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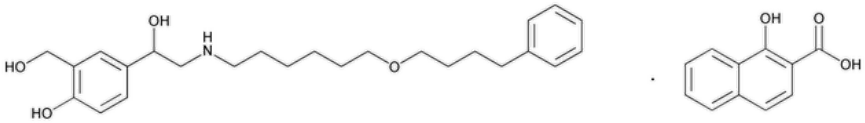
Salmeterol Xinafoate



$C_{25}H_{37}NO_4 \cdot C_{11}H_8O_3$ 603.75

1,3-Benzenedimethanol, 4-hydroxy-α^1-[[[6-(4-phenylbut oxy)hexyl]amino]methyl]-, (±)-, 1-hydroxy-2-naphthalenecarboxylate (salt); (±)-4-Hydroxy-α^1-[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-*m*-xylene-α,α'-diol 1-hydroxy-2-naphthoate (salt) CAS RN®: 94749-08-3; UNII: 6EW8Q962A5.

DEFINITION

Salmeterol Xinafoate contains NLT 98.0% and NMT 102.0% of salmeterol xinafoate ($C_{25}H_{37}NO_4 \cdot C_{11}H_8O_3$), calculated on the water- and solvent-free basis.

IDENTIFICATION

Change to read:

• **A.** ▲**Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 197A, 197K, or 197M▲ (CN 1-May-2020)

• **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

• **Procedure**

[Note—It is recommended that solutions containing salmeterol be protected from light.]

Buffer A: 0.1 M sodium dodecyl sulfate

Buffer B: 0.1 M ammonium acetate

Mobile phase: Acetonitrile, *Buffer A*, and *Buffer B* (52:24:24). Adjust with glacial acetic acid to a pH of 3.8. [Note—This may need as much as 75 mL of glacial acetic acid for each liter.]

System suitability solution: 0.25 mg/mL of USP Salmeterol Xinafoate RS and 0.02 mg/mL of USP Salmeterol Related Compound B RS in *Mobile phase*

Standard solution: 0.25 mg/mL of USP Salmeterol Xinafoate RS in *Mobile phase*

Sample solution: 0.25 mg/mL of Salmeterol Xinafoate in *Mobile phase*

Chromatographic system

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

Mode: LC

Detector: UV 278 nm

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

Flow rate: 2 mL/min

Injection volume: 20 µL

System suitability

Sample: *System suitability solution*

[Note—The relative retention times for salmeterol related compound B and salmeterol are about 0.9 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 1.0 between salmeterol and salmeterol related compound B

Relative standard deviation: NMT 1.0% for salmeterol

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of salmeterol xinafoate ($C_{25}H_{37}NO_4 \cdot C_{11}H_8O_3$) in the portion of Salmeterol Xinafoate taken:

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

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

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

C_U = concentration of Salmeterol Xinafoate in the *Sample solution* (mg/mL)

Acceptance criteria: 98.0%–102.0% on the water- and solvent-free basis

IMPURITIES

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

• **Organic Impurities**

[Note—It is recommended that solutions containing salmeterol be protected from light.]

Buffer A, Buffer B, and **Chromatographic system:** Proceed as directed in the *Assay*.

Diluent: Acetonitrile and water (50:50)

Solution A: Acetonitrile, *Buffer A*, and *Buffer B* (52:24:24). Adjust with glacial acetic acid to a pH of 3.8.

Solution B: Acetonitrile

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	100	0
16.0	100	0
36.0	30	70
45.0	30	70
45.1	100	0
50[a]	100[a]	0[a]

[a] The required equilibration time may be modified to achieve a stable baseline.

System suitability solution: 5.0 mg/mL of USP Salmeterol Xinafoate RS and 0.3 mg/mL each of USP Salmeterol Related Compound A RS and USP Salmeterol Related Compound B RS in *Diluent*

Sample solution: 5.0 mg/mL of Salmeterol Xinafoate in *Diluent*

System suitability

Sample: *System suitability solution*

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

Suitability requirements

Resolution: NLT 1.0 between salmeterol and salmeterol related compound B

Tailing factor: NMT 2.5 for salmeterol

Analysis

[Note—Disregard the peak due to hydroxynaphthoic acid and any peaks from blank injections.]

Sample: *Sample solution*

Calculate the percentage of any individual impurity in the portion of Salmeterol Xinafoate taken:

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

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

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

Acceptance criteria: See *Table 2*. [NOTE—Calculate the total impurities from the sum of all impurity peaks greater than or equal to 0.05%.]

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Hydroxynaphthoic acid[a]	0.2	—
Salmeterol related compound A	0.3	0.2
Salmeterol-phenylethoxy[b]	0.5	0.1
Salmeterol-phenylpropoxy[c]	0.7	0.1
Salmeterol-*O*-alkyl[d]	0.8	0.3
Salmeterol related compound B	0.9	0.1
Salmeterol	1.0	—
Salmeterol-deoxy[e]	1.6	0.2
Salmeterol-*N*-alkyl[f]	2.7	0.2
Any unspecified impurity	—	0.10
Total impurities	—	0.9

[a] 1-Hydroxy-naphthalene-2-carboxylic acid. This is the counter ion of salmeterol and is included for identification only.

[b] 4-[1-Hydroxy-2-(6-phenethoxyhexylamino)ethyl]-2-(hydroxymethyl)phenol.

[c] 4-{1-Hydroxy-2-[6-(3-phenylpropoxy)hexylamino]ethyl}-2-(hydroxymethyl)phenol.

[d] 4-{1-Hydroxy-2-[4-{1-hydroxy-2-[6-(4-phenylbutoxy)hexylamino]ethyl}-2-(hydroxymethyl)phenoxy]ethyl}-2-(hydroxymethyl)phenol.

[e] 4-{1-Hydroxy-2-[6-(4-phenylbutoxy)hexylamino]ethyl}-2-methylphenol.

[f] 4-{1-Hydroxy-2-[(2-hydroxy-5-{1-hydroxy-2-[6-(4-phenylbutoxy)hexylamino]ethyl}benzyl)[6-(4-phenylbutoxy)hexyl]amino]ethyl}-2-(hydroxymethyl)phenol.

SPECIFIC TESTS

• **WATER DETERMINATION ⟨921⟩, *Method I***

Sample: 0.5 g

Acceptance criteria: NMT 0.25%

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in tight containers. Store at a temperature not exceeding 30°.

• **USP REFERENCE STANDARDS ⟨11⟩**

USP Salmeterol Xinafoate RS

USP Salmeterol Related Compound A RS

4-[1-Hydroxy-2-(4-phenylbutylamino)ethyl]-2-(hydroxymethyl)phenol.

$C_{19}H_{25}NO_3$ 315.41

USP Salmeterol Related Compound B RS

4-{1-Hydroxy-2-[6-(4-phenylbutan-2-yloxy)hexylamino]ethyl}-2-(hydroxymethyl)phenol.

$C_{25}H_{37}NO_4$ 415.57

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

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

Chromatographic Database Information: Chromatographic Database

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