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Albuterol Extended-Release Tablets

DEFINITION

Albuterol Extended-Release Tablets contain albuterol sulfate equivalent to NLT 90.0% and NMT 110.0% of the labeled amount of albuterol ($C_{13}H_{21}NO_3$).

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*.

Change to read:

• **B.** ▲**Spectroscopic Identification Tests ⟨197⟩, *Ultraviolet-Visible Spectroscopy*: 197U**▲ (CN 1-May-2020)

Standard solution: 80 µg/mL of albuterol from USP Albuterol Sulfate RS in methanol

Sample solution: 80 µg/mL of albuterol in methanol, prepared as follows. Transfer a suitable number of Tablets to a volumetric flask, and dilute with methanol to volume. Stir for 30 min, and centrifuge.

Wavelength range: 210–350 nm

Cell path: 0.2 cm

Acceptance criteria: The *Sample solution* exhibits maxima and minima only at the same wavelengths as the *Standard solution*.

ASSAY

• **Procedure**

Buffer: 0.65 g/L of sodium 1-octane sulfonate and 21.7 g/L of ammonium acetate in water

Mobile phase: Glacial acetic acid, 2-propanol, methanol, and *Buffer* (4:3:1:92)

Diluent: 10 mL/L of triethylamine in water

Standard stock solution: 0.2 mg/mL of USP Albuterol Sulfate RS in *Diluent*

Standard solution: 0.02 mg/mL of USP Albuterol Sulfate RS in *Diluent*, from the *Standard stock solution*. Transfer an aliquot of the *Standard stock solution* to a suitable volumetric flask, and add 4% of the flask volume of methanol. Allow to cool to room temperature, and dilute with *Diluent* to volume.

Sample solution: Nominally 0.016 mg/mL of albuterol, prepared as follows. Transfer Tablets (NLT 10) to a suitable volumetric flask, add 10% of the flask volume of methanol, and sonicate for 30 min with regular swirling. Add 60% of the flask volume of *Diluent*, and sonicate for 30 min with swirling. Stir for 60 min, allow the solution to cool to room temperature, and dilute with *Diluent* to volume. Centrifuge a portion of this solution at 2500 rpm for 15 min. Transfer 10 mL of the supernatant into a 50-mL volumetric flask, add 1 mL of methanol, cool to room temperature, and dilute with *Diluent* to volume. Pass the solution though a 1-µm glass fiber or equivalent filter, and discard the first 3 mL of the filtrate.

Chromatographic system

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

Mode: LC

Detector: UV 276 nm

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

Column temperature: 30°

Flow rate: 1 mL/min

Injection volume: 40 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Column efficiency: NLT 2000 theoretical plates

Tailing factor: NMT 2.0

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 from the *Sample solution*

r_S = peak response 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 = 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

• **Dissolution** ⟨711⟩

Medium: 0.1 N hydrochloric acid; 900 mL

Apparatus 2: 50 rpm, with helix sinker

Time: 1, 2, 4, and 9 h

Buffer, Mobile phase, Chromatographic system, and **System suitability:** Proceed as directed in the *Assay*, except to use an *Injection volume* of 50 µL.

Standard stock solution: 0.2 mg/mL of albuterol, using USP Albuterol Sulfate RS, in *Medium*

Standard solution: Dilute the *Standard stock solution* with *Medium* to obtain a final concentration of (*L*/1000) mg/mL of albuterol, where *L* is the label claim in mg/Tablet of albuterol.

Sample solution: Pass a portion of the solution under test through a suitable filter.

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the concentration (C_i) of albuterol ($C_{13}H_{21}NO_3$) in the sample withdrawn from the vessel at each time point (*i*):

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

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

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

Calculate the percentage of the labeled amount of albuterol ($C_{13}H_{21}NO_3$) released at each time point (*i*):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$

$$\text{Result}_2 = \{[C_2 \times (V - V_S)] + [C_1 \times V_S]\} \times (1/L) \times 100$$

$$\text{Result}_3 = \{[C_3 \times (V - (2 \times V_S))] + [(C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

$$\text{Result}_4 = \{[C_4 \times (V - (3 \times V_S))] + [(C_3 + C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

C_i = concentration of albuterol in the portion of sample withdrawn at time point *i* (mg/mL)

V = volume of the *Medium* (900 mL)

L = label claim (mg/Tablet)

V_S = volume of the *Sample solution* withdrawn from the *Medium* (mL)

Tolerances: See *Table 1*.

Table 1

Time point (*i*)	Time (h)	Amount released (%)
1	1	25–45
2	2	45–65

Time point (*i*)	Time (h)	Amount released (%)
3	4	65–85
4	9	NLT 80

The cumulative percentages of the labeled amount of albuterol ($C_{13}H_{21}NO_3$), released at the times specified, conform to *Acceptance Table 2* in *Dissolution ⟨711⟩*.

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

IMPURITIES

- **Organic Impurities, Procedure 1**

Buffer: 6.8 g/L of monobasic potassium phosphate in water. Adjust with hydrochloric acid to a pH of 3.0.

Mobile phase: Methanol and *Buffer* (5:95)

System suitability solution: 2 µg/mL each of USP Albuterol Sulfate RS and USP Albuterol Related Compound B RS in *Mobile phase*

Standard solution: 2.4 µg/mL of USP Albuterol Sulfate RS, 0.80 µg/mL of USP Levalbuterol Related Compound C RS, and 0.25 µg/mL of USP Levalbuterol Related Compound D RS (equivalent to 0.20 µg/mL free base) in *Mobile phase*

Sensitivity solution: 0.06 µg/mL of USP Albuterol Sulfate RS in *Mobile phase*

Sample solution: Transfer an amount of powder from NLT 20 Tablets to a suitable volumetric flask to obtain a solution with a final nominal concentration of 0.2 mg/mL of albuterol. Add 70% of the flask volume of *Mobile phase*, and sonicate for 10 min. Stir for 30 min, and dilute with *Mobile phase* to volume. Pass the solution though a 1-µm glass fiber or equivalent filter, and discard the first 3 mL of the filtrate.

Chromatographic system

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

Mode: LC

Detector: UV 225 nm

Column: 4.6-mm × 25-cm; 5-µm packing L11

Column temperature: 30°

Flow rate: 1.5 mL/min

Injection volume: 80 µL

Run time: 5 times the retention time of albuterol

System suitability

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

[Note—Identify the impurities using the relative retention times shown in *Table 2*.]

Suitability requirements:

Tailing factor: NMT 2.0 for each compound, *Standard solution*

Resolution: NLT 2 between albuterol and albuterol related compound B, *System suitability solution*

Relative standard deviation: NMT 10.0% for each compound, *Standard solution*

Analysis

Samples: *Standard solution*, *Sensitivity solution*, and *Sample solution*

[Note—Identify the impurities using the relative retention times shown in *Table 2*.]

Calculate the percentage of levalbuterol related compound C in the portion of Tablets taken:

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

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

r_S = peak response of levalbuterol related compound C from the *Standard solution*

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

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

Calculate the percentage of 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 levalbuterol related compound D from the *Sample solution*

r_S = peak response of the levalbuterol related compound D from the *Standard solution*

C_S = concentration of USP Levalbuterol Related Compound D RS (as the free base) in the *Standard solution* (mg/mL)

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

Calculate the percentage of any other impurity 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 the impurity 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 = 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*. Disregard peaks eluting after levalbuterol related compound C or with areas less than that of the *Sensitivity solution*.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Albuterol related compound B[a]	0.88	—[b]
Albuterol	1.0	—
Chloroalbuterone[c]	1.7	—[b]
Chloroalbuterol[d]	2.5	—[b]
Albuterol related compound A[e]	2.7	—[b]
Levalbuterol related compound D[f]	3.2	0.1
Levalbuterol related compound C[g,h]	3.5	0.4
Any other individual unspecified impurity	—	0.2

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

[b] Process impurity 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 for the drug product.

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

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

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

[f] 5-[2-{(1,1-Dimethylethyl)amino}-1-hydroxyethyl]-2-hydroxy-benzaldehyde.

[g] α-[{(1,1-Dimethylethyl)amino}methyl]-4-hydroxy-3-(methoxymethyl)-benzenemethanol.

[h] Disregard peaks eluting after levalbuterol related compound C.

- **Organic Impurities, Procedure 2**

Buffer: 6.8 g/L of monobasic potassium phosphate in water. Adjust with hydrochloric acid to a pH of 3.0.

Mobile phase: Methanol and *Buffer* (30:70)

Diluent: Methanol and *Buffer* (5:95)

Peak identification solution: 2.4 µg/mL of USP Albuterol Sulfate RS, 1.0 µg/mL of USP Levalbuterol Related Compound C RS, and 1.2 µg/mL of USP Levalbuterol Related Compound D RS in *Diluent*

Standard solution: 2.4 µg/mL of USP Albuterol Sulfate RS and 1.0 µg/mL of USP Albuterol Related Compound E RS in *Diluent*

Sensitivity solution: 0.06 µg/mL of USP Albuterol Sulfate RS in *Diluent* from *Standard solution*

Sample solution: Transfer an amount of powder from NLT 20 Tablets to a suitable volumetric flask to obtain a solution with a final concentration of 0.2 mg/mL of albuterol. Add 70% of the flask volume of *Diluent*, and sonicate for 10 min. Stir for 30 min, and dilute with *Diluent* to volume. Pass the solution though a glass fiber or equivalent filter of 1-µm pore size, and discard the first 3 mL of the filtrate.

Chromatographic system

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

Mode: LC

Detector: UV 225 nm

Column: 4.6-mm × 25-cm; 5-µm packing L11

Flow rate: 0.7 mL/min

Injection volume: 80 µL

Run time: 5 times the retention time of albuterol

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0 for each compound

Relative standard deviation: NMT 10.0% for each compound

Analysis

Samples: *Standard solution*, *Peak identification solution*, *Sensitivity solution*, and *Sample solution*

Calculate the percentage of albuterol related compound E 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 from the *Sample solution*

r_S = peak response of albuterol related compound E from the *Standard solution*

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

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

Calculate the percentage of any other impurity 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 the impurity 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 = 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 3*. Disregard the levalbuterol related compound C peak and any peak eluting before it. Disregard peaks with areas less than that of the *Sensitivity solution*.

Table 3

Compound	Relative Retention Time	Acceptance Criteria, NMT (%)
Albuterol	1.0	—
Levalbuterol related compound C	1.79	—
Levalbuterol related compound D	1.83	—
Albuterol related compound E[a]	3.67	0.5
Any other individual unspecified impurity	—	0.2

Compound	Relative Retention Time	Acceptance Criteria, NMT (%)
Total impurities	—	1.5[b]

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

[b] From the sum of the impurities in *Procedure 1* and *Procedure 2*.

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight, light-resistant containers. Store at controlled room temperature.
- **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}.
$C_{26}H_{40}N_2O_5$ 460.61

USP Levalbuterol Related Compound C RS
α-[{(1,1-Dimethylethyl)amino}methyl]-4-hydroxy-3-(methoxymethyl)-benzenemethanol.
$C_{14}H_{23}N0_3$ 253.34

USP Levalbuterol Related Compound D RS
5-[2-{(1,1-Dimethylethyl)amino}-1-hydroxyethyl]-2-hydroxy-benzaldehyde sulfate salt.
$(C_{13}H_{19}NO_3)_2 \cdot H_2SO_4$ 572.67

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

Topic/Question	Contact	Expert Committee
ALBUTEROL EXTENDED-RELEASE 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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