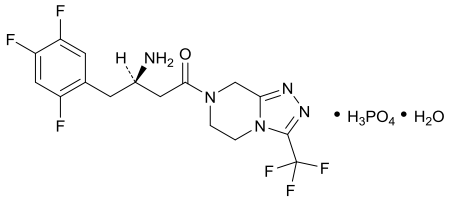
Sitagliptin Phosphate Hydrate

シタグリプチンリン酸塩水和物



$C_{16}H_{15}F_6N_5O.H_3PO_4.H_2O$: 523.32

(3*R*)-3-Amino-1-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-4-(2,4,5-trifluorophenyl)butan-1-one monophosphate monohydrate [*654671-77-9*]

Sitagliptin Phosphate Hydrate contains not less than 98.0% and not more than 102.0% of sitagliptin phosphate ($C_{16}H_{15}F_6N_5O.H_3PO_4$: 505.31), calculated on the anhydrous basis.

Description Sitagliptin Phosphate Hydrate occurs as a white powder.

It is soluble in water, sparingly soluble in methanol, very slightly soluble in acetonitrile and in ethanol (99.5), and practically insoluble in 2-propanol.

Identification (1) Determine the absorption spectrum of a solution of Sitagliptin Phosphate Hydrate (1 in 10,000) as directed under Ultraviolet-visible Spectrophotometry <*2.24*>, and compare the spectrum with the Reference Spectrum or the spectrum of a solution of Sitagliptin Phosphate RS prepared in the same manner as the sample solution: both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared absorption spectrum of Sitagliptin Phosphate Hydrate as directed in the paste method under Infrared Spectrophotometry <*2.25*>, and compare the spectrum with the Reference Spectrum or the spectrum of Sitagliptin Phosphate RS: both spectra exhibit similar intensities of absorption at the same wave numbers. Alternatively, perform the test by the potassium bromide disk method or the ATR method, and compare the spectrum with the spectrum of Sitagliptin Phosphate RS: both spectra exhibit similar intensities of absorption at the same wave numbers.

(3) A solution of Sitagliptin Phosphate Hydrate (1 in 25) responds to Qualitative Tests <*1.09*> (1) for phosphate.

Purity (1) Related substances—Use the sample solution obtained in the Assay as the sample solution. Pipet 1 mL of the sample solution, add a mixture of diluted phosphoric acid (1 in 1000) and acetonitrile for liquid chromatography (19:1) to make exactly 1000 mL, and use this solution as the standard solution. Perform the test with exactly 20 μL each of the sample solution and standard solution as directed under Liquid Chromatography <*2.01*> according to the following conditions. Determine each peak area by the automatic integration method: the area of the peak other than sitagliptin obtained from the sample solution is not larger than the peak area of sitagliptin from the standard solution, and the total area of the peaks other than sitagliptin from the sample solution is not larger than 5 times the peak area of sitagliptin from the standard solution. For this calculation the peak area not larger than 1/2 times the peak area of sitagliptin from the standard solution is excluded.

Operating conditions —

Detector, column, column temperature, mobile phase and flow rate: Proceed as directed in the operating conditions in the Assay.

Time span of measurement: About 5.5 times as long as the retention time of sitagliptin.

System suitability —

System performance: Proceed as directed in the system suitability in the Assay.

Test for required detectability: Pipet 5 mL of the standard solution, and add a mixture of diluted phosphoric acid (1 in 1000) and acetonitrile for liquid chromatography (19:1) to make exactly 10 mL. Confirm that the SN ratio of the peak of sitagliptin obtained with 20 μL of this solution is not less than 10.

System repeatability: When the test is repeated 6 times with 20 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of sitagliptin is not more than 2.0%.

(2) Enantiomer—Dissolve 80 mg of Sitagliptin Phosphate Hydrate in a mixture of methanol and water (9:1) to make 10 mL, and use this solution as the sample solution. Perform the test with 10 μL of the sample solution as directed under Liquid Chromatography <*2.01*> according to the following conditions. Determine the total peak area, A_T, of sitagliptin and related substance A (enantiomer), having the relative retention time of about 0.9 to sitagliptin, and the peak area, A_S, of related substance A (enantiomer), and calculate the amount of the enantiomer by the following equation: not more than 0.5%.

$$\text{Amount (\%) of enantiomer} = A_S / A_T \times 100$$

Operating conditions —

Detector: An ultraviolet absorption photometer (wavelength: 268 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 25 cm in length, packed with amylose tris-(3,5-dimethylphenylcarbamate)-immobilized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 35℃.

Mobile phase: A mixture of ethanol (99.5), heptane, water and diethylamine (600:400:1:1).

Flow rate: 0.8 mL per minute.

System suitability—

Test for required detectability: Pipet 1 mL of the sample solution, and dissolve in a mixture of methanol and water (9:1) to make exactly 100 mL. Pipet 1 mL of this solution, add a mixture of methanol and water (9:1) to make exactly 10 mL. Confirm that the SN ratio of the peak of sitagliptin obtained with 10 μL of this solution is not less than 10.

System performance: Dissolve 8 mg of Sitagliptin Phosphate RS for System Suitability in 1 mL of a mixture of methanol and water (9:1). When the procedure is run with 10 μL of this solution under the above operating conditions, the resolution between the peak of related substance A (enantiomer) and sitagliptin is not less than 1.5.

Water <*2.48*> 3.3 – 3.7% (0.3 g, volumetric titration, direct titration).

Residue on ignition <*2.44*> Not more than 0.2% (1 g, platinum crucible).

Assay Weigh accurately about 20 mg each of Sitagliptin Phosphate Hydrate and Sitagliptin Phosphate RS (separately determine the water <*2.48*> in the same manner as Sitagliptin Phosphate Hydrate), dissolve each in a mixture of diluted phosphoric acid (1 in 1000) and acetonitrile for liquid chromatography (19:1) to make exactly 200 mL, and use these solutions as the sample solution and the standard solution, respectively. Perform the test with exactly 20 μL each of the sample solution and standard solution as directed under Liquid Chromatography <*2.01*> according to the following conditions, and determine the peak areas, A_T and A_S, of sitagliptin in each solution.

Amount (mg) of sitagliptin phosphate ($C_{16}H_{15}F_6N_5O.H_3PO_4$)
$= M_S \times A_T / A_S$

M_S: Amount (mg) of Sitagliptin Phosphate RS taken, calculated on the anhydrous basis

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 205 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 15 cm in length, packed with cyanopropylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 30℃.

Mobile phase: Dissolve 1.36 g of sodium dihydrogen phosphate in 900 mL of water, adjust to pH 2.0 with phosphoric acid, and add water to make 1000 mL. To 850 mL of this solution add 150 mL of acetonitrile for liquid chromatography.

Flow rate: 1.0 mL per minute.

System suitability—

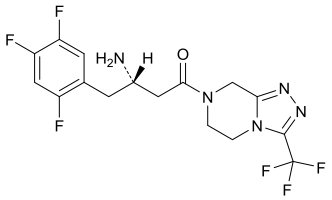
System performance: Place 10 mg of Sitagliptin Phosphate RS and 1 mg of sodium stearyl fumarate in a vial, and add 1 mL of water. Stopper the vial tightly, and heat at 80℃ for 20 to 48 hours. Take out the contents of the vial, wash the vial 3 times with a mixture of diluted phosphoric acid (1 in 1000) and acetonitrile for liquid chromatography (19:1), combine the washings and the content, and add a mixture of diluted phosphoric acid (1 in 1000) and acetonitrile for liquid chromatography (19:1) to make 100 mL. Stir this solution for 1 hour, and centrifuge for 10 minutes or until the solution becomes clear. Use the supernatant liquid as the solution for system suitability test. When the procedure is run with 20 μL of the solution for system suitability test under the above operating conditions, the resolution between sitagliptin and the peak having the relative retention time of about 1.2 to sitagliptin is not less than 1.5.

System repeatability: When the test is repeated 6 times with 20 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of sitagliptin is not more than 1.0%.

Containers and storage Containers—Tight containers.

Others

Related substance A (enantiomer): (3*S*)-3-Amino-1-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazine-7(8*H*)-yl]-4-(2,4,5-trifuluorophenyl)butane-1-one



Add the following to 9.01 Reference Standards (1):

Sitagliptin Phosphate RS

Sitagliptin Phosphate RS for System Suitability

Add the following to 9.41 Reagents, Test Solutions:

Sodium stearyl fumarate $C_{22}H_{39}NaO_4$ A white crystalline powder.

Content: not less than 99.0% and not more than 101.5%, calculated on the anhydrous basis. Assay — Weigh accurately about 0.6 g of sodium stearyl fumarate, add 8 mL of chloroform and 140 mL of acetic acid (100), and warm to dissolve. After cooling, titrate <*2.50*> with 0.1 mol/L perchloric acid VS (potentiometric titration). Perform a blank determination in the same manner, and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 39.05 mg of $C_{22}H_{39}NaO_4$

Add the following to 9.42 Solid Supports/Column Packings for Chromatography:

Amylose tris-(3,5-dimethylphenylcarbamate)-immobilized silica gel for liquid chromatography Prepared for liquid chromatography.