

Propranolol Hydrochloride Extended-Release Capsules

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Expert Committee	Chemical Medicines Monographs 2

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 2 Expert Committee intends to revise the Propranolol Hydrochloride Extended-Release Capsules monograph.

Based on the supporting data received from a manufacturer awaiting FDA approval, the Expert Committee proposes to add *Dissolution Test 5*.

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 Donald Min, Senior Scientific Liaison to the Chemical Medicines Monographs 2 Expert Committee (301-230-7457 or ddm@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](#).

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

Change to read:

- **SPECTROSCOPIC IDENTIFICATION TESTS** (197), *Infrared Spectroscopy*: 197M▲ (CN 1-May-2020)

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- μ m or finer pore size before use.

Mobile phase: Acetonitrile and Buffer (7:13)

Diluent: Acetonitrile and water (7:13)

Standard stock solution: 200 μ g/mL of USP Propranolol Hydrochloride RS in methanol

Standard solution: 20 μ g/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 μ g/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 \times 15-cm; 5- μ m packing L1

Flow rate: 2 mL/min

Injection size: 20 μ L

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 (μ g/mL)

C_U = nominal concentration of propranolol hydrochloride in the Sample solution (μ g/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 $T_i = 1.5$ 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*.

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

Acid stage medium: 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 1000 mL); 900 mL

Buffer stage medium: pH 6.8 phosphate buffer (dissolve 21.72 g of anhydrous dibasic sodium phosphate and 4.94 g of citric acid monohydrate in 1000 mL of water); 900 mL

Apparatus 1: 100 rpm

Times: 1.5, 4, 8, 14, and 24 h

Standard stock solution: 1.3–1.8 mg/mL of USP Propranolol Hydrochloride RS in water

Acid stage standard solution: Dilute a portion of the *Standard stock solution* with *Acid stage medium* to a concentration of about 30% of the label claim.

Buffer stage standard solutions: Dilute a portion of the *Standard stock solution* with *Buffer stage medium* to concentrations equivalent to 10%, 50%, and 100% of the label claim.

Acid stage sample solution: Pass a portion of the solution under test through a suitable filter. Dilute with *Acid stage medium*, if necessary.

Buffer stage sample solution: Pass a portion of the solution under test through a suitable filter. Dilute with *Buffer stage medium*, if necessary.

Instrumental conditions

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

Mode: UV

Analytical wavelength: 319 nm

Blank: *Acid stage medium* or *Buffer stage medium*

System suitability

Samples: *Buffer stage standard solutions*

Plot the absorbance of the *Buffer stage standard solution* versus the concentration of the propranolol hydrochloride in the *Buffer stage standard solution*, in mg/mL, and draw the straight line best fitting the four plotted points. From the graph, determine the concentration of propranolol hydrochloride in the *Buffer stage sample solution*.

Suitability requirements

Linear correlation coefficient: NLT 0.99

Analysis

Samples: *Acid stage standard solution*, *Buffer stage standard solutions*, *Acid stage sample solution*, and *Buffer stage sample solution*

Proceed as directed in *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*, and conduct the test for 1.5 h. For the *Buffer stage*, use 900 mL of *Buffer stage medium*, 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 in *Tolerances*.

Calculate the percentage of propranolol hydrochloride ($C_{16}H_{21}NO_2 \cdot HCl$) dissolved in *Acid stage medium*:

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

- A_U = absorbance from the *Acid stage sample solution*
- A_S = absorbance from the *Acid stage standard solution*
- C_S = concentration of USP Propranolol Hydrochloride RS in the *Acid stage standard solution* (mg/mL)
- D = dilution factor, if needed
- V = volume of *Acid stage medium*, 900 mL
- L = label claim (mg/Capsule)

Determine the concentration of propranolol hydrochloride in the portion of the *Buffer stage sample solution* from the linear regression analysis.

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 the *Buffer stage*:

$$\text{Result}_1 = C_7 \times V \times (1/L) \times 100$$

$$\text{Result}_2 = \{[C_2 \times (V - V_5)] + (C_7 \times V_5)\} \times (1/L) \times 100$$

$$\text{Result}_3 = \{[C_3 \times [V - (2 \times V_5)]] + [(C_2 + C_7) \times V_5]\} \times (1/L) \times 100$$

$$\text{Result}_4 = \{[C_4 \times [V - (3 \times V_5)]] + [(C_3 + C_2 + C_7) \times V_5]\} \times (1/L) \times 100$$

- C_i = concentration of propranolol hydrochloride in the portion of sample withdrawn at time point (i) (mg/mL)
- V = volume of *Buffer stage medium*, 900 mL
- L = label claim (mg/Capsule)
- V_5 = volume of the *Buffer stage sample solution* withdrawn 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 (h)	Amount Dissolved (%)
1.5	NMT 25
4	30–50
8	50–70
14	65–85
24	NLT 80▲ (TBD)

- **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