Propafenone Hydrochloride Extended-Release Capsules

Type of Posting: Revision Bulletin
Posting Date: 07–Mar–2019
Official Date: 08–Mar–2019
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 4 to accommodate FDA-approved drug products with different conditions and/or tolerances than the existing dissolution tests.

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

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

Should you have any questions, please contact Donald Min, 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 20 Capsules to an appropriate volumetric flask. Add about 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:

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

\[r_U = \text{peak response of propafenone from the Standard solution}\]

\[r_S = \text{peak response of propafenone from the Sample solution}\]

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

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

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.

In instrumentation
  - **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:

\[
\text{Result} = \left( \frac{A_U}{A_S} \right) \times \left( \frac{C_S}{C_U} \right) \times V \times 100
\]

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

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

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

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

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

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):

\[
\text{Result} = \left( \frac{A_U}{A_S} \right) \times C_S
\]

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

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

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

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

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

\[
\text{Result}_3 = \left(\frac{(C_i \times (V - V_3)) + (C_i \times V_3)}{L} \times \left(\frac{1}{L}\right)\right) \times 100
\]

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

\[
V = \text{volume of } Medium, \text{ 1000 mL}
\]

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

\[
V_i = \text{volume of } Medium \text{ taken (mL)}
\]

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 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 \((C_{21}H_{27}NO_3 \cdot HCl)\) dissolved:

\[
\text{Result}_i = \left(\frac{A_i}{A_0} \times C_i \times D \times V \times \left(\frac{1}{L}\right)\right) \times 100
\]

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

\[
A_0 = \text{absorbance of the Standard solution}
\]

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

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

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

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

**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°, 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 \(i\):

\[
\text{Result}_i = \left(\frac{A_i}{A_0} \times C_i \times D\right)
\]

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

\[
A_0 = \text{absorbance of the Standard solution}
\]

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

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

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

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

\[
\text{Result}_3 = \left(\frac{(C_i \times V_j) + (C_i \times V_3)}{L} \times \left(\frac{1}{L}\right)\right) \times 100
\]

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

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

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

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

**Tolerances:** See Table 2.
If the product complies with this test, the labeling indicates that the product meets USP Dissolution Test 3.

**Acid stage**

<table>
<thead>
<tr>
<th>Acid stage medium: 0.08 N hydrochloric acid; 900 mL</th>
<th>Apparatus 2: 50 rpm, with sinkers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time: 2 h</td>
<td></td>
</tr>
<tr>
<td>Phosphate buffer: Dissolve 190.06 g of tribasic sodium phosphate in 1 L of water.</td>
<td></td>
</tr>
<tr>
<td>Diluent: Phosphate buffer and Acid stage medium (12:88). Adjust the pH to 6.8 with phosphoric acid or sodium hydroxide if necessary; 1000 mL.</td>
<td></td>
</tr>
<tr>
<td>Standard solution: (L/1000) mg/mL of USP Propafenone Hydrochloride RS, where L is the label claim in mg/Capsule, prepared as follows. Transfer a suitable amount of USP Propafenone Hydrochloride RS to a suitable volumetric flask. Dissolve with 10% of sodium hydroxide if necessary. Transfer a suitable amount of USP Propafenone Hydrochloride RS to a suitable volumetric flask. Dissolve with 10% of final volume of methanol with aid of sonication. Dilute with Diluent to volume.</td>
<td></td>
</tr>
</tbody>
</table>

**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 concentration (C) of propafenone hydrochloride (C₃₁₂_H₁₇_NO₃ · HCl) in the sample withdrawn at each time point (i):

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

\[ A_j \] = absorbance of the Sample solution

\[ A_i \] = 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 Acid stage medium, 900 mL

**Tolerances:** See Table 3.

**Buffer stage**

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

<table>
<thead>
<tr>
<th>Buffer stage medium: After the samples are withdrawn at 2 h, add 110 mL or appropriate amount of Phosphate buffer, preheated at 37°C, to Acid stage medium, and adjust the pH to 6.8 with phosphoric acid or sodium hydroxide if necessary; 1000 mL.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Times: 4 and 12 h</td>
</tr>
</tbody>
</table>
| Sample solution: At the specified time points, withdraw 10 mL of the solution and centrifuge. Use the supernatant.

The percentages of the labeled amount of propafenone hydrochloride (C₃₁₂_H₁₇_NO₃ · 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. |
| Standard solution: 0.325 mg/mL of USP Propafenone Hydrochloride RS in Diluent [Note—Sonication may be needed for dissolution.] |

**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

The percentages of the labeled amount of propafenone hydrochloride (C₃₁₂_H₁₇_NO₃ · HCl) dissolved at the specified time points conform to Dissolution (711), Acceptance Table 2.

---

**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>

**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>

© 2019 The United States Pharmacopeial Convention All Rights Reserved.
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:

\[
\text{Result}_1 = \left( \frac{A_2}{A_1} \right) \times \left( \frac{C_2}{L} \right) \times V \times 100
\]

\(A_1\) = absorbance of the Sample solution
\(A_2\) = absorbance of the Standard solution
\(C_2\) = 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 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\(^\circ\), 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 \((C_{21}H_{27}NO_3 \cdot HCl)\) in the sample withdrawn from the vessel at each time point \((i)\):

\[
\text{Result}_1 = \left( \frac{A_2}{A_1} \right) \times C_1
\]

\(A_1\) = absorbance of the Sample solution
\(A_2\) = absorbance of the Standard solution
\(C_1\) = 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 \((i)\):

\[
\text{Result}_2 = \left( \frac{C_2 \times V + (C_1 \times V_i)}{(1/L) \times 100}
\text{Result}_3 = \left( \frac{(C_1 \times V) + [C_2 + C_1 \times V_i]}{(1/L) \times 100}
\text{Result}_4 = \left( \frac{(C_2 \times V) + [C_1 + C_2 + C_1 \times V_i]}{(1/L) \times 100}
\]

\(C_1\) = concentration of propafenone hydrochloride in the portion of sample withdrawn at time point \((i)\) (mg/mL)
\(V\) = volume of Medium, 1000 mL
\(V_i\) = volume of Medium taken, 5 mL
\(L\) = label claim (mg/Capsule)

**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>
</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.

- **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.

**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>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 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:

\[
\text{Result} = \left( \frac{r_a}{r_s} \right) \times \left( \frac{C_b}{C_d} \right) \times 100
\]

- \( r_a \) = peak response of each unspecified degradation product from the Sample solution.
- \( r_s \) = peak response of propafenone from the Standard solution.
- \( C_b \) = concentration of USP Propafenone Hydrochloride RS in the Standard solution (\( \text{mg/mL} \)).
- \( C_d \) = nominal concentration of propafenone hydrochloride in the Sample solution (\( \text{mg/mL} \)).

Acceptance criteria: See Table 6 (88-8-Mar-2019).

Change to read:

Table 6 (88-8-Mar-2019)

<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 ( ^a )</td>
<td>0.81</td>
<td>-</td>
</tr>
<tr>
<td>Propafenone</td>
<td>1.00</td>
<td>-</td>
</tr>
<tr>
<td>Propafenone glycerol analog ( ^a )</td>
<td>2.53</td>
<td>-</td>
</tr>
<tr>
<td>Flavone ( ^d )</td>
<td>2.83</td>
<td>-</td>
</tr>
<tr>
<td>Propafenone dimer ( ^e )</td>
<td>2.88</td>
<td>-</td>
</tr>
<tr>
<td>Propafenone chloroglycerol analog ( ^f )</td>
<td>2.91</td>
<td>-</td>
</tr>
<tr>
<td>Propafenone glycyldiol analog ( ^g )</td>
<td>2.96</td>
<td>-</td>
</tr>
<tr>
<td>Propafenone phenol ( ^h )</td>
<td>3.29</td>
<td>-</td>
</tr>
<tr>
<td>Propafenone glycerol dimer ( ^i )</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>

\( ^a \) 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-((2ZS)-2,3-Dihydroxypropoxy)phenyl]-3-phenylpropan-1-one.

\( ^d \) 2-Pheny lacroman-4-one.

\( ^e \) 1',1'-Propylaminobis(2-hydroxypropane-1,3-diol)oxy-2,1-phenylene|bis(3-phenyl)propan-1-one.

\( ^f \) 1-[2-(2-Chloro-2-hydroxypropoxy)phenyl]-3-phenylpropan-1-one.

\( ^g \) 1-[2-((RS)-(O)-Oxiranylmethyl)oxy]phenyl]-3-phenylpropan-1-one.

\( ^h \) 1-(2-Hydroxyphenyl)-3-phenylpropan-1-one.

\( ^i \) 1',1'-[2-(2,2'-1-(2-Hydroxypropane-1,3-diol)oxy-2,1-phenylene)bis(3-phenyl)propan-1-one].

Diluent: Methanol and water (80:20).

Standard solution: 2.0 \( \mu g/mL \) of USP Propafenone Related Compound A RS in Diluent.

Sensitivity solution: 0.2 \( \mu g/mL \) 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-\( \mu m \) 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-\( \mu m \) packing L1

Column temperature: 60°

Flow rate: 0.4 mL/min

Injection volume: 4 \( \mu L \)

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:

\[
\text{Result} = \left( \frac{r_a}{r_s} \right) \times \left( \frac{C_b}{C_d} \right) \times 100
\]

- \( r_a \) = peak response of propafenone related compound A from the Sample solution.
- \( r_s \) = peak response of propafenone related compound A from the Standard solution.
- \( C_b \) = concentration of USP Propafenone Related Compound A RS in the Standard solution (\( \text{mg/mL} \)).

© 2019 The United States Pharmacopeial Convention All Rights Reserved.

C203749-M1034-CHM22015, rev. 00 20190307
6 Propafenone

\( C_U \) = nominal concentration of propafenone hydrochloride in the Sample solution (mg/mL)

**Acceptance criteria:** See Table ▲8 ▲ (RB 8-Mar-2019)

<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.

- **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
    - \( (RS,\text{E})\)-1-[2-(2-Hydroxy-3-(propylamino)propoxy)phenyl]-3-phenylprop-2-en-1-one.
    - \( C_{21}H_{23}NO_4 \) \ 339.43