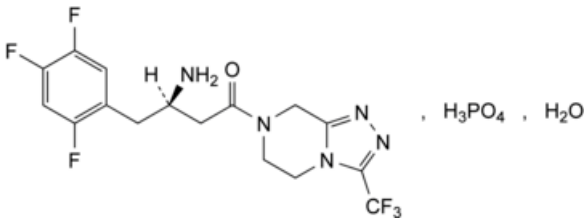
Edition: BP 2025 (Ph. Eur. 11.6 update)

Sitagliptin Phosphate Monohydrate

General Notices

(Ph. Eur. monograph 2778)



$C_{16}H_{18}F_6N_5O_5P,H_2O$ 523.3 *654671-77-9*

Action and use

Dipeptidylpeptidase-4 inhibitor; treatment of diabetes mellitus.

Preparations

Sitagliptin Tablets

Metformin and Sitagliptin Tablets

Metformin and Sitagliptin Prolonged-release Tablets

Ph Eur

DEFINITION

(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 phosphate monohydrate.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Soluble in water, very slightly soluble in anhydrous ethanol, practically insoluble in heptane.

It shows polymorphism (5.9).

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *sitagliptin phosphate monohydrate CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *methanol R*, evaporate to dryness and record new spectra using the residues.

B. Enantiomeric purity (see Tests).
C. Dissolve 0.200 g in *water R* and dilute to 5.0 mL with the same solvent. The solution gives reaction (a) of phosphates (2.3.1).

TESTS

Enantiomeric purity

Liquid chromatography (2.2.29): use the normalisation procedure.

Solvent mixture *water R*, *methanol R* (10:90 *V/V*).

Test solution Dissolve 80 mg of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 8 mg of *sitagliptin containing impurity A CRS* in 1 mL of the solvent mixture.

Column:

— *size*: *l* = 0.25 m, *Ø* = 4.6 mm;

— *stationary phase*: *amylose derivative of silica gel for chiral separation R* (5 µm);

— *temperature*: 35 °C.

Mobile phase *water for chromatography R*, *diethylamine R*, *heptane R*, *anhydrous ethanol R* (1:1:400:600 *V/V/V/V*).

Flow rate 0.8 mL/min.

Detection Spectrophotometer at 268 nm.

Injection 10 µL.

Run time 1.6 times the retention time of sitagliptin.

Identification of impurities Use the chromatogram supplied with *sitagliptin containing impurity A CRS* and the chromatogram obtained with reference solution (b) to identify the peak due to impurity A.

Relative retention With reference to sitagliptin (retention time = about 15 min): impurity A = about 0.9.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to impurity A and sitagliptin.

Limit:

— *impurity A*: maximum 0.5 per cent;

— *reporting threshold*: 0.1 per cent (reference solution (a)).

Related substances

Liquid chromatography (2.2.29).

Solvent mixture acetonitrile R, 0.1 per cent *V/V* solution of phosphoric acid R (5:95 *V/V*).

Test solution Dissolve 25.0 mg of the substance to be examined in the solvent mixture and dilute to 250.0 mL with the solvent mixture.

Reference solution (a) Dissolve 25.0 mg of sitagliptin phosphate monohydrate CRS in the solvent mixture and dilute to 250.0 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (c) In order to prepare the fumarate adduct *in situ*, heat 1 mL of water R, 1 mg of sodium stearyl fumarate R and 10 mg of the substance to be examined in a tightly closed vial at 80 °C for about 30 h. Dilute to 100 mL with the solvent mixture and stir for 1 h. Centrifuge a portion of the solution and use the clear supernatant.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: end-capped cyanosilyl silica gel for chromatography R (5 µm);

— *temperature*: 30 °C.

Mobile phase Mix 15 volumes of acetonitrile R1 and 85 volumes of a 1.36 g/L solution of potassium dihydrogen phosphate R previously adjusted to pH 2.0 with phosphoric acid R.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 205 nm.

Injection 20 µL of the test solution and reference solutions (b) and (c).

Run time 5.5 times the retention time of sitagliptin.

Relative retention With reference to sitagliptin (retention time = about 5.5 min): fumarate adduct = about 1.2.

System suitability Reference solution (c):

— resolution: minimum 1.5 between the peaks due to sitagliptin and the fumarate adduct.

Calculation of percentage contents:

— for each impurity, use the concentration of sitagliptin phosphate monohydrate in reference solution (b).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent.

Water (2.5.12)

3.3 per cent to 3.7 per cent, determined on 0.300 g.

Sulfated ash (2.4.14)

Maximum 0.2 per cent, determined on 1.0 g in a platinum crucible.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Injection Test solution and reference solution (a).

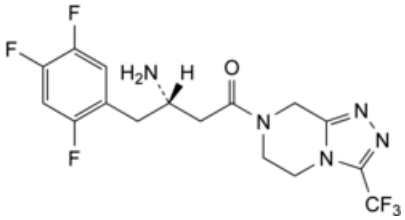
Run time Twice the retention time of sitagliptin.

Calculate the percentage content of $C_{16}H_{18}F_6N_5O_5P$ taking into account the assigned content of *sitagliptin phosphate monohydrate CRS*.

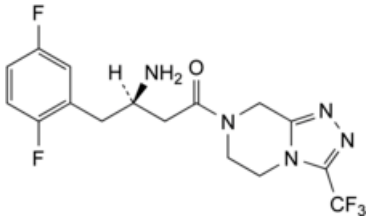
IMPURITIES

Specified impurities A.

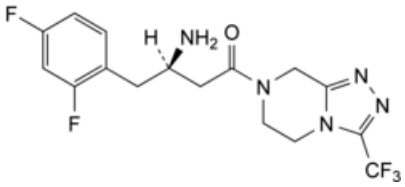
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) B, C.



A. (3*S*)-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,



B. (3*R*)-3-amino-4-(2,5-difluorophenyl)-1-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]butan-1-one,



C. (3*R*)-3-amino-4-(2,4-difluorophenyl)-1-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]butan-1-one.

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