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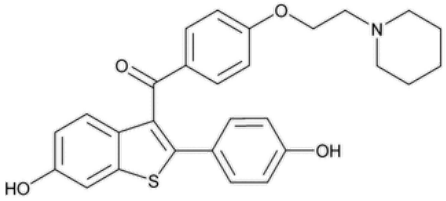
Raloxifene Hydrochloride



• HCl

$C_{28}H_{27}NO_4S \cdot HCl$ 510.04

Methanone, [6-hydroxy-2-(4-hydroxyphenyl)benzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]-, hydrochloride;
6-Hydroxy-2-(*p*-hydroxyphenyl)benzo[*b*]thien-3-yl-*p*-(2-piperidinoethoxy)phenyl ketone, hydrochloride CAS RN®: 82640-04-8; UNII: 4F86W47BR6.

DEFINITION

Raloxifene Hydrochloride contains NLT 97.5% and NMT 102.0% of raloxifene hydrochloride ($C_{28}H_{27}NO_4S \cdot HCl$), calculated on the dried basis.

IDENTIFICATION

Change to read:

• **A.** ▲**Spectroscopic Identification Tests** ⟨197⟩, *Infrared Spectroscopy*: **197K**▲ (CN 1-May-2020)

• **B.** **Identification Tests—General,** *Chloride*⟨191⟩**:** It meets the requirements, the sample being dissolved in methanol.

ASSAY

• **Procedure**

Buffer: Dissolve 7.2 g of monobasic potassium phosphate in 1000 mL of water. Add 1.5 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)

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

Standard solution: 0.05 mg/mL of USP Raloxifene Hydrochloride RS in *Mobile phase*

Sample solution: 0.05 mg/mL of Raloxifene Hydrochloride in *Mobile phase*

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

Sample: *System suitability solution*

Suitability requirements

Resolution: NLT 2.0 between raloxifene and raloxifene related compound C

Tailing factor: NMT 2.0 for raloxifene

Relative standard deviation: NMT 0.7% for raloxifene

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of raloxifene hydrochloride ($C_{28}H_{27}NO_4S \cdot HCl$) in the portion of Raloxifene Hydrochloride 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 = concentration of the *Sample solution* (mg/mL)

Acceptance criteria: 97.5%–102.0% on the dried basis

IMPURITIES

- **Residue on Ignition ⟨281⟩:** NMT 0.1%
- **Organic Impurities**

Solution A: Dissolve 9.0 g of monobasic potassium phosphate in 1000 mL of water. Add 0.6 mL of phosphoric acid, and further adjust with phosphoric acid or potassium hydroxide solution to a pH of 3.0 ± 0.1.

Solution B: Acetonitrile

Mobile phase: See *Table 1*. [Note—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	75	25
9.00	75	25
40.25	50	50
42.25	75	25
49.00	75	25

Diluent A: *Solution A* and acetonitrile (70:30)

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 solution: 0.003 mg/mL of USP Raloxifene Hydrochloride RS in *Diluent A*

Sample solution: 3 mg/mL of Raloxifene Hydrochloride in *Diluent A*

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 raloxifene

Analysis

Samples: *Standard solution* and *Sample solution*

Record the chromatograms for NLT two 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 Raloxifene Hydrochloride taken:

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

r_U = peak response of each impurity in the *Sample solution*

r_S = peak response of raloxifene in the *Standard solution*

C_S = concentration of USP Raloxifene Hydrochloride RS in the *Standard solution* (mg/mL)

C_U = concentration of the *Sample solution* (mg/mL)

Acceptance criteria: See *Table 2*. The reporting level for impurities is 0.05%.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Raloxifene 3,7-diketone[a]	0.74	0.20
Raloxifene	1.00	—
Any unspecified individual impurity	—	0.10
Total impurities	—	0.5

[a] Methanone, [6-hydroxy-2-(4-hydroxyphenyl)benzo[*b*]thien-3,7-diyl]bis[4-[2-(1-piperidinyl)ethoxy]phenyl].

SPECIFIC TESTS

• **Loss on Drying ⟨731⟩**

Analysis: Dry a sample at 105° for 3 h.

Acceptance criteria: NMT 0.5%

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in well-closed containers, and store at room temperature.

• **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

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
RALOXIFENE HYDROCHLORIDE	Documentary Standards Support	SM52020 Small Molecules 5
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM52020 Small Molecules 5

Chromatographic Database Information: Chromatographic Database

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