## Clarithromycin Extended-Release Tablets

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In accordance with the Rules and Procedures of the 2015-2020 Council of Experts, the Chemical Medicines Monographs 1 Expert Committee has revised the Clarithromycin Extended-Release Tablets monograph. The purpose for the revision is to add *Dissolution Test* 5 for a drug product approved by the FDA. This analytical procedure is validated using Acquity UPLC BEH C18 brand of L1 column. The typical retention time for clarithromycin is about 1.2 min.

The Clarithromycin Extended-Release Tablets Revision Bulletin supersedes the currently official monograph. The Revision Bulletin will be incorporated in the *Second Supplement to USP 40–NF 35*.

Should you have any questions, please contact Morgan Puderbaugh, Scientific Liaison (301-998-6833 or mxp@usp.org).

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# Clarithromycin Extended-Release Tablets

## DEFINITION

Clarithromycin Extended-Release Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of clarithromycin ($C_{38}H_{69}NO_{13}$).

## IDENTIFICATION

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

## ASSAY

• **PROCEDURE**

**Buffer A:** 0.067 M monobasic potassium phosphate

**Mobile phase:** Methanol and *Buffer A* (13:7). Adjust with phosphoric acid to a pH of 4.0. Pass through a suitable filter.

**Standard stock solution:** 625 µg/mL of clarithromycin from USP Clarithromycin RS in methanol. Shake and sonicate, if necessary, to facilitate dissolution.

**Standard solution:** 125 µg/mL of clarithromycin in *Mobile phase* from *Standard stock solution*. Pass through a suitable filter.

**System suitability stock solution:** 625 µg/mL of USP Clarithromycin Related Compound A RS in methanol

**System suitability solution:** 125 µg/mL of USP Clarithromycin Related Compound A RS from *System suitability stock solution* and 125 µg/mL of clarithromycin from *Standard stock solution* in *Mobile phase*

**Sample stock solution:** Transfer nominally 2000 mg of clarithromycin from finely powdered Tablets to a 500-mL volumetric flask with the aid of methanol. Add about 350 mL of methanol, and shake by mechanical means for 30 min. Dilute with methanol to volume, and sonicate for 30 min. Cool to room temperature, and allow to stand for at least 16 h. Mix, allow any insoluble matter to settle, and use the supernatant.

**Sample solution:** Transfer 3.0 mL of the *Sample stock solution* to a 100-mL volumetric flask, and dilute with *Mobile phase* to volume. Pass through a suitable filter.

**Chromatographic system**

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

**Mode:** LC

**Detector:** UV 210 nm

**Columns**

**Guard (optional):** Packing L1

**Analytical:** 4.6-mm × 15-cm; packing L1

**Column temperature:** 50°

**Flow rate:** 1 mL/min

**Injection volume:** 20–50 µL

**System suitability**

**Samples:** *Standard solution* and *System suitability solution*

[NOTE—The relative retention times for clarithromycin and clarithromycin related compound A are about 0.75 and 1.0, respectively.]

**Suitability requirements**

**Resolution:** NLT 2.0 between clarithromycin and clarithromycin related compound A, *System suitability solution*

**Tailing factor:** 0.9–1.5, *Standard solution*

**Relative standard deviation:** NMT 2.0%, *Standard solution*

**Analysis**

**Samples:** *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of clarithromycin ($C_{38}H_{69}NO_{13}$) in the portion of Tablets 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 clarithromycin in the *Standard solution* (µg/mL)
$C_U$ = nominal concentration of clarithromycin in the *Sample solution* (µg/mL)

**Acceptance criteria:** 90.0%–110.0%

## PERFORMANCE TESTS

***Change to read:***

• **DISSOLUTION** ⟨711⟩

**Test 1**

**Buffer B:** Dissolve 816.5 g of monobasic potassium phosphate and 48 g of sodium hydroxide in about 4 L of water, mix, and dilute with water to 20 L. Adjust with either concentrated phosphoric acid or 1 N sodium hydroxide to a pH of 6.0 ± 0.05.

**Medium:** *Buffer B*; 900 mL

**Apparatus 2:** 75 rpm

**Times:** 30, 45, 60, and 120 min

**Standard solutions:** Prepare five solutions of USP Clarithromycin RS dissolved in acetonitrile and diluted with *Medium*, with known concentrations over a range of about 60–600 µg/mL.

**Sample solution:** Use portions of the solution under test passed through a polyethylene filter of 35-µm pore size.

**Chromatographic system:** Proceed as directed in the *Assay*, except the *Injection volume* is 50 µL.

**Analysis**

**Samples:** *Standard solutions* and *Sample solution*

Perform a linear regression analysis to generate a standard curve using the peak area of each *Standard solution* versus its concentration. Determine the percentage of the labeled amount of clarithromycin ($C_{38}H_{69}NO_{13}$) dissolved at each specified time interval, using the peak area of each *Sample solution* and the linear regression statistics for the *Standard solutions*.

**Tolerances:** The percentages of the labeled amounts of clarithromycin ($C_{38}H_{69}NO_{13}$) dissolved at the times specified conform to *Table 1*.

**Table 1**

| Level | Time (min) | Amount Dissolved, Individual Limits (%) | Amount Dissolved, Average Limits (%) |
|---|---|---|---|
| L1 | 30 | NMT 65 | — |
| | 45 | 55–85 | — |
| | 60 | NLT 75 | — |
| | 120 | NLT 85 | — |
| L2 | 30 | NMT 75 | NMT 65 |
| | 45 | 45–95 | 55–85 |
| | 60 | NLT 65 | NLT 75 |
| | 120 | NLT 75 | NLT 85 |

**Table 1** *(Continued)*

| Level | Time (min) | Amount Dissolved, Individual Limits (%) | Amount Dissolved, Average Limits (%) |
|---|---|---|---|
| | 30 | NMT 2 Tablets release more than 75%, and no individual Tablet releases more than 85% | NMT 65 |
| | 45 | NMT 2 Tablets are outside the range of 45%–95%, and no individual Tablet is outside the range of 35%–105% | 55–85 |
| | 60 | NMT 2 Tablets release less than 65%, and no individual Tablet releases less than 55% | NLT 75 |
| L3 | 120 | NMT 2 Tablets release less than 75%, and no individual Tablet releases less than 65% | NLT 85 |

**Test 2**

If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.

**Buffer C:** 0.05 M phosphate buffer with a pH of 6.8, containing 0.5% of sodium lauryl sulfate

**Medium:** *Buffer C*; 900 mL, degassed by sonication and vacuum

**Apparatus 1:** 100 rpm

**Times:** 2, 12, and 24 h

**Buffer D:** 9.2 g/L of monobasic sodium phosphate monohydrate in water, adjusted with phosphoric acid to a pH of 2.5 prior to final dilution

**Mobile phase:** Methanol and *Buffer D* (65:35)

**Standard solution:** 0.56 mg/mL of USP Clarithromycin RS in a solution of methanol and *Medium* (1 in 10). Dissolve first in methanol using 10% of the final volume, and dilute with *Medium* to volume.

**Sample solution:** Centrifuge the solution under test at 2500 rpm for 10 min.

**Chromatographic system**

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

**Mode:** LC

**Detector:** UV 210 nm

**Column:** 4.6-mm × 15-cm; 5-µm packing L1

**Column temperature:** 50°

**Flow rate:** 1 mL/min

**Injection volume:** 5 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 clarithromycin ($C_{38}H_{69}NO_{13}$) dissolved at each time point ($Q_T$):

$$Q_2 = (r_U/r_S) \times (C_S/L) \times V \times 100$$

$$Q_{12} = [Q_2 \times (V_S/V)] + [(r_U/r_S) \times (C_S/L) \times (V - V_S) \times 100]$$

$$Q_{24} = [Q_2 \times (V_S/V)] + [Q_{12} \times V_S/(V - 2V_S)] + [(r_U/r_S) \times (C_S/L) \times (V - 2V_S) \times 100]$$

$r_U$ = peak response from the *Sample solution*
$r_S$ = peak response from the *Standard solution*
$C_S$ = concentration of clarithromycin in the *Standard solution* (mg/mL)
$V$ = volume of *Medium*, 900 mL
$V_S$ = volume of the sample withdrawn at each time point (mL)
$L$ = label claim (mg/Tablet)

**Tolerances:** The percentages of the labeled amounts of clarithromycin ($C_{38}H_{69}NO_{13}$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

**Table 2**

| Time (h) | Amount Dissolved (%) |
|---|---|
| 2 | NMT 20 |
| 12 | 45–70 |
| 24 | NLT 80 |

**Test 3**

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

**Buffer E:** Dissolve 3.59 g of sodium acetate trihydrate and 11.0 mL of 2 N acetic acid in 1000 mL of water. Adjust with 2 N acetic acid to a pH of 4.75.

**Medium:** *Buffer E*; 1000 mL

**Apparatus 1:** 10 mesh; 50 rpm

**Times:** 1, 2, 4, 8, and 12 h

**Buffer F:** 9.12 g/L of monobasic potassium phosphate in water

**Mobile phase:** Methanol and *Buffer F* (65:35). Adjust with phosphoric acid to a pH of 4.0.

**Standard stock solution:** 625 µg/mL of clarithromycin from USP Clarithromycin RS in methanol. Shake and sonicate, if necessary, to dissolve.

**Standard solution:** 125 µg/mL of clarithromycin from *Standard stock solution* in *Mobile phase*

**System suitability stock solution:** 625 µg/mL of USP Clarithromycin Related Compound A RS in methanol

**System suitability solution:** 125 µg/mL of clarithromycin related compound A from *System suitability stock solution* and 125 µg/mL of clarithromycin from *Standard stock solution* in *Mobile phase*

**Sample solution:** Withdraw 10 mL of the solution under test from each vessel and replace with 10 mL of *Medium*. Transfer 3 mL of the withdrawn solution to a 25-mL volumetric flask, and dilute with *Mobile phase* to volume. Pass through a filter of 0.45-µm pore size.

**Chromatographic system**
(See *Chromatography* ⟨621⟩, *System Suitability*.)
**Mode:** LC
**Detector:** UV 210 nm
**Column:** 4.6-mm × 15-cm; 5-µm packing L1
**Column temperature:** 50°
**Flow rate:** 1 mL/min
**Injection volume:** 50 µL

**System suitability**
**Samples:** *Standard solution* and *System suitability solution*
[NOTE—The relative retention times for clarithromycin and clarithromycin related compound A are about 0.75 and 1.0, respectively.]
**Suitability requirements**
**Resolution:** NLT 2.0 between clarithromycin and clarithromycin related compound A, *System suitability solution*
**Tailing factor:** 0.9–2, *Standard solution*
**Relative standard deviation:** NMT 2.0%, *Standard solution*

**Analysis**
**Samples:** *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of clarithromycin ($C_{38}H_{69}NO_{13}$) dissolved at each time point ($Q_T$):

$$Q_1 = (r_U/r_S) \times (C_S/L) \times V \times 100$$

$$Q_2 = [Q_1 \times (V_S/V)] + [(r_U/r_S) \times (C_S/L) \times (V - V_S) \times 100]$$

$$Q_4 = [Q_1 \times (V_S/V)] + [Q_2 \times V_S/(V - 2V_S)] + [(r_U/r_S) \times (C_S/L) \times (V - 2V_S) \times 100]$$

$$Q_8 = [Q_1 \times (V_S/V)] + [Q_2 \times V_S/(V - 2V_S)] + [Q_4 \times V_S/(V - 3V_S)] + [(r_U/r_S) \times (C_S/L) \times (V - 3V_S) \times 100]$$

$$Q_{12} = [Q_1 \times (V_S/V)] + [Q_2 \times V_S/(V - 2V_S)] + [Q_4 \times V_S/(V - 3V_S)] + [Q_8 \times V_S/(V - 4V_S)] + [(r_U/r_S) \times (C_S/L) \times (V - 4V_S) \times 100]$$

$r_U$ = peak response from the *Sample solution*
$r_S$ = peak response from the *Standard solution*
$C_S$ = concentration of clarithromycin in the *Standard solution* (mg/mL)
$V$ = volume of *Medium*, 1000 mL
$V_S$ = volume of the sample withdrawn at each time point (mL)
$L$ = label claim (mg/Tablet)

**Tolerances:** The percentages of the labeled amount of clarithromycin ($C_{38}H_{69}NO_{13}$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

**Table 3**

| Time (h) | Amount Dissolved (%) |
|---|---|
| 1 | NMT 15 |
| 2 | 10–30 |
| 4 | 35–55 |
| 8 | NLT 80 |
| 12 | NLT 90 |

**Test 4**
If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 4*.
**Buffer G:** 6.8 g/L of potassium dihydrogen phosphate and 0.18 g/L of sodium hydroxide in water. Adjust with dilute sodium hydroxide or phosphoric acid to a pH of 6.0 ± 0.1.
**Medium:** *Buffer G*; 900 mL
**Apparatus 2:** 50 rpm
**Times:** 2, 4, 8, and 12 h
**Buffer H:** 6.8 g/L of potassium dihydrogen phosphate in water. Adjust with dilute sodium hydroxide or phosphoric acid to a pH of 4.5 ± 0.1.
**Mobile phase:** Methanol and *Buffer H* (64:36)
**Standard solution:** 0.4 mg/mL of USP Clarithromycin RS in methanol and *Medium* (4:96). Dissolve first in *Medium*, using 60% of the final volume. Sonicate about 10 min until dissolved. Add methanol, using 4% of the final volume. Dilute with *Medium* to volume.
**Sample solution:** Use the solution under test, passed through a suitable filter of 0.45-µm pore size.
**Chromatographic system**
(See *Chromatography* ⟨621⟩, *System Suitability*.)
**Mode:** LC
**Detector:** UV 203 nm
**Column:** 4.0-mm × 12.5-cm; 5-µm packing L7
**Column temperature:** 30°
**Flow rate:** 1 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*
Determine the concentration, in mg/mL, of clarithromycin ($C_{38}H_{69}NO_{13}$) in the *Sample solution* at each time point:

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

$r_U$ = peak response from the *Sample solution*
$r_S$ = peak response from the *Standard solution*
$C_S$ = concentration of the *Standard solution* (mg/mL)

Calculate the percentage of the labeled amount of clarithromycin ($C_{38}H_{69}NO_{13}$) dissolved at each time point ($Q_T$):

$$Q_2 = (r_U/r_S) \times (C_S/L) \times V \times 100$$

$$Q_4 = [Q_2 \times (V_S/V)] + [(r_U/r_S) \times (C_S/L) \times (V - V_S) \times 100]$$

$$Q_8 = [Q_2 \times (V_S/V)] + [Q_4 \times V_S/(V - 2V_S)] + [(r_U/r_S) \times (C_S/L) \times (V - 2V_S) \times 100]$$

$$Q_{12} = [Q_2 \times (V_S/V)] + [Q_4 \times V_S/(V - 2V_S)] + [Q_8 \times V_S/(V - 3V_S)] + [(r_U/r_S) \times (C_S/L) \times (V - 3V_S) \times 100]$$

$r_U$ = peak response from the *Sample solution*

$r_S$ = peak response from the *Standard solution*
$C_S$ = concentration of clarithromycin in the *Standard solution* (mg/mL)
$V$ = volume of *Medium*, 900 mL
$V_S$ = volume of the sample withdrawn at each time point (mL)
$L$ = label claim (mg/Tablet)

**Tolerances:** The percentages of the labeled amount of clarithromycin ($C_{38}H_{69}NO_{13}$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

**Table 4**

| Time (h) | Amount Dissolved (%) |
|---|---|
| 2 | NMT 25 |
| 4 | 20–40 |
| 8 | 45–75 |
| 12 | NLT 80 |

**Test 5**

If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 5*.

**Medium:** Phosphate buffer, pH 6.0 (6.8 g/L of monobasic potassium phosphate and 0.18 g/L of sodium hydroxide in water. Adjust with dilute sodium hydroxide or phosphoric acid to a pH of 6.0 ± 0.1); 900 mL

**Apparatus 2:** 50 rpm, with sinker (see *Dissolution* ⟨711⟩, *Figure 2a*)

**Times:** 2, 4, 8, and 14 h

**Buffer:** 9.11 g/L of monobasic potassium phosphate in water. Adjust with dilute sodium hydroxide or phosphoric acid to a pH of 2.5 ± 0.05.

**Mobile phase:** Acetonitrile and *Buffer* (55:45)

**Standard solution:** 0.55 mg/mL of USP Clarithromycin RS in *Medium*. Sonicate to dissolve prior to dilution to final volume.

**Sample solution:** Pass a portion of the solution under test through a suitable filter of 0.22-µm pore size. Replace the portion of solution withdrawn with an equal volume of *Medium*.

**Chromatographic system**
(See *Chromatography* ⟨621⟩, *System Suitability*.)
**Mode:** LC
**Detector:** UV 210 nm
**Column:** 2.1-mm × 10-cm; 1.7-µm packing L1
**Column temperature:** 50°
**Flow rate:** 0.25 mL/min
**Injection volume:** 2 µL

**System suitability**
**Sample:** *Standard solution*
**Suitability requirements**
**Relative standard deviation:** NMT 2.0%

**Analysis**
**Samples:** *Standard solution* and *Sample solution*
Calculate the concentration ($C_i$) of clarithromycin ($C_{38}H_{69}NO_{13}$) in the sample withdrawn from the vessel at each time point ($i$):

$$\text{Result}_i = (r_U/r_S) \times C_S$$

$r_U$ = peak response from the *Sample solution*
$r_S$ = peak response from the *Standard solution*
$C_S$ = concentration of the *Standard solution* (mg/mL)

Calculate the percentage of the labeled amount of clarithromycin ($C_{38}H_{69}NO_{13}$) dissolved at each time point ($i$):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$

$$\text{Result}_2 = [(C_2 \times V) + (C_1 \times V_S] \times (1/L) \times 100$$

$$\text{Result}_3 = \{(C_3 \times V) + [(C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

$$\text{Result}_4 = \{(C_4 \times V) + [(C_3 + C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

$C_i$ = concentration of clarithromycin in the portion of sample withdrawn at the specified time point (mg/mL)
$V$ = volume of *Medium*, 900 mL
$L$ = label claim (mg/Tablet)
$V_S$ = volume of the *Sample solution* withdrawn at each time point and replaced with *Medium* (mL)

**Tolerances:** See *Table 5*.

**Table 5**

| Time Point ($i$) | Time (h) | Amount Dissolved (%) |
|---|---|---|
| 1 | 2 | NMT 25 |
| 2 | 4 | 20–40 |
| 3 | 8 | 45–75 |
| 4 | 14 | NLT 80 |

The percentages of the labeled amount of clarithromycin ($C_{38}H_{69}NO_{13}$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*. (RB 1-Feb-2017)

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

## ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed containers, protected from light. Store at 25°, excursions permitted 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 Clarithromycin RS
  USP Clarithromycin Related Compound A RS
  6,11-Di-*O*-methylerythromycin A.
  $C_{39}H_{71}NO_{13}$ 762.00