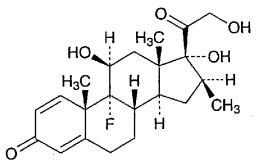
Betamethasone

ベタメタゾン



$C_{22}H_{29}FO_5$: 392.46

9-Fluoro-11β,17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione [*378-44-9*]

Betamethasone, when dried, contains not less than 96.0% and not more than 103.0% of $C_{22}H_{29}FO_5$.

Description Betamethasone occurs as a white to pale yellowish white, crystalline powder. It has no odor.

It is sparingly soluble in methanol, in ethanol (95), in acetone and in 1,4-dioxane, very slightly soluble in diethyl ether and in chloroform, and practically insoluble in water.

Melting point: about 240°C (with decomposition).

Identification **(1)** Dissolve 2 mg of Betamethasone in 40 mL of ethanol (95), add 5 mL of 2,6-di-*tert*-butylcresol TS and 5 mL of sodium hydroxide TS, and heat on a water bath for 20 minutes under a reflux condenser: a green color develops.

(2) Dissolve 0.01 g of Betamethasone in 1 mL of methanol by heating, and add 1 mL of Fehling's TS immediately: a red-brown precipitate is produced.

(3) Proceed 0.01 g of Betamethasone as directed under the Oxygen Flask Combustion Method, using a mixture of 0.5 mL of 0.01 mol/L sodium hydroxide TS and 20 mL of water as an absorbing liquid, and prepare the test solution: the test solution so obtained responds to the Qualitative Tests for fluoride.

(4) Dissolve 1.0 mg of Betamethasone in 10 mL of ethanol (95). Mix 2.0 mL of the solution with 10 mL of phenylhydrazinium hydrochloride TS, heat in a water bath at 60°C for 20 minutes, and cool the solution. Determine the absorption spectrum of the solution as directed under the Ultraviolet-visible Spectrophotometry, using as the blank the solution prepared with 2.0 mL of ethanol (95) in the same manner as the former solution, and compare the spectrum with the Reference Spectrum or the spectrum of a solution of Betamethasone Reference Standard prepared in the same manner as the sample solution: both spectra exhibit similar intensities of absorption at the same wavelengths.

(5) Determine the infrared absorption spectrum of Betamethasone, previously dried, as directed in the potassium bromide disk method under the Infrared Spectrophotometry, and compare the spectrum with the Reference Spectrum or the spectrum of previously dried Betamethasone Reference Standard: both spectra exhibit similar intensities of absorption at the same wave numbers. If any difference appears between the spectra, dissolve Betamethasone and Betamethasone Reference Standard in acetone, respectively, then evaporate the acetone to dryness, and repeat the test on the residues.

Optical rotation $[\alpha]_D^{20}$: +115 – +121° (after drying, 0.1 g, 1,4-dioxane, 10 mL, 100 mm).

Purity **(1)** Heavy metals—Proceed with 0.5 g of Betamethasone according to Method 2, and perform the test. Prepare the control solution with 1.5 mL of Standard Lead Solution (not more than 30 ppm).

(2) Other steroids—Dissolve 0.010 g of Betamethasone in 5 mL of a mixture of chloroform and methanol (9:1), and use this solution as the sample solution. Pipet 1 mL of the sample solution, add a mixture of chloroform and methanol (9:1) to make exactly 100 mL, and use this solution as the standard solution. Perform the test with these solutions as directed under the Thin-layer Chromatography. Spot 5 μL each of the sample solution and the standard solution on a plate of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of dichloromethane, diethyl ether, methanol and water (385:75:40:6) to a distance of about 12 cm, and air-dry the plate. Examine under ultraviolet light (main wavelength: 254 nm): the spots other than the principal spot from the sample solution are not more intense than the spot from the standard solution.

Loss on drying Not more than 0.5% (0.5 g, in vacuum, phosphorus (V) oxide, 4 hours).

Residue on ignition Not more than 0.5% (0.1 g, platinum crucible).

Assay Dissolve about 0.02 g each of Betamethasone and Betamethasone Reference Standard, previously dried and accurately weighed, in methanol to make exactly 50 mL. Pipet 5 mL each of these solutions, add exactly 5 mL each of the internal standard solution, then add methanol to make 50 mL, and use these solutions as the sample solution and the standard solution, respectively. Perform the test with 10 μL each of these solutions as directed under the Liquid Chromatography according to the following conditions, and calculate the ratios, Q_T and Q_S, of the peak area of betamethasone to that of the internal standard, respectively.

$$\text{Amount (mg) of } C_{22}H_{29}FO_5 = \text{amount (mg) of Betamethasone Reference Standard} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of butyl parahydroxybenzoate in methanol (2 in 3500).

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 240 nm).

Column: A stainless steel column about 4 mm in inside diameter and 15 to 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: Room temperature.

Mobile phase: A mixture of water and acetonitrile (3:2).

Flow rate: Adjust the flow rate so that the retention time of betamethasone is about 4 minutes.

Selection of column: Proceed with 10 μL of the standard solution under the above operating conditions, and calculate the resolution. Use a column giving elution of betamethasone and the internal standard in this order with the resolution between these peaks being not less than 10.

Containers and storage Containers—Tight containers. Storage—Light-resistant.

Betamethasone Dipropionate

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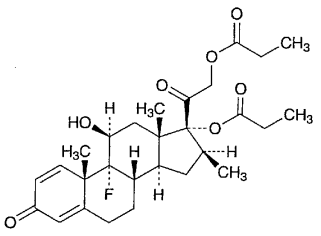

$C_{28}H_{37}FO_7$: 504.59

9-Fluoro-11β,17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17,21-dipropionate [*5593-20-4*]

Betamethasone Dipropionate, when dried, contains not less than 97.0% and not more than 103.0% of $C_{28}H_{37}FO_7$, and not less than 3.4% and not more than 4.1% of fluorine (F:19.00).

Description Betamethasone Dipropionate occurs as a white to pale yellowish white, crystalline powder. It is odorless.

It is freely soluble in acetone, in 1,4-dioxane and in chloroform, soluble in methanol, sparingly soluble in ethanol (95), slightly soluble in diethyl ether, and practically insoluble in water and in hexane.

It is affected gradually by light.

Identification (1) To 1 mL of a solution of Betamethasone Dipropionate in methanol (1 in 10,000) add 4 mL of isoniazid TS, and heat on a water bath for 2 minutes: a yellow color develops.

(2) Proceed with 0.01 g of Betamethasone Dipropionate as directed under the Oxygen Flask Combustion Method, using a mixture of 0.5 mL of 0.01 mol/L sodium hydroxide TS and 20 mL of water as the absorbing liquid: the test solution so obtained responds to the Qualitative Tests for fluoride.

(3) Determine the absorption spectrum of a solution of Betamethasone Dipropionate in methanol (3 in 200,000) as directed under the Ultraviolet-visible Spectrophotometry, and compare the spectrum with the Reference Spectrum: both spectra exhibit similar intensities of absorption at the same wavelengths.

(4) Determine the infrared absorption spectrum of Betamethasone Dipropionate, previously dried, as directed in the potassium bromide disk method under the Infrared Spectrophotometry, and compare the spectrum with the Reference Spectrum: both spectra exhibit similar intensities of absorption at the same wave numbers.

Melting point 176 - 180°C

Optical rotation $[\alpha]_D^{20}$: +63 - +70° (after drying, 0.05 g, 1,4-dioxane, 10 mL, 100 mm).

Purity (1) Fluoride—To 0.10 g of Betamethasone Dipropionate add 10.0 mL of diluted 0.01 mol/L sodium hydroxide TS (1 in 20), shake for 10 minutes, and filter through a membrane filter (0.4-μm pore size). Place 5.0 mL of the filtrate in a 20-mL volumetric flask, and add 10 mL of a mixture of alizalin complexone TS, acetic acid-potassium acetate buffer solution, pH 4.3, and cerium (III) nitrate TS (1:1:1), add water to make 20 mL, allow to stand for 1 hour, and use this solution as the sample solution. Separately, place 1.0 mL of Standard Fluorine Solution in a 20-mL volumetric flask, add 5.0 mL of diluted 0.01 mol/L sodium hydroxide TS (1 in 20), then 10 mL of a mixture of alizalin complexone TS, acetic acid-potassium acetate buffer solution, pH 4.3, and cerium (III) nitrate TS (1:1:1), proceed in the same manner as the preparation of the sample solution, and use this solution as the standard solution. Place 5.0 mL of diluted 0.01 mol/L sodium hydroxide TS (1 in 20) in a 20-mL volumetric flask, and proceed in the same manner as the preparation of the sample solution. Using this solution as the blank, determine the absorbances of the sample solution and the standard solution at 600 nm as directed under the Ultraviolet-visible Spectrophotometry: the absorbance of the sample solution is not greater than that of the standard solution (not more than 0.012%).

(2) Heavy metals—Proceed with 1.0 g of Betamethasone Dipropionate according to Method 2, and perform the test. Prepare the control solution with 2.0 mL of Standard Lead Solution (not more than 20 ppm).

(3) Other steroids—Conduct this procedure without exposure to daylight, using light-resistant vessels. Dissolve 0.010 g of Betamethasone Dipropionate in 10 mL of chloroform, and use this solution as the sample solution. Pipet 3 mL of the sample solution, add chloroform to make exactly 100 mL, and use this solution as the standard solution. Perform the test as directed under the Thin-layer Chromatography with these solutions. Spot 20 μL each of the sample solution and the standard solution on a plate of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of chloroform and acetone (7:1) to a distance of about 10 cm, and air-dry the plate. Examine under ultraviolet light (main wavelength: 254 nm): the spots other than the principal spot from the sample solution are not more intense than the spot from the standard solution.

Loss on drying Not more than 1.0% (0.5 g, 105°C, 3 hours).

Residue on ignition Not more than 0.2% (0.5 g, platinum crucible).

Assay (1) Betamethasone dipropionate—Weigh accurately about 0.015 g of Betamethasone Dipropionate, previously dried, and dissolve in methanol to make exactly 100 mL. Pipet 5 mL of this solution, and dilute with methanol to exactly 50 mL. Determine the absorbance A of this solution at the wavelength of maximum absorption at about 239 nm as directed under the Ultraviolet-visible Spectrophotometry.

$$\text{Amount (mg) of } C_{28}H_{37}FO_7 = \frac{A}{312} \times 10{,}000$$

(2) Fluorine—Weigh accurately about 0.01 g of Betamethasone Dipropionate, previously dried, and proceed as directed in the procedure of determination for fluorine under the Oxygen Flask Combustion Method, using a mixture