Erythromycin Delayed-Release Tablets

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Expert Committee                Biologics Monographs 4–Antibiotics
Reason for Revision             Compliance

In accordance with the Rules and Procedures of the 2015–2020 Council of Experts, the Biologics Monographs 4–Antibiotics Expert Committee has revised the Erythromycin Delayed-Release Tablets monograph. The purpose for the revision is to add Dissolution Test 3 to accommodate FDA-approved drug products with different dissolution conditions and tolerances than the existing dissolution tests.

- *Dissolution Test 3* was validated using a Waters XBridge C18 brand of L1 column. The typical retention time for erythromycin A is about 7.8 and 3.8 min in the analysis of acid and buffer stage, respectively.

- The definition of *P* in the Acid stage of Dissolution Test 3 was updated for clarity.

The Erythromycin Delayed-Release Tablets Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Julie Zhang, Scientific Liaison to the Biologics Monographs 4–Antibiotics Expert Committee (301-816-8350 or julie.zhang@usp.org).
Erythromycin Delayed-Release Tablets

**DEFINITION**

Erythromycin Delayed-Release Tablets contain NLT 90.0% and NMT 120.0% of the labeled amount of erythromycin (C_{13}H_{22}NO_{12}).

**IDENTIFICATION**

- **A. THIN-LAYER CHROMATOGRAPHY**
  - **Standard solution:** 2.5 mg/mL of USP Erythromycin RS in methanol
  - **Sample solution:** Nominally 2.5 mg/mL of erythromycin from powdered Tablets in methanol
  - **Chromatographic system**
    - (See Chromatography (621), General Procedures, Thin-Layer Chromatography.)
  - **Mode:** TLC
  - **Adsorbent:** 0.25-mm layer of chromatographic silica gel
  - **Application volume:** 10 μL
  - **Developing solvent system:** Methanol and chloroform (85:15)
  - **Spray reagent:** Alcohol, p-methoxybenzaldehyde, and sulfuric acid (90:5:5)
  - **Analysis**
    - **Samples:** Standard solution and Sample solution
    - Place the plate in an unlined chromatographic chamber, and develop the chromatogram until the solvent front has moved about 7 cm. Remove the plate from the chamber, mark the solvent front, and allow the solvent to evaporate. Spray the plate with Spray reagent. Heat the plate at 100° for 10 min, and examine the chromatogram, in which erythromycin appears as a black-to-purple spot.
    - **Acceptance criteria:** The Rf value of the principal spot of the Sample solution corresponds to that of the Standard solution.

**ASSAY**

- **ANTIBIOTICS—MICROBIAL ASSAYS**
  - (81)
  - **Sample solution:** Place NLT 4 Tablets in a high-speed glass blender jar with 200 mL of methanol, and blend for 3 min. Add 300 mL of Buffer B,3, and blend for 3 min.
  - **Analysis:** Proceed as directed in the chapter. Dilute the Sample solution with Buffer B,3 to obtain a Test Dilution having a concentration that is nominally equivalent to the median level of the standard.
  - **Acceptance criteria:** 90.0%–120.0%

**PERFORMANCE TESTS**

**Change to read:**

- **Dissolution** (711)
  - **Test 1:** If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 1.
  - **Acid stage medium:** Simulated gastric fluid TS, without pepsin; 900 mL
  - **Apparatus 1:** 100 rpm
  - **Time:** 60 min
  - **Solution A:** 3.6 g/L of dibasic sodium phosphate in water; Adjust with diluted phosphoric acid to a pH of 9.0.
  - **Solution B:** 6.8 g/L of monobasic potassium phosphate and 1.2 g/L of sodium hydroxide in water
  - **Sample solution 1:** 2.5 mg each of USP Erythromycin B RS and USP Erythromycin C RS to a 50-mL volumetric flask, add 12.5 mL of methanol, sonicate to dissolve, and dilute with Solution B to volume. [Note—The typical retention times of erythromycin C and erythromycin B are 4.2 and 13.4 min, respectively.]
  - **Standard solution:** 2.5 mg/mL of USP Erythromycin RS prepared as follows. Transfer 2.5 mg each of USP Erythromycin B RS and USP Erythromycin C RS to a 50-mL volumetric flask, add 12.5 mL of methanol, sonicate to dissolve, and dilute with Solution B to volume. [Note—The typical retention time of erythromycin A is 7.8 min.]
  - **Sample solution 1:** Determine the average Tablet weight by weighing NLT 20 Tablets. Carefully transfer the appropriate number of intact Tablets into a suitable volumetric flask (5 Tablets into a 500-mL flask for 250-mg Tablets, 8 Tablets into a 1000-mL flask for 333-mg Tablets, and 5 Tablets into a 1000-mL flask for 500-mg Tablets). Add methanol to about 25% of the final volume, and sonicate at room temperature for about 30 min with intermittent shaking. Further add about 25% of the final volume of Solution B and sonicate at room temperature for about 30 min with intermittent shaking. Dilute to volume with Solution B and mix well.

**Buffer:** pH 1.2 buffer (see Reagents, Indicators, and Solutions—Buffer Solutions)

**Solution A:** 1 g/L of bromocresol purple in pH 4.5 phosphate buffer

**Standard solution:** Dissolve USP Erythromycin RS in Medium to obtain a concentration similar to that of the Sample solution.

**Sample solution:** If necessary, dilute a filtered portion of the solution under test with Medium to obtain a solution containing about 0.28 mg/mL of erythromycin.

**Detector:** UV 410 nm

**Analysis**

**Samples:** Standard solution and Sample solution

Transfer 2.0 mL of the Standard solution and the Sample solution to individual separators of a suitable size. Add 6 mL of Buffer and 8 mL of Solution A, and mix. Extract with 40.0 mL of chloroform. Determine the amount of erythromycin (C_{13}H_{22}NO_{12}) dissolved from UV absorbances of the chloroform extracts.

**Tolerances:** NLT 75% (Q) of the labeled amount of erythromycin (C_{13}H_{22}NO_{12}) is dissolved.

**Test 2:** If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 2. Proceed as directed under Test 1, except to use Apparatus 2 at 75 rpm.

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

**Acid stage medium:** Simulated gastric fluid TS, without enzyme; 900 mL

**Apparatus 1:** 100 rpm

**Time:** 60 min

**Solution A:** 3.6 g/L of dibasic sodium phosphate in water; Adjust with diluted phosphoric acid to a pH of 9.0.

**Mobile phase:** Solution A and acetonitrile (1:1)

**Solution B:** 6.8 g/L of monobasic potassium phosphate and 1.2 g/L of sodium hydroxide in water

**Peak identification solution:** 0.05 mg/mL of USP Erythromycin B RS and USP Erythromycin C RS prepared as follows. Transfer 2.5 mg each of USP Erythromycin B RS and USP Erythromycin C RS to a 50-mL volumetric flask, add 12.5 mL of methanol, sonicate to dissolve, and dilute with Solution B to volume.

[Note—The typical retention times of erythromycin C and erythromycin B are 4.2 and 13.4 min, respectively.]

**Standard solution:** 2.5 mg/mL of USP Erythromycin RS prepared as follows. Transfer 125 mg of USP Erythromycin RS to a 50-mL volumetric flask, add 12.5 mL of methanol, sonicate to dissolve, and dilute with Solution B to volume. [Note—The typical retention time of erythromycin A is 7.8 min.]

**Sample solution 1:** Determine the average Tablet weight by weighing NLT 20 Tablets. Carefully transfer the appropriate number of intact Tablets into a suitable volumetric flask (5 Tablets into a 500-mL flask for 250-mg Tablets, 8 Tablets into a 1000-mL flask for 333-mg Tablets, and 5 Tablets into a 1000-mL flask for 500-mg Tablets). Add methanol to about 25% of the final volume, and sonicate at room temperature for about 30 min with intermittent shaking. Further add about 25% of the final volume of Solution B and sonicate at room temperature for about 30 min with intermittent shaking. Dilute to volume with Solution B and mix well.
Centrifuge at 5000 rpm for 5 min and pass the supernatant through a polyvinylidene fluoride (PVDF) or other suitable filter of 0.45-µm pore size. Discard the first 5 mL of the filtrate.

**Sample solution 2:** At the end of Acid stage dissolution, discard Acid stage medium and carefully transfer 1 Tablet from the dissolution vessel into a suitable volumetric flask (use a 100-mL flask for 250-mg Tablets, 200-mL flask for 333-mg Tablets, and 200-mL flask for 500-mg Tablets). Add methanol to about 25% of the final volume, and sonicate at room temperature for about 30 min with intermittent shaking. Further add about 25% of the final volume of Solution B and sonicate at room temperature for about 30 min with intermittent shaking. Dilute to volume with Solution B and mix well. Centrifuge at 5000 rpm for 5 min and pass the supernatant through a PVDF or other suitable filter of 0.45-µm pore size. Discard the first 5 mL of the filtrate.

**Blank:** Solution B and methanol (75:25)

**Chromatographic system**

(See Chromatography (621), System Suitability).

**Mode:** LC

**Detector:** UV 215 nm

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

**Temperature**

Autosampler: 4°

Column: 50°

**Flow rate:** 1.5 mL/min

**Injection volume:** 25 µL

**System suitability**

**Sample:** Standard solution

[NOTE—The relative retention times of erythromycin C, erythromycin A, and erythromycin B are 0.53, 1.00, and 1.75, respectively.]

**Suitability requirements**

Tailing factor: NMT 2.0 for erythromycin A peak

Relative standard deviation: NMT 2.0% of the sum of erythromycin A, erythromycin B, and erythromycin C

**Analysis**

**Samples:** Standard solution, Sample solution 1, and Sample solution 2

Calculate the erythromycin content (A) as a percentage of the labeled amount of erythromycin:

\[
\text{Result} = \left(\frac{r_0}{r_s}\right) \times W \times P \times \left(\frac{1}{D_0}\right) \times D_i \times \left(\frac{1}{L}\right) \times 100
\]

- \(r_0\) = peak response of sum of erythromycin A, erythromycin B, and erythromycin C from Sample solution 1
- \(r_s\) = peak response of sum of erythromycin A, erythromycin B, and erythromycin C from the Standard solution
- \(W\) = standard weight of USP Erythromycin RS to prepare the Standard solution (mg)
- \(P\) = content of erythromycin A, erythromycin B, and erythromycin C in USP Erythromycin RS (mg/mg)
- \(D_0\) = dilution factor used in preparing the Standard solution (mL)
- \(D_i\) = dilution factor used in preparing Sample solution 1 (mL)
- \(L\) = label claim (mg/Tablet)

Calculate the percentage (T) of the labeled amount of erythromycin retained:

\[
\text{Result} = \left(\frac{r_0}{r_s}\right) \times W \times P \times \left(\frac{1}{D_0}\right) \times D_i \times \left(\frac{1}{L}\right) \times 100
\]

- \(r_0\) = peak response of sum of erythromycin A, erythromycin B, and erythromycin C from Sample solution 2
- \(r_s\) = peak response of sum of erythromycin A, erythromycin B, and erythromycin C from the Standard solution
- \(W\) = standard weight of USP Erythromycin RS to prepare the Standard solution (mg)
- \(P\) = content of erythromycin A, erythromycin B, and erythromycin C in USP Erythromycin RS (mg/mg)
- \(D_i\) = dilution factor used in preparing the Standard solution (mL)
- \(L\) = label claim (mg/Tablet)

**Buffer stage**

**Buffer stage medium:** 6.8 g/L monobasic potassium phosphate in water with pH 6.8 adjusted by 5 N sodium hydroxide; 900 mL

**Apparatus 1:** 100 rpm

**Time:** 35 min

**Solution A and Mobile phase:** Prepare as directed in Acid stage.

**Standard solution:** Transfer a suitable amount of USP Erythromycin RS into an appropriate volumetric flask. See Table 1. Add methanol to about 5% of the final volume and sonicate to dissolve. Dilute with Buffer stage medium to volume with intermittent shaking and mix well. [NOTE—The typical retention time of erythromycin A is 3.8 min.]

<table>
<thead>
<tr>
<th>Tablet Label Claim (mg)</th>
<th>Weight of USP Erythromycin RS (mg)</th>
<th>Volumetric Flask (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>250</td>
<td>59</td>
<td>200</td>
</tr>
<tr>
<td>333</td>
<td>39</td>
<td>100</td>
</tr>
<tr>
<td>500</td>
<td>59</td>
<td>100</td>
</tr>
</tbody>
</table>

**Sample solution:** Prepare as directed in Acid stage with a new set of Tablets. After 60 min with Acid stage medium, immediately replace with Buffer stage medium. After 35 min, pass a portion of the solution through a PVDF or other suitable filter of 0.45-µm pore size.
Chromatographic system
(See Chromatography (621), System Suitability.)

Mode: LC
Detector: UV 210 nm
Column: 4.6-mm x 15-cm; 5-µm packing L1
Temperature
- Autosampler: 5°
- Column: 50°
Flow rate: 2.0 mL/min
Injection volume: 100 µL

System suitability

Suitability requirements
- Tailing factor: NMT 2.0 for erythromycin A peak
- Relative standard deviation: NMT 2.0% of erythromycin A

Analysis

Samples: Standard solution and Sample solution

Calculate the percentage of the labeled amount of erythromycin 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 erythromycin A from the Sample solution
\( r_S \) = peak response of erythromycin A from the Standard solution
\( C_S \) = concentration of erythromycin A in the Standard solution (mg/mL)

\( L \) = label claim (mg/Tablet)
\( V \) = volume of buffer medium

Tolerances: NLT 80% (Q) of the labeled amount of erythromycin is dissolved. ▲ (RB 25-Jul-2019)

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

**Specific Tests**

- **Water Determination** (921), Method I
  - Analysis: Use 20 mL of methanol containing 10% of imidazole in place of methanol in the titration vessel.
  - Acceptance criteria: NMT 6.0%

**Additional Requirements**

- **Packaging and Storage:** Preserve in tight containers.
- **Labeling:** The labeling indicates the Dissolution Test with which the product complies.

**Change to read:**

- **USP Reference Standards** (11)
  - USP Erythromycin RS
  - USP Erythromycin B RS
  - USP Erythromycin C RS

▲ (RB 25-Jul-2019)