DEPARTMENT OF DRUG ADMINISTRATION

National Medicines Laboratory

ANALYTICAL METHOD VALIDATION COMMITTEE

Metformin (Sustained Release) & Linagliptin Tablets

Analytical Profile No.: LMS 074/075/AP 029

Metformin (Sustained Release) & Linagliptin Tablets contain not less than 90 % and not more than 110 % of the stated amount of Metformin and Linagliptin.

1. Identification:

1.1 Metformin HCl: In the assay, the principle peak in the chromatogram obtained with the test solution should correspond to the peak in the chromatogram obtained with the reference solution of Metformin HCl.

1.2. Linagliptin: In the assay, the principle peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with the reference solution of Linagliptin.

Tests:

2. Dissolution:

2.1 Linagliptin: *Determine by liquid chromatography*

2.1.1 Dissolution Parameters:

Apparatus: Basket

Medium and Volume: 900 ml of 0.1 N HCl

Speed and Time: 50 rpm for 45 min

Withdraw a suitable volume of the medium and filter through a membrane filter of 0.2 µm.

2.1.2 Test Solution: Use the filtrate.

2.1.3 Reference Solution: Weigh accurately about 13.5 mg Linagliptin reference standard and transfer into 100 ml volumetric flask. Add about 60 ml of 0.1 N HCl, sonicate for 15 minutes, cool and make up the volume to 100 ml with 0.1 N HCl. Dilute 2 ml of the resulting solution to 100 ml with 0.1 N HCl. Filter the resulting solution through a membrane filter of 0.2 µm.

2.1.4 Chromatographic condition and Procedure: Proceed as directed under the Assay.

2.1.5 Limit: Not less than 80 % (D) of the stated amount.

2.2 Metformin: *Determine by UV Spectroscopy*

2.2.1 Dissolution Parameters:

Apparatus: Basket

Medium and volume: 1000 ml phosphate buffer pH 6.8

Speed and Time: 100 rpm for 1 hr, 3 hr and 10 hr

Withdraw a suitable volume of the medium and filter.

2.2.2 Test Solution: Dilute 1 ml of the filtrate to 100 ml with dissolution medium.

2.2.3 Reference Solution: Weigh accurately about 25 mg Metformin hydrochloride reference standard and transfer into 100 ml volumetric flask. Dissolve with water and make up the volume to 100 ml with water. Dilute 2 ml of the resulting solution to 100 ml with dissolution medium.

2.2.4 Procedure: Measure the absorbance of the test and reference solution at about 232 nm and calculate the percentage release of Metformin in the tablet.

2.2.5 Limit:

25 % to 50 % of the stated amount in 1st hour

45 % to 70 % of the stated amount in 3rd hour

NLT 80 % of the stated amount in 10th hour

3. Uniformity of content (Linagliptin): *Determine by liquid chromatography*

3.1 Test Solution: Weigh 10 tablets and transfer individually to 100 ml volumetric flask. Add 60 ml of mobile phase and sonicate for 15 min to disperse the tablet. Make up the volume with mobile phase. Filter the final solution through 0.2 µm membrane filter. (25 ppm)

3.2 Reference Solution: Weigh accurately about 12.5 mg Linagliptin reference standard in 50 ml volumetric flask and add 35 ml mobile phase. Dissolve by sonication and dilute to 50 ml with mobile phase. Dilute 5 ml of resulting solution to 50 ml with mobile phase. Filter the resulting solution through 0.2 µm membrane filter. (25 ppm)

3.3 Chromatographic system and Procedure: Proceed as directed under Assay.

3.4 Limit: 85-115% of the stated amount.

4 Assay: *Determine by liquid chromatography*

4.1 Test Solution: Weigh individually 20 tablets & crush them into fine powder. Weigh accurately the powder equivalent to 500 mg of Metformin HCl in 100 ml flask, add 70 ml of mobile phase & sonicate for 15 minutes to dissolve. After sonication, cool to room temperature and make volume to 100 ml with mobile phase. Filter the final solution through 0.2 µm membrane filter.

Note: Adjust the concentration of the standard preparation and sample preparation depending upon the strength of Metformin and Linagliptin Tablet.

4.2 Reference Solution:

4.2.1 Linagliptin Standard solution: Weigh accurately about 12.5 mg Linagliptin reference standard into separate 100 ml volumetric flask. Add about 70 ml of mobile phase and sonicate for about 10 minutes and make up the volume to 100 ml with mobile phase.

4.2.2 Metformin HCl Reference Solution: Weigh accurately about 42.5 mg Metformin HCl RS and transfer into 20 ml volumetric flask and sonicate to dissolve.

4.2.3 Mix Reference Solution: Transfer 2 ml of Linagliptin Reference Solution to Metformin HCl Reference Solution and make up the volume with mobile phase. Filter the resulting solution through 0.2 µm membrane filter.

4.3 Chromatographic system:

Column: C18, (150*4.6 mm), 5 µm

Flow rate: 1.0 ml/min

Wavelength: 265 nm (Metformin) & 295 nm (Linagliptin)

Injection volume: 20 µl

Detector: PDA Detector

Column temperature: 25 °C

Mobile phase: Buffer: Acetonitrile (70:30)

Buffer: 0.02 M Phosphate buffer

4.4 Procedure: Inject 20 µl of reference solution five times as per above mentioned chromatographic condition. In the chromatogram obtained from the standard preparation, the column efficiency determined from the major peak should not be less than 2000 theoretical plates, the tailing factor should be not more than 2.0, the relative standard deviation of replicate injections should not be more than 2.0 % and resolution between two peaks should be not less than 2. Inject 20 µl of the sample preparation and chromatograph as per above mentioned chromatographic condition. Calculate the content of Linagliptin and Metformin in each tablet.

5. Other tests: As per pharmacopoieal requirement.