Propafenone Hydrochloride Extended-Release Capsules

**Type of Posting**  Notice of Intent to Revise
**Posting Date**  27–Apr–2018
**Targeted Official Date**  To Be Determined, Revision Bulletin
**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 Propafenone 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 4* to the monograph.

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.

The revision also necessitates a change in the table numbering in the tests for *Organic Impurities* and *Content of Propafenone Related Compound A*.

See below for additional information about the proposed text.\(^1\)

Should you have any questions, please contact Donald Min, Ph.D., Senior Scientific Liaison to the Chemical Medicines Monographs 2 Expert Committee (301-230-7457 or ddm@usp.org).

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\(^1\) 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 which 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 which are posted without prior publication for comment in *Pharmacopeial Forum*, must also meet the requirements outlined in the USP Guideline on Use of Accelerated Processes for Revisions to the *USP–NF* for Revision Bulletins.
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 × 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) dissolved:
  \[
  \text{Result} = \left( \frac{r_u}{r_d} \right) \times \left( \frac{C_d}{C_u} \right) \times 100
  \]
  \[
  r_u = \text{peak response of propafenone from the Sample solution}
  \]
  \[
  r_d = \text{peak response of propafenone from the Standard solution}
  \]
  \[
  C_d = \text{concentration of USP Propafenone Hydrochloride RS in the Standard solution (mg/mL)}
  \]
  \[
  C_u = \text{nominal concentration of propafenone hydrochloride in the Sample solution (mg/mL)}
  \]
  Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

CHANGE TO READ:

• DISSOLUTION (711)

Test 1
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:
  \[
  \text{Result} = \left( \frac{A_u}{A_d} \right) \times \left( \frac{C_d}{C_s} \right) \times V \times 100
  \]
  \[
  A_u = \text{absorbance of the Sample solution}
  \]
  \[
  A_d = \text{absorbance of the Standard solution}
  \]
  \[
  C_d = \text{concentration of USP Propafenone Hydrochloride RS in the Standard solution (mg/mL)}
  \]
  \[
  L = \text{label claim (mg/Capsule)}
  \]
  \[
  V = \text{volume of Medium, 900 mL}
  \]
  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.
  Times: 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):
  \[
  \text{Result}_i = \left( \frac{A_u/A_d}{} \right) \times C_i
  \]
  \[
  A_u = \text{absorbance of the Sample solution}
  \]
2 Propafenone

$A_i$ = absorbance of the Standard solution

$C_i$ = concentration of the Standard solution (mg/mL)

Calculate the percentage of the labeled amount of propafenone hydrochloride (C$_2$H$_7$NO$_3$·HCl) dissolved at each time point ($i$):

Result$_i = C_i \times V \times (1/L) \times 100$

Result$_1 = \left(\left(\frac{C_1 \times (V - V_2)}{L} \times (1/L) \times 100\right) + \left(\frac{C_2 \times V_2}{L} \times (1/L) \times 100\right)\right)

$C_i$ = 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)

$V_1$ = volume of Medium taken (mL)

Tolerances: See Table 1.

<table>
<thead>
<tr>
<th>Time Point ($i$)</th>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>5–25</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>40–70</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
<td>NLT 75</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of propafenone hydrochloride (C$_2$H$_7$NO$_3$·HCl) dissolved at the times specified conform to Dissoiution (711), Acceptance Table 2.

Test 2: If the product complies with this test, the labeling indicates that the product meets USP Dissoiution 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 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$_2$H$_7$NO$_3$·HCl) dissolved at each time point ($i$):

Result$_1 = (A_i/A_f) \times C_i \times D \times V \times (1/L) \times 100$

$A_i$ = absorbance of the Sample solution

$A_f$ = absorbance of the Standard solution

$C_i$ = 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$_2$H$_7$NO$_3$·HCl) in the sample withdrawn from the vessel at each time point ($i$):

Result$_2 = \left(\left(\frac{C_2 \times (V - V_2)}{L} \times (1/L) \times 100\right) + \left(\frac{C_3 \times V_2}{L} \times (1/L) \times 100\right)\right)

$C_i$ = concentration of propafenone hydrochloride (C$_2$H$_7$NO$_3$·HCl) dissolved at each time point ($i$):

Result$_3 = \left(\left(\frac{C_3 \times (V - V_2)}{L} \times (1/L) \times 100\right) + \left(\frac{C_4 \times V_2}{L} \times (1/L) \times 100\right)\right)

Result$_3 = \left(\left(\frac{C_3 \times (V - V_2)}{L} \times (1/L) \times 100\right) + \left(\frac{C_4 \times V_2}{L} \times (1/L) \times 100\right)\right)

Result$_3 = \left(\left(\frac{C_3 \times (V - V_2)}{L} \times (1/L) \times 100\right) + \left(\frac{C_4 \times V_2}{L} \times (1/L) \times 100\right)\right)
Notice of Intent to Revise
Official: To Be Determined

\[ C_i = \text{concentration of propafenone hydrochloride in the portion of sample withdrawn at time point (i) (mg/mL)} \]

\[ V = \text{volume of Buffer stage medium, 1000 mL} \]

\[ V_s = \text{volume of the Sample solution withdrawn from the Buffer stage medium (mL)} \]

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

**Tolerances:** See Table 2.

<table>
<thead>
<tr>
<th>Time Point (i)</th>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>5–25</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>45–65</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

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

**Acid stage**

**Acid stage medium:** 0.08 N hydrochloric acid; 900 mL

**Apparatus 2:** 50 rpm, with sinkers

**Time:** 2 h

**Phosphate buffer:** Dissolve 190.06 g of tribasic sodium phosphate in 1 L of water.

**Diluent:** Phosphate buffer and Acid stage medium (12:88). Adjust the pH to 6.8 with phosphoric acid or sodium hydroxide if necessary.

**Standard solution:** \((U/1000) \text{ mg/mL of USP Propafenone Hydrochloride RS, where } L \text{ is the label claim in mg/Capsule, prepared as follows. Transfer a suitable amount of USP Propafenone Hydrochloride RS to a suitable volumetric flask. Dilute with 10% of final volume of methanol with aid of sonication. Dilute with Diluent to volume. Sample solution: At the specified time point, withdraw 10 mL of the solution under test and centrifuge. Use the supernatant.}

**Instrumental conditions**

**Mode:** UV

**Analytical wavelengths:** 305 nm

**Cell:** 0.2 cm

**Blank:** Diluent

**Analysis**

**Samples:** Standard solution and Sample solution Calculate the percentage of the labeled amount of propafenone hydrochloride \((C_{21}H_{27}NO_3 \cdot HCl)\) dissolved:

\[ \text{Result}_1 = (A_u/A_s) \times (C/L) \times V \times 100 \]

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

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

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

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

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

**Tolerances:** See Table 3.

<table>
<thead>
<tr>
<th>Time Point (i)</th>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>NMT 30</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>35–60</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

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

**Acid stage**

**Acid stage medium:** 0.08 N hydrochloric acid; 900 mL

**Apparatus 2:** 50 rpm

**Time:** 2 h

**Diluent:** Dissolve 6.8 g of monobasic potassium phosphate with 1 L of water. Adjust with sodium hydroxide to a pH of 6.8.
Propafenone

**Standard solution:** 0.325 mg/mL of USP Propafenone Hydrochloride RS in Diluent

**Sample solution:** At the specified time point, withdraw 5 mL of the solution and pass through a suitable filter. Replace the portion of solution withdrawn with an equal volume of Medium.

**Instrumental conditions**

- **Mode:** UV
- **Analytical wavelengths:** 305 and 375 nm
- **Cell:** 0.2 cm
- **Blank:** Diluent

**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 (C₁₃H₁₇N₂O₂·HCl) dissolved:

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

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

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

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

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

\[
V = \text{volume of Medium, 900 mL}
\]

**Tolerances:** See Table 4.

**Buffer stage**

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

- **Buffer:** Dissolve 108.88 g of monobasic potassium phosphate and 14.4 g of sodium hydroxide with 1 L of water. 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 the vessel containing 900 mL of 0.08 N hydrochloric acid.

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

**Analysis**

- **Samples:** Standard solution and Sample solution
  - Calculate the concentration (C) of propafenone hydrochloride (C₁₃H₁₇N₂O₂·HCl) in the sample withdrawn from the vessel at each time point (i):

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

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

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

\[
C_i = \text{concentration of the Standard solution (mg/mL)}
\]

Calculate the percentage of the labeled amount of propafenone hydrochloride (C₁₃H₁₇N₂O₂·HCl) dissolved at each time point (i):

\[
\text{Result}_i = \left( \frac{C_i \times V}{V_i} + \left( \frac{C_i \times V}{V_i} \right) \times \left( \frac{1}{L_i} \right) \times 100
\]

\[
\text{Result}_i = \left( \frac{C_i \times V}{V_i} + \left[ \left( C_i + C_i \right) \times V_i \right] \times \left( \frac{1}{L_i} \right) \times 100
\]

\[
\text{Result}_i = \left( \frac{C_i \times V}{V_i} + \left[ \left( C_i + C_i + C_i \right) \times V_i \right] \times \left( \frac{1}{L_i} \right) \times 100
\]

\[
C_i = \text{concentration of propafenone hydrochloride in the portion of sample withdrawn at time point (i) (mg/mL)}
\]

**Tolerances:** See Table 4.

### Table 4

<table>
<thead>
<tr>
<th>Time Point (h)</th>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>15-35</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>26-46</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>56-76</td>
</tr>
<tr>
<td>4</td>
<td>12</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of propafenone hydrochloride (C₁₃H₁₇N₂O₂·HCl) dissolved at the times specified conform to Dissolution (711), Acceptance Table 2. (TBD)

**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 5. (TBD)

### Table 5 (TBD)

<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>70</td>
<td>70</td>
</tr>
<tr>
<td>30</td>
<td>70</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 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:  
Result = (r_d/r_s) x (C_s/C_o) x 100  

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propafenone related compound B&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.81</td>
<td>—</td>
</tr>
<tr>
<td>Propafenone</td>
<td>1.00</td>
<td>—</td>
</tr>
<tr>
<td>Propafenone glycerol analog&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2.53</td>
<td>—</td>
</tr>
<tr>
<td>Flavone&lt;sup&gt;d&lt;/sup&gt;</td>
<td>2.83</td>
<td>—</td>
</tr>
<tr>
<td>Propafenone dimer&lt;sup&gt;e&lt;/sup&gt;</td>
<td>2.88</td>
<td>—</td>
</tr>
<tr>
<td>Propafenone chloroglycerol analog&lt;sup&gt;f&lt;/sup&gt;</td>
<td>2.91</td>
<td>—</td>
</tr>
<tr>
<td>Propafenone glycidyl analog&lt;sup&gt;g&lt;/sup&gt;</td>
<td>2.96</td>
<td>—</td>
</tr>
<tr>
<td>Propafenone phenol&lt;sup&gt;h&lt;/sup&gt;</td>
<td>3.29</td>
<td>—</td>
</tr>
<tr>
<td>Propafenone glycerol dimer&lt;sup&gt;i&lt;/sup&gt;</td>
<td>3.80</td>
<td>—</td>
</tr>
<tr>
<td>Any unspecified degradation product</td>
<td>—</td>
<td>0.15</td>
</tr>
<tr>
<td>Total degradation products</td>
<td>—</td>
<td>0.50</td>
</tr>
</tbody>
</table>

<sup>a</sup> Process impurities; do not include in total degradation products.  
<sup>b</sup> (RS)-1-[2-(2-Hydroxy-3-(propylamino)propoxy)phenyl]-3-phenylprop-2-en-1-one.  
<sup>c</sup> 1-[2-(2-((RS)-2,3-Dihydroxypropoxy)phenyl]-3-phenylprop-2-en-1-one.  
<sup>d</sup> 1,1'-[(Propyliminobis(2-hydroxypropane-3,1-diyl)oxy-2,1-phenylene]bis(3-phenylprop-1-one).  
<sup>e</sup> 1,1'-[2-(2-Chloro-2-hydroxypropoxy)phenyl]-3-phenylprop-1-one.  
<sup>f</sup> 1-[2-[[((RS)-Oxiranylmethoxy]phenyl]-3-phenylprop-1-one.  
<sup>g</sup> 1-[2-(2-Hydroxyphenoxy)-3-phenylprop-1-one.  
<sup>h</sup> 1,1'-[2-(2-Hydroxyprop-1,3-diy)bis(ox)(2,1-phenylene)]bis(3-phenylprop-1-one).  
<sup>i</sup> 1,1'-[2-(2-Hydroxyprop-1,3-diy)bis(ox)(2,1-phenylene)]bis(3-phenylprop-1-one).

Acceptance criteria: See Table 6.<sup>a</sup> Disregard any peaks below 0.03% (peak area less than that of the Sensitivity solution).

Table 6.<sup>a</sup>  

<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>
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<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°  
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 = (r_d/r_s) x (C_s/C_o) x 100  

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 7.<sup>a</sup>  

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### 6 Propafenone

\[ C_u = \text{nominal concentration of propafenone hydrochloride in the Sample solution (mg/mL)} \]

**Acceptance criteria:** See Table 8 (TBD)

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Acceptance Criteria, NMT (%)</th>
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</thead>
<tbody>
<tr>
<td>Propafenone</td>
<td>1.0</td>
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<tr>
<td>Propafenone related compound A*</td>
<td>1.9</td>
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</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.
- **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-phenylpropanoyl)phenoxy]propyl]-N-propylformamide.
    - C\(_22\)H\(_{27}\)NO\(_4\) 369.45
  - USP Propafenone Related Compound B RS
    - (R\(_5\),E)-1-[2-[2-Hydroxy-3-(propylamino)propoxy]phenyl]-3-phenylprop-2-en-1-one.
    - C\(_{21}\)H\(_{25}\)NO\(_3\) 339.43

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