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Albuterol Tablets

DEFINITION

Albuterol Tablets contain an amount of albuterol sulfate [$(C_{13}H_{21}NO_3)_2 \cdot H_2SO_4$] equivalent to NLT 90.0% and NMT 110.0% of the labeled amount of albuterol ($C_{13}H_{21}NO_3$).

IDENTIFICATION

Change to read:

• **A.** ▲The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.▲ (USP 1-May-2023)

Change to read:

• **B.** ▲The UV spectrum of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.▲ (USP 1-May-2023)

ASSAY

Change to read:

• **Procedure**

Solution A: 10 mL/L of glacial acetic acid in water

Solution B: 1.13 g of sodium 1-hexanesulfonate in 1200 mL of water. Add 12 mL of glacial acetic acid.

Diluent: Methanol and water (40:60)

Mobile phase: Methanol and *Solution B* (40:60)

Standard stock solution: 0.12 mg/mL of USP Albuterol Sulfate RS prepared as follows. ▲Transfer a suitable amount of USP Albuterol Sulfate RS to a suitable volumetric flask. Add 60% of the flask volume of *Solution A* and sonicate for about 5 min. Dilute with methanol to volume.▲ (USP 1-May-2023)

Standard solution: 0.03 mg/mL of USP Albuterol Sulfate RS▲ (USP 1-May-2023) from *Standard stock solution*▲in *Diluent*▲ (USP 1-May-2023)

Sample solution: Nominally 0.025 mg/mL of albuterol prepared as follows. Transfer a number of whole Tablets, equivalent to 50 mg of albuterol, to a suitable volumetric flask. Add 60% of the flask volume of *Solution A*, shake by mechanical means for ▲about▲ (USP 1-May-2023) 45 min, and sonicate for ▲about▲ (USP 1-May-2023) 10 min. Allow to cool to room temperature and dilute with methanol to volume. Pass through a suitable filter of 0.45-µm or finer pore size.

Chromatographic system

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

Mode: LC

Detector: UV 276 nm. ▲For *Identification B*, use a diode array detector in the range of 200–400 nm.▲ (USP 1-May-2023)

Column: 4.6-mm × 15-cm; ▲5-µm▲ (USP 1-May-2023) packing L1

Flow rate: 1.5 mL/min

Injection volume: 25 µL

▲**Run time:** NLT 2.5 times the retention time of albuterol▲ (USP 1-May-2023)

System suitability

Sample: *Standard solution*

Suitability requirements

▲▲ (USP 1-May-2023)

Tailing factor: NMT 2.5

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

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

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

r_U = peak response ▲of albuterol▲ (USP 1-May-2023) from the *Sample solution*

r_S = peak response ▲of albuterol▲ (USP 1-May-2023) 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 = number of moles of albuterol per mole of albuterol sulfate, 2

M_{r1} = molecular weight of albuterol, 239.31

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

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

• **Dissolution ⟨711⟩** ▲▲ *(USP 1-May-2023)*

Medium: Water; 500 mL

Apparatus 2: 50 rpm

Time: 30 min

Diluent, Mobile phase, and **Standard stock solution:** Prepare as directed in the *Assay*.

Standard solution: 0.03 mg/mL of USP Albuterol Sulfate RS in *Diluent*, from *Standard stock solution*. If necessary, dilute with *Diluent* to a concentration corresponding to the *Sample solution*.

Sample solution: Pass a portion of the solution under test through a ▲suitable▲ (USP 1-May-2023) filter of 0.45-µm pore size.

Chromatographic system

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

Mode: LC

Detector: UV 276 nm

Column: 4.6-mm × 15-cm; ▲5-µm▲ (USP 1-May-2023) packing L1

Flow rate: 1.5 mL/min

Injection volume: 100 µL

▲**Run time:** NLT 2.5 times the retention time of albuterol▲ (USP 1-May-2023)

System suitability

Sample: *Standard solution*

Suitability requirements

▲▲ (USP 1-May-2023)

Tailing factor: NMT 2.5

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of albuterol ($C_{13}H_{21}NO_3$) dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times M \times (M_{r1}/M_{r2}) \times (1/L) \times 100$$

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)

V = volume of *Medium*, 500 mL

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

M_{r1} = molecular weight of albuterol, 239.31

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

L = label claim (mg/Tablet)

Tolerances: NLT 80% (Q) of the labeled amount of albuterol ($C_{13}H_{21}NO_3$) is dissolved.

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

IMPURITIES

Change to read:

• **Organic Impurities**

▲**Solution A:** 9.5 g/L of sodium borate in water. Adjust with a sodium hydroxide solution to a pH of 10.1.

Solution B: Acetonitrile

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	95	5
1	95	5
9	47	53
9.5	47	53
9.6	95	5
11	95	5

System suitability solution: 0.002 mg/mL each of USP Albuterol Related Compound B RS and USP Levalbuterol Related Compound H RS in water

Sensitivity solution: 0.001 mg/mL of USP Albuterol Sulfate RS in water

Standard solution: 0.0025 mg/mL each of USP Albuterol Sulfate RS, USP Albuterol Related Compound E RS, USP Levalbuterol Related Compound C RS, and USP Levalbuterol Related Compound D RS in water

Sample solution: Nominally 1.0 mg/mL of albuterol from Tablets prepared as follows. Transfer a number of Tablets (NLT 20) to a suitable volumetric flask and add 80% of the flask volume of water. Sonicate for 15 min. Dilute with water to volume. Pass through a suitable filter of 0.2-µm pore size.

Chromatographic system

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

Mode: LC

Detector: UV 231 nm

Column: 2.1-mm × 10-cm; 1.7-µm packing L1

Temperatures

Autosampler: 4°

Column: 30°

Flow rate: 0.37 mL/min

Injection volume: 6 µL

System suitability

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

[Note—See *Table 2* for the relative retention times.]

Suitability requirements

Resolution: NLT 1.5 between levalbuterol related compound H and albuterol related compound B, *System suitability solution*

Relative standard deviation: NMT 5.0% for albuterol, albuterol related compound E, levalbuterol related compound C, and levalbuterol related compound D, *Standard solution*

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

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of albuterol related compound E, levalbuterol related compound C, and levalbuterol related compound D in the portion of Tablets taken:

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

r_U = peak response of albuterol related compound E, levalbuterol related compound C, or levalbuterol related compound D from the *Sample solution*

r_S = peak response of albuterol related compound E, levalbuterol related compound C, or levalbuterol related compound D from the *Standard solution*

C_S = concentration of the corresponding Reference Standard in the *Standard solution* (mg/mL)

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

Calculate the percentage of any unspecified degradation product in the portion of Tablets taken:

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

r_U = peak response of each unspecified degradation product 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 = number of moles of albuterol per mole of albuterol sulfate, 2

M_{r1} = molecular weight of albuterol, 239.31

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

Acceptance criteria: See *Table 2*. The reporting threshold is 0.1%.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Albuterol	1.00	—
Levalbuterol related compound D	1.40	0.1
Albuterol related compound D[a,b]	1.45	—
Levalbuterol related compound H[a]	1.50	—
Albuterol related compound B[a]	1.53	—
Levalbuterol related compound C	1.82	0.2
Albuterol related compound C[a,c]	1.84	—
Albuterol related compound A[a,d]	1.99	—
Levalbuterol related compound E[a,e]	2.04	—
Albuterol related compound E	2.25	0.5
Levalbuterol related compound F[a,f]	3.19	—
Any unspecified degradation product	—	0.2
Total degradation products	—	3.5▲ (USP 1-May-2023)

[a] Process impurity is included in the table for identification only. Process impurities are controlled in the drug substance and are not to be reported or included in the total impurities of the drug product.

[b] 4-[2-(*tert*-Butylamino)-1-hydroxyethyl]-2-chloro-6-(hydroxymethyl)phenol.

[c] 2-(*tert*-Butylamino)-1-[3-chloro-4-hydroxy-5-(hydroxymethyl)phenyl]ethanone.

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

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

[f] (*R*)-1-[4-(Benzyloxy)-3-(hydroxymethyl)phenyl]-2-(*tert*-butylamino)ethan-1-ol; also known as α-{[(1,1-Dimethylethyl)amino]methyl}-4-(phenylmethoxy)-1,3-benzenedimethanol.

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 Sulfate RS

▲USP Albuterol Related Compound B RS

2-(*tert*-Butylamino)-1-[4-hydroxy-3-(hydroxymethyl)phenyl]ethanone.

$C_{13}H_{19}NO_3$ 237.29

USP Albuterol Related Compound E RS

2,2'-Oxybis(methylene)bis{4-[2-(*tert*-butylamino)-1-hydroxyethyl]phenol}diacetate.

$C_{26}H_{40}N_2O_5 \cdot 2(C_2H_4O_2)$ 580.72

USP Levalbuterol Related Compound C RS

4-[2-(*tert*-Butylamino)-1-hydroxyethyl]-2-(methoxymethyl)phenol;
Also known as 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);
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

USP Levalbuterol Related Compound H RS

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

$C_{14}H_{23}NO_3 \cdot C_2H_4O_2$ 313.39▲ (USP 1-May-2023)

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

Topic/Question	Contact	Expert Committee
ALBUTEROL TABLETS	Documentary Standards Support	SM52020 Small Molecules 5
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM52020 Small Molecules 5

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