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Ipratropium Bromide and Albuterol Sulfate Inhalation Solution

DEFINITION

Ipratropium Bromide and Albuterol Sulfate Inhalation Solution is an isotonic sterile solution of ipratropium bromide and albuterol sulfate. It may contain chelating agents, isotonicity agents, and pH adjusting agents. It contains NLT 90.0% and NMT 110.0% of the labeled amount of ipratropium bromide ($C_{20}H_{30}BrNO_3$) and albuterol ($C_{13}H_{21}NO_3$) as albuterol sulfate.

IDENTIFICATION

- **A.** The retention times of the major peaks of the *Sample solution* correspond to those of the *Standard solution*, as obtained in the *Assay*.
- **B.** The UV spectra of the major peaks of the *Sample solution* correspond to those of the *Standard solution*, as obtained in the *Assay*.

ASSAY

Change to read:

- **Procedure**

Buffer: 2.7 g/L of monobasic potassium phosphate in water

Solution A: Acetonitrile and *Buffer* (5:95). [Note—The pH of the solution is about 4.7.]

Solution B: Acetonitrile and *Buffer* (40:60). [Note—The pH of the solution is about 5.4.]

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	100	0
3	100	0
30	50	50
35	100	0
40	100	0

System suitability solution: 0.1 mg/mL of USP Ipratropium Bromide RS, 0.5 mg/mL of USP Albuterol Sulfate RS, and 0.05 mg/mL each of USP Ipratropium Bromide Related Compound B RS and USP Ipratropium Bromide Related Compound C RS in water

Standard solution: 0.04 mg/mL of USP Ipratropium Bromide RS and 0.25 mg/mL of USP Albuterol Sulfate RS in water

Sample solution: Nominally 0.04 mg/mL of ipratropium bromide and 0.25 mg/mL of albuterol sulfate from the pooled contents of NLT 20 vials of Inhalation Solution prepared as follows. Transfer a suitable volume of the pooled composite Inhalation Solution to a suitable volumetric flask. Dilute with water to obtain the final nominal concentration.

Chromatographic system

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

Mode: LC

Detector: UV 210 nm. For *Identification B*, use a diode array detector in the range of 200–300 nm.

Column: 4.6-mm × 15-cm; 5-µm packing L7

Column temperature: 15°

Flow rate: 1 mL/min

Injection volume: 20 µL

System suitability

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

[Note—The relative retention times for the components relative to ipratropium are shown in *Table 2*.]

Table 2

Component	Relative Retention Time
Albuterol	0.3
Ipratropium related compound C	0.7
Ipratropium	1.0
Ipratropium related compound B	1.05

Suitability requirements

Resolution: NLT 2.0 between ipratropium and ipratropium related compound B, *System suitability solution*

Tailing factor: NMT 2.0 for ▲albuterol and ipratropium,▲ (USP 1-May-2021) *Standard solution*

Relative standard deviation: NMT 1.0% for ▲albuterol and ipratropium,▲ (USP 1-May-2021) *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)

Calculate the percentage of the labeled amount of albuterol ($C_{13}H_{21}NO_3$) in the portion of Inhalation Solution taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times N \times 100$$

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

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

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

C_U = nominal concentration of albuterol in the *Sample solution* (mg/mL)

M_{r1} = molecular weight of albuterol, 239.31

M_{r2} = molecular weight of albuterol sulfate, 576.70

N = number of moles of albuterol per mole of albuterol sulfate, 2

Acceptance criteria

Ipratropium bromide: 90.0%–110.0%

Albuterol: 90.0%–110.0%

PERFORMANCE TESTS

• **Uniformity of Dosage Units ⟨905⟩:** Meets the requirements

IMPURITIES

Change to read:

• **Organic Impurities**

Solution A: Dissolve 2.7 g of monobasic potassium phosphate in 1 L of water. Adjust with phosphoric acid to a pH of 3.9.

Solution B: Acetonitrile

Mobile phase: See *Table 3*.

Table 3

Time (min)	Solution A (%)	Solution B (%)
0	95	5
3	95	5
40	84	16
60	60	40
75	60	40
77	95	5
85	95	5

System suitability solution: 0.18 mg/mL of USP Ipratropium Bromide RS, 1 mg/mL of USP Albuterol Sulfate RS, and 0.005 mg/mL each of USP Levalbuterol Related Compound D RS, USP Ipratropium Bromide Related Compound B RS, and USP Ipratropium Bromide Related Compound C RS in water

Standard solution: 0.9 µg/mL of USP Ipratropium Bromide RS and 5 µg/mL of USP Albuterol Sulfate RS in water

Sample solution: Nominally 170 µg/mL of ipratropium bromide and 833 µg/mL of albuterol prepared by pooling the contents of 10 vials of Inhalation Solution into a suitable vessel. Shake well and inject as such.

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

Column: 4.6-mm × 25-cm; 5-µm packing L7

Column temperature: 30°

Flow rate: 1 mL/min

Injection volume: 50 µL

System suitability

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

[Note—See *Table 4* for relative retention times.]

Suitability requirements

Resolution: NLT 1.5 between ipratropium related compound C and ipratropium; NLT 2.0 between ipratropium and ipratropium related compound B, *System suitability solution*

Tailing factor: NMT 2.0 for ▲albuterol and ipratropium,▲ (USP 1-May-2021) *Standard solution*

Relative standard deviation: NMT 5.0% for albuterol and ipratropium, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of levalbuterol related compound D in the portion of Inhalation Solution taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times (M_{r1}/M_{r2}) \times N \times 100$$

r_U = peak response of levalbuterol related compound D from the *Sample solution*

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

C_S = concentration of USP Albuterol Sulfate RS in the *Standard solution* (µg/mL)

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

F = relative response factor of ▲levalbuterol related compound D▲ (USP 1-May-2021) (see *Table 4*)

M_{r1} = molecular weight of albuterol, 239.31

M_{r2} = molecular weight of albuterol sulfate, 576.70

N = number of moles of albuterol per mole of albuterol sulfate, 2

Calculate the percentage of atropic acid and ipratropium related compound C 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 ▲atropic acid or ipratropium related compound C▲ (USP 1-May-2021) 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 of the corresponding degradation product (see *Table 4*)

Calculate the percentage of each unspecified degradation product in the portion of Inhalation Solution taken:

$$\text{Result} = (r_U/r_T) \times 100$$

r_U = peak response of each unspecified degradation product from the *Sample solution*

r_T = sum of all the peak responses from the *Sample solution*

Acceptance criteria: See *Table 4*. The reporting threshold is 0.1%.

Table 4

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Bromide[a]	0.07	—	—
Albuterol	0.24	—	—
Albuterol related compound A[b,c]	0.59	—	—
Levalbuterol related compound D	0.70	2.5	0.1
Albuterol related compound E[c,d]	0.83	—	—
Ipratropium related compound C▲[e]▲ (USP 1-May-2021)	0.91	2.5	0.50
Ipratropium	1.0	—	—
Ipratropium related compound B[c]	1.10	—	—
▲Ipratropium atropic analog▲ (USP 1-May-2021) [c,f]	1.58	—	—
Levalbuterol related compound F[c,g]	1.60	—	—
Atropic acid[h]	1.64	3.7	0.50
Any individual unspecified degradation product	—	—	0.20
Total degradation products	—	—	1.0

[a] Counter ion of ipratropium bromide; not to be included in total degradation products.

[b] 4-{2-[(1,1-Dimethylethyl)amino]-1-hydroxyethyl}-2-methylphenol.

[c] Process impurity; controlled in the drug substance.

[d] 2,2'-Oxybis(methylene)bis{4-[2-(*tert*-butylamino)-1-hydroxyethyl]phenol}; also known as 1,1'[Oxybis[methylene(4-hydroxy-1,3-phenylene)]]bis[2-[(1,1-dimethylethyl)amino]ethanol].

[e] Also known as tropic acid.

[f] (1*R*,3*r*,5*S*,8*r*)-8-Isopropyl-8-methyl-3-[(2-phenylacryloyl)oxy]-8-azabicyclo[3.2.1]octan-8-ium; also known as (1*R*,3*r*,5*S*,8*r*)-8-Methyl-8-(1-methylethyl)-3-[(2-phenylpropenoyl)oxy]-8-azoniabicyclo[3.2.1]octane ▲or apo-ipratropium.▲ (USP 1-May-2021)

[g] 1-[4-(Benzyloxy)-3-(hydroxymethyl)phenyl]-2-(*tert*-butylamino)ethanol; also known as α-{[(1,1-Dimethylethyl)amino]methyl}-4-(phenylmethoxy)-1,3-benzenedimethanol or (1*RS*)-2-[(1,1-Dimethylethyl)amino]-1-[4-(benzyloxy)-3-(hydroxymethyl)phenyl]ethanol.

[h] 2-Phenylacrylic acid.

SPECIFIC TESTS

• **Sterility Tests ⟨71⟩:** Meets the requirements

• **pH ⟨791⟩:** 3.4–4.5

• **Particulate Matter**

(See *Particulate Matter in Injections ⟨788⟩, Method 1 Light Obscuration Particle Count Test*.)

Sample: Pool the contents of NLT 20 units.

Acceptance criteria: See *Table 5*.

Table 5

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

• **Osmolality and Osmolarity ⟨785⟩:** 278–349 mOsmol/kg

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Protect from light. Store in pouch until the time of use. Store at controlled room temperature.

Change to read:

• **USP Reference Standards ⟨11⟩**

USP Albuterol Sulfate RS

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▲ (USP 1-May-2021) (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.

▲▲ (USP 1-May-2021)

$C_{20}H_{30}BrNO_3$ ▲412.37▲ (USP 1-May-2021)

USP Ipratropium Bromide Related Compound C RS

▲3-Hydroxy-2-phenylpropionic acid;
(Also known as▲ (USP 1-May-2021) 2*RS*)-3-Hydroxy-2-phenylpropanoic acid.

$C_9H_{10}O_3$ 166.17

USP Levalbuterol Related Compound D RS

5-[2-{(1,1-Dimethylethyl)amino}-1-hydroxyethyl]-2-hydroxy-benzaldehyde sulfate ▲(2:1);▲ (USP 1-May-2021)

Also known as 5-[2-(*tert*-Butylamino)-1-hydroxyethyl]-2-hydroxybenzaldehyde sulfate ▲(2:1) (salt).▲ (USP 1-May-2021)

$(C_{13}H_{19}NO_3)_2 \cdot H_2SO_4$ 572.67

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

Topic/Question	Contact	Expert Committee
IPRATROPIUM BROMIDE AND ALBUTEROL SULFATE INHALATION SOLUTION	Documentary Standards Support	SM52020 Small Molecules 5
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