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Ipratropium Bromide Inhalation Solution

DEFINITION

Ipratropium Bromide Inhalation Solution is an isotonic sterile solution of ipratropium bromide monohydrate ($C_{20}H_{30}BrNO_3 \cdot H_2O$). It may contain isotonicity agents and pH-adjusting agents. It contains NLT 90.0% and NMT 110.0% of the labeled amount of ipratropium bromide ($C_{20}H_{30}BrNO_3$).

IDENTIFICATION

• **A.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

• **B.** The UV spectrum of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

Protect solutions containing ipratropium bromide from light.

ASSAY

• **Procedure**

Phosphate solution: Dissolve 8.9 g of dibasic sodium phosphate dihydrate in 100 mL of water.

Buffer: Dissolve 14.3 g of monobasic sodium phosphate dihydrate and 2 g of tetrapropylammonium chloride in 1 L of water. Adjust with *Phosphate solution* to a pH of 5.5.

Solution A: *Buffer*

Solution B: Methanol

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	87	13
7.0	87	13
7.1	10	90
9.0	10	90
9.1	87	13
12.0	87	13

Diluent: Methanol and *Buffer* (13:87)

System suitability solution: 0.1 mg/mL each of USP Ipratropium Bromide RS and USP Ipratropium Bromide Related Compound C RS in *Diluent*. Sonicate to dissolve.

Standard solution: 0.1 mg/mL of USP Ipratropium Bromide RS in *Diluent*. Sonicate to dissolve.

Sample solution: Nominally 0.1 mg/mL of ipratropium bromide from Inhalation Solution prepared as follows. Pool the contents from NLT 8 vials of Inhalation Solution. Transfer a suitable volume of the pooled Inhalation Solution to a suitable volumetric flask and dilute with *Diluent* to volume.

Chromatographic system

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

Mode: LC

Detector: UV 220 nm. For *Identification B*, use a diode array detector in the range of 200–400 nm.

Column: 3.9-mm × 15-cm; 4-µm packing L1

Column temperature: 30°

Flow rate: 2 mL/min

Injection volume: 25 µL

System suitability

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

[NOTE—The relative retention times for ipratropium bromide related compound C and ipratropium are 0.65 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 2.5 between ipratropium bromide related compound C and ipratropium, *System suitability solution*

Tailing factor: NMT 2.0, *Standard solution*

Relative standard deviation: NMT 1.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of ipratropium bromide ($C_{20}H_{30}BrNO_3$) in the portion of Inhalation Solution 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 = nominal concentration of ipratropium bromide in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

• **UNIFORMITY OF DOSAGE UNITS ⟨905⟩:** Meets the requirements

IMPURITIES

Change to read:

• **ORGANIC IMPURITIES**

Buffer: 13.6 g/L of monobasic potassium phosphate in water. Adjust with 10% phosphoric acid to a pH of 4.0.

Solution A: Acetonitrile and *Buffer* (5:95)

Solution B: Acetonitrile and *Buffer* (30:70)

Mobile phase: See *Table 2*.

Table 2

Time (min)	Solution A (%)	Solution B (%)
0	82	18
5.0	82	18
19.0	77	23
34.0	77	23
37.0	73	27
46.0	67	33
48.0	67	33
59.0	50	50
68.0	0	100
74.0	0	100
74.1	82	18
85.0	82	18

Diluent: Acetonitrile and water (5:95)

System suitability solution: 10 µg/mL of USP Ipratropium Bromide RS and 1 µg/mL each of USP Ipratropium Bromide Related Compound B RS and USP Ipratropium Bromide Related Compound C RS in *Diluent*

Sensitivity solution: 0.1 µg/mL of USP Ipratropium Bromide RS in *Diluent*

Standard solution: 1 µg/mL of USP Ipratropium Bromide RS in *Diluent*

Sample solution: Nominally 200 µg/mL of ipratropium bromide from the pooled contents of NLT 8 vials of Inhalation Solution

Chromatographic system

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

Mode: LC

Detector: UV 220 nm

Column: 4.6-mm × ▲25-cm▲ (ERR 1-Apr-2024); 5-µm packing L1

Column temperature: 30°

Flow rate: 1.2 mL/min

Injection volume: 100 µL

System suitability

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

[NOTE—See *Table 3* for the relative retention times.]

Suitability requirements

Resolution: NLT 4.0 between ipratropium bromide related compound B and ipratropium, *System suitability solution*

Tailing factor: NMT 2.0, *Standard solution*

Relative standard deviation: NMT 5.0%, *Standard solution*

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

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of any specified and unspecified degradation products in the portion of Inhalation Solution taken:

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

r_U = peak response of the degradation product 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* (µg/mL)

C_U = nominal concentration of ipratropium bromide in the *Sample solution* (µg/mL)

F = relative response factor for the corresponding degradation product (see *Table 3*)

Acceptance criteria: See *Table 3*. The reporting threshold is 0.05%.

Table 3

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Ipratropium bromide related compound C	0.46	3.0	1.0
Ipratropium	1.0	—	—
Ipratropium bromide related compound B[a]	1.16	—	—
Desmethyl ipratropium[a,b]	1.31	—	—
Atropic acid[a,c]	1.59	—	—
Ipratropium atropic analog[a,d]	1.88	—	—
Any unspecified degradation product	—	1.0	0.1
Total degradation products	—	—	1.5

[a] Process impurity is controlled in the drug substance and it is not included in the total degradation products.

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

[c] 2-Phenylacrylic acid.

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

SPECIFIC TESTS

- **Sterility Tests ⟨71⟩:** Meets the requirements
- **pH ⟨791⟩:** 3.0–4.0
- **Particulate Matter in Injections ⟨788⟩,** *Method 1 Light Obscuration Particle Count Test*

  Sample: Pool the contents of NLT 10 units.

  Acceptance criteria: See *Table 4*.

Table 4

Particle Size (µm)	Limit NMT (particles/container)
≥10	6000
≥25	600

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Store between 15° and 30°. Protect from light.
- **USP Reference Standards ⟨11⟩**

USP Ipratropium Bromide RS

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 INHALATION SOLUTION	Documentary Standards Support	SM52020 Small Molecules 5

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