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Levalbuterol Inhalation Solution

DEFINITION

Levalbuterol Inhalation Solution is a sterile, aqueous solution of Levalbuterol Hydrochloride, prepared with Sodium Chloride. It contains NLT 90.0% and NMT 110.0% of the labeled amount of levalbuterol ($C_{13}H_{21}NO_3$).

IDENTIFICATION

• **A.** The retention time of the major peak of the *Sample solution* corresponds to that of the *System suitability solution*, as obtained in the test for *Limit of S-Albuterol*.

• **B.** The UV spectrum of the major peak of the *Sample solution* corresponds to that of the major peak of the *System suitability solution*, as obtained in the test for *Limit of S-Albuterol*.

ASSAY

• **Procedure**

Solution A: Dilute 1 mL of phosphoric acid with water to 1 L.

Solution B: Acetonitrile, methanol, and water (35:35:30). To each liter of the solution add 1 mL of phosphoric acid.

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	91.5	8.5
15	91.5	8.5
15.01	0	100
20	0	100
20.01	91.5	8.5
30	91.5	8.5

Diluent: Dissolve 9.0 g of sodium chloride in 950 mL of water. Adjust with dilute sulfuric acid to a pH of 4.0, and dilute with water to 1000 mL.

Standard solution: 0.1 mg/mL of USP Levalbuterol Hydrochloride RS in *Diluent*

Sample solution: Nominally 0.1 mg/mL of levalbuterol hydrochloride (equivalent to 0.087 mg/mL of levalbuterol free base) in *Diluent* from an appropriately diluted volume of Inhalation Solution

Chromatographic system

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

Mode: LC

Detector: UV 220 nm

Column: 4.6-mm × 15-cm; 5-µm packing L1

Column temperature: 35°

Flow rate: 1 mL/min

Injection volume: 10 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.3

Relative standard deviation: NMT 1.0%

Analysis

Samples: *Standard solution* and *Sample solution*

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

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

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

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

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

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

M_{r1} = molecular weight of levalbuterol (free base), 239.31

M_{r2} = molecular weight of levalbuterol hydrochloride, 275.77

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

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

IMPURITIES

Change to read:

• **Limit of *S*-Albuterol**

Mobile phase: Acetonitrile and methanol (50:50). To each liter of the solution add 3 mL of acetic acid and 1 mL of triethylamine.

Diluent: Prepare as directed in the *Assay*.

System suitability solution: 0.10 mg/mL of USP Levalbuterol Hydrochloride RS and 0.04 mg/mL of USP Albuterol RS in *Diluent*

Sample solution: Inhalation Solution

Chromatographic system

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

Mode: LC

Detector: UV 225 nm. For *Identification B* use a diode array detector in the range of 200–400 nm.

Column: 4.6-mm × 25-cm; 5-µm packing L63

Flow rate: 1 mL/min

Injection volume: 40 µL

Run time: NLT 1.5 times the retention time of levalbuterol

System suitability

Sample: *System suitability solution*

[Note—The relative retention times for levalbuterol and (*S*)-albuterol are 1.0 and 1.16, respectively.]

Suitability requirements

Resolution: NLT 3.0 between levalbuterol and (*S*)-albuterol

Tailing factor: NMT 1.6 for levalbuterol and NMT 2.0 for (*S*)-albuterol

Analysis

Sample: *Sample solution*

Calculate the percentage of (*S*)-albuterol in the portion of Inhalation Solution taken:

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

r_U = peak response of (*S*)-albuterol from the *Sample solution*

r_T = sum of the peak responses of levalbuterol and (*S*)-albuterol from the *Sample solution*

Acceptance criteria: NMT 2.50% of (*S*)-albuterol ▲▲ (IRA 1-Nov-2022)

Change to read:

• **Organic Impurities**

Solution A, Solution B, Diluent, and **Sample solution:** Prepare as directed in the *Assay*.

Mobile phase: See *Table 2*.

Table 2

Time (min)	Solution A (%)	Solution B (%)
0	100	0

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Time (min)	Solution A (%)	Solution B (%)
30	70	30
50	28	72
50.01	0	100
55	0	100
55.01	100	0
70	100	0

System suitability solution: 100 µg/mL of USP Levalbuterol Hydrochloride RS and 0.05 µg/mL each of USP Levalbuterol Related Compound A RS, ▲USP Albuterol Related Compound A RS,▲ (IRA 1-Nov-2022) USP Levalbuterol Related Compound C RS, and USP Levalbuterol Related Compound D RS in *Diluent*

Sensitivity solution: 0.05 µg/mL of USP Levalbuterol Hydrochloride RS in *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 220 nm

Column: 4.6-mm × 15-cm; 5-µm packing L1

Column temperature: 45°

Flow rate: 1 mL/min

Injection volume: 50 µL

System suitability

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

▲[NOTE—The relative retention times in *Table 3* are provided as information that could aid in peak assignment.]

Table 3▲ (IRA 1-Nov-2022)

Name	Relative Retention Time
5-Hydroxyalbuterol[a]	0.90
Levalbuterol	1.0
Levalbuterol related compound A	1.2
Levalbuterol related compound H[b]	1.3
▲Albuterol related compound A▲ (IRA 1-Nov-2022)	1.5
Levalbuterol related compound C	1.6
Levalbuterol related compound D	1.7
Levalbuterol related compound E[c]	2.1
Levalbuterol related compound F[d]	3.5

[a] 5-[2-(*tert*-Butylamino)-1-hydroxyethyl]-3-(hydroxymethyl)benzene-1,2-diol.

[b] 4-[2-(*tert*-Butylamino)-1-methoxyethyl]-2-(hydroxymethyl)phenol.

[c] ▲4-[2-(*tert*-Butylamino)-1-hydroxyethyl]-2-(ethoxymethyl)phenol; also known as▲ (IRA 1-Nov-2022) α-{[(1,1-Dimethylethyl)amino]methyl}-3-(ethoxymethyl)-4-hydroxy-benzenemethanol.

[d] ▲1-[4-(Benzyloxy)-3-(hydroxymethyl)phenyl]-2-(*tert*-butylamino)ethan-1-ol▲ (IRA 1-Nov-2022) .

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Suitability requirements

Resolution: NLT 4.9 between levalbuterol and levalbuterol related compound A; NLT 1.5 between ▲albuterol related compound A▲ (IRA 1-Nov-2022) and levalbuterol related compound C, *System suitability solution*

Tailing factor: NMT 4.0 for the levalbuterol peak, *System suitability solution*

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

Analysis

Sample: *Sample solution*

Calculate the percentage of each ▲degradation product▲ (IRA 1-Nov-2022) in the portion of Inhalation Solution taken:

$$\text{Result} = (r_U/r_T) \times (1/F) \times 100$$

r_U = peak response of each ▲degradation product▲ (IRA 1-Nov-2022) from the *Sample solution*

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

F = relative response factor for each ▲degradation product▲ (IRA 1-Nov-2022) (see *Table 4*)

Acceptance criteria: See *Table 4*. The reporting threshold is 0.05%.

Table 4

Name	Relative Response Factor	Acceptance Criteria, NMT (%)
5-Hydroxyalbuterol▲▲ (IRA 1-Nov-2022)	1.0	0.10
▲▲ (IRA 1-Nov-2022)	▲▲ (IRA 1-Nov-2022)	▲▲ (IRA 1-Nov-2022)
▲▲ (IRA 1-Nov-2022)	▲▲ (IRA 1-Nov-2022)	▲▲ (IRA 1-Nov-2022)
▲▲ (IRA 1-Nov-2022)	▲▲ (IRA 1-Nov-2022)	▲▲ (IRA 1-Nov-2022)
▲▲ (IRA 1-Nov-2022)	▲▲ (IRA 1-Nov-2022)	▲▲ (IRA 1-Nov-2022)
▲▲ (IRA 1-Nov-2022)	▲▲ (IRA 1-Nov-2022)	▲▲ (IRA 1-Nov-2022)
Levalbuterol related compound D	3.0	0.08
▲▲ (IRA 1-Nov-2022)	▲▲ (IRA 1-Nov-2022)	▲▲ (IRA 1-Nov-2022)
▲▲ (IRA 1-Nov-2022)	▲▲ (IRA 1-Nov-2022)	▲▲ (IRA 1-Nov-2022)
▲Any unspecified degradation product▲ (IRA 1-Nov-2022)	▲1.0▲ (IRA 1-Nov-2022)	0.10
▲Total degradation products▲ (IRA 1-Nov-2022)	—	0.70

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SPECIFIC TESTS

- **Sterility Tests ⟨71⟩**: Meets the requirements
- **pH ⟨791⟩**: 3.3–4.5
- **Particulate Matter in Injections ⟨788⟩**: See *Table 5*.

Table 5

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Particle Size (µm)	Limit NMT (particles/container)
≥10	250
≥25	25
≥100	2
≥300	1

• **Osmolality and Osmolarity ⟨785⟩, *Osmolality*:** 280–320 mOsmol/kg

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in low-density polyethylene single-use ampuls, with a multilayer foil overwrap. Store at controlled room temperature.

• **Labeling:** The outer label indicates that the unit-dose container should be discarded if the solution is not colorless.

Change to read:

• **USP Reference Standards ⟨11⟩**

USP Albuterol RS

▲ USP Albuterol Related Compound A RS

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

$(C_{13}H_{21}NO_2)_2 \cdot H_2SO_4$ 544.70▲ (IRA 1-Nov-2022)

USP Levalbuterol Hydrochloride RS

USP Levalbuterol Related Compound A RS

▲4-[2-(*tert*-Butylamino)ethyl]-2-(hydroxymethyl)phenol; Also known as▲ (IRA 1-Nov-2022) 4-(2-*tert*-Butylamino-ethyl)-2-hydroxymethyl-phenol.

$C_{13}H_{21}NO_2$ ▲223.32▲ (IRA 1-Nov-2022)

USP Levalbuterol Related Compound C RS

▲4-[2-(*tert*-Butylamino)-1-hydroxyethyl]-2-(methoxymethyl)phenol; Also known as▲ (IRA 1-Nov-2022) α-{[(1,1-Dimethylethyl)amino]methyl}-4-hydroxy-3-(methoxymethyl)-benzenemethanol.

$C_{14}H_{23}NO_3$ 253.34

USP Levalbuterol Related Compound D RS

5-[2-(*tert*-Butylamino)-1-hydroxyethyl]-2-hydroxybenzaldehyde sulfate (2:1)▲▲ (IRA 1-Nov-2022) ;

Also known as 5-[2-{(1,1-Dimethylethyl)amino}-1-hydroxyethyl]-2-hydroxy-benzaldehyde sulfate(2:1).

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

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

Topic/Question	Contact	Expert Committee
LEVALBUTEROL INHALATION SOLUTION	Documentary Standards Support	SM52020 Small Molecules 5

Chromatographic Database Information: Chromatographic Database

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