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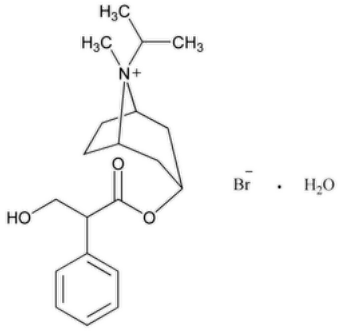
Ipratropium Bromide

To view the Notice from the Expert Committee that posted in conjunction with this accelerated revision, please click www.uspnf.com/rb-ipratropium-br-20230728.



$C_{20}H_{30}BrNO_3 \cdot H_2O$ 430.38
$C_{20}H_{30}BrNO_3$ 412.37

8-Azoniabicyclo[3.2.1]octane, 3-(3-hydroxy-1-oxo-2-phenylpropoxy)-8-methyl-8-(1-methylethyl)-, bromide, monohydrate(*endo,syn*)-, (±)-;
(8*r*)-3α-Hydroxy-8-isopropyl-1α*H*,5α*H*-tropanium bromide (±)-tropate monohydrate;
(1*R*,3*r*,5*S*,8*r*)-3-[(3-Hydroxy-2-phenylpropanoyl)oxy]-8-isopropyl-8-methyl-8-azabicyclo[3.2.1]octan-8-ium bromide monohydrate CAS RN®: 66985-17-9; UNII: J697UZ2A9J..
Anhydrous CAS RN®: 22254-24-6; UNII: VJV4X1P2Z1..

DEFINITION
Ipratropium Bromide contains NLT 98.0% and NMT 102.0% of ipratropium bromide ($C_{20}H_{30}BrNO_3$), calculated on the anhydrous basis.

IDENTIFICATION
- **A. Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 197M
- **B. Identification Tests—General ⟨191⟩, *Chemical Identification Tests, Bromide***
  Sample solution: 10 mg/mL of Ipratropium Bromide in water
  Acceptance criteria: Meets the requirements
- **C.** 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**
  Solution A: 89 g/L of dibasic sodium phosphate dihydrate in water
  Buffer: 14.3 g/L of monobasic sodium phosphate dihydrate and 2.0 g/L of tetrapropylammonium chloride in water. Adjust with *Solution A* to a pH of 5.5.
  Mobile phase: Methanol and *Buffer* (13:87). [Note—Do not use the *Mobile phase* after 36 h.]
  System suitability solution: 0.5 mg/mL of USP Ipratropium Bromide RS and 0.1 mg/mL of USP Ipratropium Bromide Related Compound C RS in *Mobile phase*
  Standard solution: 0.5 mg/mL of USP Ipratropium Bromide RS in *Mobile phase*
  Sample solution: 0.5 mg/mL of Ipratropium Bromide in *Mobile phase*
  Chromatographic system
  (See *Chromatography ⟨621⟩, System Suitability*.)
  Mode: LC
  Detector: UV 220 nm
  Column: 3.9-mm × 15-cm; 4-µm packing L1
  Column temperature: 30°
  Flow rate: 1.5 mL/min
  Injection volume: 5 µL
  Run time: NLT 6 times the retention time of ipratropium
  System suitability
  Samples: *System suitability solution* and *Standard solution*

[NOTE—The relative retention times for ipratropium bromide related compound C and ipratropium are about 0.7 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 4 between ipratropium bromide related compound C and ipratropium, *System suitability solution*

Tailing factor: NMT 2.5, *Standard solution*

Relative standard deviation: NMT 0.73%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of ipratropium bromide ($C_{20}H_{30}BrNO_3$) in the portion of Ipratropium Bromide taken:

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

r_U = peak response of ipratropium from the *Sample solution*

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

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

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

Acceptance criteria: 98.0%–102.0% on the anhydrous basis

IMPURITIES

- **Residue on Ignition ⟨281⟩:** NMT 0.1%
- **Limit of Ipratropium Bromide Related Compound A**

Buffer: 3.9 g/L of ammonium acetate in water. Adjust with glacial acetic acid to a pH of 4.0.

Mobile phase: Acetonitrile and *Buffer* (90:10)

Diluent: 0.01 N hydrochloric acid

Standard stock solution: 10 µg/mL of USP Ipratropium Bromide Related Compound A RS in *Diluent*

Standard solution: 0.1 µg/mL of USP Ipratropium Bromide Related Compound A RS from *Standard stock solution* in *Diluent*

Sensitivity solution: 0.01 µg/mL of USP Ipratropium Bromide Related Compound A RS from *Standard solution* in *Diluent*

Sample solution: 100 µg/mL of Ipratropium Bromide in *Diluent*

Chromatographic system

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

Mode: LC

Detector: Mass spectrometer

Ionization: Electrospray positive ion. [NOTE—Adjustments to the electrospray source parameters including the probe temperature, cone voltage, and capillary voltage may be necessary to meet *Suitability requirements*.]

Acquisition mode: Selected ion monitoring (SIM) mode with m/z of 184.2 for the ipratropium related compound A cation

Column: 3.0-mm × 5-cm; 5-µm packing L9

Column temperature: 20°

Flow rate: 0.6 mL/min

Injection volume: 5 µL

Run time: NLT 1.5 times the retention time of ipratropium bromide related compound A

System suitability

Samples: *Standard solution* and *Sensitivity solution*

Suitability requirements

Relative standard deviation: NMT 10.0%, *Standard solution*

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

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of ipratropium bromide related compound A in the portion of Ipratropium Bromide taken:

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

r_U = peak response of ipratropium bromide related compound A from the *Sample solution*

r_S = peak response of ipratropium bromide related compound A from the *Standard solution*

C_S = concentration of USP Ipratropium Bromide Related Compound A RS in the *Standard solution* (µg/mL)

C_U = concentration of Ipratropium Bromide in the *Sample solution* (µg/mL)

Acceptance criteria: NMT 0.10%

- **Organic Impurities**

Solution A, Buffer, Mobile phase, and **Chromatographic system:** Proceed as directed in the *Assay*.

System suitability solution: 0.03 mg/mL of USP Ipratropium Bromide RS and 0.01 mg/mL of USP Ipratropium Bromide Related Compound B RS in *Mobile phase*

Sensitivity solution: 0.005 mg/mL of USP Ipratropium Bromide RS in *Mobile phase*

Standard solution: 0.03 mg/mL of USP Ipratropium Bromide RS in *Mobile phase*

Sample solution: 10 mg/mL of Ipratropium Bromide in *Mobile phase*

System suitability

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

[NOTE—See *Table 1* for the relative retention times.]

Suitability requirements

Resolution: NLT 4 between ipratropium and ipratropium bromide related compound B, *System suitability solution*

Tailing factor: NMT 2.5, *Standard solution*

Relative standard deviation: NMT 5%, *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 Ipratropium Bromide taken:

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

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

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

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

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

F = relative response factor (see *Table 1*)

Acceptance criteria: See *Table 1*. The reporting threshold is 0.05%. Disregard the bromide counterion peak eluting at a relative retention time of about 0.1.

Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Ipratropium bromide related compound C[a]	0.7	3.8	0.10
Ipratropium	1.0	1.0	—
Ipratropium bromide related compound B	1.3	1.0	0.10
Desmethyl ipratropium[b]	2.3	1.0	0.10
Ipratropium atropic analog[c]	5.1	2.0	0.10
Any unspecified impurity	—	1.0	0.10
Total impurities	—	—	0.25

[a] Also known as tropic acid.

[b] (1*R*,3*r*,5*S*)-8-Isopropyl-8-azabicyclo[3.2.1]octan-3-yl 3-hydroxy-2-phenylpropanoate.

[c] (1*R*,3*r*,5*S*,8*r*)-8-Isopropyl-8-methyl-3-[(2-phenylacryloyl)oxy]-8-azabicyclo[3.2.1]octan-8-ium.

Add the following:

▲SPECIFIC TESTS

• **WATER DETERMINATION ⟨921⟩, *Method I*:** 3.9%–4.4%▲ (RB 1-Aug-2023)

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in tight, light-resistant containers, and store at controlled room temperature.

• **USP Reference Standards** ⟨11⟩

USP Ipratropium Bromide RS

USP Ipratropium Bromide Related Compound A RS

(1*R*,3*r*,5*S*,8*r*)-3-Hydroxy-8-isopropyl-8-methyl-8-azabicyclo[3.2.1]octan-8-ium bromide;
Also known as (1*R*,3*r*,5*S*,8*r*)-3-Hydroxy-8-methyl-8-(1-methylethyl)-8-azoniabicyclo[3.2.1]octane, bromide.
$C_{11}H_{22}BrNO$ 264.20

USP Ipratropium Bromide Related Compound B RS

(1*R*,3*r*,5*S*,8*s*)-3-[(3-Hydroxy-2-phenylpropanoyl)oxy]-8-isopropyl-8-methyl-8-azabicyclo[3.2.1]octan-8-ium bromide;
Also known as (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, bromide.
$C_{20}H_{30}BrNO_3$ 412.37

USP Ipratropium Bromide Related Compound C RS

3-Hydroxy-2-phenylpropionic acid;
Also known as (2*RS*)-3-Hydroxy-2-phenylpropanoic acid.
$C_9H_{10}O_3$ 166.17

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

Topic/Question	Contact	Expert Committee
IPRATROPIUM BROMIDE	Documentary Standards Support	SM52020 Small Molecules 5

Chromatographic Database Information: Chromatographic Database

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