Glipizide and Metformin Tablets

Glipizide and Metformin Hydrochloride Tablets

Glipizide and Metformin Tablets contain not less than 90.0 per cent and not more than 110.0 per cent of the stated amounts of glipizide, $C_{21}H_{27}N_5O_4S$ and metformin hydrochloride, $C_4H_{11}N_5$, HCl.

Usual strengths. Glipizide, 2.5 mg and Metformin Hydrochloride, 250 mg; Glipizide, 5 mg and Metformin Hydrochloride, 250; Glipizide, 5 mg and Metformin Hydrochloride, 500 mg.

Identification

In the Assay of glipizide, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with reference solution (a) and in the Assay of 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).

Tests

NOTE - Protect the solution from light.

Dissolution (2.5.2).
Apparatus. No 2 (Paddle),
Medium. 1000 ml of 0.05 M phosphate buffer pH 6.8 prepared by dissolving 6.48 g of *monobasic potassium phosphate* and 0.83 g of *sodium hydroxide* in 1000 ml of *water,* adjusted to pH 6.8 with *dilute sodium hydroxide solution, [Note-Control of the pH is critical]*,
Speed and time. 50 rpm and 45 minutes for glipizide and 30 minutes for metfonnin hydrochloride.

For Glipizide -

Withdraw a suitable volume of the medium and filter.

Determine by liquid chromatography (2.4.14)

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

Reference solution. A 0.005 per cent w/v solution of *glipizide IPRS* in *methanol.* Dilute a suitable volume of the solution with the dissolution medium to obtain the same concentration as expected in the test solution.

Chromatographic system
- a stainless steel column 15 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm),
- mobile phase: a mixture of 48 volumes of a buffer solution prepared by dissolving 3.4 g of *monobasic potassium phosphate* in 800 ml of *water,* adjusted to pH 6.0 with *10 M sodium hydroxide,* dilute to 1000 with *water* and 52 volumes of *methanol*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 220 nm,
- injection volume: 50 µl.

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

Inject the reference solution and the test solution.

Calculate the content of $C_{21}H_{27}N_5O_4S$ in the medium.

Q. Not less than 80 per cent of the stated amount of $C_{21}H_{27}N_5O_4S$.

For Metformin Hydrochloride –

Withdraw a suitable volume of the medium and filter. Measure the absorbance of the filtrate, suitably diluted with dissolution medium if necessary, at the maximum at about 233 nm (2.4.7). Calculate the content of $C_4H_{11}N_5$,HCl, in the medium from the absorbance obtained from a solution of known concentration of *metformin hydrochloride IPRS* in the dissolution medium.

Q. Not less than 80 per cent of the stated amount of $C_4H_{11}N_5$,HCl.

Related substances. Determine by liquid chromatography (2.4.14).

For Glipizide –

Solvent mixture. 60 volumes of *acetonitrile* and 40 volumes of *water*.

Buffer solution. Dissolve 2.6 g of *dibasic ammonium phosphate* in 1000 ml of *water*, adjusted to pH 8.0 with *ammonium hydroxide.*

Test solution. Disperse 5 intact tablets in the solvent mixture (50.0 per cent of the final volume) in a suitable volumetric flask with the aid of ultrasound for 30 minutes and shake vigorously for another 30 minutes to dissolve and dilute to volume with *water* to obtain a solution containing 0.005 per cent w/v of Glipizide (solution A). To 5.0 ml of solution A, add 5.0 ml of the solvent mixture and dilute to 20.0 ml with *water*.

Chromatographic system
- a stainless steel column 15 cm x 4.6 mm, packed with octylsilane bonded to porous silica (5 µm),
  - mobile phase: A. a mixture of 25 volumes of the buffer solution, 70 volumes of *water* and 5 volumes of *acetonitrile*,
    B. a mixture of 25 volumes of the buffer solution, 25 volumes of *water* and 50 volumes of *acetonitrile*,
  - a gradient programme using the conditions given below,
    - flow rate: 1 ml per minute,
    - spectrophotometer set at 223 nm,
    - injection volume: 50 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	100	0
3	100	0
18	0	100
20	0	100
22	100	0
30	100	0

Name	Relative retention time	Correction factor
Glipizide related compound A[1]	0.92	0.71
Glipizide	1.0	

[1]N-{2-[(4-aminosulfonyl) phenyl]ethyl}-5-methyl-pyrazinecarboxamide

Inject the test solution, the area of any peak corresponding to glipizide related compound A is not more than 2.0 per cent, the area of any other secondary peak (eluting after approximately 8 minutes) is not more than 0.5 per cent and the sum of areas of all the secondary peaks other than glipizide related compound A is not more than 1.0 per cent, calculated by area normalisation. Ignore the peak due to metformin hydrochloride and any peak with an area less than 0.05 per cent.

For Metformin Hydrochloride –

Buffer solution. Dissolve 9.41 g of *sodium 1-hexanesulfonate* in 1000 ml of *water*, adjusted to pH 2.0 with *trifluoroacetic acid.*

Solution B. 60 volumes of *water* and 40 volumes of *acetonitrile*.

Solvent mixture. 63 volumes of *water*, 30 volumes of the buffer solution and 7 volumes of *acetonitrile*.

Test solution. Dilute a suitable volume of solution A (obtained from test solution of Glipezide) with the solvent mixture to obtain a solution containing 0.01 per cent w/v of Metformin Hydrochloride.

Chromatographic system
- a stainless steel column 15 cm x 4.6 mm, packed with phenyl groups bonded to porous silica (3.5 µm),
- mobile phase: a mixture of 30 volumes of the buffer solution, 20 volumes of solution B and 50 volumes of *water,*
- flow rate: 1 ml per minute,
- spectrophotometer set at 218 nm,

– injection volume: 25 µl.

Inject the test solution. The area of any secondary peak is not more than 0.1 per cent and the sum of the areas of all the secondary peaks is not more than 0.5 per cent, calculated by area normalization and ignore the peak due to glipizide and any peak with an area less than 0.05 per cent.

Uniformity of content. Complies with the test stated under Tablets.

Determine by liquid chromatography (2.4.14), as described under Related substances of Glipizide with the following modifications.

Test solution. Disperse 1 intact tablet in the solvent mixture (50.0 per cent of the final volume) in a suitable volumetric flask with the aid of ultrasound for 30 minutes and shake vigorously for another 30 minutes to dissolve and dilute to volume with *water* to obtain a solution containing 0.00125 per cent w/v of Glipizide.

Reference solution. Dissolve 10 mg of *glipizide IPRS* in 60 ml of *acetonitrile,* with the aid of ultrasound for 20 minutes with intermittent shaking and dilute to 100.0 ml with *water*. To 25.0 ml of the solution, add 75 ml of the solvent mixture and dilute to 200.0 ml with *water.*

Inject the reference solution and the test solution.

Calculate the content of $C_{21}H_{27}N_5O_4S$ in the tablet.

Other tests. Comply with the tests stated under Tablets.

Assay

For Glipizide –

Determine by liquid chromatography (2.4.14), as described under Related substances for glipizide with the following modifications.

Reference solution (a). Dissolve 10 mg of *glipizide IPRS* in 60 ml of *acetonitrile,* with the aid of ultrasound for 20 minutes with intermittent shaking and dilute to 100.0 ml with *water*. To 25.0 ml of the solution, add 75 ml of the solvent mixture and dilute to 200.0 ml with *water.*

Reference solution (b). Dissolve 2.5 mg of *glipizide related compound A IPRS* in 150 ml of *acetonitrile,* with the aid of ultrasound for 30 minutes and dilute to 250.0 ml with *acetonitrile.* Dilute 1.0 ml of the solution to 50.0 ml with reference solution (a).

The relative retention time with reference of glipizide for glipizide related compound A is about 0.92.

Inject reference solution (a) and (b). The test is not valid unless the resolution between the peaks due to glipizide related compound A and glipizide is not less than 1.2 in the chromatogram obtained with reference solution (b) and the relative standard deviation for the replicate injections is not more than 2.0 per cent in the chromatogram obtained with reference solution (a).

Inject reference solution (a) and the test solution.

Calculate the content of $C_{21}H_{27}N_5O_4S$ in the tablets.

For Metformin Hydrochloride –

Determine by liquid chromatography (2.4.14), as described under Related substances for metformin hydrochloride with the following modifications.

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

Reference solution (b). A 0.0005 per cent w/v solution of *dicyandiamide IPRS* in *water*. Dilute 1.0 ml of the solution to 100.0 ml with reference solution (a).

The relative retention time with reference of metformin for dicyandiamide is about 0.26.

Inject reference solution (a) and (b). The test is not valid unless the resolution between the peaks due to dicyandiamide and metformin is not less than 3.0 in the chromatogram obtained with reference solution (b) and the relative standard deviation for the replicate injections is not more than 2.0 per cent in the chromatogram obtained with reference solution (a).

Inject reference solution (a) and the test solution.

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

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