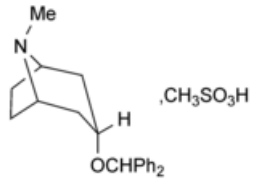
Edition: BP 2025 (Ph. Eur. 11.6 update)

Benzatropine Mesilate

General Notices



$C_{21}H_{25}NO,CH_4O_3S$ 403.5 *132-17-2*

Action and use

Anticholinergic.

Preparations

Benzatropine Injection

Benzatropine Tablets

DEFINITION

Benzatropine Mesilate is (1*R*,3*R*,5*S*)-3-benzhydryloxytropane methanesulfonate. It contains not less than 98.0% and not more than 100.5% of $C_{21}H_{25}NO,CH_4O_3S$, calculated with reference to the dried substance.

PRODUCTION

Risk assessment should be used to evaluate the potential for genotoxic methanesulfonate esters to be formed in the presence of low molecular weight alcohols. If a risk of methanesulfonate ester formation is identified through risk assessment, these impurities should not exceed the threshold of toxicological concern.

CHARACTERISTICS

A white, crystalline powder. It melts at about 144°.

Very soluble in *water*; freely soluble in *ethanol (96%)*; practically insoluble in *ether*.

IDENTIFICATION

A. Dry the substance at 105° for 3 hours. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of benzatropine mesilate (*RS 026*).

B. The *light absorption*, Appendix II B, in the range 230 to 350 nm of a 0.1% w/v solution in *2M hydrochloric acid* exhibits two maxima, at 253 and 258 nm. The *absorbance* at 253 nm is about 0.96 and at 258 nm is about 1.1.
C. Dissolve 10 mg in 2 mL of *water*, pour into 5 mL of hot *picric acid solution R1* and allow to cool. The *melting point* of the precipitate, after drying at 105°, is about 185°, Appendix V A.

TESTS

Tropine

Carry out the method for *thin-layer chromatography*, Appendix III A, using *silica gel G* as the coating substance and a mixture of 75 volumes of *ethanol (96%)* and 15 volumes of *13.5M ammonia* as the mobile phase. Apply separately to the plate 10 µL of each of two solutions in *acetone* containing (1) 4.0% w/v of the substance being examined and (2) 0.020% w/v of *tropine*. After removal of the plate, allow it to dry in air and spray with *sodium iodobismuthate solution* and then with a 0.4% w/v solution of *sulfuric acid*. Any spot corresponding to tropine in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2).

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1) mix with the aid of ultrasound 50 mg of the substance being examined with 15 mL of mobile phase A, dilute to 50 mL with the same solvent and filter. For solution (2) dilute 1 volume of solution (1) to 100 volumes with mobile phase A and further dilute 1 volume of the resulting solution to 5 volumes with the same solvent. For solution (3) mix with the aid of ultrasound 50 mg of *desmethyl benzatropine hydrochloride BPCRS* with 15 mL of mobile phase A, dilute to 100 mL and dilute 1 volume of the resulting solution to 100 volumes with the same solvent. Solution (4) contains 0.01% w/v each of *benzatropine mesilate BPCRS* and *desmethyl benzatropine hydrochloride BPCRS* in mobile phase A.

The chromatographic procedure may be carried out using (a) a stainless steel column (25 cm × 4.6 mm) packed with *phenylsilyl silica gel for chromatography* (5 µm) (Zorbax SB-Phenyl 5µ is suitable). Carry out a linear gradient elution with a flow rate of 1 mL per minute using the following conditions. Use a detection wavelength of 220 nm.

Mobile phase A A mixture of 5 volumes of a 1M potassium phosphate buffer prepared as described for mobile phase B, 20 volumes of *acetonitrile* and 75 volumes of *water*.

Mobile phase B A mixture of 35 volumes of *water*, 60 volumes of *acetonitrile* and 5 volumes of a 1M potassium phosphate buffer prepared in the following manner: dissolve 136.1 g of *potassium dihydrogen orthophosphate* in 900 mL of *water*, add 5 mL of *orthophosphoric acid (85%)* and dilute to 1000 mL.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-20	70→30	30→70	linear gradient
20-30	30→0	70→100	linear gradient
30-55	0	100	isocratic
55-65	70	30	isocratic

Inject 20 µL of solution (4). The test is not valid unless the *resolution factor* between the two principal peaks is at least 1. If necessary adjust the concentration of *acetonitrile* or adjust the time program of the linear gradient elution.

Inject separately 20 µL of mobile phase A as a blank and 20 µL each of solutions (1), (2) and (3). In the chromatogram obtained with solution (1) the area of any peak corresponding to desmethyl benzatropine is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.5%), the area of any other *secondary peak* is not greater that the area of the principal peak in the chromatogram obtained with solution (2) (0.2%) and the sum of the areas of any such peaks is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%). In solution (1) disregard any peaks corresponding to the peaks in the chromatogram obtained with the blank solution.

Loss on drying

When dried to constant weight at 105°, loses not more than 5.0% of its weight. Use 1 g.

Sulfated ash

Not more than 0.1%, Appendix IX A.

ASSAY

Dissolve 0.6 g in 25 mL of *water*, add 5 mL of *dilute sodium carbonate solution* and extract with four 10 mL quantities of *chloroform*. Wash the combined extracts with 10 mL of *water*, extract the washings with 5 mL of *chloroform* and add the chloroform to the combined extracts. Filter and wash the filter with 5 mL of *chloroform*. To the combined filtrate and washings add 25 mL of *1,4-dioxan* and titrate with *0.1M perchloric acid VS* using 0.15 mL of a 0.1% w/v solution of *methyl red* in *methanol* as indicator. Each mL of *0.1M perchloric acid VS* is equivalent to 40.35 mg of $C_{21}H_{25}NO,CH_4O_3S$.