COA, Spec and MOA

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Method of Analysis

Lisinopril Dihydrate BP

1. DESCRIPTION

White or almost white, crystalline powder.

2. SOLUBILITY

Soluble in water, practically insoluble in anhydrous ethanol and in heptane.

3. IDENTIFICATION

A. By Specific optical rotation

-47 to -43

Dissolve 0.5 g in zinc acetate solution and dilute to 50.0 mL with the same solvent.

B By Infrared absorption spectrophotometry

Test IR spectrum should be match with standard IR spectrum

4. RELATED SUBSTANCES

Liquid chromatography.

Test solution. Dissolve 50 mg of the substance to be examined in mobile phase A and dilute to 10.0 mL with mobile phase A.

Reference solution (a) Dissolve 5 mg of lisinopril for system suitability A CRS (containing impurities A and E) in mobile phase A and dilute to 1.0 mL with mobile phase A.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 10.0 mL with mobile phase A.

Reference solution (c) Dissolve the contents of a vial of lisinopril impurity F CRS in 1.0 mL of mobile phase A.

Reference solution (d) Dissolve 5 mg of lisinopril for peak identification CRS (containing impurity G) in mobile phase A and dilute to 1.0 mL with mobile phase A.

Column:

— size: l = 0.25 m, Ø = 4.6 mm;

— stationary phase: base-deactivated end-capped octadecylsilyl silica gel for chromatography (5 µm);

— temperature: 50 °C.

Mobile phase:

— mobile phase A: mix 3 volumes of acetonitrile and 97 volumes of a 3.12 g/L solution of sodium dihydrogen phosphate R previously adjusted to pH 3.8 with dilute phosphoric acid ;

— mobile phase B: mix 20.5 volumes of acetonitrile and 79.5 volumes of a 3.12 g/L solution of sodium dihydrogen phosphate previously adjusted to pH 3.5 with dilute phosphoric acid;

Flow rate 1.6 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 50 µL.

Identification of impurities Use the chromatogram supplied with lisinopril for system suitability A CRS and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A and E; use the chromatogram obtained with reference solution (c) to identify the peak due to impurity F; use the chromatogram supplied with lisinopril for peak identification CRS and the chromatogram obtained with reference solution (d) to identify the peak due to impurity G.

Relative retention With reference to lisinopril (retention time = about 14 min): impurity A = about 0.7; impurity E = about 1.2; impurity F = about 1.9; impurity G = about 2.9.

System suitability:

— resolution: minimum 1.5 between the peaks due to lisinopril and impurity E in the chromatogram obtained with reference solution (a);

— signal-to-noise ratio: minimum 45 for the principal peak in the chromatogram obtained with reference solution (b).

Calculation of percentage contents:

— correction factor: multiply the peak area of impurity F by 2.1;

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

Limits:

— impurities A, E, F: for each impurity, maximum 0.2 per cent;

— impurity G: maximum 0.15 per cent;

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

— total: maximum 0.5 per cent;

— reporting threshold: 0.05 per cent; disregard any peak with a retention time less than 3 min.

5. WATER

8.0 per cent to 9.5 per cent

Clean the receiving tube and the condenser of the apparatus, thoroughly rinse with water, and dry. Introduce 200 mL of toluene and about 2 mL of water into the dry flask. Distil for 2 h, and then allow cooling for about 30 min and reading the water volume to the nearest 0.05 mL. Place in the flask 10.0g of a quantity of the substance, weighed with an accuracy of 1 per cent, expected to give about 2 mL to 3 mL of water. If the substance has a pasty consistency, weigh it in a boat of metal foil. Add a few pieces of porous material and heat the flask gently for 15 min. When the toluene begins to boil, distil at the rate of about two drops per second until most of the water has distilled over, then increase the rate of distillation to about four drops per second. When the water has all distilled over, rinse the inside of the condenser tube with toluene. Continue the distillation for 5 min, remove the heat, allow the receiving tube to cool to room temperature and dislodge any droplets of water which adhere to the walls of the receiving tube. When the water and toluene have completely separated, read the volume of water and calculate the content present in the substance as millilitres per kilogram, using the formula:

$$\frac{1000\,(n_2 - n_1)}{m}$$

m = the mass in grams of the substance to be examined,

n_1 = the number of millilitres of water obtained in the first distillation,

n_2 = the total number of millilitres of water obtained in the 2 distillations.

6. SULFATED ASH

Not more than 0.1%

Ignite silica at 600 ± 50 °C for 30 min and allow cooling in a desiccator over silica gel and weighing it. Place the 1.0 g of the substance in the crucible and weigh it. Moisten the substance with a 1 ml of sulfuric acid and heat gently at as low a temperature as practicable until the sample is thoroughly charred. After cooling, moisten the residue with 1 ml of sulfuric acid, heat gently until white fumes are no longer evolved and ignite at 600 ± 50 °C until the residue is completely incinerated. Ensure that flames are not produced at any time during the procedure. Allow the crucible to cool in a desiccator over silica gel or other suitable desiccant, weigh it again and calculate the percentage of residue.

7. ASSAY

98.5 per cent to 101.5 per cent (anhydrous substance).

Dissolve 0.350 g in 50 mL of water . Titrate with 0.1 M sodium hydroxide, determining the end-pointpotentiometrically.

1 mL of 0.1 M sodium hydroxide is equivalent to 40.55 mg of $C_{21}H_{31}N_3O_5$.

CERTIFICATE OF ANALYSIS

QUALITY CONTROL DEPARTMENT **ANALYTICAL REPORT**

NAME OF THE DRUG SUBSTANCE	LISINOPRIL DIHYDRATE BP	**BATCH / LOT NO.**	LPD201800901
QUANTITY RECEIVED	100.0 kg	**SAMPLE COLLECTED ON**	03/09/2018
QUANTITY SAMPLED	100 gm	**ANALYTICAL REPORT NO**	ARN/LPD/747
DATE OF MFG.	09/2018	**DATE OF REPORT**	09/09/2018
DATE OF EXPIRY	08/2022	**SPECIFICATION**	BP 2018

TEST	SPECIFICATION	RESULTS
Description	White or almost white, crystalline powder.	White or almost white, crystalline powder.
Solubility	Soluble in water, practically insoluble in anhydrous ethanol and in heptane.	Soluble in water, practically insoluble in anhydrous ethanol and in heptane.
Identification		
Specific optical rotation	-47 to -43	Positive for Lisinopril
By Infrared absorption spectrophotometry	Test IR spectrum should be match with standard IR spectrum	Positive for Lisinopril
Related Substances		
Impurity A	Not more than 0.1 %	Not detected
Impurity E	Not more than 0.1 %	Not detected

Impurity F	Not more than 0.1 %	Not detected
Impurity G	Not more than 0.15 %	Not detected
Unspecified Impurity	Not more than 0.10 %	0.03%
Total Impurities	Not more than 0.5%	0.08%
Water	8.0 per cent to 9.5 per cent	8.6 %
Sulfated ash	Not more than 0.1%	0.01 %
Assay	98.5 per cent to 101.5 per cent	100.39 %

Opinion: In the opinion undersigned, the sample referred to the above is of Standard Quality as defined in the Act. And the Rules there under for the reason given below. The sample complies above standards as per BP. The opinion is in respect of the tests carried and mentioned above.

ANALYSED BY: **APPROVEDBY:**

Lisinopril Dihydrate BP

S.NO	TEST	SPECIFICATION	METHOD
1	Description	White or almost white, crystalline powder.	Physical method (as per BP 2018)
2	Solubility	Soluble in water, practically insoluble in anhydrous ethanol and in heptane.	Physical method (as per BP 2018)
3	Identification		
	Specific optical rotation	-47 to -43	Physical method (as per BP 2018)
	By Infrared absorption spectrophotometry	Test IR spectrum should be match with standard IR spectrum	Spectroscopical method (as per BP 2018)
4	Related Substances		
	Impurity A	Not more than 0.1 %	LC method (as per BP 2018)
	Impurity E	Not more than 0.1 %	LC method (as per BP 2018)
	Impurity F	Not more than 0.1 %	LC method (as per BP 2018)
	Impurity G	Not more than 0.15 %	LC method (as per BP 2018)
	Unspecified Impurity	Not more than 0.10 %	LC method (as per BP 2018)
	Total Impurities	Not more than 0.5%	LC method (as per BP 2018)

5	Water	8.0 per cent to 9.5 per cent	Physical method (as per BP 2018)
6	Sulfated ash	Not more than 0.1%	Chemical method (as per BP 2018)
7	Assay	98.5 per cent to 101.5 per cent	Potentiometric method (as per BP 2018)

Comments on specification: Lisinopril Dihydrate active raw material confirms to BP.