Status: Currently Official on 14-Feb-2025
Official Date: Official as of 01-Dec-2024
Document Type: USP Monographs
DocId: GUID-1E95A7FE-1FD9-41E3-9A32-A2A4E7D5F493_7_en-US
DOI: https://doi.org/10.31003/USPNF_M1097_07_01
DOI Ref: 3mydw

Fluticasone Propionate Nasal Spray

DEFINITION

Fluticasone Propionate Nasal Spray is a white, opaque suspension of Fluticasone Propionate in water. It is supplied in a form suitable for nasal administration. It contains NLT 95.0% and NMT 115.0% of the labeled amount of fluticasone propionate ($C_{25}H_{31}F_3O_5S$).

IDENTIFICATION

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

Sample: Transfer 30 g of Nasal Spray equally into two 50-mL centrifuge tubes. Add 10 mL of water to each tube, insert the stopper, and shake vigorously for 2 min. Centrifuge at about 3500 rpm for about 10 min, and discard the supernatant. Add 10 mL of water to each tube, insert the stopper, and shake vigorously for 2 min. Centrifuge at about 3500 rpm for about 10 min, and discard the supernatant. Add 10 mL of water to each tube, insert the stopper, and shake vigorously for about 2 min. Centrifuge at 3500 rpm for 10 min, and discard the supernatant. To one tube add 10 mL of methanol. Shake to disperse the residue, and transfer to the other tube. Shake the other tube for 1 min. Centrifuge at about 3500 rpm for about 10 min. Decant the supernatant into an agate mortar. Evaporate the methanol either by carefully blowing dry with compressed air or nitrogen, or by allowing the methanol to evaporate naturally. If using an air or nitrogen line, use a suitable in-line filter to avoid contamination. Allow the residue to dry overnight in a desiccator over silica gel.

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

• **Procedure**

Diluent: Acetonitrile and 0.001 M hydrochloric acid (60:40)

Buffer: 1.2 g/L of monobasic ammonium phosphate. Adjust with phosphoric acid to a pH of 3.5.

Mobile phase: Methanol, acetonitrile, and *Buffer* (50:15:35)

System suitability solution: 50 µg/mL of USP Phenylethyl Alcohol RS, 10 µg/mL of USP Fluticasone Propionate RS, and 1 µg/mL of USP Fluticasone Propionate Related Compound D RS in *Diluent*

Standard solution: 10 µg/mL of USP Fluticasone Propionate RS in *Diluent*

Sample solution: Nominally 10 µg/mL of fluticasone propionate prepared as follows. Transfer an amount of the Nasal Spray containing 0.5 mg of fluticasone propionate to a 50-mL volumetric flask. Add about 40 mL of *Diluent*, and sonicate the flask for 10 min. Dilute with *Diluent* to volume, and shake. Allow to stand for 10 min until the supernatant is a clear solution. Inject the clear supernatant into the chromatograph.

Chromatographic system

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

Mode: LC

Detector: UV 210 and 239 nm

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

Column temperature: 40°

Flow rate: 1.5 mL/min

Injection volume: 20 µL

System suitability

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

Record the chromatogram at 210 nm for 5 min and then change the wavelength to 239 nm.

[Note—The relative retention times for phenylethyl alcohol, fluticasone propionate, and fluticasone propionate related compound D are about 0.42, 1.0, and 1.10, respectively.]

Suitability requirements

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

Relative standard deviation: NMT 2.0%, *Standard solution*

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 Nasal Spray 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 Fluticasone Propionate RS in the *Standard solution* (µg/mL)

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

Acceptance criteria: 95.0%–115.0%

OTHER COMPONENTS

• **Content of Phenylethyl Alcohol**

Diluent, Mobile phase, System suitability solution, Chromatographic system, and **System suitability:** Proceed as directed in the *Assay*.

Standard solution: 0.05 mg/mL of USP Phenylethyl Alcohol RS in *Diluent*

Sample solution: Transfer 1.0 g of the Nasal Spray to a 50-mL volumetric flask. Add about 40 mL of *Diluent*, and sonicate for 10 min. Dilute with *Diluent* to volume, and shake. Allow to stand for 10 min until the supernatant is clear. Use the clear supernatant for analysis.

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the quantity, in mg/g, of phenylethyl alcohol in the portion of Nasal Spray taken:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times (1/W)$$

r_U = peak response of phenylethyl alcohol from the *Sample solution*

r_S = peak response of phenylethyl alcohol from the *Standard solution*

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

V = volume of the *Sample solution*, 50 mL

W = weight of the Nasal Spray in the *Sample solution* (g)

Acceptance criteria

For 50 sprays: 1.75–2.63 mg/g

For 120 sprays: 1.88–2.63 mg/g

• **Content of Benzalkonium Chloride**

Buffer: Dissolve 10.8 g of monobasic sodium phosphate dihydrate in 90 mL of water, and adjust with phosphoric acid to a pH of 2.5. Dilute with water to 100 mL.

Solution A: Mix 50 mL of *Buffer*, 750 mL of water, and 200 mL of methanol. Add 5 mL of triethylamine. Mix and adjust with phosphoric acid to a pH of 2.5.

Solution B: Mix 1 L of methanol with 50 mL of phosphoric acid.

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	55	45
3.0	5	95
3.2	55	45
5.0	55	45

Diluent: Methanol, water, and hydrochloric acid (693:297:10)

System suitability solution: 0.04 mg/mL of USP Benzalkonium Chloride RS in *Diluent* prepared as follows. Transfer a suitable volume of USP Benzalkonium Chloride RS to a suitable volumetric flask and dilute to volume with *Diluent*.

Standard stock solution: 200 µg/mL of USP Benzalkonium Bromide RS in water. [Note—Sonication for about 2 min may be used to ensure complete dissolution. A few drops of methanol may be used to resolve the formation of foam prior to dilution.]

Standard solution: 20 µg/mL of USP Benzalkonium Bromide RS. Transfer an aliquot of *Standard stock solution* to a suitable volumetric flask. Dilute with *Diluent* to volume.

Sample solution: Transfer 1.0 g of the Nasal Spray to a 10-mL volumetric flask. Dilute with *Diluent* to volume. Centrifuge if necessary. [Note—Centrifuging at about 4000 rpm for about 15 min may be suitable. Supernatant may be passed through a suitable filter with a pore size of NMT 0.2 µm with a glass syringe.]

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

Column: 4.6-mm × 3.0-cm; 2.6-µm packing L1

Column temperature: 50°

Flow rate: 2 mL/min

Injection volume: 100 µL

System suitability

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

[NOTE—See *Table 2* for relative retention times. The C_{10} benzalkonium homolog may not be present.]

Suitability requirements

Resolution: NLT 2.5 between the pairs of C_{12} and C_{14} benzalkonium homologs and the C_{14} and C_{16} benzalkonium homologs, *System suitability solution*

Tailing factor: NMT 2.0, *Standard solution*

Relative standard deviation: NMT 2%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the sum of the corrected benzalkonium peak responses (r_{CU}) in the portion of *Sample solution* taken:

$$\text{Result} = \Sigma[r_U \times (1/F)]$$

r_U = peak response of each C_{10}, C_{12}, C_{14}, and C_{16} benzalkonium homolog from the *Sample solution*

F = relative response factor for the corresponding benzalkonium homolog relative to benzalkonium bromide (see *Table 2*)

Table 2

Benzalkonium Chloride Homolog	Relative Retention Time	Relative Response Factor
C_{10}	0.65	1.2
C_{12}	1.0	1.1
C_{14}	1.35	1.0
C_{16}	1.59	0.98

Calculate the amount of benzalkonium chloride in the portion of Nasal Spray taken:

$$\text{Result} = (r_{CU}/r_S) \times C_S \times (V/W)$$

r_{CU} = sum of the corrected peak responses of the benzalkonium homologs from the *Sample solution*

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

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

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

W = weight of Nasal Spray in the *Sample solution* (g)

Acceptance criteria: 140–220 µg/g

PERFORMANCE TESTS

• **DELIVERED DOSE UNIFORMITY** ⟨within container⟩

Diluent: Acetonitrile and 0.001 M hydrochloric acid (60:40)

Buffer: 1.2 g/L of monobasic ammonium phosphate. Adjust with phosphoric acid to a pH of 3.5.

Mobile phase: Methanol, acetonitrile, and *Buffer* (50:15:35)

System suitability solution: 5 µg/mL of USP Fluticasone Propionate RS and 0.5 µg/mL of USP Fluticasone Propionate Related Compound D RS in *Diluent*

Standard solution: 4 µg/mL of USP Fluticasone Propionate RS in *Diluent*

Sample solution: Wipe the pump clean. Shake the bottle for 30 s, and mechanically prime the bottle. Hold a 25-mL volumetric flask in an inverted position, and discharge the first two actuations (1 dose) into the flask. Turn the flask to the upright position immediately after each actuation. Insert the stopper into the flask after collecting two actuations. Discharge actuations 3–48 (50-spray pack) or 3–118 (120-spray pack) to waste. Wipe the bottle clean, and collect the last two actuations (49 and 50 or 119 and 120) in a second 25-mL volumetric flask. Turn the flask to the upright position immediately after each actuation, and insert the stopper into the flask. Add 20 mL of *Diluent* to each flask, and shake well for 10 min to disperse the suspension. Dilute with *Diluent* to volume, and mix thoroughly. Allow the flask to stand until the excipients have settled. Inject the clear supernatant. Repeat this procedure with four additional bottles.

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: 1.5 mL/min

Injection volume: 50 µL

System suitability

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

[Note—The relative retention times for fluticasone propionate and fluticasone propionate related compound D are about 1.0 and 1.10, respectively.]

Suitability requirements

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

Relative standard deviation: NMT 2.0%, *Standard solution*

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 each dose 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 Fluticasone Propionate RS in the *Standard solution* (µg/mL)

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

Acceptance criteria

Tier 1

1. Mean dose delivered from 10 doses is within 85%–115% of the labeled amount of fluticasone propionate.
2. NMT 1 dose is outside 80%–120% of the labeled amount of fluticasone propionate.
3. No doses are outside 75%–125% of the labeled amount of fluticasone propionate.

If the criteria in *Tier 1* cannot be met, proceed to *Tier 2*.

Tier 2

If 2 or 3 doses are outside 80%–120% of the label claim, test an additional 10 bottles.

1. Mean dose delivered from 30 doses is within 85%–115% of the labeled amount of fluticasone propionate.
2. NMT 3 doses are outside 80%–120% of the labeled amount of fluticasone propionate.
3. No doses are outside 75%–125% of the labeled amount of fluticasone propionate.

- **Delivered Dose Uniformity** (within batch)

Diluent, Buffer, Mobile phase, System suitability solution, Standard solution, Chromatographic system, and **System suitability:** Proceed as directed in the test for *Delivered Dose Uniformity.*

Sample solution: Wipe the pump clean. Shake the bottle for 30 s, and mechanically prime the bottle. Hold a 25-mL volumetric flask in an inverted position, and discharge the first two actuations into the flask. Turn the flask to the upright position immediately after each actuation. Insert the stopper into the flask after collecting two actuations (1 dose). Repeat this procedure with nine additional bottles.

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 each dose 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 Fluticasone Propionate RS in the *Standard solution* (µg/mL)

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

Acceptance criteria

Tier 1

1. Mean dose delivered from 10 doses is within 85%–115% of the labeled amount of fluticasone propionate.
2. NMT 1 dose is outside 80%–120% of the labeled amount of fluticasone propionate.
3. No doses are outside 75%–125% of the labeled amount of fluticasone propionate.

If the criteria in *Tier 1* cannot be met, proceed to *Tier 2*.

Tier 2

If 2 or 3 doses are outside 80%–120% of the label claim, test an additional 20 bottles.

1. Mean dose delivered from 30 doses is within 85%–115% of the labeled amount of fluticasone propionate.
2. NMT 3 doses are outside 80%–120% of the labeled amount of fluticasone propionate.
3. No doses are outside 75%–125% of the labeled amount of fluticasone propionate.

IMPURITIES

Change to read:

• **Organic Impurities**

Diluent: Acetonitrile and 0.001 M hydrochloric acid (60:40)

Solution A: Methanol and acetonitrile (77:23)

Buffer: 1.2 g/L of monobasic ammonium phosphate in water. Adjust with phosphoric acid to a pH of 3.4.

Mobile phase: *Solution A* and *Buffer* (60:40)

System suitability solution: 0.1 mg/mL of USP Fluticasone Propionate RS and 0.05 mg/mL of USP Fluticasone Propionate Related Compound D RS in *Diluent*

Identification solution: 0.5 mg/mL of USP Phenylethyl Alcohol RS and 0.08 mg/mL of USP Benzalkonium Chloride RS in a mixture of *Diluent* and water (4:1)

Sample solution: 0.2 g/mL of Nasal Spray in *Diluent*. Shake the flask vigorously to dissolve. Pass through a filter of 0.5-µm pore size.

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: 1.5 mL/min

Injection volume: 50 µL

System suitability

Sample: *System suitability solution*

[Note—See *Table 3* for the relative retention times.]

Suitability requirements

Resolution: NLT 2 between fluticasone propionate related compound D and fluticasone propionate

Analysis

Samples: *Identification solution* and *Sample solution*

Calculate the percentage of each degradation product in the portion of Nasal Spray taken:

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

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

r_T = sum of all the peak responses from the *Sample solution*, excluding the peaks from the *Identification solution*

Acceptance criteria: See *Table 3*.

Table 3

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Fluticasone acetate[a]	0.7	0.3
6-Ketofluticasone propionate[b]		

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Fluticasone propionate	1.0	—
Fluticasone propionate related compound D	1.1	0.3
Fluticasone propionate dimer[c]	2.1	0.3
Any individual unspecified degradation product	—	0.2
Total degradation products	—	1.5

[a] ▲6α,9-Difluoro-17-{[(fluoromethyl)sulfanyl]carbonyl}-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-dien-17α-yl acetate; also known as *S*-Fluoromethyl 17α-acetyloxy-6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioate.▲ (CN 1-Dec-2024)

[b] ▲9-Fluoro-17-{[(fluoromethyl)sulfanyl]carbonyl}-11β-hydroxy-16α-methyl-3,6-dioxoandrosta-1,4-dien-17α-yl propanoate.▲ (CN 1-Dec-2024)

[c] ▲6α,9-Difluoro-17-{[(fluoromethyl)sulfanyl]carbonyl}-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-dien-17α-yl 6α,9-difluoro-11β,17-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carboxylate.▲ (CN 1-Dec-2024)

SPECIFIC TESTS

• **Microbial Enumeration Tests ⟨61⟩** and **Tests for Specified Microorganisms ⟨62⟩:** Meets the requirements of the tests for absence of *Staphylococcus aureus*, *Escherichia coli*, *Salmonella* species, and *Pseudomonas aeruginosa*. The total aerobic microbial count does not exceed 25 cfu/mL, and the total combined molds and yeasts count does not exceed 25 cfu/mL.

• **pH ⟨791⟩:** 5.0–7.0

• **Particle Size**

Analysis: Remove the pump system after shaking the test bottle to ensure product uniformity. Transfer 1 drop of the Nasal Spray onto a clean microscope slide. Examine 10 random fields of view on the slide using 400× magnification. Drug substance particles are irregular in shape, whereas the excipient particles are elongated and angular. Record the number of individual drug substance particles that are less than 5 µm in diameter, greater than 5 µm but less than 15 µm in diameter, and greater than 15 µm in diameter. Calculate the percentage of each category by number.

Acceptance criteria: See *Table 4*.

Table 4

Particle Size (µm)	Acceptance Criteria (%)
<5	NLT 98
>5 to <15	NMT 1.8
>15	NMT 0.2

• **Foreign Particulates**

Analysis: Shake the required number of bottles to ensure uniformity. Remove the pump system carefully to minimize contamination of the sample. Collect about 100 g of Nasal Spray, and pass it through a wetted 250-µm screen. Rinse each bottle with a portion of water equal to twice the volume of each bottle. Pass the rinse through the 250-µm screen. Visually observe the screen and filtrate for any foreign particulates. Also examine the screen under a microscope using transmitted light.

Acceptance criteria: No foreign particulates greater than 250 µm are visible.

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight, light-resistant containers. Store between 4° and 30°.

Change to read:

• **USP Reference Standards ⟨11⟩**

USP Benzalkonium Bromide RS
USP Benzalkonium Chloride RS
USP Fluticasone Propionate RS
USP Fluticasone Propionate Related Compound D RS

▲6α,9-Difluoro-11β-hydroxy-16α-methyl-17-[(methylsulfanyl)carbonyl]-3-oxoandrosta-1,4-dien-17α-yl propanoate;
Also known as *S*-Methyl-6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxyandrosta-1,4-diene-17β-carbothioate.▲ (CN 1-Dec-2024)

USP Phenylethyl Alcohol RS

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

Topic/Question	Contact	Expert Committee
FLUTICASONE PROPIONATE NASAL SPRAY	Documentary Standards Support	SM52020 Small Molecules 5

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
Pharmacopeial Forum: Volume No. PF 42(6)

Current DocID: GUID-1E95A7FE-1FD9-41E3-9A32-A2A4E7D5F493_7_en-US

DOI: https://doi.org/10.31003/USPNF_M1097_07_01

DOI ref: 3mydw