Sitagliptin and Metformin Tablets

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Manufacturers, regulatory authorities, health authorities, researchers, and other stakeholders are invited to provide their feedback and comments on this draft proposal. Comments and samples received after the last date will not be considered by the IPC before finalizing the monograph.

Please send any comments you may have on this draft document to arnd-ipc@gov.in , with a copy to Dr. Gaurav Pratap Singh (email: gpsingh.ipc@gov.in) before the last date for comments.

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Sitagliptin and Metformin Tablets

Sitagliptin Phosphate and Metformin Hydrochloride Tablets

Metformin and Sitagliptin Tablets contain Sitagliptin Phosphate equivalent to not less than 95.0 per cent and not more than 105.0 per cent of the stated amount of sitagliptin, $C_{16}H_{15}F_6N_5O$ and metformin hydrochloride, $C_4H_{11}N_5$, HCl.

Usual strengths. Sitagliptin, 50 mg and Metformin hydrochloride, 500 mg; Sitagliptin, 50 mg and Metformin hydrochloride, 850 mg; Sitagliptin, 50 mg and Metformin hydrochloride, 1000 mg; Sitagliptin, 100 mg and Metformin hydrochloride, 500 mg; Sitagliptin, 100 mg and Metformin hydrochloride, 1000 mg.

Identification

A. In the Assay, (For Metformin Hydrochloride) the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with reference solution (a).

B. In the Assay, (For Sitagliptin) the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with reference solution (a).

Tests

Dissolution (2.5.2).
Apparatus No. 2 (Paddle),
Medium. 900 ml of *0.025 M sodium chloride*,
Speed and time. 75 rpm and 20 minutes.

Withdraw a suitable volume of the medium and filter.

Determine by liquid chromatography (2.4.14).

Test solution (a). Use the filtrate, dilute if necessary, with the dissolution medium.

Test solution (b). Use the filtrate, dilute if necessary, with the dissolution medium to obtain a solution containing 0.0055 per cent w/v of sitagliptin.

Reference solution. Dissolve a suitable quantity of *sitagliptin phosphate monohydrate IPRS* and *metformin hydrochloride IPRS* in the dissolution medium and dilute with the dissolution medium to obtain a solution having a known concentration similar to the expected concentration of the test solution.

Chromatographic system
- a stainless steel column 5 cm × 4.6 mm, packed with strong cation-exchange silica (5 µm) (such as Phenomenex Luna SCX),
- column temperature: 30º,
- mobile phase: a mixture of 75 volumes of *0.05 M potassium dihydrogen orthophosphate*, adjusted to pH 3.5 with *orthophosphoric acid* and 25 volumes of *acetonitrile*,
- flow rate: 2 ml per minute,
- spectrophotometer set at 255 nm,
- injection volume: 10 µl.

Inject the reference solution. The test is not valid unless the resolution between the peaks due to sitagliptin and metformin is not less than 1.6.

Inject the reference solution and test solution (a) for metformin hydrochloride and test solution (b) for sitagliptin.

Calculate the content of $C_4H_{11}N_5$, HCl and $C_{16}H_{15}F_6N_5O$ in the medium.

Q. Not less than 80 per cent of the stated amount of $C_4H_{11}N_5$, HCl and $C_{16}H_{15}F_6N_5O$.

Related substances. Determine by liquid chromatography (2.4.14).

For Metformin Hydrochloride —

Solvent mixture. 95 volumes of 0.1 per cent v/v solution of *orthophosphoric acid* and 5 volumes of *acetonitrile*.

Test solution. Disperse a quantity of the powdered tablets containing 1 g of Metformin Hydrochloride in the solvent mixture, with the aid of ultrasound with intermittent shaking and dilute to 500.0 ml with the solvent mixture, filter. Dilute a suitable volume of the filtrate to obtain a solution containing 0.01 per cent w/v of Metformin Hydrochloride.

Reference solution (a). A 0.001 per cent w/v solution of *metformin hydrochloride IPRS* in the solvent mixture. Dilute 1.0 ml of the solution to 100.0 ml with the solvent mixture.

Reference solution (b). To 20.0 ml of 0.02 per cent w/v solution of *metformin hydrochloride IPRS* in the solvent mixture, add 0.1 ml of *0.1 M sodium hydroxide*, heat at 80° for 2 hours, allow to cool to room temperature and add 3.0 ml of *orthophosphoric acid* (generation of metformin degradant 1 and metformin degradant 2). Add 2.0 ml of 0.01 per cent w/v solution of *sitagliptin phosphate monohydrate IPRS* in the solvent mixture and mix.

Chromatographic system
- a stainless steel column 5 cm × 4.6 mm, packed with strong cation-exchange silica (5 µm) (such as Phenomenex Luna SCX),
- column temperature: 30º,
- mobile phase: a mixture of 84 volumes of *0.05 M potassium dihydrogen orthophosphate*, adjusted to pH 3.5 with *orthophosphoric acid* and 16 volumes of *acetonitrile*,
- flow rate: 2 ml per minute,
- spectrophotometer set at 205 nm,
- injection volume: 20 µl.

Name	Relative retention time
Metformin degradant 1[1]	0.4
Metformin degradant 2[2]	0.6
Sitagliptin	0.8
Metformin (Retention time: about 3 minutes)	1.0

[1]unknown structure.
[2]unknown structure.

Inject reference solution (b) to identify the peaks due to metformin degradant 1, metformin degradant 2 and sitagliptin.

Inject reference solution (b). The test is not valid unless the resolution between the peaks due to metformin degradant 2 and sitagliptin is not less than 1.0 and between the peaks due to sitagliptin and metformin is not less than 1.6.

Inject reference solution (a) and the test solution. In the chromatogram obtained with the test solution, the area of any secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent) and the sum of the areas of all the secondary peaks is not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent). Ignore the peaks due to sitagliptin and sitagliptin related impurities and any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

For Sitagliptin —

Solvent mixture. 95 volumes of *0.1 per cent v/v* solution of *orthophosphoric acid* and 5 volumes of *acetonitrile*.

Test solution. Disperse a quantity of the powdered tablets containing 0.25 g of sitagliptin in the solvent mixture, with the aid of ultrasound with intermittent shaking and dilute to 500.0 ml with solvent mixture, filter. Dilute 4.0 ml of the filtrate to 25.0 ml with the solvent mixture.

Reference solution (a). A solution of *sitagliptin phosphate monohydrate IPRS* containing 0.0016 per cent w/v of sitagliptin in the solvent mixture. Dilute 1.0 ml of the solution to 100.0 ml with the solvent mixture.

Reference solution (b). (*for tablets containing sodium stearyl fumarate*) Disperse one intact tablet in 10 ml of *water,* with the aid of ultrasound, until the tablet is completely dispersed. Heat in a tightly closed vial at 80° for 30 hours, allow to cool and dilute to 100.0 ml with the solvent mixture and stir for 1 hour. Centrifuge a portion of the solution and use supernatant liquid. (*generation of sitagliptin fumarate adduct and sitagliptin acid hydrolysis product)*

(*for tablets that do not containing sodium stearyl fumarate*). To 10 mg of *sitagliptin phosphate monohydrate IPRS* and 1 mg of *sodium stearyl fumarate*, add 1 ml of *water.* Heat in a tightly closed vial at 80° for 30 hours, allow to cool and dilute to 100.0 ml with the solvent mixture and stir for 1 hour, centrifuge a portion of the solution and use supernatant liquid. (*generation of sitagliptin fumarate adduct and sitagliptin acid hydrolysis product*)

Chromatographic system
- a stainless steel column 10 cm × 3.0 mm, packed with end-capped octadecylsilane bonded to porous silica (3 µm) (such as YMC-Pack Pro C18),
- column temperature: 42º,
- mobile phase: A. a mixture of 95 volumes *0.025 M potassium dihydrogen orthophosphate*, adjusted to pH 2.5 with *orthophosphoric acid* and 5 volumes of *acetonitrile*,
  B. a mixture of 50 volumes of *acetonitrile* and 50 volumes of *methanol*,
- flow rate: 0.75 ml per minute,
- a gradient programme using the conditions given below,
- spectrophotometer set at 267 nm,
- injection volume: 20 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	87	13
14	35	65
14.1	87	13
17	87	13

Name	Relative retention time	Correction factor
Metformin	0.1	---
Sitagliptin acid hydrolysis product[1]	0.5	0.8
Sitagliptin	1.0	---
Sitagliptin fumarate adduct[2]	1.2	0.6
Sitagliptin triazecine analog[3]	1.7	---
Sitagliptin styrylacetyl analoge[4]	2.3	---
Sitagliptin phenylcrotonyl analog[5]	2.4	---

[1](3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoic acid,
[2]2-[[(2*R*)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-1-(2,4,5-trifluorophenyl)butan-2-yl]amino]butanedioic acid,
[3]3-(trifluoromethyl)-10-[(2,4,5-trifluorophenyl)methyl]-6,7,10,11-tetrahydro[1,2,4]triazolo[3,4-c][1,4,7]triazecine-8,12(5*H*,9*H*)-dione,
[4](3*E*)-1-[3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-α]pyrazin-7(8*H*)-yl]-4-(2,4,5-trifluorophenyl)but-3-en-1-one,
[5](2*E*)-1-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-α]pyrazin-7(8*H*)-yl]-4-(2,4,5-trifluorophenyl)but-2-en-1-one.

Inject reference solution (b) and (c). The test is not valid unless the resolution between the peaks due to sitagliptin and sitagliptin fumarate adduct is not less than 1.5 in the chromatogram obtained with reference solution (b) and the signal-to-noise ratio is not less than 20 in the chromatogram obtained with reference solution (a).

Inject reference solution (a) and the test solution. In the chromatogram obtained with the test solution, the area of any secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent) and the sum of the areas of all the secondary peaks is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent). Ignore the peaks due to metformin and metformin related impurities and any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent).

Uniformity of dosage units (2.5.4). Complies with the test stated under Uniformity of dosage units.

Other tests. Comply with the tests stated under Tablets.

Assay. Determine by liquid chromatography (2.4.14).

For Metformin Hydrochloride —

Solvent mixture. 95 volumes of *0.1 per cent v/v* solution of *orthophosphoric acid* and 5 volumes of *acetonitrile*.

Test solution. Weigh and powder 20 tablets. Disperse a quantity of the powder containing 1 g of Metformin Hydrochloride in solvent mixture, with the aid of ultrasound with intermittent shaking and dilute to 500.0 ml with solvent mixture, filter. Dilute a suitable volume of the filtrate with the solvent mixture to obtain a solution containing 0.01 per cent w/v of Metformin Hydrochloride.

Reference solution (a). A 0.01 per cent w/v solution of *metformin hydrochloride IPRS* in the solvent mixture.

Reference solution (b). Prepare a solution of *sitagliptin phosphate monohydrate IPRS* in reference solution (a) having a concentration of sitagliptin equivalent to that in the test solution.

Use chromatographic system as described under Related substances for Metformin Hydrochloride.

Inject reference solution (b). The test is not valid unless the resolution between the peaks due to sitagliptin and metformin is not less than 1.6.

Inject reference solution (a) and the test solution.

Calculate the content of $C_4H_{11}N_5$, HCl in the tablet.

For Sitagliptin —

Solvent mixture. 95 volumes of *0.1 per cent v/v* solution of *orthophosphoric acid* and 5 volumes of *acetonitrile*.

Test solution. Weigh and powder 20 tablets. Disperse a quantity of the powder containing 0.25 g of sitagliptin in the solvent mixture, with the aid of ultrasound with intermittent shaking and dilute to 500.0 ml with the solvent mixture, filter. Dilute 4.0 ml of the filtrate to 25.0 ml with the solvent mixture.

Reference solution (a). A solution of *sitagliptin phosphate monohydrate IPRS* containing 0.008 per cent w/v of sitagliptin in the solvent mixture.

Reference solution (b). (*for tablets containing sodium stearyl fumarate*) Disperse one intact tablet in 10 ml of *water,* with the aid of ultrasound, until the tablet is dispersed. Heat in a tightly closed vail at 80° for 30 hours, allow to cool and dilute to 100.0 ml with the solvent mixture and stir for 1 hour, centrifuge a portion of the solution and use supernatant liquid. (*generation of sitagliptin fumarate adduct and sitagliptin acid hydrolysis product)*.

Reference solution (b). (*for tablets that do not containing sodium stearyl fumarate*) To 10 mg of *sitagliptin phosphate monohydrate IPRS* and 1 mg of *sodium stearyl fumarate*, add 1 ml of *water,* heat in a tightly closed vial at 80° for 30 hours, allow to cool and dilute to 100.0 ml with the solvent mixture and stir for 1 hour, centrifuge a portion of the solution and use supernatant liquid. (*generation of sitagliptin fumarate adduct and sitagliptin acid hydrolysis product*).

Use chromatographic system as described under Related substances for Sitagliptin.

Inject reference solution (b). The test is not valid unless the resolution between the peaks due to sitagliptin and sitagliptin fumarate adduct is not less than 2.5.

Inject reference solution (a) and the test solution.

Calculate the content of $C_{16}H_{15}F_6N_5O$ in the tablet.

1 mg of sitagliptin phosphate monohydrate $C_{16}H_{20}F_6N_5O_6P$ is equivalent to 0.7783 mg of sitagliptin, $C_{16}H_{15}F_6N_5O$.

Labelling. The label states the strength in terms of the equivalent amount of sitagliptin.

Storage. Store protected from light and moisture, at temperature not exceeding 30º.