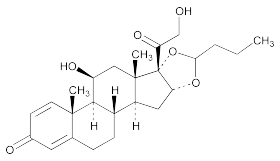
Budesonide



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

Pregna-1,4-diene-3,20-dione, 16α,17-[1*R*-butylidenebis(oxy)]-11*β*,21-dihydroxy and pregna-1,4-diene-3,20-dione,16α,17-[1*S*-butylidenebis(oxy)]-11*β*,21-dihydroxy;
(*RS*)-11*β*,16α,17,21-Tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with butyraldehyde [51372-29-3; 51372-28-2; 51333-22-3].

DEFINITION

Change to read:

Budesonide is a mixture of two epimeric forms, epimer A(C-22S) and epimer B(C-22R). It contains NLT •40.0%• (RB 1-Jun-2011) and NMT 51.0% of epimer A, and the sum of both epimers is NLT 98.0% and NMT 102.0% of $C_{25}H_{34}O_6$, calculated on the dried basis.

[NOTE—Protect all solutions containing budesonide from light.]

IDENTIFICATION

- **A. INFRARED ABSORPTION** ⟨197K⟩
- **B. ULTRAVIOLET ABSORPTION** ⟨197U⟩

Sample solution: 25 µg/mL
Medium: Methanol
Acceptance criteria: Meets the requirements

ASSAY

Change to read:

- **PROCEDURE**

Buffer: 3.17 mg/mL of monobasic sodium phosphate and 0.23 mg/mL of phosphoric acid. The pH is 3.2 ± 0.1.
Mobile phase: Acetonitrile and *Buffer* (32:68)
Standard solution: Dissolve a quantity of USP Budesonide RS in acetonitrile and dilute quantitatively with *Buffer* to obtain a solution having a concentration of 0.5 mg/mL, keeping the proportion of acetonitrile in this solution to NMT 30%.
Sample solution: Dissolve 25 mg of Budesonide in 15 mL of acetonitrile in a 50-mL volumetric flask, and dilute with *Buffer* to volume.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 254 nm
Column: 4.6-mm × 15-cm; 5-µm packing L1
Flow rate: 1.5 mL/min
Injection size: 20 µL
System suitability
Sample: *Standard solution*
[NOTE—The relative retention time for epimer A is 1.1 with respect to epimer B.]
Suitability requirements
Resolution: NLT 1.5 between the two budesonide epimer peaks
Column efficiency: NLT 5500 theoretical plates, determined from the budesonide epimer B peak
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of 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 $C_{25}H_{34}O_6$ 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%•(RB 1-Jun-2011)–51.0% on the dried basis
Both epimers: 98.0%–102.0% on the dried basis

IMPURITIES

- **PROCEDURE 1: LIMIT OF 21-ACETATE OF BUDESONIDE**

Buffer: 3.17 mg/mL of monobasic sodium phosphate and 0.23 mg/mL of phosphoric acid. The pH is 3.2 ± 0.1.
Mobile phase: Acetonitrile and *Buffer* (45:55)
Standard solution: Dissolve a quantity of USP Budesonide RS in acetonitrile, and dilute quantitatively with *Buffer* to obtain a solution having a concentration of 0.5 mg/mL, keeping the proportion of acetonitrile in this solution to NMT 30%.
Sample solution: Dissolve 25 mg of Budesonide in 15 mL of acetonitrile in a 50-mL volumetric flask, and dilute with *Buffer* to volume.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 254 nm
Column: 4.6-mm × 15-cm; 5-µm packing L1
Flow rate: 1.5 mL/min
Injection size: 20 µL
System suitability
Sample: *Standard solution*
[NOTE—The relative retention times for the first eluted epimer of the 21-acetate of budesonide, the second eluted epimer of the 21-acetate of budesonide, the first eluted epimer of budesonide (epimer B), and the second eluted epimer of budesonide (epimer A) are 3.1, 3.2, 1.0, and 1.1, respectively.]
Suitability requirements
Column efficiency: NLT 5500 theoretical plates, determined from the budesonide epimer B peak
Analysis
Sample: *Sample solution*
Calculate the percentage of the 21-acetate of budesonide in the portion of Budesonide taken:

$$\text{Result} = (r_{T1}/r_{T2}) \times 100$$

r_{T1} = sum of the peak areas for the two epimers of the 21-acetate of budesonide
r_{T2} = sum of the peak areas of the two budesonide peaks

Acceptance criteria: NMT 0.10% of the 21-acetate of budesonide is found.

- **PROCEDURE 2: LIMIT OF 11-KETOBUDESONIDE**

Buffer: 3.17 mg/mL of monobasic sodium phosphate and 0.23 mg/mL of phosphoric acid. The pH is 3.2 ± 0.1.
Mobile phase: Acetonitrile, isopropanol, and *Buffer* (26:9:65)
Standard solution: Dissolve a quantity of USP Budesonide RS in acetonitrile, and dilute quantitatively with *Buffer* to obtain a solution having a concentration of 0.5 mg/mL, keeping the proportion of acetonitrile in this solution to NMT 30%.
Sample solution: Dissolve 25 mg of Budesonide in 15 mL of acetonitrile in a 50-mL volumetric flask, and dilute with *Buffer* to volume.
Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 254 nm
Column: 4.6-mm × 15-cm; 3.5-µm packing L1
Column temperature: 50°
[NOTE—Preheat the *Mobile phase* to 50°.]
Flow rate: 1.5 mL/min
Injection size: 20 µL
System suitability
Sample: *Standard solution*
[NOTE—The relative retention times for the two epimers of 11-ketobudesonide are 0.73 and 0.78, respectively; the relative retention times for 21-dehydrobudesonide, 14,15-dehydrobudesonide, and the first eluted epimer of budesonide (epimer B) are 0.68, 0.84, and 1.0, respectively.]
Suitability requirements
Column efficiency: NLT 5500 theoretical plates, determined from the budesonide epimer B peak
Analysis
Sample: *Sample solution*
Calculate the percentage of 11-ketobudesonide in the portion of Budesonide taken:

$$\text{Result} = (r_{T1}/r_{T2}) \times 100$$

r_{T1} = sum of the peak areas for the two ketobudesonide peaks
r_{T2} = sum of the peak areas of the two budesonide peaks

Acceptance criteria: NMT 0.2% of 11-ketobudesonide is found.

- **PROCEDURE 3**

Buffer: 3.17 mg/mL of monobasic sodium phosphate and 0.23 mg/mL of phosphoric acid. The pH is 3.2 ± 0.1.
Mobile phase: Acetonitrile and *Buffer* (32:68)
Standard solution: Dissolve a quantity of USP Budesonide RS in acetonitrile, and dilute quantitatively with *Buffer* to obtain a solution having a concentration of 0.5 mg/mL, keeping the proportion of acetonitrile in this solution to NMT 30%.
Sample solution: Dissolve 25 mg of Budesonide in 15 mL of acetonitrile in a 50-mL volumetric flask, and dilute with *Buffer* to volume.
Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 254 nm
Column: 4.6-mm × 15-cm; 5-µm packing L1
Flow rate: 1.5 mL/min
Injection size: 20 µL
System suitability
Sample: *Standard solution*
Suitability requirements
Column efficiency: NLT 5500 theoretical plates, determined from the budesonide epimer B peak
Analysis
Sample: *Sample solution*
Calculate the percentage of each impurity in the portion of Budesonide taken:

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

r_U = peak area for each impurity
r_T = sum of the areas of all of the peaks

Acceptance criteria: See *Table 1*.

Table 1

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
16α-Hydroxyprednisolone[a]	0.11	0.2
D-Homobudesonide[b]	0.36	0.10
21-Dehydrobudesonide (epimers)[c]	0.61; 0.66	0.07[d]
14,15-Dehydrobudesonide[e]	0.86	0.10
Total specified impurities	—	0.4[f]
Any other individual impurity	—	0.10
Total unspecified impurities	—	0.4

[a] 11β,16α,17,21-Tetrahydroxypregna-1,4-diene-3,20-dione.
[b] 16α,17-[(1*RS*)-Butylidenebis(oxy)]-11β-hydroxy-17-(hydroxymethyl)-D-homoandrosta-1,4-diene-3,17a-dione.
[c] 16α,17-[(1*RS*)-Butylidenebis(oxy)]-11β-hydroxy-3,20-dioxopregna-1,4-dien-21-al.
[d] Limit includes both epimers.
[e] 16α,17-[(1*RS*)-Butylidenebis(oxy)]-11β,21-dihydroxypregna-1,4,14-triene-3,20-dione.
[f] Total specified impurities includes 11-ketobudesonide obtained in the test for *Limit of 11-Ketobudenoside* and the impurities listed above.

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**⟩**:** Dry a sample at 105° to constant weight: it loses NMT 0.3% of its weight.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight, light-resistant containers. Store at controlled room temperature.
- **USP REFERENCE STANDARDS** ⟨**11**⟩
USP Budesonide RS