Vildagliptin and Metformin Tablets

Vildagliptin and Metformin Hydrochloride Tablets

Vildagliptin and Metformin Tablets contain not less than 95.0 per cent and not more than 105.0 per cent of the stated amounts of vildagliptin, $C_{17}H_{25}N_3O_2$ and metformin hydrochloride, $C_4H_{11}N_5$,HCl.

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

Identification

In the Assay, the principal peaks in the chromatogram obtained with test solution (a) and test solution (b) correspond to the principal peaks in the chromatogram obtained with reference solution (a).

Tests

Dissolution (2.5.2).
Apparatus No. 1 (Basket),
Medium. 900 ml of *0.01 M hydrochloric acid*,
Speed and time. 100 rpm and 30 minutes.

Withdraw a suitable volume of the medium and filter.

Determine by liquid chromatography (2.4.14).
Buffer solution. A solution prepared by dissolving 1.7 g of *potassium dihydrogen phosphate* in 1000 ml of *water*, adjusted to pH 3.0 with *orthophosphoric acid*. Add 8.0 g of *ammonium hexafluorophosphate* and mix.

Test solution (a). Use the filtrate.

Test solution (b). Dilute the filtrate, if necessary, with the dissolution medium to obtain a solution of known concentration similar to the expected concentration of the reference solution.

Reference solution. A solution containing 0.00556 per cent w/v, each of, *vildagliptin IPRS* and *metformin hydrochloride IPRS* in the dissolution medium.

Chromatographic system
- a stainless steel column 15 cm x 4.6 mm, packed with octadecylsilane bonded to spherical silica (3.0 µm), (Such as Atlantis d C18 100 Å),
- column temperature: 40º,
- mobile phase: a mixture of 40 volumes of the buffer solution, 33 volumes of *water* and 27 volumes of *acetonitrile*,
- flow rate: 1.8 ml per minute,
- spectrophotometer set at 218 nm,
- injection volume: 10 µl.

Inject the reference solution. The test is not valid unless the tailing factor is not more than 2.0 and the relative standard deviation for replicate injections is not more than 2.0 for both the peaks.

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

Calculate the content of $C_{17}H_{25}N_3O_2$ and $C_4H_{11}N_5$, HCl in the medium.

Q. Not less than 80 per cent of the stated amount of $C_{17}H_{25}N_3O_2$ and $C_4H_{11}N_5$,HCl .

Benzyltrimethylammonium hydroxide. Not more than 0.4 per cent.

Determine by gas chromatography (2.4.13).

NOTE - Use freshly prepared solutions.

Internal standard solution. A 0.5 per cent v/v solution of *benzyl alcohol* in *acetone.* Dilute 1.0 ml of the solution to 10.0 ml with *acetone.* Dilute 2.0 ml of the solution to 200.0 ml with *acetone.*

Test solution. Disperse a quantity of the powdered tablets containing 62.5 mg of Vildagliptin in the internal standard and vortex for 2 minutes. Then stir the solution for 45 minutes, with the aid of magnetic stirrer, dilute to 50.0 ml with the internal standard and centrifuge at 4000 rpm for 30 minutes. Use supernatant liquid.

Reference solution (a). A solution containing 0.000625 per cent w/v of *benzyltrimethylammonium hydroxide IPRS (1- amino-adamantan-3-ol)* in the internal standard solution.

Reference solution (b). Dilute 2.0 ml of reference solution (a) to 10.0 ml with the internal standard solution.

Reference solution (c). A 0.125 per cent w/v solution of *vildagliptin IPRS* in reference solution (a).

Chromatographic system
- a fused-silica capillary column, 15 m x 0.25 mm coated with crossbond 5 per cent diphenyl and 95 per cent dimethylpolysiloxane with film thickness of 1.0 µm (Such as Rtx-5 amine),
- temperature:
  column 100° for 4 minutes, 100° to 290° @ 35° per minutes and hold at 290°, for 14 minutes,
- inlet port at 250° and detector at 300°,
- flame ionisation detector,
- split ratio of 5:1,
- flow rate: 1.0 ml per minute using nitrogen as the carrier gas,
- injection volume: 1 µl.

Inject reference solution (a), (b) and (c). The test is not valid unless the resolution between the peaks due to benzyltrimethyl ammonium hydroxide and benzyl alcohol is not less than 2.5 in the chromatogram obtained with reference solution (c), the relative standard deviation of the peak area ratio due to benzyltrimethylammonium hydroxide and internal standard for replicate injections is not more than 10.0 per cent in the chromatogram obtained with reference solution (a) and the signal-to-noise ratio is not less than 10 in the chromatogram obtained with reference solution (b).

Inject reference solution (a) and the test solution.

Calculate the content of benzyltrimethyl ammonium hydroxide, using ratio of the peak area of benzyltrimethyl ammonium hydroxide to that of peak area of the internal standard.

Related substances. Determine by liquid chromatography (2.4.14).

Buffer solution. Dissolve 1.7 g of *potassium dihydrogen phosphate* in 1000 ml of *water* and adjusted to pH 3.0 with *ortho phosphoric acid,* add 8 g of *ammonium hexafluorophosphate* and mix.

Solvent mixture. 90 volumes of *water,* 10 volumes of *acetonitrile* and 0.1 volume of *orthophosphoric acid*.

Solution A. 40 volumes of the buffer solution*,* 60 volumes of *water* and 2.5 volumes of *acetonitrile.*

Test solution (a). Disperse 10 intact tablets in the solvent mixture, with the aid of magnetic stirrer for 45 minutes, dilute to 500.0 ml with the solvent mixture. Centrifuge to get a clear supernatant, filter. Dilute 10.0 ml of the filtrate to 20.0 ml with the solvent mixture.

Test solution (b). Dilute a suitable volume of test solution (a) with solution A to obtain a solution having 0.02 per cent w/v of Metformin Hydrochloride.

Reference solution (a). A solution containing 0.05 per cent w/v of *vildagliptin IPRS* and 0.02 per cent w/v of *metformin hydrochloride IPRS* in the solvent mixture.

Reference solution (b). Dilute 1.0 ml of reference solution (a) to 100.0 ml with the solvent mixture.

Reference solution (c). A 0.005 per cent w/v solution of *dicyandiamide IPRS* in the solvent mixture.

Reference solution (d). Dilute 5.0 ml of reference solution (b) and 0.2 ml of reference solution (c) to 50.0 ml with the solvent mixture.

Reference solution (e). A solution containing 0.0125 per cent w/v, each of, *vildagliptin impurities A, B, C IPRS* and *dicyandiamide IPRS* in the solvent mixture. Dilute 2.0 ml of the solution to 50.0 ml with reference solution (a).

Chromatographic system

- a stainless steel column 15 cm x 4.6 mm, packed with octadecylsilane bonded to spherical silica (3.0 µm) (Such as Waters, Atlantis d C18 100 Å**),**
- column temperature: 35º,
- mobile phase A: a mixture of 40 volumes of a buffer solution and 60 volumes of *water,*
  B: a mixture of 40 volumes of a buffer solution and 60 volumes of *acetonitrile*,
- a gradient programme using the conditions given below,
- flow rate: 1 ml per minute,
- spectrophotometer set at 210 nm (for vildagliptin) and 218 nm (for metformin hydrochloride),
- injection volume: 10 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	97	3
1	97	3
2	85	15
5	75	25
12	25	75
12.1	97	3
18	97	3

Name	Relative retention time	Correction factor
Dicyandiamide[1]	0.21	0.36
Metformin hydrochloride	0.41	---
Vildagliptin impurity A[2]	0.87	0.58
Vildagliptin impurity B[3]	0.83	0.77
Vildagliptin impurity C[4]	0.95	0.68
Vildagliptin	1.0	---

[1] 1-cyanoguanidine
[2] 2-(3-hydroxy-adamantan-1-yl)-1-imino-hexahydro-pyrrolo[1,2-a]pyrazin-4-one. (Cyclic amidine).
[3] (S)1-[(3-Hydroxyadamant-1-ylamino)-acetyl]-2-prolinamide. (Amide).
[4] 2-(3-Hydroxy adamantan-1-yl)-hexahydro-pyrrolo[1,2-a]pyrazine-1,4-dione. (Diketopiperazine).

Inject reference solution (b), (d) and (e) at 210 nm. The test is not valid unless the resolution between the peaks due to vildagliptin impurity B and vildagliptin impurity A is not less than 1.8 in the chromatogram obtained with reference solution (e), the tailing factor is not more than 2.0 and the relative standard deviation for replicate injections is not more than 5.0 per cent for both the peaks in the chromatogram obtained with reference solution (b). The signal-to-noise ratio is not less than 10 in the chromatogram obtained with reference solution (d) for all the three peaks.

Inject reference solution (b) and test solution (a) at 210 nm. In the chromatogram obtained with test solution (a), the area of any peak corresponding to vildagliptin impurity A and vildagliptin impurity C, each of, is not more than the area of vildagliptin peak in the chromatogram obtained with reference solution (b) (1.0 per cent), the area of any peak corresponding to vildagliptin impurity B is not more than twice the area of vildagliptin peak in the chromatogram obtained with reference solution (b) (2.0 per cent), the area of any other secondary peak is not more than 0.2 times the area of the vildagliptin peak in the chromatogram obtained with reference solution (b) (0.2 per cent) and the sum of the areas of all the secondary peaks is not more than 3.5 times the area of vildagliptin peak in the chromatogram obtained with reference solution (b) (3.5 per cent). Ignore the peaks due to metformin hydrochloride and any peak with an area less than 0.05 times the area of the vildagliptin peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Inject reference solution (b) and test solution (b) at 218 nm. In the chromatogram obtained with the test solution (b), the area of any peak corresponding to dicyandiamide is not more than 0.02 times the area of principal peak in the chromatogram obtained with reference solution (b) (0.02 per cent), the area of any other secondary peak is not more than 0.1 the area of the metformin hydrochloride peak in the chromatogram obtained with reference solution (b) (0.1 per cent), and the sum of the areas of all the secondary peaks is not more than 0.6 times the area of metformin hydrochloride peak in the chromatogram obtained with reference solution (b) (0.6 per cent). Ignore the peak due to vildagliptin.

Uniformity of content (2.5.4). Complies with the test stated under Tablets.
Determine by liquid chromatography (2.4. 14), as described under Dissolution, using the following modifications.

Solvent mixture. 90 volumes of *water,* 10 volumes of *acetonitrile* and 0.1 volume of *orthophosphoric acid*.

Test solution. Disperse one intact tablet in the solvent mixture, with the aid of ultrasound and dilute to 200.0 ml with the solvent mixture, filter.

Reference solution. A 0.025 per cent w/v solution of *vildagliptin IPRS* in the solvent mixture.

Inject the reference solution. The test is not valid unless the tailing factor is not more than 2.0 and the relative standard deviation for replicate injections is not more than 2.0.

Inject the reference solution and the test solution.

Calculate the content of $C_{17}H_{25}N_3O_2$ in the tablet.

Other tests. Comply with the tests stated under Tablets.

Assay. Determine by liquid chromatography (2.4.14), as described under Related substances.

Inject reference solution (a). The test is not valid unless the tailing factor is not more than 2.0 and the relative standard deviation for replicate injections is not more than 2.0 per cent for both the peaks.

Inject reference solution (a) and test solution (a) and (b).

Calculate the content of $C_{17}H_{25}N_3O_2$ in test solution (a) and $C_4H_{11}N_5$, HCl in test solution (b) in the tablets.

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

4.2. General reagents. Page 890

Insert before **Ammonium Mercurithiocyanate Solution.**

Ammonium Hexafluorophosphate; NH_4PF_6 = 163.0
General laboratory reagent grade of commerce.