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

Ipratropium Nebuliser Solution

General Notices

Action and use

Anticholinergic (antimuscarinic) bronchodilator.

DEFINITION

Ipratropium Nebuliser Solution is a solution of Ipratropium Bromide in Water for Injections and may contain sodium chloride.

The nebuliser solution complies with the requirements stated under Preparations for Inhalation and with the following requirements.

Content of ipratropium bromide, $C_{20}H_{30}NO_3Br,H_2O$

95.0 to 110.0% of the stated amount.

IDENTIFICATION

Evaporate a volume of the nebuliser solution containing 1.5 mg of Ipratropium Bromide to dryness on a water bath. Shake the residue with 5 mL of *methanol* and filter (Whatman GF/C is suitable). Evaporate the filtrate to dryness on a water bath and dry the residue at room temperature at a pressure of 1 kPa for 15 minutes. The *infrared absorption spectrum* of the dried residue, Appendix II A, is concordant with a spectrum prepared from a mixture of 5 mg of *ipratropium bromide BPCRS* and 45 mg of *sodium chloride* dissolved in the minimum quantity of *water*, evaporated to dryness on a water bath and treated in a similar manner to the substance being examined beginning at the words “Shake the residue with 5 mL of *methanol*,…”.

TESTS

Acidity

pH, 3.0 to 4.0, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a quantity of the nebuliser solution, if necessary, with sufficient 0.001M *hydrochloric acid* to produce a solution containing 0.02% w/v of Ipratropium Bromide.
(2) Dilute 1 volume of solution (1) to 200 volumes with 0.001M *hydrochloric acid*.
(3) 0.005% w/v of *ipratropium bromide impurity B EPCRS* and 0.005% w/v of *ipratropium bromide BPCRS* in 0.001M *hydrochloric acid*.
(4) Dilute 1 volume of solution (2) to 5 volumes with 0.001M *hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

(a) Stainless steel column (12.5 cm × 4.6 mm) packed with *octylsilyl silica gel for chromatography* (5 µm) (Columbus C8 is suitable).
(b) Use isocratic elution using the mobile phase described below.
(c) Use a flow rate of 0.5 mL per minute.
(d) Use an ambient column temperature.
(e) Detection wavelength of 210 nm.
(f) Inject 20 µL of each solution.
(g) For solution (1) allow the chromatography to proceed for 6 times the retention time of ipratropium.

MOBILE PHASE

A mixture of 4 volumes of freshly distilled *triethylamine*, 50 volumes of *propan-2-ol R1*, 100 volumes of *acetonitrile R1* and 850 volumes of a 0.1% w/v solution of *sodium methanesulfonate* adjusted to pH 3.0 with *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions, the retention time of ipratropium is about 11 minutes.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to ipratropium bromide and impurity B is at least 1.2.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the sum of the areas of any such peaks is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a quantity of the nebuliser solution, if necessary, with sufficient 0.001M *hydrochloric acid* to produce a solution containing 0.02% w/v of Ipratropium Bromide.
(2) 0.02% w/v of *ipratropium bromide BPCRS* in 0.001M *hydrochloric acid*.
(3) 0.005% w/v of *ipratropium bromide impurity B EPCRS* and 0.005% w/v of *ipratropium bromide BPCRS* in 0.001M *hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic procedure described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the two principal peaks is at least 1.2.

DETERMINATION OF CONTENT

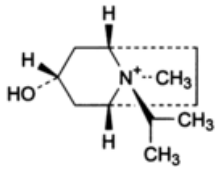
Calculate the content of $C_{20}H_{30}NO_3Br,H_2O$ in the solution using the declared content of $C_{20}H_{30}NO_3Br,H_2O$ in *ipratropium bromide BPCRS*.

STORAGE

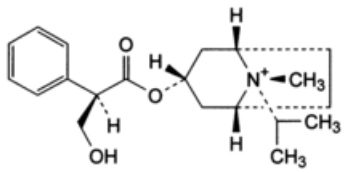
Ipratropium Nebuliser Solution should be stored protected from light in a sealed container.

IMPURITIES

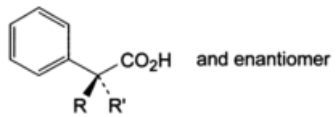
The impurities limited by the requirements of this monograph include.



A. (1*R*,3*r*,5*S*,8*r*)-3-hydroxy-8-methyl-8-(1-methylethyl)-8-azoniabicyclo[3.2.1]octane,



B. (1*R*,3*r*,5*S*,8*s*)-3-[[(2*RS*)-3-hydroxy-2-phenylpropanoyl]oxy]-8-methyl-8-(1-methylethyl)-8- azoniabicyclo[3.2.1]octane,



C. R = CH_2-OH, R′ = H: (2*RS*)-3-hydroxy-2-phenylpropanoic acid (DL-tropic acid),

D. R + R′ = CH_2: 2-phenylpropenoic acid (atropic acid).