## Propranolol Hydrochloride Extended-Release Capsules

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In accordance with the Rules and Procedures of the 2015–2020 Council of Experts, the Chemical Medicines Monographs 2 Expert Committee has revised the Propranolol Hydrochloride Extended-Release Capsules monograph. The purpose for the revision is to add *Dissolution Test 6* to accommodate FDA-approved drug products with different dissolution conditions and/or tolerances than the existing dissolution tests.

The Propranolol Hydrochloride Extended-Release Capsules Revision Bulletin supersedes the currently official monograph.

See below for additional information about the proposed text.[1]

Should you have any questions, please contact Donald Min, Senior Scientific Liaison (301-230-7457 or ddm@usp.org).

[1] Note: The addition of *Dissolution Test* 5 to the Propranolol Hydrochloride Extended-Release Capsules monograph is currently being proposed under the pending monograph process.

*Revision Bulletin*
Official: August 1, 2020

# Propranolol Hydrochloride Extended-Release Capsules

**DEFINITION**
Propranolol Hydrochloride Extended-Release Capsules contain NLT 90.0% and NMT 110.0% of the labeled amount of propranolol hydrochloride ($C_{16}H_{21}NO_2 \cdot HCl$).

**IDENTIFICATION**
● **Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 197M
**Sample:** Transfer the contents of a number of Capsules, equivalent to 160 mg of propranolol hydrochloride, to a glass mortar. Add 5 mL of water, and triturate the mixture with a glass pestle. Transfer the suspension to a centrifuge tube with the aid of 10 mL of water. Add 1 mL of 1 N sodium hydroxide. Add 15 mL of ether, and shake by mechanical means for 5 min. Centrifuge the mixture, and transfer as much of the ether layer as possible to a second centrifuge tube. Add 0.1 mL of hydrochloric acid to the ether extract, and shake. Centrifuge, and discard the ether layer. Add 15 mL of ether to the precipitate, and shake by mechanical means for 5 min. Centrifuge, and discard the ether layer. Dry the precipitate in vacuum at 45° for 30 min. Transfer a small amount of the dried precipitate to a mortar, and grind to a fine powder.

**ASSAY**
● **Procedure**
**Buffer:** 6.8 mg/mL of monobasic potassium phosphate. Pass the solution through a filter of 0.5-µm or finer pore size before use.
**Mobile phase:** Acetonitrile and *Buffer* (7:13)
**Diluent:** Acetonitrile and water (7:13)
**Standard stock solution:** 200 µg/mL of USP Propranolol Hydrochloride RS in methanol
**Standard solution:** 20 µg/mL in *Diluent* from *Standard stock solution*
**Sample stock solution:** Transfer the contents of Capsules (NLT 10) to a suitable volumetric flask. Add methanol (60% of the volume of the flask), and swirl by mechanical means for 2 h. Allow to stand for 16 h, then sonicate for 30 min, and swirl for 30 min. Dilute with methanol to volume, and centrifuge a portion of the solution. Use the clear supernatant for further use.
**Sample solution:** Nominally equivalent to 20 µg/mL of propranolol hydrochloride in *Diluent* from *Sample stock solution*
**Chromatographic system**
(See *Chromatography ⟨621⟩, System Suitability*.)
**Mode:** LC
**Detector:** UV 220 nm
**Column:** 4-mm × 15-cm; 5-µm packing L1
**Flow rate:** 2 mL/min
**Injection size:** 20 µL
**System suitability**
**Sample:** *Standard solution*
[Note—The retention time for propranolol is about 5–9 min.]
**Suitability requirements**
**Column efficiency:** NLT 1000 theoretical plates
**Tailing factor:** NMT 3
**Relative standard deviation:** NMT 2%
**Analysis**
**Samples:** *Standard solution* and *Sample solution*
Calculate the percentage of $C_{16}H_{21}NO_2 \cdot HCl$ in each Capsule 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 Propranolol Hydrochloride RS in the *Standard solution* (µg/mL)
$C_U$ = nominal concentration of propranolol hydrochloride in the *Sample solution* (µg/mL)

**Acceptance criteria:** 90.0%–110.0%

**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*.
**pH 1.2 buffer solution:** Dissolve 2.0 g of sodium chloride in water, add 7.0 mL of hydrochloric acid, and dilute with water to 1 L.
**pH 6.8 buffer solution:** 21.72 mg/mL of anhydrous dibasic sodium phosphate and 4.94 mg/mL of citric acid monohydrate in water
**Media:** Proceed as directed under *Dissolution ⟨711⟩, Procedure, Apparatus 1 and Apparatus 2, Delayed-Release Dosage Forms, Method B Procedure*, using 900 mL of *pH 1.2 buffer solution* during the *Acid stage*, and conduct the test for 1.5 h. For the *Buffer stage*, use 900 mL of *pH 6.8 buffer solution*, conduct the test for 2.5 h (this is the 4-h time point: 1.5 h in *Acid stage* plus 2.5 h in *Buffer stage*), conduct the test for the additional time points, always considering $T_1$ = 1.5 h, and use the acceptance criteria given under *Tolerances*.
**Apparatus 1:** 100 rpm
**Times:** 1.5, 4, 8, 14, and 24 h
**Standard solution:** USP Propranolol Hydrochloride RS at a known concentration in water
**Sample solution:** Pass a portion of the solution under test through a suitable filter. Dilute with *Medium*, if necessary.

**Spectrometric conditions**

(See *Ultraviolet-Visible Spectroscopy* ⟨857⟩.)

**Mode:** UV

**Analytical wavelength:** Maximum absorbance at 320 nm, with respect to a baseline drawn from 355 nm through 340 nm

**Analysis**

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

**Tolerances:** The percentages of the labeled amount of $C_{16}H_{21}NO_2 \cdot HCl$ dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

| Time (h) | Amount Dissolved |
|---|---|
| 1.5 | NMT 30% |
| 4 | 35%–60% |
| 8 | 55%–80% |
| 14 | 70%–95% |
| 24 | 81%–110% |

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

**pH 1.2 buffer solution:** Dissolve 2.0 g of sodium chloride in water, add 7.0 mL of hydrochloric acid, and dilute with water to 1 L.

**pH 7.5 buffer solution:** Dissolve 6.8 g of monobasic potassium phosphate and 1.6 g of sodium hydroxide in 900 mL of water, adjust with 1 N sodium hydroxide to a pH of 7.5, and dilute with water to 1 L.

**Media:** Proceed as directed under *Dissolution* ⟨711⟩*, Procedure, Apparatus 1 and Apparatus 2, Delayed-Release Dosage Forms, Method B Procedure*, using 900 mL of *pH 1.2 buffer solution* during the *Acid stage*, and conduct the test for 1 h. For the *Buffer stage*, use 900 mL of *pH 7.5 buffer solution*, conduct the test for 2 h (this is the 3-h time point: 1 h in *Acid stage* plus 2 h in *Buffer stage*), conduct the test for the additional time points, always considering $T_1$ = 1 h, and use the acceptance criteria given under *Tolerances*.

**Apparatus 1:** 50 rpm

**Times:** 1, 3, 6, and 12 h

**Standard solution:** USP Propranolol Hydrochloride RS at a known concentration in water

**Sample solution:** Pass a portion of the solution under test through a suitable filter. Dilute with *Medium*, if necessary.

**Spectrometric conditions** and **Analysis:** Proceed as directed under *Test 1*.

**Tolerances:** The percentages of the labeled amount of $C_{16}H_{21}NO_2 \cdot HCl$ dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

| Time (h) | Amount Dissolved |
|---|---|
| 1 | NMT 20% |
| 3 | 20%–45% |
| 6 | 45%–80% |
| 12 | NLT 80% |

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

**Acid stage medium:** *pH 1.2 buffer solution* (prepared by dissolving 2.0 g of sodium chloride in water, adding 7.0 mL of hydrochloric acid, and diluting with water to 1000 mL); 900 mL

**Buffer stage medium:** pH 6.8 phosphate buffer; 900 mL

**Apparatus 1:** 100 rpm

**Standard stock solution:** 1 mg/mL of USP Propranolol Hydrochloride RS in water

**Working standard solution:** Quantitatively dilute the *Standard stock solution* with water to obtain a final concentration of about (*L*/1000) mg per mL, where *L* is the Capsule label claim in mg.

**Analysis:** Conduct the test in *Acid stage medium* for 1.5 h, sample, and pass through a suitable filter of 0.45-µm or finer pore size. Replace the *Acid stage medium* with the *Buffer stage medium*, and conduct the test for 2.5 h (this is the 4-h time point: 1.5 h in *Acid stage medium* plus 2.5 h in *Buffer stage medium*), conduct the test for the additional time points, always considering $T_1$ = 1.5 h, and use the acceptance criteria given under *Tolerances*.

Determine the amount of $C_{16}H_{21}NO_2 \cdot HCl$ dissolved, using UV absorbances at the wavelength of maximum absorbance at about 320 nm, with respect to a baseline drawn from 355 nm through 340 nm, using a 1-cm cell and water as the blank.

Determine the percentage of propranolol hydrochloride dissolved using the spectrophotometric procedure as directed for *Test 1*.

**Tolerances:** The percentages of the labeled amount of $C_{16}H_{21}NO_2 \cdot HCl$ dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

| Time (h) | Amount Dissolved |
|---|---|
| 1.5 | NMT 15% |
| 4 | NMT 30% |
| 8 | 25%–60% |
| 14 | 55%–85% |
| 24 | NLT 75% |

**Test 4:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 4*.

**Acid stage medium:** *pH 1.2 buffer solution* (prepared by dissolving 2.0 g of sodium chloride in water, adding 7.0 mL of hydrochloric acid, and diluting with water to 1000 mL); 900 mL, deaerated
**Buffer stage medium:** pH 6.8 phosphate buffer; 900 mL, deaerated
**Apparatus 1:** 100 rpm
**Times:** 1.5 h in acid stage; 4, 8, 14, and 24 h in buffer stage
**Standard solution:** 0.18 mg/mL of USP Propranolol Hydrochloride RS in water
**Analysis:** Conduct the test in *Acid stage medium* for 1.5 h, sample, and pass through a suitable filter of 10-µm or finer pore size. Replace the *Acid stage medium* with the *Buffer stage medium*, and conduct the test for 2.5 h (this is the 4-h time point: 1.5 h in *Acid stage medium* plus 2.5 h in *Buffer stage medium*), conduct the test for the additional time points, always considering $T_1$ = 1.5 h, and use the acceptance criteria given under *Tolerances*. Determine the amount of $C_{16}H_{21}NO_2 \cdot HCl$ dissolved, using UV absorbances at the wavelength of maximum absorbance at about 320 nm, with respect to a baseline drawn from 355 nm through 340 nm, using a 1-cm cell and water as the blank.
**Tolerances:** The percentages of the labeled amount of $C_{16}H_{21}NO_2 \cdot HCl$ dissolved at the times specified conform to *Dissolution ⟨711⟩*, *Acceptance Table 2*.

| Time (h) | Amount Dissolved |
|---|---|
| 1.5 | NMT 30% |
| 4 | 27%–52% |
| 8 | 52%–77% |
| 14 | 70%–95% |
| 24 | 81%–110% |

**Test 6:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 6*.
**Acid stage medium:** *pH 1.2 buffer solution* (Dissolve 2.0 g of sodium chloride in 1000 mL water, and add 7.0 mL of hydrochloric acid. Adjust with hydrochloric acid or 50% sodium hydroxide solution to a pH of 1.2); 900 mL
**Buffer stage medium:** pH 6.8 phosphate buffer (Dissolve 54.8 g of sodium phosphate dibasic, dodecahydrate and 4.94 g of citric acid monohydrate in 1000 mL of water. Adjust with phosphoric acid or 50% sodium hydroxide solution to a pH of 6.8); 900 mL
**Apparatus 1:** 100 rpm
**Times:** 1.5 h in acid stage; 4, 8, 14, and 20 h in buffer stage
**Standard solution:** 0.18 mg/mL of USP Propranolol Hydrochloride RS in water
**Acid stage sample solution:** Withdraw a portion of the solution under test and pass through a suitable filter.
**Buffer stage sample solution:** Withdraw a portion of the solution under test and pass through a suitable filter.
**Instrumental conditions**
(See *Ultraviolet-Visible Spectroscopy ⟨857⟩*.)
**Mode:** UV
**Analytical wavelength:** 320 nm
**Cell length:** 1 cm
**Blank:** *Acid stage medium* or *Buffer stage medium*
**System suitability**
**Sample:** *Standard solution*
**Suitability requirement**
**Relative standard deviation:** NMT 2.0%
**Analysis**
**Samples:** *Standard solution*, *Acid stage sample solution*, and *Buffer stage sample solution*
Proceed as directed under *Dissolution ⟨711⟩, Procedure, Apparatus 1 and Apparatus 2, Delayed-Release Dosage Forms, Method B Procedure*, using 900 mL of *Acid stage medium* during the *Acid stage*. Conduct the test in *Acid stage medium* for 1.5 h. For the *Buffer stage*, use 900 mL of *Buffer stage medium* and conduct the test for the additional time points and use the acceptance criteria given under *Tolerances*.
Calculate the percentage of the labeled amount of propranolol hydrochloride ($C_{16}H_{21}NO_2 \cdot HCl$) dissolved in *Acid stage medium* ($Q_A$):

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

$A_U$ = absorbance from the *Acid stage sample solution*
$A_S$ = absorbance from the *Standard solution*
$C_S$ = concentration of USP Propranolol Hydrochloride RS in the *Standard solution* (mg/mL)
$V$ = volume of *Acid stage medium*, 900 mL
$L$ = label claim (mg/Capsule)

Determine the concentration of propranolol hydrochloride ($C_{16}H_{21}NO_2 \cdot HCl$) at each time point ($i$) in the *Buffer stage medium*:

$$\text{Result}_i = (A_U/A_S) \times C_S$$

$A_U$ = absorbance from the *Buffer stage sample solution*
$A_S$ = absorbance from the *Standard solution*
$C_S$ = concentration of USP Propranolol Hydrochloride RS in the *Standard solution* (mg/mL)

Calculate the percentage of the labeled amount of propranolol hydrochloride ($C_{16}H_{21}NO_2 \cdot HCl$) dissolved at each time point ($i$) in both the *Acid stage medium* and the *Buffer stage medium*:

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

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

$$\text{Result}_4 = [(\{C_3 \times [V - (2 \times V_S)]\}) + [(C_2 + C_1) \times V_S]) \times (1/L) \times 100] + Q_A$$

$$\text{Result}_5 = [(\{C_4 \times [V - (3 \times V_S)]\}) + [(C_3 + C_2 + C_1) \times V_S]) \times (1/L) \times 100] + Q_A$$

$C_i$ = concentration of propranolol hydrochloride in the portion of the sample withdrawn at time point ($i$) (mg/mL)

$V$ = volume of *Buffer stage medium*, 900 mL

$L$ = label claim (mg/Capsule)

$Q_A$ = percentage of the labeled amount of propranolol hydrochloride dissolved in*Acid stage medium*

$V_S$ = volume of the *Buffer stage sample solution* withdrawn at each time point from the *Buffer stage medium* (mL)

**Tolerances:** The percentages of the labeled amount of propranolol hydrochloride ($C_{16}H_{21}NO_2 \cdot HCl$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

| Time point (*i*) | Time (h) | Amount Dissolved (%) |
|---|---|---|
| 1 | 1.5 | NMT 20 |
| 2 | 4 | 25–45 |
| 3 | 8 | 55–75 |
| 4 | 14 | 70–90 |
| 5 | 20 | NLT 80 |

▲ (RB 1-Aug-2020)

- **Uniformity of Dosage Units** ⟨905⟩**:** Meet the requirements

**Procedure for content uniformity**

**Standard solution:** 40 µg/mL of USP Propranolol Hydrochloride RS in methanol

**Sample stock solution:** Transfer the contents of 1 Capsule to a suitable volumetric flask. Add methanol (70% of the volume of the flask), swirl occasionally for 30 min, sonicate for 1 min, and then swirl occasionally for an additional 30 min. Dilute with methanol to volume, and centrifuge a portion of the solution. Use the clear supernatant for preparing the *Sample solution*.

**Sample solution:** Equivalent to 40 µg/mL in methanol from *Sample stock solution*

**Spectrometric conditions**

(See *Ultraviolet-Visible Spectroscopy* ⟨857⟩.)

**Mode:** UV

**Analytical wavelength:** 290 nm

**Cell:** 1 cm

**Blank:** Methanol

Calculate the percentage of $C_{16}H_{21}NO_2 \cdot HCl$ in the Capsule taken:

$$\text{Result} = (A_U/A_S) \times (C_S/C_U) \times 100$$

$A_U$ = absorbance of the *Sample solution*

$A_S$ = absorbance of the *Standard solution*

$C_S$ = concentration of USP Propranolol Hydrochloride RS in the *Standard solution* (µg/mL)

$C_U$ = concentration of the *Sample solution* (µg/mL)

**ADDITIONAL REQUIREMENTS**

- **Packaging and Storage:** Preserve in well-closed containers.
- **Labeling:** The labeling states the *Dissolution Test* with which the product complies.
- **USP Reference Standards** ⟨11⟩

USP Propranolol Hydrochloride RS

**Page Information:**

Not Applicable

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