Propafenone Hydrochloride Extended-Release Capsules

Type of Posting: Revision Bulletin
Posting Date: 27–May–2016
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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$_3$ · 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 x 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$_3$ · HCl) in the portion of Capsules taken:

$$\text{Result} = \left( \frac{r_o}{r_S} \right) \times \left( \frac{C_S}{C_o} \right) \times 100$$

$r_o$ = 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)
$C_o$ = 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: (88-1-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$_3$ · HCl) dissolved:

$$\text{Result}_i = \left( \frac{A_o/A_S} {C_i/L} \right) \times V \times 100$$

$A_o$ = absorbance of the Sample solution
$A_S$ = absorbance of the Standard solution
$C_i$ = 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) of propafenone hydrochloride (C$_{21}$H$_{27}$NO$_3$ · HCl) in the sample withdrawn from the vessel at each time point (i):

$$\text{Result}_i = \left( \frac{A_o/A_S} {C_i} \right) \times C_o$$

$A_o$ = absorbance of the Sample solution
$A_S$ = absorbance of the Standard solution

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Propafenone

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C1 = concentration of the Standard solution (mg/mL)

Calculate the percentage of the labeled amount of propafenone hydrochloride (C21H27NO3 · HCl) dissolved at each time point (i):

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

\[ \text{Result}_1 = \left[ \left( C_1 \times (V - V_3) \right) + (C_2 \times V_3) \right] \times (1/L) \times 100 \]

C1 = 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)

V3 = volume of Medium taken (mL)

Tolerances: See Table 1.

<table>
<thead>
<tr>
<th>Time Point (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5-25</td>
</tr>
<tr>
<td>2</td>
<td>40-70</td>
</tr>
<tr>
<td>3</td>
<td>NLT 75</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of propafenone hydrochloride (C21H27NO3 · 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 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: 0.021 mg/mL of USP Propafenone Hydrochloride RS in Acid stage medium from 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 (C21H27NO3 · HCl) dissolved:

\[ \text{Result}_1 = \left( \frac{A_i}{A_o} \right) \times (C_i) \times D \times V \times (1/L) \times 100 \]

\[ \text{Result}_2 = \left[ \left( C_1 \times V \right) + (C_2 \times V_3) \right] \times (1/L) \times 100 \]

\[ \text{Result}_3 = \left[ \left( C_1 \times V \right) + (C_2 \times V_3) \right] \times (1/L) \times 100 \]

\[ C_i = \text{concentration of USP Propafenone Hydrochloride RS in the Standard solution (mg/mL)} \]

\[ D = \text{dilution factor (mL/mL)} \]

\[ V = \text{volume of Acid stage medium, 900 mL} \]

\[ L = \text{label claim (mg/Capsule)} \]

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°C, 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

Analytical wavelength: 305 nm

Cell: 1 cm

Blank: Buffer stage medium

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) of propafenone hydrochloride (C21H27NO3 · HCl) in the sample withdrawn from the vessel at each time point (i):

\[ \text{Result} = \left( \frac{A_i}{A_o} \right) \times C_i \times D \]

\[ A_i = \text{absorbance of the Sample solution} \]

\[ A_o = \text{absorbance of the Standard solution} \]

\[ C_i = \text{concentration of USP Propafenone Hydrochloride RS in the Standard solution (mg/mL)} \]

\[ D = \text{dilution factor (mL/mL)} \]

\[ V = \text{volume of Buffer stage medium, 900 mL} \]

\[ L = \text{label claim (mg/Capsule)} \]

Tolerances: See Table 2.
Propafenone 3

**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.

**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:

\[
\text{Result} = \left( \frac{c_u}{c_s} \right) \times \left( \frac{C_s}{C_u} \right) \times 100
\]

- \( c_u \) = peak response of each unspecified degradation product from the Sample solution
- \( c_s \) = 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. Disregard any peaks below 0.03% (peak area less than that of the Sensitivity solution).

**Table 2**

<table>
<thead>
<tr>
<th>Time Point (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5–25</td>
</tr>
<tr>
<td>2</td>
<td>45–65</td>
</tr>
<tr>
<td>3</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

**Table 3**

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Solution A (%)</th>
<th>Solution B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>65</td>
<td>35</td>
</tr>
<tr>
<td>8</td>
<td>65</td>
<td>35</td>
</tr>
<tr>
<td>20</td>
<td>30</td>
<td>70</td>
</tr>
<tr>
<td>30</td>
<td>30</td>
<td>70</td>
</tr>
<tr>
<td>31</td>
<td>65</td>
<td>35</td>
</tr>
<tr>
<td>36</td>
<td>65</td>
<td>35</td>
</tr>
</tbody>
</table>

**Diluent:** 50% Methanol in water

**System suitability solution:** 0.1 mg/mL each of USP Propafenone Hydrochloride RS and USP Propafenone Related Compound B R5 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°C

**Flow rate:** 1 mL/min

**Injection volume:** 20 µL

**System suitability**

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

**Suitability requirements**

**Resolution:** NLT 9.0 between propafenone related compound B and propafenone, System suitability solution

**Relative standard deviation:** NMT 5.0%, Standard solution

**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
Propafenone

Mobile phase: See Table 5.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Solution A (%)</th>
<th>Solution B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>4.0</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>7.0</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>10.0</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>12.0</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>12.5</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>15.0</td>
<td>100</td>
<td>0</td>
</tr>
</tbody>
</table>

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°C
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:

Result = \( \frac{r_U}{r_S} \times \left( \frac{C_S}{C_U} \right) \times 100 \)

\( r_U \) = 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.

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propafenone</td>
<td>1.0</td>
<td>—</td>
</tr>
<tr>
<td>Propafenone related compound A*</td>
<td>1.9</td>
<td>0.20</td>
</tr>
</tbody>
</table>

* 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.

• USP REFERENCE STANDARDS (11)
USP Propafenone Hydrochloride RS
USP Propafenone Related Compound A RS
N-[2-Hydroxy-3-[2-(3-phenylpropionyl)phenoxyl]propyl]-N-propylformamide. C₂₂H₂₇NO₄ 369.45
USP Propafenone Related Compound B RS
(RS, E)-1-[2-[2-Hydroxy-3-(propylamino)propoxy]phenyl]-3-phenylprop-2-en-1-one. C₂₁H₂₃NO₃ 339.43

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