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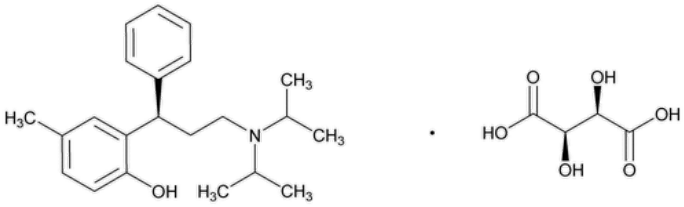
Tolterodine Tartrate



$C_{22}H_{31}NO \cdot C_4H_6O_6$ 475.57

(*R*)-2-[3-[Bis(1-methylethyl)amino]-1-phenylpropyl]-4-methylphenol (2*R*,3*R*)-2,3-dihydroxybutanedioate (1:1) (salt);
(+)-(*R*)-2-[α-[2-(Diisopropylamino)ethyl]benzyl]-*p*-cresol L-tartrate (1:1) (salt);

(*R*)-2-[3-(Diisopropylamino)-1-phenylpropyl]-4-methylphenol tartrate CAS RN®: 124937-52-6; UNII: 5T619TQR3R.

DEFINITION

Tolterodine Tartrate contains NLT 97.0% and NMT 103.0% of tolterodine tartrate ($C_{22}H_{31}NO \cdot C_4H_6O_6$), calculated on the as-is basis.

IDENTIFICATION

Change to read:

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

• **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: Acetonitrile, water, and phosphoric acid (330:670:1)

Standard solution: 0.35 mg/mL of USP Tolterodine Tartrate RS in *Mobile phase*

Sample solution: 0.35 mg/mL of Tolterodine Tartrate in *Mobile phase*

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: UV 285 nm

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

Flow rate: 1.0 mL/min

Injection volume: 5 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Relative standard deviation: NMT 1.0% from six replicate injections

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of tolterodine tartrate ($C_{22}H_{31}NO \cdot C_4H_6O_6$) in the portion of Tolterodine Tartrate 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 Tolterodine Tartrate RS in the *Standard solution* (mg/mL)

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

Acceptance criteria: 97.0%–103.0% on the as-is basis

IMPURITIES

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

Solution A: Acetonitrile, water, and perchloric acid (100:900:1.5)

Solution B: Acetonitrile, water, and perchloric acid (500:500:1.5)

Solution C: Acetonitrile

Mobile phase: See *Table 1*. Return to original conditions, and re-equilibrate the system.

Table 1

Time (min)	Solution A (%)	Solution B (%)	Solution C (%)
0	75	25	0
5	75	25	0
22	0	100	0
47	0	0	100
57	0	0	100

Diluent: Acetonitrile and water (50:50)

System suitability solution: 10 mg/mL of USP Tolterodine System Suitability Mixture RS in *Diluent*. See *Table 2* for relative retention times of the main components of the mixture.

Table 2

Component of USP Tolterodine System Suitability Mixture RS	Relative Retention Time
p-Cresol	0.75
trans-Cinnamic acid	0.81
Monoisopropyl tolterodine	0.88
Tolterodine	1.0
Diol impurity	1.18
Tolterodine dimer[a]	1.44
6-Methyl-4-phenylchroman-2-ol[a]	1.48
Diol acetate impurity	1.54
6-Methyl-4-phenylchroman-2-one	1.59

[a] Undefined stereochemistry.

Standard solution: 0.01 mg/mL of USP Tolterodine Tartrate RS in *Diluent*

Sensitivity solution: 0.005 mg/mL of USP Tolterodine Tartrate RS in *Diluent* from the *Standard solution*

Sample solution: 10 mg/mL of Tolterodine Tartrate in *Diluent*

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: UV 220 nm

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

Column temperature: 65°

Flow rate: 1.0 mL/min

Injection volume: 10 µL

System suitability

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

Suitability requirements

Resolution: NLT 1.5 between diol acetate impurity and 6-methyl-4-phenylchroman-2-one, *System suitability solution*

Relative standard deviation: NMT 3.0%, *Standard solution*

Signal-to-noise ratio: NLT 10, *Sensitivity solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Tolterodine Tartrate taken:

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

r_U = peak response for each impurity from the *Sample solution*

r_S = peak response of tolterodine from the *Standard solution*

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

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

F = relative response factor (see *Table 3*)

Acceptance criteria: See *Table 3*. Disregard any peak below 0.05% and any peak eluting at retention times of less than 4 min.

Table 3

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Monoisopropyl tolterodine	0.88	1.6	0.25
Tolterodine	1.0	—	—
6-Methyl-4-phenylchroman-2-ol	1.48	1.9	0.25
Any other individual impurity	—	1.0	0.1
Total impurities	—	—	0.5

• **Enantiomeric Purity**

Buffer: Prepare pH 7.1 buffer as follows. Transfer 21.0 mL of 1 M solution of monobasic sodium phosphate and 53.3 mL of 0.5 M solution of dibasic sodium phosphate dihydrate to a 1000-mL volumetric flask, and dilute with water to volume. Dilute 100.0 mL of this solution with water to 1000.0 mL.

Mobile phase: Add 0.97 g of tetrabutylammonium bromide to a mixture of 930 mL of *Buffer* and 70 mL of isobutyl alcohol.

System suitability solution: 0.02 mg/mL each of USP Tolterodine Tartrate RS and USP Tolterodine S-Enantiomer RS in *Mobile phase*

Standard solution: 0.0004 mg/mL of USP Tolterodine S-Enantiomer RS in *Mobile phase*

Sample solution: 0.04 mg/mL of Tolterodine Tartrate in *Mobile phase*

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: UV 220 nm

Column: 2-mm × 10-cm; 5-µm packing L41

Flow rate: 0.2 mL/min

Injection volume: 20 µL

System suitability

Sample: *System suitability solution*

[NOTE—The relative retention times for tolterodine *S*-enantiomer and tolterodine are 0.9 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 1.4 between tolterodine *S*-enantiomer and tolterodine

Column efficiency: NLT 1500 theoretical plates for tolterodine

Relative standard deviation: NMT 3% for each of tolterodine *S*-enantiomer and tolterodine

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of tolterodine *S*-enantiomer in the portion of Tolterodine Tartrate taken:

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

r_U = peak response of tolterodine *S*-enantiomer from the *Sample solution*

r_S = peak response of tolterodine *S*-enantiomer from the *Standard solution*

C_S = concentration of USP Tolterodine S-Enantiomer RS in the *Standard solution* (mg/mL)

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

Acceptance criteria: NMT 1.0%

SPECIFIC TESTS

• **LOSS ON DRYING ⟨731⟩**

Analysis: Dry under vacuum at 100° for 2 h.

Acceptance criteria: NMT 0.5%

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in well-closed containers. Store at room temperature.

• **USP REFERENCE STANDARDS ⟨11⟩**

USP Tolterodine S-Enantiomer RS

(*S*)-2-[3-(Diisopropylamino)-1-phenylpropyl]-4-methylphenol tartrate.

$C_{22}H_{31}NO \cdot C_4H_6O_6$ 475.57

USP Tolterodine System Suitability Mixture RS

The mixture contains tolterodine tartrate and the following impurities (other impurities may also be present):

p-Cresol. C_7H_8O 108.14

trans-Cinnamic acid. $C_9H_8O_2$ 148.16

Monoisopropyl tolterodine;
(*R*)-2-[3-(Isopropylamino)-1-phenylpropyl]-4-methylphenol. $C_{19}H_{25}NO$ 283.41

Diol impurity;
2-(3-Hydroxy-1-phenylpropyl)-4-methylphenol. $C_{16}H_{18}O_2$ 242.32

Tolterodine dimer;
N,*N*-Bis[3-(2-hydroxy-5-methylphenyl)-3-phenylpropyl]-*N*-isopropylamine. $C_{35}H_{41}NO_2$ 507.72

6-Methyl-4-phenylchroman-2-ol. $C_{16}H_{16}O_2$ 240.30

Diol acetate impurity;
3-(2-Hydroxy-5-methylphenyl)-3-phenylpropyl acetate. $C_{18}H_{20}O_3$ 284.35

6-Methyl-4-phenylchroman-2-one. $C_{16}H_{14}O_2$ 238.29

USP Tolterodine Tartrate RS

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

Topic/Question	Contact	Expert Committee
TOLTERODINE TARTRATE	Documentary Standards Support	SM32020 Small Molecules 3
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM32020 Small Molecules 3

Chromatographic Database Information: Chromatographic Database

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