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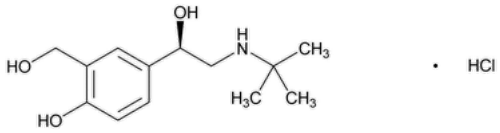
Levalbuterol Hydrochloride

Change to read:



$C_{13}H_{21}NO_3 \cdot HCl$ 275.77

▲Phenol, 4-[2-(*tert*-butylamino)-1-hydroxyethyl]-2-(hydroxymethyl), hydrochloride, (*R*)-;
(*R*)-α-[(*tert*-Butylamino)methyl]-4-hydroxy-*m*-xylene-α,α'-diol hydrochloride;▲ (IRA 1-Nov-2022)
(*R*)-α[1]-[(*tert*-Butylamino)methyl]-4-hydroxy-*m*-xylene-α,α'-diol hydrochloride CAS RN®: 50293-90-8; ▲UNII: WDQ1526QJM.▲ (IRA 1-Nov-2022)

DEFINITION

Levalbuterol Hydrochloride contains NLT 98.0% and NMT 102.0% of levalbuterol hydrochloride ($C_{13}H_{21}NO_3 \cdot HCl$), calculated on the anhydrous basis.

IDENTIFICATION

• **A. Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 197K

Change to read:

• **B.** The retention time of the major peak of the ▲*Identification sample solution*▲ (IRA 1-Nov-2022) corresponds to that of the levalbuterol peak of the *System suitability solution*, as obtained in the test for *Limit of S-Albuterol*.

ASSAY

Change to read:

• **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: *Solution A*

Standard solution: 100 µg/mL of USP Levalbuterol Hydrochloride RS in *Diluent*

Sample solution: 100 µg/mL of Levalbuterol Hydrochloride 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: 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 0.73%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of levalbuterol hydrochloride ($C_{13}H_{21}NO_3 \cdot HCl$) in the portion of Levalbuterol Hydrochloride taken:

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

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

r_S = peak response ▲of levalbuterol▲ (IRA 1-Nov-2022) from the *Standard solution*

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

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

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

IMPURITIES

• **Residue on Ignition ⟨281⟩:** NMT 0.1%

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: *Mobile phase*

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: 0.8 mg/mL of Levalbuterol Hydrochloride in *Diluent*

▲**Identification sample solution:**▲ (IRA 1-Nov-2022) 0.1 mg/mL ▲of Levalbuterol Hydrochloride▲ (IRA 1-Nov-2022) from the *Sample solution* ▲in *Diluent*▲ (IRA 1-Nov-2022)

Chromatographic system

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

Mode: LC

Detector: UV 225 nm

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

Flow rate: 1 mL/min

Injection volume: 10 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 2.0 between levalbuterol and (*S*)-albuterol

Tailing factor: NMT 2.2 for levalbuterol and (*S*)-albuterol

Analysis

Sample: *Sample solution*▲▲ (IRA 1-Nov-2022)

Calculate the percentage of (*S*)-albuterol in the portion of Levalbuterol Hydrochloride 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 for levalbuterol and (*S*)-albuterol from the *Sample solution*

Acceptance criteria: NMT 0.2% of (*S*)-albuterol

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
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: 0.03 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
Levalbuterol	1.0
Levalbuterol related compound A	1.2
Levalbuterol related compound H[a]	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[b]	2.1
Levalbuterol related compound F[c]	3.5

[a] 4-[2-(*tert*-Butylamino)-1-methoxyethyl]-2-(hydroxymethyl)phenol ▲▲ (IRA 1-Nov-2022) .

[b] ▲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.

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

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 levalbuterol, *System suitability solution*

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

Analysis

Sample: *Sample solution*

Calculate the percentage of each impurity in the portion of Levalbuterol Hydrochloride taken:

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

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

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

F = relative response factor for each impurity (see Table 4)

Acceptance criteria: See Table 4. The reporting threshold is 0.03%.

Table 4

Name	Relative Response Factor	Acceptance Criteria, NMT (%)
▲▲ (IRA 1-Nov-2022)	▲▲ (IRA 1-Nov-2022)	▲▲ (IRA 1-Nov-2022)
Levalbuterol related compound A	1.0	0.1
Levalbuterol related compound H▲▲ (IRA 1-Nov-2022)	1.0	0.15
▲Albuterol related compound A▲ (IRA 1-Nov-2022)	1.0	0.10
Levalbuterol related compound C	1.0	0.15
Levalbuterol related compound D	3.0	0.05
Levalbuterol related compound E▲▲ (IRA 1-Nov-2022)	1.0	0.1
Levalbuterol related compound F▲▲ (IRA 1-Nov-2022)	1.2	0.10
Any ▲▲ (IRA 1-Nov-2022) unspecified impurity	▲1.0▲ (IRA 1-Nov-2022)	0.10
Total impurities	—	0.5

SPECIFIC TESTS

- **pH** ⟨791⟩

Sample solution: 10 mg/mL of Levalbuterol Hydrochloride

Acceptance criteria: 4.5–5.5

- **Water Determination** ⟨921⟩, *Method I*, *Method Ic*: NMT 0.3%

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight, light-resistant containers. Store at controlled room temperature.

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 HYDROCHLORIDE	Documentary Standards Support	SM52020 Small Molecules 5

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
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