Raloxifene Hydrochloride Tablets

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Expert Committee: Chemical Medicines Monographs 5
Reason for Revision: Compliance

In accordance with the Rules and Procedures of the 2015-2020 Council of Experts, the Chemical Medicines Monographs 5 Expert Committee has revised the Raloxifene Hydrochloride Tablets monograph. The purpose for the revision is to add a dissolution test to accommodate a drug product which was approved with different conditions and acceptance criteria.

Dissolution Test 3 was validated using an Inertsil ODS 3V brand of 4.6-mm x 25-cm, 5-µm packing L1 column. The typical retention time for raloxifene is 4 minutes.

The Raloxifene Hydrochloride Tablets Revision Bulletin supersedes the currently official monograph. The Revision Bulletin will be incorporated into the Second Supplement to USP 41–NF 36.

Should you have any questions, please contact Ren-Hwa Yeh, Ph.D., Senior Scientific Liaison, (301–998–6818 or RHY@usp.org).
**Assay**

**Sample**
Transfer a sufficient quantity of powdered Tablets to a volumetric flask of suitable size, add Diluent, and shake to disintegrate the Tablets. Sonicate if necessary. Dilute with Diluent to obtain a solution having a concentration of 0.06 mg/mL of USP Raloxifene Hydrochloride RS in water.

**Standard solution**
Prepare as directed in the test for **Organic Impurities**.

Diluent
Dissolve 7.2 g of monobasic potassium phosphate in 1000 mL of water. Add 1.3 mL of phosphoric acid, and further adjust with phosphoric acid or potassium hydroxide solution to a pH of 2.5 ± 0.1.

Mobile phase
Acetonitrile and Buffer (33:67) (1:1).

**System suitability solution**
Prepare a solution containing 12 mg/mL of USP Raloxifene Hydrochloride RS in water.

**System suitability requirements**
- **Resolution**: NLT 2.0 between raloxifene and raloxifene related compound C, **System suitability solution**
- **Tailing factor**: NMT 2.0 for raloxifene, **System suitability solution**
- **Relative standard deviation**: NMT 1.0%, **Standard solution**

**System suitability sample**
Transfer a quantity of powdered Tablets, equivalent to 120 mg of raloxifene hydrochloride, to a suitable container. Add 20 mL of water, and shake to form a uniform slurry. Centrifuge, and discard the supernatant. Add 5 mL of isopropyl alcohol, shake to form a slurry, filter, and rinse the residue with isopropyl alcohol. Dry the residue at 105°C for 30 min. Alternatively, add 40 mL of water to the powdered Tablets and vortex to form a uniform slurry. Centrifuge, and discard the supernatant. Repeat the washing process. Add 40 mL of methanol to the residue, vortex to form a uniform slurry, and centrifuge. Transfer the clear liquid to an appropriate container and evaporate to dryness.

**Analysis**
Prepare a potassium bromide dispersion with a known concentration equivalent to the expected concentration of raloxifene hydrochloride (C_{28}H_{27}NO_{4}S·HCl) in the portion of Tablets taken:

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

- \( r_V \) = peak response from the **Sample solution**
- \( r_S \) = peak response from the **Standard solution**
- \( C_S \) = concentration of USP Raloxifene Hydrochloride RS in the **Standard solution** (mg/mL)
- \( C_U \) = nominal concentration of raloxifene hydrochloride from the **Sample solution** (mg/mL)

**Acceptance criteria**: 93.0%–107.0%

**Permeability Tests**

**Change to read**

- **Dissolution** (711) Test 1
  - Medium: 0.1% polysorbate 80; 1000 mL
  - Apparatus 2: 50 rpm
  - Time: 30 min
  - Mobile phase: Acetonitrile, water, and triethylamine (500:500:2). Adjust with phosphoric acid to a pH of 4.0.
  - Triethylamine phosphate suspension: Add 2.0 mL of triethylamine to 500 mL of acetonitrile, and adjust with phosphoric acid to a pH of 4.0. [Note—Triethylamine phosphate will precipitate; keep the suspension well mixed.]

**Standard solution**
Prepare a solution having a known concentration equivalent to the expected concentration of the **Sample solution** by dissolving USP Raloxifene Hydrochloride RS in a small volume (NMT 10% of the final volume) of methanol. Dilute with Medium to volume, and mix the resulting solution with **Triethylamine phosphate suspension** (1:1). **Sample solution**
Pass a portion of the solution under test through an appropriate filter of 0.45-µm pore size. Mix the resulting solution and **Triethylamine phosphate suspension** (1:1).

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

**Mode**: LC
Detector: UV 290 nm
Column: 4.6-mm × 15-cm; 3.5-µm base-deactivated packing L10. If the analyte peak splits, use a guard column containing packing L3.
Flow rate: 2 mL/min
Injection volume: 50 µL

**System suitability**
**Sample**: **Standard solution**
**Suitability requirements**
**Relative standard deviation**: NMT 2.0%

**Analysis**
**Samples**: **Standard solution** and **Sample solution**
Determine the percentage of the labeled amount of raloxifene hydrochloride (C_{28}H_{27}NO_{4}S·HCl) dissolved:

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

- \( r_V \) = peak response from the **Sample solution**
- \( r_S \) = peak response from the **Standard solution**
- \( C_S \) = concentration of USP Raloxifene Hydrochloride RS in the **Standard solution** (mg/mL)
- \( L \) = label claim (mg/Tablet)
- \( F \) = factor
If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 2.

Medium: 1% sodium dodecyl sulfate in 0.05 M phosphate buffer prepared as follows. 1.7 g/L of sodium hydroxide and 7 g/L of monobasic sodium phosphate monohydrate. Adjust to a pH of 7.5, if necessary. Add 10 g of sodium dodecyl sulfate per L; 900 mL.

Apparatus: 75 rpm

Time: 45 min

Buffer: 2.8 g/L of sodium dodecyl sulfate. Adjust with glacial acetic acid to a pH of 4.0.

Diluent: Acetonitrile and water (50:50)

Mobile phase: Acetonitrile and Buffer (55:45)

Standard stock solution: 0.48 mg/mL of USP Raloxifene Hydrochloride RS in Diluent

Standard solution: 0.072 mg/mL of USP Raloxifene Hydrochloride RS in Medium from the Standard stock solution

Sample solution: Pass a portion of the solution under test through a suitable filter.

Chromatographic system

Mode: LC

Detector: UV 286 nm

Column: 3.9-mm × 15-cm; 5-µm packing L1

Column temperature: 30°

Flow rate: 1 mL/min

Injection volume: 10 µL

Run time: NLT 1.7 times the retention time of raloxifene

System suitability

Sample: Standard solution

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 1.0%

Analysis

Samples: Standard solution and Sample solution

Calculate the percentage of the labeled amount of raloxifene hydrochloride (C28H27NO4S·HCl) dissolved:

\[ \text{Result} = \left( \frac{r_U}{r_S} \right) \times C_S \times V \times (1/L) \times 100 \]

with occasional shaking and then dilute with Medium to volume.

Standard solution: 0.06 mg/mL of USP Raloxifene Hydrochloride RS in Medium from the Standard stock solution

Sample solution: Centrifuge a portion of the solution under test and use the clear supernatant. [NOTE—The use of a centrifuge speed of 2000 rpm for 10 min may be suitable.]

Chromatographic system

(See Chromatography (621), System Suitability.)

Mode: LC

Detector: UV 290 nm

Column: 4.6-mm × 25-cm; 5-µm packing L1

Flow rate: 1 mL/min

Injection volume: 10 µL

Run time: NLT 1.7 times the retention time of raloxifene

System suitability

Sample: Standard solution

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 1.0%

Analysis

Samples: Standard solution and Sample solution

Calculate the percentage of the labeled amount of raloxifene hydrochloride (C28H27NO4S·HCl) dissolved.

\[ \text{Result} = \left( \frac{r_U}{r_S} \right) \times C_S \times V \times (1/L) \times 100 \]

with occasional shaking and then dilute with Medium to volume.

Table 1

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Solution A (%)</th>
<th>Solution B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>5.00</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>36.25</td>
<td>0</td>
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</tr>
<tr>
<td>38.25</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>48.00</td>
<td>100</td>
<td>0</td>
</tr>
</tbody>
</table>

Diluent A: Acetonitrile and Buffer (60:40)

Diluent B: Tetrahydrofuran and methanol (70:30)

Raloxifene related compound C solution: 0.15 mg/mL of USP Raloxifene Related Compound C RS in Diluent B
System suitability solution: Transfer 15 mg of USP Raloxifene Hydrochloride RS to a 50-mL volumetric flask, add 1.0 mL of Raloxifene related compound C solution, and dilute with Diluent A to volume.

Standard stock solution: 0.06 mg/mL of USP Raloxifene Hydrochloride RS in Diluent A

Standard solution: Mix 5 mL of the Standard stock solution and 45 mL of Diluent A, and dilute with Solution A to 100.0 mL (0.003 mg/mL).

Sample solution: Transfer a sufficient quantity of Tablets to a volumetric flask of a suitable size to obtain a solution of raloxifene hydrochloride having a concentration of 6 mg/mL, based on the label claim. Add Diluent A, and shake to disintegrate the Tablets. Sonicate, if necessary, and add Diluent A to volume. Transfer 5 mL of this solution to a 10-mL volumetric flask, and dilute with Solution A to volume to obtain a solution having a concentration of 3 mg/mL of raloxifene hydrochloride, based on the label claim. Filter, and use the clear solution.

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

Mode: LC
Detector: UV 280 nm
Column: 4.6-mm × 25-cm; 5-µm base-deactivated packing L7
Column temperature: 35°
Flow rate: 1 mL/min
Injection volume: 10 µL

System suitability
Sample: System suitability solution
Suitability requirements
Resolution: NLT 3.0 between raloxifene and raloxifene related compound C
Tailing factor: NMT 2.0 for the raloxifene peak

Analysis
Samples: Standard solution and Sample solution
Record the chromatograms for NLT 2 times the retention time of the raloxifene peak, and measure all of the peak responses.

Calculate the percentage of each impurity in the portion of Tablets taken:

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

\(r_U\) = peak response of each impurity from the Sample solution
\(r_S\) = peak response of raloxifene from the Standard solution
\(C_S\) = concentration of USP Raloxifene Hydrochloride RS in the Standard solution (mg/mL)
\(C_U\) = nominal concentration of raloxifene hydrochloride from the Sample solution (mg/mL)

Acceptance criteria: See Table 2.

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raloxifene</td>
<td>1.00</td>
<td>—</td>
</tr>
<tr>
<td>Raloxifene related compound C&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.17</td>
<td>0.3</td>
</tr>
<tr>
<td>Any unspecified individual impurity</td>
<td></td>
<td>0.2</td>
</tr>
<tr>
<td>Total impurities</td>
<td>—</td>
<td>1.0</td>
</tr>
</tbody>
</table>

<sup>a</sup>1-(2-{4-[6-Hydroxy-2-(4-hydroxyphenyl)benzothiophene-3-carbonyl]phenoxy}ethyl)piperidine 1-oxide.

ADDITIONAL REQUIREMENTS
• Packaging and Storage: Preserve in tight containers, and store at controlled room temperature.
• Labeling: When more than one Dissolution test is given, the labeling states the test used only if Test 1 is not used.

USP Reference Standards (11)
USP Raloxifene Hydrochloride RS
USP Raloxifene Related Compound C RS
C<sub>28</sub>H<sub>37</sub>NO<sub>5</sub> · H<sub>2</sub>O 507.60