Propafenone Hydrochloride Extended-Release Capsules

Type of Posting	Revision Bulletin
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Expert Committee	Chemical Medicines Monographs 2
Reason for Revision	Compliance

In accordance with the Rules and Procedures of the 2015-2020 Council of Experts, the Chemical Medicines Expert Committee 2 has revised the Propafenone Hydrochloride Extended-Release Capsules monograph. The purpose for the revision is to add *Dissolution Test 2* to be consistent with the FDA approved specifications for a generic drug product.

Minor editorial changes have been made to update the monograph to the current *USP* style.

Propafenone Hydrochloride Extended-Release Capsules Revision Bulletin supersedes the currently monograph. The Revision Bulletin will be incorporated to *USP40–NF35*.

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

Propafenone Hydrochloride Extended-Release Capsules

DEFINITION

Propafenone Hydrochloride Extended-Release Capsules contain NLT 90.0% and NMT 110.0% of the labeled amount of propafenone hydrochloride ($C_{21}H_{27}NO_3 \cdot HCl$).

IDENTIFICATION

- **A. INFRARED ABSORPTION** ⟨197K⟩
- **B.** 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: Dissolve 1.36 g/L of monobasic potassium phosphate in water, and adjust with phosphoric acid to a pH of 3.0 ± 0.1.
Mobile phase: Methanol and *Buffer* (50:50)
Diluent: 50% Methanol in water
Standard solution: 0.1 mg/mL of USP Propafenone Hydrochloride RS in *Diluent*
Sample stock solution: Nominally 1 mg/mL of propafenone hydrochloride prepared as follows. Transfer a suitable amount of finely powdered contents from NLT 20 Capsules to an appropriate volumetric flask. Add about 60% of the final volume of *Diluent,* and sonicate with occasional swirling until the contents are completely disintegrated. Dilute with *Diluent* to volume and pass through a suitable filter of 0.45-µm pore size.
Sample solution: Nominally 0.1 mg/mL of propafenone hydrochloride in *Diluent* from the *Sample stock solution*
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 250 nm
Column: 4.6-mm × 15-cm; 5-µm packing L7
Flow rate: 1 mL/min
Injection volume: 20 µL
Run time: NLT 2 times the retention time of propafenone
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 propafenone hydrochloride ($C_{21}H_{27}NO_3 \cdot HCl$) in the portion of Capsules taken:

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

r_U = peak response of propafenone from the *Sample solution*
r_S = peak response of propafenone from the *Standard solution*
C_S = concentration of USP Propafenone Hydrochloride RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of propafenone hydrochloride in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

- **DISSOLUTION** ⟨711⟩

Test 1: ● (RB 1-Jun-2016)
Acid stage
Medium: 0.08 N hydrochloric acid; 900 mL
Apparatus 2: 50 rpm
Time: 1 h
Diluent: 6.8 g/L of monobasic potassium phosphate in water. Adjust with sodium hydroxide to a pH of 6.8.
Standard solution: (*L*/1000) mg/mL of USP Propafenone Hydrochloride RS in *Diluent*, where *L* is the label claim in mg/Capsule
Sample solution: At the specified time point, withdraw about 10 mL of the solution and pass through a suitable filter of 0.45-µm pore size. Discard at least the first 4 mL of the filtrate. Analyze the *Sample solution* immediately.
Instrumental conditions
Mode: UV
Analytical wavelengths: 305 and 375 nm
Cell: 0.2 cm
Blank: *Medium*
Analysis
Samples: *Standard solution* and *Sample solution*
Measure and subtract the absorbance at 375 nm from the absorbance at 305 nm to obtain the absorbances for the *Sample solution* and *Standard solution*.
Calculate the percentage of the labeled amount of propafenone hydrochloride ($C_{21}H_{27}NO_3 \cdot HCl$) dissolved:

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

A_U = absorbance of the *Sample solution*
A_S = absorbance of the *Standard solution*
C_S = concentration of USP Propafenone Hydrochloride RS in the *Standard solution* (mg/mL)
L = label claim (mg/Capsule)
V = volume of *Medium*, 900 mL
Tolerances: See *Table 1*.
Buffer stage
Proceed as directed in the *Acid stage*, except for the following parameters.
Buffer: Dissolve 108.88 g of monobasic potassium phosphate in water, add 14.4 g of sodium hydroxide, mix to dissolve, and dilute with water to 1 L. Adjust with 2 N sodium hydroxide to a pH of 6.8.
Solution A: *Buffer* and 2 N sodium hydroxide (64:36)
Medium: At 2 h of dissolution time, add 100 mL of *Solution A*, preheated at 37°, to 900 mL of 0.08 N hydrochloric acid.
Time: 4 and 12 h
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the concentration (C_i) of propafenone hydrochloride ($C_{21}H_{27}NO_3 \cdot HCl$) in the sample withdrawn from the vessel at each time point (i):

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

A_U = absorbance of the *Sample solution*
A_S = absorbance of the *Standard solution*

C_S = concentration of the *Standard solution* (mg/mL)

Calculate the percentage of the labeled amount of propafenone hydrochloride ($C_{21}H_{27}NO_3 \cdot HCl$) dissolved at each time point (i):

$$\text{Result}_2 = C_2 \times V \times (1/L) \times 100$$

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

C_i = concentration of propafenone hydrochloride in the portion of sample withdrawn at time point (i) (mg/mL)
V = volume of *Medium*, 1000 mL
L = label claim (mg/Capsule)
V_S = volume of *Medium* taken (mL)

Tolerances: See *Table 1*.

Table 1

Time Point (*i*)	Time (h)	Amount Dissolved (%)
1	1	5–25
2	4	40–70
3	12	NLT 75

The percentages of the labeled amount of propafenone hydrochloride ($C_{21}H_{27}NO_3 \cdot HCl$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

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

Acid stage

Acid stage medium: 0.08 N hydrochloric acid; 900 mL

Apparatus 2: 50 rpm, with sinkers

Time: 1 h

Standard stock solution: 0.42 mg/mL of USP Propafenone Hydrochloride RS prepared as follows. Transfer a suitable amount of USP Propafenone RS to a suitable volumetric flask. Add methanol, NMT 10% of the final volume, and sonicate to dissolve. Dilute with *Acid stage medium* to volume.

Standard solution: 0.021 mg/mL of USP Propafenone Hydrochloride RS in *Acid stage medium* from the *Standard stock solution*

Sample solution: Pass the solution through a suitable filter of 0.45-µm pore size. Dilute with *Acid stage medium* to a concentration similar to that of the *Standard solution*.

Instrumental conditions

Mode: UV

Analytical wavelength: 305 nm

Cell: 1 cm

Blank: *Acid stage medium*

Analysis

After 1 h in the *Acid stage medium* and the collection of the *Sample solution*, replace the portion of solution withdrawn with an equal volume of *Acid stage medium*. Continue for an additional 1 h in *Acid stage medium*.

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of propafenone hydrochloride ($C_{21}H_{27}NO_3 \cdot HCl$) dissolved:

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

A_U = absorbance of the *Sample solution*
A_S = absorbance of the *Standard solution*
C_S = concentration of USP Propafenone Hydrochloride RS in the *Standard solution* (mg/mL)
D = dilution factor (mL/mL)
V = volume of *Acid stage medium*, 900 mL
L = label claim (mg/Capsule)

Tolerances: See *Table 2*.

Buffer stage

Proceed as directed in the *Acid stage*, except for the following parameters.

Buffer stage medium: After 2 h in the *Acid stage*, add 100 mL of phosphate buffer (68 g of monobasic potassium phosphate and 42 g of sodium hydroxide in 1000 mL of water), preheated at 37°, to 900 mL of *Acid stage medium*; 1000 mL.

Times: 6 and 15 h

Standard stock solution: 0.48 mg/mL of USP Propafenone Hydrochloride RS prepared as follows. Transfer a suitable amount of USP Propafenone Hydrochloride RS to a suitable volumetric flask. Add methanol, NMT 10% of the final volume, and sonicate to dissolve. Dilute with *Buffer stage medium* to volume.

Standard solution: 0.048 mg/mL of USP Propafenone Hydrochloride RS in *Buffer stage medium* from *Standard stock solution*

Sample solution: Withdraw a 10-mL aliquot at each time point. Pass the solution through a suitable filter of 0.45-µm pore size. Dilute with *Buffer stage medium* to a concentration similar to that of the *Standard solution*.

Blank: *Buffer stage medium*

Instrumental conditions: See *Acid stage*.

Analysis

At the specified time points, replace the portion of solution withdrawn with 10 mL of *Buffer stage medium*.

Samples: *Standard solution* and *Sample solution*

Calculate the concentration (C_i) of propafenone hydrochloride ($C_{21}H_{27}NO_3 \cdot HCl$) in the sample withdrawn from the vessel at each time point (i):

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

A_U = absorbance of the *Sample solution*
A_S = absorbance of the *Standard solution*
C_S = concentration of USP Propafenone Hydrochloride RS in the *Standard solution* (mg/mL)
D = dilution factor (mL/mL)

Calculate the percentage of the labeled amount of propafenone hydrochloride ($C_{21}H_{27}NO_3 \cdot HCl$) dissolved at each time point (i):

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

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

C_i = concentration of propafenone hydrochloride in the portion of sample withdrawn at time point (i) (mg/mL)
V = volume of *Buffer stage medium*, 1000 mL
V_S = volume of the *Sample solution* withdrawn from the *Buffer stage medium* (mL)
L = label claim (mg/Capsule)

Tolerances: See *Table 2*.

Table 2

Time Point (*i*)	Time (h)	Amount Dissolved (%)
1	1	5–25
2	6	45–65
3	15	NLT 80

The percentages of the labeled amount of propafenone hydrochloride ($C_{21}H_{27}NO_3 \cdot HCl$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.● (RB 1-Jun-2016)

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

IMPURITIES

Change to read:

- **ORGANIC IMPURITIES**

Keep all solutions containing propafenone hydrochloride in amber glassware.

Solution A: 0.015 M dibasic potassium phosphate. Adjust with phosphoric acid to a pH of 2.5 ± 0.2.

Solution B: Acetonitrile

Mobile phase: See ●*Table 3*.● (RB 1-Jun-2016)

●**Table 3**● (RB 1-Jun-2016)

Time (min)	Solution A (%)	Solution B (%)
0	65	35
8	65	35
20	30	70
30	30	70
31	65	35
36	65	35

Diluent: 50% Methanol in water

System suitability solution: 0.1 mg/mL each of USP Propafenone Hydrochloride RS and USP Propafenone Related Compound B RS in *Diluent*

Standard solution: 2.0 µg/mL of USP Propafenone Hydrochloride RS in *Diluent*. Sonicate if necessary.

Sensitivity solution: 0.3 µg/mL of USP Propafenone Hydrochloride RS in *Diluent* from the *Standard solution*

Sample solution: Nominally 1 mg/mL of propafenone hydrochloride, prepared as follows. Transfer a suitable amount of finely powdered contents from NLT 20 Capsules to an appropriate volumetric flask. Add about 40% of the final volume of *Diluent* and sonicate for about 15 min. Dilute with *Diluent* to volume and pass through a suitable filter of 0.45-µm pore size.

Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 220 nm
Column: 4.6-mm × 15-cm; 5-µm packing L7
Column temperature: 30°
Flow rate: 1 mL/min
Injection volume: 20 µL

System suitability
Samples: *System suitability solution*, *Standard solution*, and *Sensitivity solution*
Suitability requirements
Resolution: NLT 3.0 between propafenone related compound B and propafenone, *System suitability solution*
Relative standard deviation: NMT 5.0%, *Standard solution*
Signal-to-noise ratio: NLT 10, *Sensitivity solution*

Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of each individual unspecified degradation product in the portion of Capsules taken:

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

r_U = peak response of each unspecified degradation product from the *Sample solution*
r_S = peak response of propafenone from the *Standard solution*
C_S = concentration of USP Propafenone Hydrochloride RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of propafenone hydrochloride in the *Sample solution* (mg/mL)

Acceptance criteria: See ●*Table 4*.● (RB 1-Jun-2016) Disregard any peaks below 0.03% (peak area less than that of the *Sensitivity solution*).

●**Table 4**● (RB 1-Jun-2016)

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Propafenone related compound B[a,b]	0.81	—
Propafenone	1.00	—
Propafenone glycerol analog[a,c]	2.53	—
Flavone[a,d]	2.83	—
Propafenone dimer[a,e]	2.88	—
Propafenone chloroglycerol analog[a,f]	2.91	—
Propafenone glycidyl analog[a,g]	2.96	—
Propafenone phenol[a,h]	3.29	—
Propafenone glycerol dimer[a,i]	3.80	—
Any unspecified degradation product	—	0.15
Total degradation products	—	0.50

[a] Process impurities; do not include in total degradation products.
[b] (*RS*,*E*)-1-{2-[2-Hydroxy-3-(propylamino)propoxy]phenyl}-3-phenylprop-2-en-1-one.
[c] 1-[2-[(2*RS*)-2,3-Dihydroxypropoxy]phenyl]-3-phenylpropan-1-one.
[d] 2-Phenylchroman-4-one.
[e] 1,1′-[Propyliminobis(2-hydroxypropane-3,1-diyl)oxy-2,1-phenylene]bis(3-phenylpropan-1-one).
[f] 1-[2-(3-Chloro-2-hydroxypropoxy)phenyl]-3-phenylpropan-1-one.
[g] 1-[2-[[(*RS*)-Oxiranyl]methoxy]phenyl]-3-phenylpropan-1-one.
[h] 1-(2-Hydroxyphenyl)-3-phenylpropan-1-one.
[i] 1,1′-(2,2′-(2-Hydroxypropane-1,3-diyl)bis(oxy)bis(2,1-phenylene))bis(3-phenylpropan-1-one).

Change to read:

- **CONTENT OF PROPAFENONE RELATED COMPOUND A**

Buffer: Dissolve 3.4 g of dibasic potassium phosphate in 1000 mL of water, and adjust with phosphoric acid to a pH of 2.5 ± 0.05.

Solution A: Methanol and *Buffer* (45:55); pass through a suitable filter of 0.2-µm pore size

Solution B: Methanol and *Buffer* (75:25); pass through a suitable filter of 0.2-µm pore size

Mobile phase: See *Table 5.* (RB 1-Jun-2016)

Table 5 (RB 1-Jun-2016)

Time (min)	Solution A (%)	Solution B (%)
0	100	0
4.0	100	0
7.0	50	50
10.0	0	100
12.0	0	100
12.5	100	0
15.0	100	0

Diluent: Methanol and water (80:20)
Standard solution: 2.0 µg/mL of USP Propafenone Related Compound A RS in *Diluent*
Sensitivity solution: 0.2 µg/mL of USP Propafenone Related Compound A RS in *Diluent* from the *Standard solution*
Sample solution: Nominally 1 mg/mL of propafenone hydrochloride prepared as follows. Transfer a suitable amount of finely powdered contents from NLT 20 Capsules to an appropriate volumetric flask. Add about 75% of the final volume of *Diluent* and sonicate with intermittent shaking for 20 min. Dilute with *Diluent* to volume and pass through a suitable filter of 0.45-µm pore size. Discard the first 4 mL of the filtrate.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 250 nm
Column: 2.1-mm × 10-cm; 1.7-µm packing L1
Column temperature: 60°
Flow rate: 0.4 mL/min
Injection volume: 4 µL
System suitability
Samples: *Standard solution* and *Sensitivity solution*
Suitability requirements
Tailing factor: NMT 2.0, *Standard solution*
Relative standard deviation: NMT 6.0%, *Standard solution*
Signal-to-noise ratio: NLT 10, *Sensitivity solution*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of propafenone related compound A in the portion of Capsules taken:

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

r_U = peak response of propafenone related compound A from the *Sample solution*
r_S = peak response of propafenone related compound A from the *Standard solution*
C_S = concentration of USP Propafenone Related Compound A RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of propafenone hydrochloride in the *Sample solution* (mg/mL)

Acceptance criteria: See *Table 6.* (RB 1-Jun-2016)

Table 6 (RB 1-Jun-2016)

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Propafenone	1.0	—
Propafenone related compound A[a]	1.9	0.20

[a] *N*-{2-Hydroxy-3-[2-(3-phenylpropanoyl)phenoxy]propyl}-*N*-propylformamide.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Keep in tight containers and store at controlled room temperature.

Add the following:

- **LABELING:** When more than one test for *Dissolution* is given, the *Labeling* section states the test for *Dissolution* used only if *Test 1* is not used. (RB 1-Jun-2016)
- **USP REFERENCE STANDARDS** ⟨11⟩
  USP Propafenone Hydrochloride RS
  USP Propafenone Related Compound A RS
  N-{2-Hydroxy-3-[2-(3-phenylpropanoyl)phenoxy]propyl}-*N*-propylformamide.
  $C_{22}H_{27}NO_4$ 369.45
  USP Propafenone Related Compound B RS
  (*RS*,*E*)-1-{2-[2-Hydroxy-3-(propylamino)propoxy]phenyl}-3-phenylprop-2-en-1-one.
  $C_{21}H_{25}NO_3$ 339.43