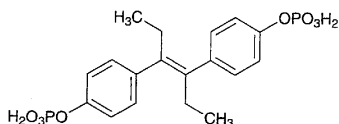


Fosfestrol

Diethylstilbestrol Diphosphate

ホスフェストロール



$C_{18}H_{22}O_8P_2$: 428.31

(*E*)-4,4'-(1,2-Diethylvinylene) bis(phenyl dihydrogen phosphate) [522-40-7]

Fosfestrol, when dried, contains not less than 98.5% of $C_{18}H_{22}O_8P_2$.

Description Fosfestrol occurs as a white, crystalline powder. It is odorless.

It is freely soluble in ethanol (95), soluble in formamide, slightly soluble in water, and practically insoluble in acetonitrile and in diethyl ether.

It dissolves in sodium hydroxide TS.

Melting point: about 234°C (with decomposition).

Identification (1) Dissolve 0.015 g of Fosfestrol in 1 mL of sulfuric acid: a yellow to orange color develops. To this solution add 10 mL of water: the color of the solution disappears.

(2) Determine the infrared absorption spectrum of Fosfestrol as directed in the potassium bromide disk method under the Infrared Spectrophotometry, and compare the spectrum with the Reference Spectrum or with the spectrum of Fosfestrol Reference Standard: both spectra exhibit similar intensities of absorption at the same wave numbers.

(3) Place 0.4 g of Fosfestrol in a crucible, wet by adding 0.1 mL of sulfuric acid, and heat to carbonize. Add 10 mL of water to the residue, stir well, and filter. Add 0.1 mL of nitric acid to the filtrate, and heat in a water bath for 15 minutes: this solution responds to the Qualitative Tests for phosphate.

pH Dissolve 0.10 g of Fosfestrol in 30 mL of water: the pH of this solution is between 1.0 and 2.5.

Purity (1) Clarity and color of solution—Dissolve 1.0 g of Fosfestrol in 15 mL of sodium hydroxide TS: the solution is clear and colorless.

(2) Chloride—Dissolve 0.10 g of Fosfestrol in 30 mL of ethanol (95), add 6 mL of dilute nitric acid and water to make 50 mL. Perform the test using this solution as the test solution. Prepare the control solution as follows: to 0.70 mL of 0.01 mol/L hydrochloric acid VS add 6 mL of dilute nitric acid, 30 mL of ethanol (95) and water to make 50 mL (not more than 0.248%).

(3) Heavy metals—Proceed with 1.0 g of Fosfestrol according to Method 4, and perform the test. Use a solution of magnesium nitrate hexahydrate in ethanol (95) (1 in 5). Prepare the control solution with 2.0 mL of Standard Lead Solution (not more than 20 ppm).

(4) Arsenic—Prepare the test solution with 1.0 g of Fosfestrol according to Method 3, and perform the test using Apparatus B. Use a solution of magnesium nitrate hexahy-

drate in ethanol (95) (1 in 5) (not more than 2 ppm).

(5) Free phosphoric acid—Weigh accurately about 0.4 g of Fosfestrol, dissolve in a mixture of water and formamide (1:1) to make exactly 200 mL, and use this solution as the sample solution. Separately, weigh accurately 0.112 g of monobasic potassium phosphate, previously dried in a desiccator (silica gel) to constant mass, dissolve in 10 mL of diluted sulfuric acid (1 in 10) and water to make exactly 1000 mL. Measure exactly 10 mL of this solution, add 100 mL of formamide and water to make exactly 200 mL, and use this solution as the standard solution. Measure exactly 10 mL each of the sample solution and the standard solution, and place in a 25-mL volumetric flask, respectively. To each of these solutions add 2.5 mL of hexaammonium heptamolybdate-sulfuric acid TS and 1 mL of 1-amino-2-naphthol-4-sulfonic acid TS, shake, add water to make 25 mL, and allow to stand at $20 \pm 1^\circ\text{C}$ for 30 minutes. Perform the test with these solutions, using a solution obtained in the same manner with 10 mL of a mixture of water and formamide (1:1) as the blank, as directed under the Ultraviolet-visible Spectrophotometry. Determine the absorbances, A_T and A_S , of the solutions obtained from the sample solution and the standard solution at 740 nm: the amount of free phosphoric acid is not more than 0.2%.

Amount (%) of free phosphoric acid (H_3PO_4)

$$= \frac{A_T}{A_S} \times \frac{1}{W} \times 80.65$$

W : Amount (mg) of Fosfestrol

(6) Related substances—Dissolve 0.020 g of Fosfestrol in 100 mL of the mobile phase, and use this solution as the sample solution. Measure exactly 5 mL of this solution, and add the mobile phase to make exactly 50 mL. Pipet 3 mL of this solution, add the mobile phase to make exactly 20 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the sample solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine each peak area of these solutions by the automatic integration method: the total area of the peaks other than the peak of fosfestrol from the sample solution is not larger than the peak area of fosfestrol from the standard solution.

Operating conditions—

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

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

Column temperature: A constant temperature of about 25°C.

Mobile phase: A mixture of a solution of potassium dihydrogenphosphate (1 in 500), acetonitrile and tetrabutylammonium hydroxide TS (70:30:1).

Flow rate: Adjust the flow rate so that the retention time of fosfestrol is about 8 minutes.

Selection of column: Dissolve 0.02 g of Fosfestrol and 8 mg of methyl parahydroxybenzoate in 100 mL of the mobile phase. Proceed with 10 μL of this solution under the above operating conditions, and calculate the resolution. Use a column giving elution of methyl parahydroxybenzoate and fosfestrol in this order with the resolution between these peaks being not less than 3.

Detection sensitivity: Adjust the detection sensitivity so that the peak height of fosfestrol obtained from 10 μ L of the standard solution is between 5 mm and 15 mm.

Time span of measurement: Three times as long as the retention time of fosfestrol.

Loss on drying Not more than 1.0% (1 g, 105°C, 4 hours).

Assay Weigh accurately about 0.2 g of Fosfestrol, previously dried, dissolve in 60 mL of water, and titrate with 0.1 mol/L sodium hydroxide VS (potentiometric titration). The end point is the second equivalent point. Perform a blank determination, and make any necessary correction.

$$\begin{aligned} \text{Each mL of 0.1 mol/L sodium hydroxide VS} \\ = 10.708 \text{ mg of } C_{18}H_{22}O_8P_2 \end{aligned}$$

Containers and storage Containers—Tight containers.

Fosfestrol Tablets

Diethylstilbestrol Diphosphate Tablets

ホスフェストロール錠

Fosfestrol Tablets contain not less than 93% and not more than 107% of the labeled amount of fosfestrol ($C_{18}H_{22}O_8P_2$: 428.31).

Method of preparation Prepare as directed under the Tablets, with Fosfestrol.

Identification (1) To a quantity of powdered Fosfestrol Tablets, equivalent to 0.5 g of Fosfestrol according to the labeled amount, add 50 mL of 0.1 mol/L hydrochloric acid TS, shake well, and filter. To the filtrate add 100 mL of diethyl ether, extract, and evaporate carefully the diethyl ether extract on a water bath to dryness. Proceed with 0.015 g of the residue as directed in the Identification (1) under Fosfestrol.

(2) Dry 0.01 g of the residue obtained in (1) at 105°C for 4 hours, and determine the infrared absorption spectrum as directed in the potassium bromide disk method under the Infrared Spectrometry: it exhibits absorption at the wave numbers of about 2970 cm^{-1} , 1605 cm^{-1} , 1505 cm^{-1} , 1207 cm^{-1} and 1006 cm^{-1} .

Dissolution test Perform the test with 1 tablet of Fosfestrol Tablets at 50 revolutions per minute according to Method 2 under the Dissolution Test, using 900 mL of water. Take 20 mL or more of the dissolved solution 20 minutes after starting the test, and filter through a membrane filter with pore size of not more than 0.8 μ m. Discard the first 10 mL of the filtrate, pipet 2 mL of the subsequent, add a solution of sodium hydroxide (1 in 250) to make exactly 20 mL, and use this solution as the sample solution. Separately, weigh accurately about 0.05 g of Fosfestrol Reference Standard, previously dried at 105°C for 4 hours, and dissolve in a solution of sodium hydroxide (1 in 250) to make exactly 100 mL. Pipet 2 mL of this solution, add a solution of sodium hydroxide (1 in 250) to make exactly 100 mL, and use this solution as the standard solution. Determine the absorbances, A_T and A_S , of the sample solution and the standard solution at 242 nm as directed under the Ultraviolet-visible Spectrophotometry.

The dissolution rate of Fosfestrol Tablets in 20 minutes is not less than 80%.

Dissolution rate (%) with respect to the labeled amount of fosfestrol ($C_{18}H_{22}O_8P_2$)

$$= W_S \times \frac{A_T}{A_S} \times \frac{1}{C} \times 180$$

W_S : Amount (mg) of Fosfestrol Reference Standard.

C : Labeled amount (mg) of fosfestrol ($C_{18}H_{22}O_8P_2$) in 1 tablet.

Assay Weigh accurately not less than 20 Fosfestrol Tablets, and powder. Weigh accurately a quantity of the powder, equivalent to about 1 g of fosfestrol ($C_{18}H_{22}O_8P_2$) according to the labeled amount, add 100 mL of a solution of sodium hydroxide (1 in 125), shake well, add water to make exactly 500 mL. Filter this solution, discard the first 30 mL of the filtrate, pipet the subsequent 2 mL of the filtrate, add 30 mL of a solution of sodium hydroxide (1 in 125) and water to make exactly 250 mL, and use this solution as the sample solution. Separately, weigh accurately about 0.08 g of Fosfestrol Reference Standard, previously dried at 105°C for 4 hours, and dissolve in a solution of sodium hydroxide (1 in 125) to make exactly 50 mL. Pipet 1 mL of this solution, add 10 mL of a solution of sodium hydroxide (1 in 125) and water to make exactly 100 mL, and use this solution as the standard solution. Determine the absorbances, A_T and A_S , of the sample solution and the standard solution at 242 nm as directed under the Ultraviolet-visible Spectrophotometry.

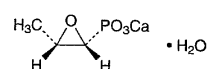
Amount (mg) of fosfestrol ($C_{18}H_{22}O_8P_2$)

$$\begin{aligned} = \text{amount (mg) of Fosfestrol Reference Standard} \\ \times \frac{A_T}{A_S} \times \frac{25}{2} \end{aligned}$$

Containers and storage Containers—Tight containers.

Fosfomycin Calcium

ホスホマイシンカルシウム



$C_3H_5CaO_4P \cdot H_2O$: 194.14

Monocalcium (2*R*,3*S*)-3-methyloxiran-2-ylphosphonate monohydrate [26016-98-8]

Fosfomycin Calcium contains not less than 725 μ g (potency) per mg, calculated on the anhydrous basis. The potency of Fosfomycin Calcium is expressed as mass (potency) of fosfomycin ($C_3H_7O_4P$: 138.06).

Description Fosfomycin Calcium occurs as a white crystalline powder.

It is slightly soluble in water, and practically insoluble in methanol and in ethanol (95).

Identification (1) Determine the infrared absorption spectrum of Fosfomycin Calcium as directed in the potassium bromide disk method under the Infrared Spectrophotometry, and compare the spectrum with the Reference Spectrum: