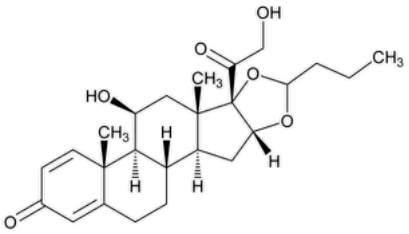
Status: Currently Official on 14-Feb-2025
Official Date: Official as of 01-Jul-2021
Document Type: USP Monographs
DocId: GUID-D0084C97-1F78-41D5-B757-1DDC46CACB2E_4_en-US
DOI: https://doi.org/10.31003/USPNF_M10458_04_01
DOI Ref: b5vgm

Budesonide

To view the Notice from the Expert Committee that posted in conjunction with this accelerated revision, please click https://www.uspnf.com/rb-budesonide-20210625.



$C_{25}H_{34}O_6$ 430.53

Pregna-1,4-diene-3,20-dione, 16,17-butylidenebis(oxy)-11,21-dihydroxy-,[11b,16a(*R*)], and 16a,17-[(*S*)-Butylidenebis(oxy)]-11b,21-dihydroxypregna-1,4-diene-3,20-dione;

(*RS*)-11b,16a,17,21-Tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with butyraldehyde CAS RN®: 51333-22-3; UNII: Q3OKS62Q6X.

S epimer CAS RN®: 51372-28-2; UNII: 168L5HT37P.

R epimer CAS RN®: 51372-29-3; UNII: 2HI1006KPH.

DEFINITION

Budesonide is a mixture of two epimeric forms, epimer A (C-22S) and epimer B (C-22R). It contains NLT 40.0% and NMT 51.0% of epimer A, and the sum of both epimers is NLT 98.0% and NMT 102.0% of budesonide ($C_{25}H_{34}O_6$), calculated on the dried basis.

[Note—Protect all solutions containing Budesonide from light.]

IDENTIFICATION

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

Sample solution: 25 µg/mL

Medium: Methanol

Acceptance criteria: Meets the requirements

ASSAY

- **Procedure**

Buffer: 0.5 mL of glacial acetic acid in 1 L of water. Adjust with potassium hydroxide to a pH of 3.9.

Mobile phase: Acetonitrile and *Buffer* (45:55)

Standard solution: 0.06 mg/mL of USP Budesonide RS prepared as follows. Transfer USP Budesonide RS to a suitable volumetric flask, dissolve in acetonitrile equivalent to 30% of the flask volume, and dilute with water to volume.

Sample solution: 0.06 mg/mL of Budesonide prepared as follows. Transfer Budesonide to a suitable volumetric flask, dissolve in acetonitrile equivalent to 30% of the flask volume, and dilute with water to volume.

Chromatographic system

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

Mode: LC

Detector: UV 240 nm

Column: 4.6-mm × 25-cm; 3-µm packing L1

Column temperature: 50°

Flow rate: 1 mL/min

Injection volume: 20 µL

System suitability

Sample: *Standard solution*

[Note—The relative retention time for epimer B is 0.96 with respect to epimer A.]

Suitability requirements

Resolution: NLT 1.2 between the two budesonide epimer peaks

Relative standard deviation: NMT 1.0%, for the sum of the peak areas of the two budesonide epimers

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of budesonide epimer A ($C_{25}H_{34}O_6$) in the portion of Budesonide taken:

$$\text{Result} = [r_{UA}/(r_{UA} + r_{UB})] \times 100$$

r_{UA} = peak area of epimer A from the *Sample solution*

r_{UB} = peak area of epimer B from the *Sample solution*

Calculate the percentage of budesonide ($C_{25}H_{34}O_6$) in the portion of Budesonide taken:

$$\text{Result} = [(r_{UA} + r_{UB})/(r_{SA} + r_{SB})] \times (C_S/C_U) \times 100$$

r_{UA} = peak area of epimer A from the *Sample solution*

r_{UB} = peak area of epimer B from the *Sample solution*

r_{SA} = peak area of epimer A from the *Standard solution*

r_{SB} = peak area of epimer B from the *Standard solution*

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

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

Acceptance criteria

Epimer A: 40.0%–51.0%

Both epimers: 98.0%–102.0% on the dried basis

IMPURITIES

Change to read:

• **Organic Impurities**

Solution A: 0.5 mL of glacial acetic acid in 1 L of water. Adjust with potassium hydroxide to a pH of 3.9.

Solution B: Acetonitrile

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	75	25
5	75	25
35	68	32
42	59	41
59	25	75
60	75	25
70	75	25

Diluent: Acetonitrile and water (3:7)

System suitability stock solution A: 0.3 mg/mL of USP Budesonide Related Compound E RS in acetonitrile

System suitability stock solution B: 0.3 mg/mL of USP Budesonide Related Compound G RS in acetonitrile

System suitability stock solution C: 0.3 mg/mL of USP Budesonide Related Compound L RS in acetonitrile

System suitability solution: 0.6 mg/mL of USP Budesonide RS and 3 µg/mL each of USP Budesonide Related Compound E RS, USP Budesonide Related Compound G RS, and USP Budesonide Related Compound L RS in *Diluent* prepared as follows. Transfer USP Budesonide RS to a suitable volumetric flask and add suitable quantities of *System suitability stock solution A*, *System suitability stock solution B*, and *System suitability stock solution C*. Dilute with acetonitrile equivalent to 30% of the final volume and dilute with water to volume.

Standard stock solution: 0.6 mg/mL of USP Budesonide RS prepared as follows. Transfer USP Budesonide RS to a suitable volumetric flask, dissolve in acetonitrile equivalent to 30% of the flask volume, and dilute with water to volume.

Sensitivity solution: 0.3 µg/mL of USP Budesonide RS in *Diluent* from the *Standard stock solution*

Standard solution: 6 µg/mL of USP Budesonide RS in *Diluent* from the *Standard stock solution*

Sample solution: 0.6 mg/mL of Budesonide prepared as follows. Transfer Budesonide to a suitable volumetric flask, dissolve in acetonitrile equivalent to 30% of the flask volume, and dilute with water to volume.

Chromatographic system

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

Mode: LC

Detector: UV 240 nm

Column: 4.6-mm × 25-cm; 3-µm packing L1

Temperatures

Autosampler: 4°

Column: 50°. [Note—The resolution between budesonide related compound E and budesonide related compound L may be improved by lowering the temperature, but to NLT 40°.]

Flow rate: 1.5 mL/min

Injection volume: 50 µL

System suitability

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

[Note—The relative retention times of the two epimers of budesonide are 0.96 (epimer B) and 1.00 (epimer A), respectively.]

Suitability requirements

Resolution: NLT 1.2 between budesonide related compound E and budesonide related compound L and NLT 3.0 between budesonide epimer A and the first epimer of budesonide related compound G, *System suitability solution*

Tailing factor: NMT 1.5 for the budesonide epimer B peak, *Standard solution*

Relative standard deviation: NMT 5.0%, for the sum of the peak areas of the two budesonide epimers, *Standard solution*

Signal-to-noise ratio: NLT 10, *Sensitivity solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Budesonide taken:

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

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

r_S = peak response of the sum of budesonide epimers from the *Standard solution*

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

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

Acceptance criteria: See *Table 2*. Disregard peaks that are less than 0.05% of the total peak areas of the budesonide epimers. Disregard peaks eluting after 60 min, which, if present, are due to the change in the gradient.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
16α-Hydroxyprednisolone[a]	0.12	0.2
Budesonide acetaldehyde acetal (epimers)[b]	0.39, 0.40	0.10[c]
Budesonide D-homo analog[d,e]	0.47	0.10
Desonide[e,f]	0.51	0.10
Budesonide glyoxal (epimers)[g]	0.76, 0.78	▲0.10▲ (RB 1-Jul-2021) [c]
Budesonide related compound E[h]	0.86	0.10

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Budesonide related compound L[j]	0.88	0.2
Budesonide epimer B	0.96	—
Budesonide epimer A	1.00	—
Budesonide related compound G (epimers)[j]	1.07, 1.08	0.10[c]
Budesonide 21-acetate (epimers)[k]	1.39, 1.40	0.10[c]
Budesonide 21-butyrate[l]	1.48	0.10
Any other individual impurity	—	0.10
Total specified impurities	—	0.4
Total unspecified impurities	—	0.4

[a] 11β,16α,17,21-Tetrahydroxypregna-1,4-diene-3,20-dione.

[b] 16α,17-[Ethylidenebis(oxy)]-11β,21-dihydroxypregna-1,4-diene-3,20-dione.

[c] Limit includes both epimers.

[d] 16α,17-[Butylidenebis(oxy)]-11β-hydroxy-17-(hydroxymethyl)-D-homoandrosta-1,4-diene-3,17a-dione; also known as D-homobudesonide.

[e] This impurity is to be reported under total unspecified impurities. Do not report it under total specified impurities.

[f] 16α,17-[1-Methylethylidenebis(oxy)]-11β, 21-dihydroxypregna-1,4-diene-3,20-dione.

[g] 16α,17-[Butylidenebis(oxy)]-11β-hydroxy-3,20-dioxopregna-1,4-dien-21-al; also known as 21-dehydrobudesonide.

[h] Also known as 14,15-dehydrobudesonide or budesonide 14-ene.

[i] Also known as 11-ketobudesonide.

[j] Also known as 1,2-dihydrobudesonide.

[k] 16α,17-[Butylidenebis(oxy)]-11β-hydroxypregna-1,4-diene-3,20-dione-21-yl acetate.

[l] 16α,17-[Butylidenebis(oxy)]-11β,21-dihydroxypregna-1,4-diene-3,20-dione-21-butyrate.

SPECIFIC TESTS

• **Microbial Enumeration Tests ⟨61⟩** and **Tests for Specified Microorganisms ⟨62⟩:** The total aerobic microbial count is NMT 10^3 cfu/g, and the total combined molds and yeast count is NMT 10^2 cfu/g.

• **Loss on Drying ⟨731⟩**

Analysis: Dry at 105° to constant weight.

Acceptance criteria: NMT 0.3%

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight, light-resistant containers. Store at controlled room temperature.

• **USP Reference Standards ⟨11⟩**

USP Budesonide RS

USP Budesonide Related Compound E RS

16α,17-[Butylidenebis(oxy)]-11β,21-dihydroxypregna-1,4,14-triene-3,20-dione.

$C_{25}H_{32}O_6$ 428.52

USP Budesonide Related Compound G RS

16α,17-[Butylidenebis(oxy)]-11β,21-dihydroxypregna-4-ene-3,20-dione.

$C_{25}H_{36}O_6$ 432.55

USP Budesonide Related Compound L RS

16α,17-[Butylidenebis(oxy)]-21-hydroxypregna-1,4-diene-3,11,20-trione.

$C_{25}H_{32}O_6$ 428.52

Topic/Question	Contact	Expert Committee
BUDESONIDE	Documentary Standards Support	SM52020 Small Molecules 5

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
Pharmacopeial Forum: Volume No. PF 40(4)

Current DocID: GUID-D0084C97-1F78-41D5-B757-1DDC46CACB2E_4_en-US

DOI: https://doi.org/10.31003/USPNF_M10458_04_01

DOI ref: b5vgm