

Packaging and storage—Preserve in collapsible tubes or in tight containers, preferably at controlled room temperature.

Identification—Filter 5 mL of the solution obtained by titration in the *Assay*. Add 1 mL of ferric chloride TS to the filtrate: a violet color is produced. Add 1 mL of 6 N acetic acid: the violet color does not change. Add 1 mL of 6 N hydrochloric acid: the violet color is discharged. A small amount of white precipitate may appear.

Alcohol content (if present) (611): from 90.0% to 110.0% of the labeled amount of C₂H₅OH.

Assay—To 25 mL of diluted alcohol add 1 drop of phenolphthalein TS and sufficient 0.1 N sodium hydroxide to produce a faint pink color. Add 5.0 g of Gel, accurately weighed, and stir. Titrate the dispersion with 0.1 N sodium hydroxide VS until a pink color is produced. [NOTE—Reserve this solution for the *Identification* test.] Each mL of 0.1 N sodium hydroxide is equivalent to 13.81 mg of C₇H₆O₃.

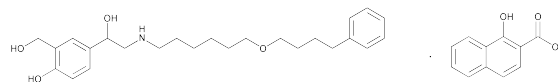
Salicylic Acid Plaster

» Salicylic Acid Plaster is a uniform mixture of Salicylic Acid in a suitable base, spread on paper, cotton cloth, or other suitable backing material. The plaster mass contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of C₇H₆O₃.

Packaging and storage—Preserve in well-closed containers, preferably at controlled room temperature.

Assay—Weigh accurately an amount of Plaster, corresponding to about 500 mg of salicylic acid, cut the portion into small strips, place them in a small flask, add 50 mL of chloroform, and shake the mixture until the plaster mass is disintegrated. Decant the chloroform extract into a 250-mL beaker, and wash the plaster backing with two 25-mL portions of chloroform, receiving the washings in the same beaker. Then wash the backing with 50 mL of alcohol to which has been added 1 mL of 6 N ammonium hydroxide, and add the washing to the chloroform extract. Again wash the backing with 40 mL of alcohol, and add the washing to the chloroform extract. Dry the backing, weigh, and subtract the weight from the weight of Plaster taken for the assay to obtain the weight of plaster mass. Stir the chloroform extract until any coagulum has separated into a compact mass, and filter the extract through purified cotton into a separator. Knead the coagulum, if any, with a glass rod to expel the solvent, and rinse the coagulum and the beaker with 10 mL of alcohol. Pour the rinsing through the cotton, then press the cotton with a glass rod to expel the solvent. Extract the filtrate with three 10-mL portions of 1 N sodium hydroxide, drawing off each portion into a 500-mL volumetric flask, and finally wash with two 25-mL portions of water, receiving the washings in the same flask. Dilute with water to volume, and pipet a 25-mL aliquot into a 500-mL iodine flask. Add 30.0 mL of 0.1 N bromine VS, then add 5 mL of hydrochloric acid, and immediately insert the stopper. Shake the flask repeatedly during 30 minutes, allow it to stand for 15 minutes, add quickly 5 mL of potassium iodide solution (1 in 5), taking precautions against the escape of bromine vapor, and at once insert the stopper in the flask. Shake thoroughly, remove the stopper, and rinse it and the neck of the flask with a small quantity of water, so that the washing flows into the flask. Add 1 mL of chloroform, shake the mixture, and titrate the liberated iodine with 0.1 N sodium thiosulfate VS, adding 3 mL of starch TS as the endpoint is approached. Perform a blank determination (see *Residual Titrations* under *Titrimetry* (541)). Each mL of 0.1 N bromine is equivalent to 2.302 mg of C₇H₆O₃.

Salmeterol Xinafoate



C₂₅H₃₇NO₄ · C₁₁H₈O₃ 603.75
 1,3-Benzenedimethanol, 4-hydroxy- α -[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-, (\pm)-, 1-hydroxy-2-naphthalene-carboxylate (salt);
 (\pm)-4-Hydroxy- α -[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-*m*-xylene- α , α' -diol 1-hydroxy-2-naphthoate (salt) [94749-08-3].

DEFINITION

Salmeterol Xinafoate contains NLT 98.0% and NMT 102.0% of C₂₅H₃₇NO₄ · C₁₁H₈O₃, calculated on the water- and solvent-free basis.

IDENTIFICATION

- **A. INFRARED ABSORPTION** (197M)
- **B.** The retention time of the major peak from the *Sample solution* corresponds to that from the *Standard solution*, as obtained in the *Assay*.

ASSAY

- **PROCEDURE**
Solution A: 0.1 M sodium dodecyl sulfate
Solution B: 0.1 M ammonium acetate
Mobile phase: Acetonitrile, *Solution A*, and *Solution B* (13:6:6). Adjust with glacial acetic acid to a pH of 3.8.
System suitability solution: 0.25 mg/mL of USP Salmeterol Xinafoate RS and 0.017 mg/mL of USP Salmeterol Related Compound B RS in *Mobile phase*, prepared by diluting *System suitability solution 1* in the test for *Organic Impurities*
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 \times 15-cm; packing L1
Flow rate: 2 mL/min
Injection size: 20 μ L
System suitability
Sample: *System suitability solution*
Suitability requirements
Resolution: NLT 1.0 between salmeterol and salmeterol related compound B
Relative standard deviation: NMT 2.0% for salmeterol

Analysis

Samples: *Standard solution* and *Sample solution*
 Calculate the percentage of C₂₅H₃₇NO₄ · C₁₁H₈O₃ 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**Inorganic Impurities**

- **RESIDUE ON IGNITION (281):** NMT 0.1%

Organic Impurities• **PROCEDURE**

[NOTE—Use freshly prepared test solutions, and protect from light.]

Solution A, Solution B, and Chromatographic system:

Proceed as directed in the Assay.

Diluent: Acetonitrile and water (1:1)

Solution C: Acetonitrile, *Solution A*, and *Solution B* (13:6:6). Adjust with glacial acetic acid to a pH of 3.8.

Solution D: Acetonitrile

Mobile phase: See the gradient table below.

| Time (min) | Solution C (%) | Solution D (%) |
|-------------------|----------------|----------------|
| 0 | 100 | 0 |
| 16.0 | 100 | 0 |
| 36.0 | 30 | 70 |
| 45.0 | 30 | 70 |
| 45.1 ^a | 100 | 0 |

^a Prior to the next injection, run the system at the initial condition until equilibration is achieved.

System suitability solution 1: 5.0 mg/mL of USP

Salmeterol Xinafoate RS and 0.34 mg/mL of USP

Salmeterol Related Compound B RS in *Diluent*

System suitability solution 2: 1.0 mg/mL of USP

Salmeterol Related Compound A RS in *Diluent*

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

System suitability

Samples: *System suitability solution 1* and *System suitability solution 2*

Suitability requirements

Resolution: NLT 1.0 between salmeterol and salmeterol related compound B, *System suitability solution 1*

Tailing factor: NMT 2.5 for salmeterol, *System suitability solution 1*

Relative standard deviation: NMT 2.0% for the salmeterol related compound A peak, *System suitability solution 2*

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 peak responses from the *Sample solution*

Acceptance criteria

Individual impurities: See *Impurity Table 1*.

Total impurities: NMT 0.9% area. [NOTE—Calculate the total impurities from the sum of all impurity peaks greater than or equal to 0.05%.]

Impurity Table 1

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

^a 1-Hydroxy-naphthalene-2-carboxylic acid.

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

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

^d 4-[1-Hydroxy-2-[6-(3-phenylpropoxy)hexylamino]ethyl]-2-(hydroxymethyl)phenol.

^e 4-[1-Hydroxy-2-[4-(1-hydroxy-2-[6-(4-phenylbutoxy)hexylamino]ethyl)-2-(hydroxymethyl)phenoxy]ethyl]-2-(hydroxymethyl)phenol.

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

^g 4-[1-Hydroxy-2-[6-(4-phenylbutoxy)hexylamino]ethyl]-2-methylphenol.

^h 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, Method I (921):** NMT 0.25%

Sample: 0.5 g

- **OPTICAL ROTATION, Specific Rotation (781S):** -0.5° to $+0.5^\circ$ ($t = 20^\circ$), calculated on the anhydrous and solvent-free basis

Sample solution: 10 mg/mL in methanol

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers, and store at a temperature not exceeding 30° .
- **LABELING:** Salmeterol Xinafoate in the form of microcrystals is so labeled.

• **USP REFERENCE STANDARDS (11)**

USP Salmeterol Xinafoate RS

USP Salmeterol Related Compound A RS

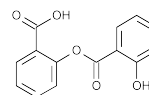
(4-[1-Hydroxy-2-(4-phenylbutylamino)ethyl]-2-(hydroxymethyl)phenol).

C₁₉H₂₅NO₃ 315.41

USP Salmeterol Related Compound B RS

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

C₂₅H₃₇NO₄ 415.57

Salsalate

C₁₄H₁₀O₅ 258.23

Benzoic acid, 2-hydroxy-, 2-carboxyphenyl ester.

Disalicylic acid.

Salicylsalicylic acid.

Salicylic acid, bimolecular ester [552-94-3].