Proceed as directed for the *Sample solution* in the *Assay*, starting with "Add about 50 mL of *Diluent*".
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the quantity of the labeled amount of omeprazole ($C_{17}H_{19}N_3O_3S$) dissolved in *Medium*, in mg:

$$\text{Result} = T - C_S \times D \times (r_U/r_S)$$

T = labeled quantity of omeprazole in the capsule (mg)
C_S = concentration of USP Omeprazole RS in the *Standard solution* (mg/mL)
D = dilution factor used in preparing the *Sample solution*
r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*

Tolerances: See *Table 2*.

Table 2

Level	Criteria
L_1	The average of the 6 units is NMT 10% of omeprazole dissolved.
L_2	The average of the 12 units is NMT 10% of omeprazole dissolved.
L_3	The average of the 24 units is NMT 10% of omeprazole dissolved.

Buffer stage
Medium: 0.05 M pH 6.8 phosphate buffer; 900 mL (see *Reagents, Indicators, and Solutions*)
Apparatus 1: 100 rpm
Time: 45 min
Analysis: Proceed as directed for *Acid resistance stage* with a new set of Capsules from the same batch. After 2 h, replace the acid *Medium* with the buffer *Medium*, and

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continue the test for 45 more min. Determine the amount of omeprazole ($C_{17}H_{19}N_3O_3S$) 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 USP Omeprazole RS in the same *Medium*.

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

The percentage of the labeled amount of omeprazole ($C_{17}H_{19}N_3O_3S$) 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

Time: 2 h

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

Solution B: Acetonitrile

Mobile phase: See *Table 3*.

Table 3

Time (min)	Solution A (%)	Solution B (%)
0	80	20
3	80	20
10	65	35
15	55	45
17	55	45
18	80	20
25	80	20

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 ($C_{17}H_{19}N_3O_3S$) retained:

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

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 *Sample solution*, 100 mL

Calculate the percentage of the labeled amount of omeprazole ($C_{17}H_{19}N_3O_3S$) 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 ($C_{17}H_{19}N_3O_3S$) 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 prefilter 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

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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 ($C_{17}H_{19}N_3O_3S$) dissolved:

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

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

Tolerances: NLT 80% (Q) of the labeled amount of omerprazole ($C_{17}H_{19}N_3O_3S$) is dissolved.▲ (TBD)

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

Change to read:

IMPURITIES

- **ORGANIC IMPURITIES**

Solution A, Solution B, Mobile phase, Diluent, Sample solution, and **Chromatographic system:** Proceed as directed in the *Assay*.
Standard solution: 1.0 µg/mL of USP Omeprazole RS in *Diluent*
Peak identification solution: 0.2 mg/mL of USP Omeprazole RS, 1.0 µg/mL of USP Omeprazole Related Compound F and G Mixture RS, and 1.0 µg/mL of 5-methoxy-1*H*-benzimidazole-2-thiol in *Diluent*. Sonicate the solution for 15 min, and then heat at 55° for 30 min. [NOTE—The heating step facilitates conversion of omeprazole related compounds F and G into a product with the relative retention time of 0.33. The remaining unconverted omeprazole related compounds F and G may elute as a very broad peak at the relative retention time of about 0.5.]
Analysis
Samples: *Standard solution*, *Peak identification solution*, and *Sample solution*
Chromatograph the *Peak identification solution*, and identify the components on the basis of their relative retention times, given in the ▲*Table 4*.▲ (TBD)
Calculate the percentage of each impurity in the portion of Capsules taken:

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

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*)▲ (TBD)

Acceptance criteria: See ▲*Table 4*.

Table 4▲ (TBD)

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Omeprazole related compounds F and G[a]	0.33	1.6	0.5
5-Methoxy-1*H*-benzimidazole-2-thiol	0.64	3.1	0.5
Any other individual impurity	—	1.0	0.5
Total impurities	—	—	2.0

[a] 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-*a*]benzimidazol-2(12*H*)-one and 1,3-dimethyl-9-methoxy-12-thioxopyrido[1′,2′:3,4]imidazo[1,2-*a*]benzimidazol-2(12*H*)-one.

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