Raloxifene Hydrochloride Tablets

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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).

Raloxifene Hydrochloride Tablets

DEFINITION

Raloxifene Hydrochloride Tablets contain NLT 93.0% and NMT 107.0% of the labeled amount of raloxifene hydrochloride ($C_{28}H_{27}NO_4S \cdot HCl$).

IDENTIFICATION

- **A. Infrared Absorption** ⟨197K⟩

  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° 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 the *Sample*. Similarly prepare the Standard, starting with a slurry containing 12 mg/mL of USP Raloxifene Hydrochloride RS in water.

  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**

  Buffer: 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)

  Diluent: Acetonitrile and *Buffer* (60:40)

  System suitability solution: Prepare as directed in the test for *Organic Impurities*.

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

  Sample solution: Transfer a sufficient quantity of 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 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 × 15-cm; 3.5-µm base-deactivated packing L7

  Column temperature: 35°

  Flow rate: 1.5 mL/min

  Injection volume: 10 µL

  System suitability

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

  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*

  Analysis

  Samples: *Standard solution* and *Sample solution*

  Calculate the percentage of the labeled amount of raloxifene hydrochloride ($C_{28}H_{27}NO_4S \cdot HCl$) in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

  r_U = 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%

PERFORMANCE 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 ($C_{28}H_{27}NO_4S \cdot HCl$) dissolved:

$$\text{Result} = (r_U/r_S) \times (C_S/L) \times F \times 100$$

  r_U = 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 = volume of *Medium*, 1000 mL
Tolerances: NLT 80% (Q) of the labeled amount of raloxifene hydrochloride is dissolved.
Test 2: 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 2: 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
(See *Chromatography* ⟨621⟩*, System Suitability*.)
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 1.3 times the retention time of raloxifene
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 raloxifene hydrochloride ($C_{28}H_{27}NO_4S \cdot HCl$) dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times (1/L) \times 100$$

r_U = 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)
V = volume of *Medium*, 900 mL
L = label claim (mg/Tablet)
Tolerances: NLT 80% (Q) of the labeled amount of raloxifene hydrochloride ($C_{28}H_{27}NO_4S \cdot HCl$) is dissolved.
● **Test 3:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 3*.
Medium: pH 2.2 phosphate buffer prepared as follows. Dissolve 3.7 g of monobasic potassium phosphate in 1 L of water. Adjust with phosphoric acid to a pH of 2.2; 1000 mL.
Apparatus 2: 50 rpm
Time: 20 min
Mobile phase: Acetonitrile, water, and triethylamine (400:600:2). Adjust with diluted phosphoric acid to a pH of 4.0.
Standard stock solution: 0.30 mg/mL of USP Raloxifene Hydrochloride RS prepared as follows. Transfer an appropriate amount of USP Raloxifene Hydrochloride RS to a suitable volumetric flask and add 50% of the flask volume of methanol. Sonicate for 20 min 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 ($C_{28}H_{27}NO_4S \cdot HCl$) dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times (1/L) \times 100$$

r_U = 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)
V = volume of *Medium*, 1000 mL
L = label claim (mg/Tablet)
Tolerances: NLT 80% (Q) of the labeled amount of raloxifene hydrochloride ($C_{28}H_{27}NO_4S \cdot HCl$) is dissolved. ● (RB 1-Feb-2018)

• **UNIFORMITY OF DOSAGE UNITS ⟨905⟩:** Meet the requirements

IMPURITIES

• **ORGANIC IMPURITIES**
Buffer: Dissolve 9.0 g of monobasic potassium phosphate in 1000 mL of water. Add 0.5 mL of phosphoric acid, and further adjust with phosphoric acid or potassium hydroxide solution to a pH of 3.0 ± 0.1.
Solution A: *Buffer* and acetonitrile (75:25)
Solution B: *Buffer* and acetonitrile (50:50)
Mobile phase: See *Table 1*. Adjust the start time of the gradient step on the basis of the instrument's dwell volume.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0.00	100	0
5.00	100	0
36.25	0	100
38.25	100	0
48.00	100	0

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:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

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 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Raloxifene	1.00	—
Raloxifene related compound C[a]	1.17	0.3
Any unspecified individual impurity	—	0.2
Total impurities	—	1.0

[a] 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
  1-(2-{4-[6-Hydroxy-2-(4-hydroxyphenyl)benzothiophene-3-carbonyl]phenoxy}ethyl)piperidine 1-oxide monohydrate.
  $C_{28}H_{27}NO_5S \cdot H_2O$ 507.60