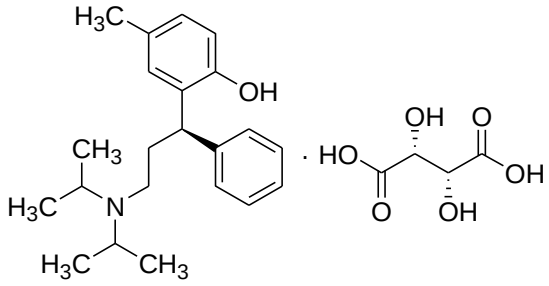
Tolterodine Tartrate



$C_{22}H_{31}NO$, $C_4H_6O_6$ Mol. Wt. 475.6

Tolterodine Tartrate is (R)-2-[3-[Bis(1-methylethyl)amino]-1-phenylpropyl]-4-methylphenol (2R,3R)-2,3-dihydroxybutanedioate (1:1) (salt).

Tolterodine Tartrate contains not less than 97.0 per cent and not more than 103.0 per cent of $C_{22}H_{31}NO$, $C_4H_6O_6$.

Category. Antimuscarinic.

Description. A white or almost white, crystalline powder.

Identification

A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *tolterodine tartrate RS* or with the reference spectrum of tolterodine tartrate.

B. In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with the reference solution.

C. It gives reaction of tartrate (2.3.1).

Tests

Enantiomeric purity. Determine by liquid chromatography (2.4.14).

Test solution. Dissolve 40 mg of the substance under examination in the mobile phase and dilute to 100.0 ml with the mobile phase. Dilute 5.0 ml of the solution to 50.0 ml with the mobile phase.

Reference solution (a). A 0.004 per cent w/v solution of *tolterodine S-enantiomer RS* in the mobile phase. Dilute 1.0 ml of the solution to 100.0 ml with the mobile phase.

Reference solution (b). A solution containing 0.002 per cent w/v each of *tolterodine tartrate RS* and *tolterodine s-enantiomer RS* in the mobile phase.

Chromatographic system

- a stainless steel column 10 cm x 2 mm, packed with immobilized α1-acid glycoprotein on spherical silica particles (5 µm) (Such as Chiralpak-AGP),
- mobile phase: a 0.097 per cent w/v solution of *tetrabutylammonium bromide* in a mixture of 93 volumes of a buffer solution prepared by diluting 2.1 ml of *1 M monobasic sodium phosphate* solution and 5.3 ml of *0.5 M dibasic sodium phosphate dehydrate* to a 1000 ml with *water*, Adjusted to pH 7.1 and 7 volumes of *isobutyl alcohol*,
- flow rate: 0.2 ml per minute,
- spectrophotometer set at 220 nm,
- injection volume: 20 µl.

The relative retention time with reference tolterodine tartrate and tolterodine S-enantiomer is about 0.9.

Inject reference solution (b). The test is not valid unless the resolution between the peaks due to tolterodine tartrate and tolterodine S-enantiomer is not less than 1.4, the column efficiency is not less than 1500 theoretical plates for tolterodine peak and the relative standard deviation for replicate injections is not more than 3.0 per cent for both the peaks

Inject reference solution (a) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to tolterodine s-enantiomer is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent).

Related substances. Determine by liquid chromatography (2.4.14)

Solvent mixture. 50 volumes of *water* and 50 volumes of *acetonitrile.*

Test solution. Dissolve 100 mg of the substance under examination in the solvent mixture and dilute to 10.0 ml with the solvent mixture.

Reference solution (a). A 0.001 per cent w/v solution of *tolterodine tartrate RS* in the solvent mixture.

Reference solution (b). Dilute 5.0 ml of reference solution (a) to 10.0 ml with the solvent mixture.

Reference solution (c). A 1.0 per cent w/v solution of *tolterodine tartrate system suitability mixture RS* in solvent mixture.

Chromatographic system

- a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm),
- column temperature: 65º,
- mobile phase: A. a mixture of 10 volumes of *acetonitrile,* 90 volumes of *water* and 0.15 volumes of *perchloric acid,*
  B. a mixture of 50 volumes of *acetonitrile,* 50 volumes of *water* and 0.15 volumes of *perchloric acid,*
  C. *acetonitrile,*
- a gradient programme using the conditions given below,
- flow rate: 1 ml per minute,
- spectrophotometer set at 220 nm,
- injection volume: 10 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)	Mobile phase C (per cent v/v)
0	75	25	0
5	75	25	0
22	0	100	0
47	0	0	100
57	0	0	100
57.1	75	25	0
60	75	25	0

Name	Relative retention time	Correction factor
p-cresol	0.75	---
Trans-cinnamic acid	0.81	---
Monoisopropyl tolterodine[1]	0.88	0.63
Tolterodine,	1.0	---
Diol impurity[2]	1.18	---
Tolterodine dimer[3]*	1.44	---
6-methyl-4-phenylchroman-2-ol*	1.48	0.53
Diol acetate impurity[4]	1.54	---
6-methyl-4-phenylchroman-2-one	1.59	---

* Undefined stereochemistry
[1](R)-2-[3-(Isopropylamino)-1-phenylpropyl]-4-methylphenol.
[2]2-(3-Hydroxy-1-phenylpropyl)-4-methylphenol.
[3]N,N-Bis[3-(2-hydroxy-5-mthylphenyl)-3-phenylpropyl]-N-isopropylamine.
[4]3-(2Hydroxy-5-methylphenyl)-3-phenylpropyl acetate.

Inject reference solutions (a), (b) and (c). The test is not valid unless the resolution between the peaks due to diol acetate impurity and 6-methyl-4-phenylchroman-2-one is not less than 1.5 obtained in the chromatogram with reference solution (c), the relative standard deviation for replicate injections is not more than 3.0 per cent obtained in the chromatogram with reference solution (a) and signal-to-noise ratio is not less than 10 in the chromatogram obtained with reference solution (b).

Inject reference solutions (a) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to monoisopropyl tolterodine1and 6-methyl-4-phenylchroman-2-ol, each of is not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.25 per cent), the area of any other secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent) and the sum of areas of all the secondary peaks is not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent). Ignore any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent) and any peak eluting at retention time of less than 4 minute.

Heavy metals (2.3.13). 1.0 g complies with the limit test for heavy metals, Method B (20 ppm).

Sulphated ash (2.3.18). Not more than 0.1 per cent.

Loss on drying (2.4.19). Not more than 0.5 per cent, determined on 1.0 g by drying in an oven at 100° under vacuum for 2 hours.

Assay. Determine by liquid chromatography (2.4.14).
Test solution. Dissolve 35 mg of the substance under examination in the mobile phase and dilute to 100.0 ml with the mobile phase.

Reference solution. A 0.035 per cent w/v solution of *tolterodine tartrate RS* in the mobile phase.

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm),
- mobile phase: a mixture of 33 volumes of *acetonitrile*, 67 volumes of *water* and 0.1 volume of *orthophosphoric acid*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 285 nm,
- injection volume: 5 µl.

Inject the reference solution. The test is not valid unless the relative standard deviation for replicate injections is not more than 1.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_{22}H_{31}NO$, $C_4H_6O_6$.

Storage. Store protected from moisture at a temperature not exceeding 30°.

Solubility. Sparingly soluble in *water*, slightly soluble in anhydrous *ethanol*, practically insoluble in *heptaane*.