Status: Currently Official on 17-Feb-2025
Official Date: Official as of 01-Sep-2022
Document Type: USP Monographs
DocId: GUID-2E4D271E-08DF-418D-88BC-D15214726312_7_en-US
DOI: https://doi.org/10.31003/USPNF_M3467_07_01
DOI Ref: 90zao

Fluticasone Propionate and Salmeterol Inhalation Powder

DEFINITION

Fluticasone Propionate and Salmeterol Inhalation Powder is a mixture of fluticasone propionate and salmeterol xinafoate for use in dry powder inhalers. The Inhalation Powder contains NLT 90% and NMT 110% of the labeled amount of fluticasone propionate ($C_{25}H_{31}F_3O_5S$) and NLT 90% and NMT 110% of the labeled amount of salmeterol ($C_{25}H_{37}NO_4$) as salmeterol xinafoate.

IDENTIFICATION

• **A. Spectroscopic Identification Tests ⟨197⟩, *Ultraviolet-Visible Spectroscopy*:** 197U

Diluent: Methanol and water (70:30)

Standard solution: A mixture of USP Fluticasone Propionate RS and USP Salmeterol Xinafoate RS according to the individual product strengths in the Inhalation Powder under test in *Diluent*

Sample solution: Dissolve a suitable number of unit doses of the Inhalation Powder under test in a suitable volume of *Diluent*.

Acceptance criteria: Meets the requirements

Change to read:

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

(IRA 1-Sep-2022)

ASSAY

Change to read:

• Procedure

Buffer: To each liter of 2.9 g/L of sodium dodecyl sulfate in water, add 1 mL of glacial acetic acid.

Solution A: Methanol and *Buffer* (20:80)

Mobile phase: Acetonitrile and *Solution A* (50:50)

Diluent: Methanol and water (70:30)

Standard solution: 10 µg/mL of USP Fluticasone Propionate RS and 3 µg/mL of USP Salmeterol Xinafoate RS in *Diluent*

Sample solution: Nominally 5–25 µg/mL of fluticasone propionate and 2.4 µg/mL of salmeterol from NLT 12 unit doses in *Diluent*

Chromatographic system

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

Mode: LC

Detectors

Fluticasone propionate: UV 239 nm

Salmeterol: Fluorescence with excitation at 225 nm and emission at 305 nm. Use emission response for quantification.

Column: 4.6-mm × 5-cm; 3.5-µm packing L1

Column temperature: 40°

Flow rate: 2 mL/min

Injection volume: 10 µL

Run time: NLT 1.5 times the retention time of salmeterol

System suitability

Sample: *Standard solution*

[Note—The relative retention times for fluticasone propionate and salmeterol are 0.6 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 3.5 between salmeterol and fluticasone propionate

Tailing factor: NMT 1.5 for salmeterol and fluticasone propionate

Relative standard deviation: NMT 2.0% for salmeterol and fluticasone propionate

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of fluticasone propionate ($C_{25}H_{31}F_3O_5S$) in the portion of Inhalation Powder taken:

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

r_U = peak response of fluticasone propionate from the *Sample solution*

r_S = peak response of fluticasone propionate from the *Standard solution*

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

C_U = nominal concentration of fluticasone propionate in the *Sample solution* (µg/mL)

Calculate the percentage of the labeled amount of salmeterol ($C_{25}H_{37}NO_4$) in the portion of ▲Inhalation Powder▲ (IRA 1-Sep-2022) taken:

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

r_U = peak response of salmeterol from the *Sample solution*

r_S = peak response of salmeterol from the *Standard solution*

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

C_U = nominal concentration of salmeterol free base in the *Sample solution* (µg/mL)

M_{r1} = molecular weight of salmeterol free base, 415.57

M_{r2} = molecular weight of salmeterol xinafoate, 603.75

Acceptance criteria: 90%–110% each for fluticasone propionate and salmeterol

Delete the following:

▲PERFORMANCE TESTS▲ (IRA 1-Sep-2022)

IMPURITIES

Change to read:

• **ORGANIC IMPURITIES**

[NOTE—Protect all solutions containing fluticasone propionate or salmeterol from light.]

Solution A: 5.7 g/L of monobasic ammonium phosphate in water adjusted with 10% phosphoric acid TS to a pH of 2.9

Solution B: Acetonitrile

Mobile phase: See ▲*Table 1*.

Table 1▲ (IRA 1-Sep-2022)

Time (min)	Solution A (%)	Solution B (%)
0	70	30
60	22	78
61	70	30
70	70	30

Diluent: Methanol, water, and phosphoric acid (70: 30: 0.05)

Acidified methanol: To each liter of methanol, add 0.5 mL of phosphoric acid.

System suitability solution: 0.15 mg/mL of USP Salmeterol Xinafoate RS, 0.05 mg/mL of USP Fluticasone Propionate RS, and 0.4 µg/mL each of USP Fluticasone Propionate Related Compound D RS and USP Fluticasone Propionate Related Compound J RS in *Diluent*

Standard solution: 2 µg/mL of USP Salmeterol Related Compound H RS and 4 µg/mL of USP Fluticasone Propionate RS in *Diluent*

Sensitivity solution: 0.05 µg/mL of USP Salmeterol Related Compound H RS and 0.1 µg/mL of USP Fluticasone Propionate RS from the *Standard solution* in *Diluent*

Sample solution: Nominally 200–500 µg/mL of fluticasone propionate prepared as follows. Transfer the contents of NLT 10 unit doses to a 10-mL volumetric flask. Add 6 mL of acidified methanol and sonicate for 10 min. Add 3 mL of water, mix, and allow the solution to equilibrate. Dilute with acidified methanol to volume.

Chromatographic system

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

Mode: LC

Detector: UV 228 nm

Column: 4.6-mm × 25-cm; 5-µm packing L1

Column temperature: 35°

Flow rate: 1 mL/min

Injection volume: 50 µL

System suitability

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

[NOTE—See ▲*Table 2*▲ (IRA 1-Sep-2022) for the relative retention times.]

Suitability requirements

Resolution: NLT 1.5 between fluticasone propionate related compound J and salmeterol; NLT 1.5 between fluticasone propionate related compound D and fluticasone propionate, *System suitability solution*

Tailing factor: NMT 2.0 for salmeterol related compound H and fluticasone propionate, *Standard solution*

Relative standard deviation: NMT 5.0% for salmeterol related compound H and fluticasone propionate, *Standard solution*

Signal-to-noise ratio: NLT 10 for both fluticasone propionate and salmeterol related compound H, *Sensitivity solution*

Analysis

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

Calculate the percentage of each fluticasone propionate related degradation product in the portion of Inhalation Powder taken:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times (W_N/W_U) \times (1/L) \times 100$$

r_U = peak response of each fluticasone propionate related degradation product from the *Sample solution*

r_S = peak response of fluticasone propionate from the *Standard solution*

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

V = volume of the *Sample solution* (mL)

W_N = nominal weight of each unit dose (mg)

W_U = weight of the unit doses in the *Sample solution* (mg)

L = label claim of fluticasone propionate (µg/unit dose)

Disregard any fluticasone propionate related degradation product peak less than the area of fluticasone propionate in the *Sensitivity solution*.

Calculate the percentage of each salmeterol related degradation product in the portion of Inhalation Powder taken:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times (W_N/W_U) \times (1/L) \times 100$$

r_U = ▲peak▲ (IRA 1-Sep-2022) response of each salmeterol related degradation product from the *Sample solution*

r_S = ▲peak▲ (IRA 1-Sep-2022) response of salmeterol related compound H from the *Standard solution*

C_S = concentration of USP Salmeterol Related Compound H RS in the *Standard solution* (µg/mL)

V = volume of the *Sample solution* (mL)

W_N = nominal weight of each unit dose (mg)

W_U = weight of the unit doses in the *Sample solution* (mg)

L = label claim of salmeterol free base (µg/unit dose)

Acceptance criteria: See ▲*Table 2*.▲ (IRA 1-Sep-2022) Disregard any salmeterol related degradation product peak less than the area of salmeterol related compound H in the *Sensitivity solution*. [NOTE—Any unspecified degradation product eluting before salmeterol is related to salmeterol. Any unspecified degradation product eluting after salmeterol is related to fluticasone propionate.]

▲Table 2▲ (IRA 1-Sep-2022)

Name	Relative Retention Time	Acceptance Criteria, (NMT %)
Salmeterol-*N*-phenylbutyl aminoalcohol[a,b]	0.14	—
Salmeterol-phenylethoxy[a,c]	0.25	—
Salmeterol-phenylpropoxy[a,d]	0.32	—

Name	Relative Retention Time	Acceptance Criteria, (NMT %)
Salmeterol-phenyl-2-butoxy [a,e]	0.37	—
Fluticasone propionate related compound J[a]	0.38	—
Salmeterol[a]	0.41	N/A
Hydroxynapthoic acid[f]	0.5	—
Salmeterol-deoxy[a,g]	0.55	—
Fluticasone propionate dithioacid[a,h]	0.67	—
Salmeterol-*N*-alkyl[i]	0.71	0.2
Salmeterol related compound H	0.74	0.9
Fluticasone propionate related compound D[a]	0.97	—
Fluticasone propionate	1.0	N/A
Fluticasone dimer[a,j]	1.09	—
Any fluticasone propionate related unspecified degradation product	—	0.1
Any salmeterol related unspecified degradation product	—	0.1
Total degradation products	—	1.3

[a] This is a process impurity that is included in this table for identification only. This impurity is controlled in the drug substance. This impurity is not to be reported for the drug product or to be included in the total degradation products.

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

[f] This is a counter ion of salmeterol that is included in this table for identification only. It is not to be reported for the drug product or to be included in the total degradation products.

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

[h] 6α,9α-Difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxyandrosta-1,4-diene-17β-carbodithioic acid.

[i] 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.

[j] 6α,9α-Difluoro-11β,17α-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carboxylic acid 6α,9α-difluoro-17β-(fluoromethylthio)carbonyl-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-yl ester.

SPECIFIC TESTS

• **Microbial Enumeration Tests ⟨61⟩** and **Tests for Specified Microorganisms ⟨62⟩:** The total aerobic microbial count does not exceed 10^1 cfu/g of powder. The total aerobic yeasts and molds count does not exceed 10^1 cfu/g of formulation. It meets the requirements of the tests for absence of *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, and *Salmonella* species.

Change to read:

• **Foreign Particulate Matter**

Particulate Matter in Injections ⟨788⟩ describes details of the test apparatus to be used for the determination of particulate matter using a microscopic particle count test methodology. Samples should be carefully prepared to avoid environmental contamination, and testing

should be performed with suitable controls, including the appropriate use of blank determinations.

Diluent: Methanol and water (65:35) passed through a filter of 0.45-µm pore size

Filter: Mixed cellulose and ester filter; 25-mm diameter and 0.45-µm pore size

Sample solution: Transfer contents of NLT 8 unit doses to a suitable container. Dissolve in 75 mL of *Diluent*.

Analysis

Sample: *Sample solution*

Pass the *Sample solution* through the filter and allow the filter to dry under conditions that will limit particulate contamination. Using a microscopic particle count test method, enumerate the number of particles present in the *Sample solution*.

Calculate the total number of particles per actuation by the formula:

$$\text{Result} = (N_{<10} + N_{10–100} + N_{>100})/8$$

$N_{<10}$ = total number of particles <10 µm present in the *Sample solution*

$N_{10–100}$ = total number of particles between 10 and 100 µm present in the *Sample solution*

$N_{>100}$ = total number of particles >100 µm present in the *Sample solution*

Acceptance criteria: See ▲*Table 3*.

Table 3▲ (IRA 1-Sep-2022)

Particle Size Range (µm)	Number of Particles/Dose (NMT)
<10	200
10–100	100
>100	10
Total	300

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight, light-resistant containers. Store at controlled room temperature, in a dry place away from direct heat or sunlight.

Delete the following:

▲• **Labeling**▲ (IRA 1-Sep-2022)

• **USP Reference Standards** ⟨11⟩

USP Fluticasone Propionate RS

USP Fluticasone Propionate Related Compound D RS

S-Methyl 6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxyandrosta-1,4-diene-17β-carbothioate.

$C_{25}H_{32}F_2O_5S$ 482.58

USP Fluticasone Propionate Related Compound J RS

6α,9α-Difluoro-11β,17α-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carboxylic acid.

$C_{21}H_{26}F_2O_5$ 396.42

USP Salmeterol Related Compound H RS

1-Hydroxy-4-[2-hydroxy-5-(1-hydroxy-2-{[6-(4-phenylbutoxy)hexyl]amino}ethyl)benzyl]-2-naphthoic acid, monohydrate.

$C_{36}H_{43}NO_6 \cdot H_2O$ 603.76

USP Salmeterol Xinafoate RS

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

Topic/Question	Contact	Expert Committee
FLUTICASONE PROPIONATE AND SALMETEROL INHALATION POWDER	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

Most Recently Appeared In:
Pharmacopeial Forum: Volume No. 48(2)
Current DocID: GUID-2E4D271E-08DF-418D-88BC-D15214726312_7_en-US
DOI: https://doi.org/10.31003/USPNF_M3467_07_01
DOI ref: 90zao