Pseudoephedrine Hydrochloride Extended-Release Tablets

Type of Posting: Revision Bulletin
Posting Date: 22–Feb–2019
Official Date: 01–Mar–2019
Expert Committee: Chemical Medicines Monographs 6
Reason for Revision: Compliance

In accordance with the Rules and Procedures of the 2015–2020 Council of Experts, the Chemical Medicines Monographs 6 Expert Committee has revised the Pseudoephedrine Hydrochloride Extended-Release Tablets monograph. The purpose for the revision is to add Dissolution Test 4 to accommodate FDA-approved drug products with different conditions and tolerances than the existing dissolution tests.

- Dissolution Test 4 was validated using the Inertsil ODS-3V brand of column with L1 packing. The typical retention time for pseudoephedrine is about 5.5 min.

The revision also necessitates a change in the table numbering in Dissolution Test 2.

The Pseudoephedrine Hydrochloride Extended-Release Tablets Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Yanyin Yang, Associate Scientific Liaison (301-692-3623 or yanyin.yang@usp.org).
Pseudoephedrine Hydrochloride Extended-Release Tablets

DEFINITION
Pseudoephedrine Hydrochloride Extended-Release Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of pseudoephedrine hydrochloride (C_10H_15NO · HCl).

IDENTIFICATION
• A. Infrared Absorption (197K)
  Sample: Triturate a number of Tablets, nominally equivalent to 180 mg of pseudoephedrine hydrochloride. Filter with about 10 mL of chloroform collected using vacuum filtration. Maintain the vacuum until no further filtrate can be collected, and evaporate the chloroform on a steam bath, taking care to avoid overheating. Recrystallize the residue from a small amount of dehydrated alcohol.
  Acceptance criteria: Meet the requirements
• 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
  Mobile phase: Alcohol and ammonium acetate solution (1 in 250) (850:150). Filter, and degas
  Standard solution: 1.2 mg/mL of USP Pseudoephedrine Hydrochloride RS in alcohol
  Sample stock solution: Transfer NLT 20 Tablets to a suitable container, add 500 mL of alcohol, and homogenize until the Tablets are dispersed. Quantitatively transfer the contents of the container to a 1000-mL volumetric flask, dilute with alcohol to volume, mix, and allow to stand for the solids to settle.
  Sample solution: Transfer 25.0 mL of the supernatant from the Sample stock solution into a 50-mL volumetric flask, dilute with alcohol to volume, and mix. Pass a portion of this solution through a filter of 0.45-µm pore size.

Chromatographic system
(See Chromatography (621), System Suitability.)
  Mode: LC
  Detector: UV 254 nm
  Column: 4.6-mm × 15-cm; packing L3
  Flow rate: 0.7 mL/min
  Injection volume: 50 µL
  Analysis
  Samples: Standard solution and Sample solution
  Calculate the percentage of the labeled amount of pseudoephedrine hydrochloride (C_10H_15NO · HCl) dissolved.
  Tolerances: See Table 1.

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>25–45</td>
</tr>
<tr>
<td>3</td>
<td>50–75</td>
</tr>
<tr>
<td>6</td>
<td>NLT 75</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of pseudoephedrine hydrochloride (C_10H_15NO · 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 it meets USP Dissolution Test 3.
  Medium: Water, 900 mL
  Apparatus 2: 50 rpm
  Times: 1, 3, and 6 h
  Standard solution: A known concentration of USP Pseudoephedrine Hydrochloride RS in Medium.
  Sample solution: Pass portions of the solution under test through a filter of 0.45-µm pore size, and suitably dilute with Medium.
  Analysis: Calculate the percentage of the labeled amount of pseudoephedrine hydrochloride (C_10H_15NO · HCl) dissolved by comparing the maximum absorbance of Sample solution with that of Standard solution at about 214 nm.
  Tolerances: See Table 2.

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25–45</td>
</tr>
<tr>
<td>3</td>
<td>60–80</td>
</tr>
</tbody>
</table>
2 Pseudoephedrine

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of pseudoephedrine hydrochloride (C₁₀H₁₅NO·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 it meets USP Dissolution Test 4.

**Medium, Apparatus, and Times:** Proceed as directed in Test 1.

**Solution A:** Acetonitrile and water (45:55)

**Mobile phase:** 2.5 g/L of docusate sodium in Solution A. Add 1.0 mL of phosphoric acid. Adjust with ammonia water, 25% to a pH of 3.2.

**Standard solution:** (L/900) mg/mL of USP Pseudoephedrine Hydrochloride RS in Medium, where L is the label claim in mg/Tablet.

**Sample solution:** Withdraw a portion of the solution under test from each vessel at the specified time point and pass through a suitable filter of 0.45-µm pore size. Replace the portion of solution withdrawn with an equal volume of Medium previously equilibrated to 37.0° ± 0.5°.

**Chromatographic system**

(See Chromatography (621), System Suitability.)

**Mode:** LC

**Detector:** UV 215 nm

**Column:** 4.6-mm × 15-cm; 5-µm packing L1

**Column temperature:** 40°

**Flow rate:** 1.5 mL/min

**Injection volume:** 10 µL

**Run time:** NLT 1.5 times the retention time of pseudoephedrine

**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 concentration (C) of pseudoephedrine hydrochloride (C₁₀H₁₅NO·HCl) in the sample withdrawn from the vessel at each time point i:

\[
\text{Result} = (r_i/r_s) \times C_s
\]

\[r_i\] = peak response of pseudoephedrine from the Sample solution

\[r_s\] = peak response of pseudoephedrine from the Standard solution

\[C_s\] = concentration of USP Pseudoephedrine Hydrochloride RS in the Standard solution

Calculate the percentages of the labeled amount of pseudoephedrine hydrochloride (C₁₀H₁₅NO·HCl) dissolved at each time point i:

\[
\text{Result}_1 = C_s \times V \times (1/L) \times 100
\]

\[
\text{Result}_2 = [(C_s \times V) + (C_i \times V_i)] \times (1/L) \times 100
\]

\[
\text{Result}_3 = [(C_s \times V) + (C_i \times V_i)] \times (1/L) \times 100
\]

**Tolerances:** See Table 3.

<table>
<thead>
<tr>
<th>Time Point (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>27-47</td>
</tr>
<tr>
<td>2</td>
<td>53-73</td>
</tr>
<tr>
<td>3</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of pseudoephedrine hydrochloride (C₁₀H₁₅NO·HCl) dissolved at the times specified conform to Dissolution (711), Acceptance Table 2.

For Tablets labeled for doing every 24 h

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

**Medium:** 0.9% sodium chloride in water; 50 mL

**Apparatus 7** (see Drug Release (724)): 30 cycles/min; 2–3 cm amplitude. To prepare the sample, see Figure 1.

Figure 1. Steps to prepare the sample. (1) Place 1 Tablet on a 5-cm × 5-cm nylon netting. (2) Fold the netting over the Tablet. Continue folding until the Tablet is enclosed in the netting. (3) Fold the netting so that the two open ends meet. The Tablet should be enveloped in the center of the netting. (4) Insert a rod (see Drug Release (724), Figure 4c) through the netting to secure the Tablet. (5) Secure the netting with HPLC plastic ferrules or other appropriate device. Trim the excess netting. Attach each sample holder to the vertically reciprocating sample holder.

**Times:** 2, 8, 14, and 24 h

**Solution A:** Transfer 200 mL of water to a 1000-mL volumetric flask. Add 3.4 mL of phosphoric acid and 5 mL of triethylamine. Add water to almost 900 mL. Adjust with 1 N sodium hydroxide to a pH of about 6.8, dilute with water to volume, and mix.

**Mobile phase:** Methanol and Solution A (100:900)

**System suitability solution:** 0.4 mg/mL of USP Pseudoephedrine Hydrochloride RS in water

**Sample solution:** Solution under test

**Standard solution:** Known concentrations of USP Pseudoephedrine Hydrochloride RS in water, in a range...
around the expected concentration of the Sample solution at each time interval.

**Chromatographic system**
(See Chromatography (621), System Suitability.)

*Mode:* LC
*Detector:* UV 254 nm
*Column:* 4.6-mm × 5-cm; packing L1
*Flow rate:* 1.5 mL/min
*Injection volume:* 10 µL

**System suitability**

*Sample:* System suitability solution

**Suitability requirements**

<table>
<thead>
<tr>
<th>Tailing factor:</th>
<th>NMT 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative standard deviation:</td>
<td>NMT 2.0%</td>
</tr>
</tbody>
</table>

**Analysis**

*Samples:* Sample solution and Standard solution

Measure the major peak responses of the Standard solution and Sample solution. Construct a calibration curve by plotting the peak response versus concentrations of the Standard solution. Determine the amount of pseudoephedrine hydrochloride (C₁₀H₁₅NO · HCl) dissolved at each time interval from a linear regression analysis of the calibration curve.

*Tolerances:* See Table ^4^ (RB 1-Mar-2019).

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>20–35</td>
</tr>
<tr>
<td>8</td>
<td>40–65</td>
</tr>
<tr>
<td>14</td>
<td>60–90</td>
</tr>
<tr>
<td>24</td>
<td>NLT 85</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of pseudoephedrine hydrochloride (C₁₀H₁₅NO · HCl) dissolved at the times specified conform to Dissolution (711), Acceptance Table 2.

**Uniformity of Dosage Units (905):** Meet the requirements.

**ADDITIONAL REQUIREMENTS**

- **Packaging and Storage:** Preserve in tight containers.
- **Labeling:** When more than one Dissolution test is given, the labeling states the Dissolution test used only if Test 1 is not used.
- **USP Reference Standards (11):** USP Pseudoephedrine Hydrochloride RS