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Fluticasone Propionate Inhalation Aerosol

DEFINITION

Fluticasone Propionate Inhalation Aerosol is a suspension of Fluticasone Propionate with suitable propellants in a pressurized container. The mean content per actuation contains NLT 85% and NMT 115% of the labeled amount of fluticasone propionate ($C_{25}H_{31}F_3O_5S$).

IDENTIFICATION

- **A. Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 197A

  Spectral range: 4000 cm^{-1} to 600 cm^{-1}

  Samples: Deposit between 5 and 20 actuations onto the zinc selenide plate of the HATR (Horizontal ATR) accessory. Dry the zinc selenide plate.

  Acceptance criteria: Meets the requirements

- **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

Change to read:

- **Procedure**

  Buffer: 0.01 M sodium dodecyl sulfate containing 0.1% glacial acetic acid

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

  Mobile phase: Acetonitrile and *Solution A* (1:1)

  Standard solution: 50 µg/mL of USP Fluticasone Propionate RS in acetonitrile and water (1:1)

  Sample solution: Nominally 50 µg/mL of fluticasone propionate prepared as follows. Shake the canister vigorously, and cool for 10 min in a dry ice–methanol bath. Remove the canister from the bath, and shake vigorously. Using a suitable device, carefully remove and keep the valve, and pour the contents into a suitable container. Allow the propellant to evaporate. Transfer the canister content to a suitable volumetric flask fitted with a suitable funnel using about 12% of the flask volume of acetonitrile. Add 50% of the flask volume of water. Swab the outer part of the valve with damp cotton wool soaked in acetonitrile. Place the swab in the neck of the funnel in the volumetric flask. Allow the valve to dry, then dismantle, and wash the components and the canister wall with acetonitrile. Collect the washings, and place in the same volumetric flask as the sample. Allow the flask to come to room temperature, and dilute with acetonitrile to volume.

  Chromatographic system

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

  Mode: LC

  Detector: UV 239 nm

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

  Column temperature: 40°

  Flow rate: 2 mL/min

  Injection volume: 10 µL

  System suitability

  Sample: *Standard solution*

  [Note—The retention time for the peak due to fluticasone propionate must be within the range of 1.0–1.6 min.]

  Suitability requirements

  Tailing factor: NMT 1.3 for the fluticasone propionate peak

  Relative standard deviation: NMT 2.0%

  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 the Inhalation Aerosol taken:

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

  r_U = ▲peak▲ (IRA 1-Sep-2022) response from the *Sample solution*

  r_S = ▲peak▲ (IRA 1-Sep-2022) response 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)

Acceptance criteria: 85%–115%

Delete the following:

▲PERFORMANCE TESTS▲ (IRA 1-Sep-2022)

IMPURITIES

Change to read:

• **Organic Impurities:** Protect the *Sample solution*▲ (IRA 1-Sep-2022) from light.

Solution A: Prepare a solution of 0.05% v/v phosphoric acid in acetonitrile.

Solution B: Prepare a solution of 0.05% v/v phosphoric acid in methanol.

Solution C: Prepare a solution of 0.05% v/v phosphoric acid in water.

Mobile phase: See ▲*Table 1*.

Table 1▲ (IRA 1-Sep-2022)

Time (min)	Solution A (%)	Solution B (%)	Solution C (%)
0	42	3	55
40	53	3	44
60	87	3	10
70	87	3	10

System suitability solution: Dissolve 2 mg of USP Fluticasone Propionate System Suitability Mixture RS in 5 mL of *Solution A*. Add 5 mL of *Solution C*, and mix.

Sample solution: Nominally 200 µg/mL of fluticasone propionate in *Solution A* prepared as follows. Place a canister into a freezing mixture of dry ice and methanol, and cool for approximately 5 min. Carefully remove the valve from the canister, and pass the contents through a filter of 0.22-µm pore size. When the filter bed is dry, wash it with two 5-mL aliquots of cyclohexane. Allow the paper to dry, then carefully transfer to an appropriate container. Dissolve the drug present on the filter paper in 50% of the final required volume of *Solution A*. Dilute with *Solution C* to volume to obtain the nominal concentration.

Chromatographic system

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

Mode: LC

Detector: UV 239 nm

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

Column temperature: 40°

Flow rate: 1 mL/min

Injection volume: 50 µL

System suitability

Sample: *System suitability solution*

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

Suitability requirements

Resolution: NLT 0.6 between the fluticasone propionate related compound B and fluticasone propionate related compound C peaks and NLT 1.5 between the fluticasone propionate related compound D and fluticasone propionate peaks

Tailing factor: NMT 1.1 for the fluticasone propionate peak

Analysis

Sample: *Sample solution*

Calculate the percentage of each impurity in the portion of Inhalation Aerosol taken:

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

r_U = ▲peak▲ (IRA 1-Sep-2022) response of each impurity from the *Sample solution*

r_T = total peak area for all peaks ≥0.05% by area of the peak due to fluticasone propionate from the *Sample solution*

Acceptance criteria: See ▲*Table 2.*

Table 2▲ (IRA 1-Sep-2022)

Name	Relative Retention Time	Acceptance Criteria (%)
Fluticasone sulfenic acid[a]	0.47	<0.2
Fluticasone propionate related compound B[b]	0.74	—
Fluticasone propionate related compound C[b]	0.76	—
Fluticasone propionate related compound D	0.95	<0.3
Fluticasone propionate	1.0	—
Chlorofluticasone propionate[c]	1.19	<0.3
Fluticasone propionate dimer[d]	1.33	<0.3
Any unspecified degradation product	—	<0.1
Total impurities[e]	—	NMT 1.0

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

[b] These are process impurities that are included in the table for identification only. These impurities are controlled in the drug substance and are not included in the total impurities.

[c] *S*-Chloromethyl-6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxyandrosta-1,4-diene-17β-carbothioate.

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

[e] Sum of all impurity peaks ≥0.05%.

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 formulation. 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 in 10 g of the formulation.

Change to read:

• **Particulate Matter in Injections ⟨788⟩**

The test described below and the specification is only applicable to a microscopic particle count test methodology. *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.

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

Sample solution: Perform testing on two previously unused inhalers. Prime each inhaler by discharging a predetermined number of actuations to waste. Discharge, and dissolve 16 actuations, 8 from each of two canisters in 50 mL of methanol.

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 number of particles per actuation by the formula:

$$\text{Result} = (N_{<10} + N_{10-100} + N_{>100})/16$$

$N_{<10}$ = 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 per Actuation (NMT)
<10	140
10–100	50
>100	5
Total	185

Delete the following:

▲• **Other Requirements**▲ (IRA 1-Sep-2022)

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in nonreactive, light-resistant aerosol containers with metered valves fitted with a dose counter and provided with oral inhalation actuators. Avoid exposure to heat. Store at controlled room temperature.

• **USP Reference Standards** ⟨11⟩

USP Fluticasone Propionate RS

USP Fluticasone Propionate System Suitability Mixture RS

It is a mixture of: Fluticasone propionate; Fluticasone propionate related compound B: [6α,9α-difluoro-11β-hydroxy-16α-methyl-2',3,4'-trioxo-17α-spiro(androsta-1,4-diene-17,5'-(1,3)oxathiolane]; Fluticasone propionate related compound C: [*S*-fluoromethyl 17α-acetyloxy-6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioate]; Fluticasone propionate related compound D: [*S*-methyl 6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxyandrosta-1,4-diene-17β-carbothioate].

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

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

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