No.F.14-1/2022-PEC
Government of Pakistan
Ministry of National Health Services, Regulation and Coordination
(Drug Regulatory Authority of Pakistan)
TF Complex Sector G-9/4
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"SAY NO TO CORRUPTION"

Islamabad, the 14th March, 2022

Subject: - **Cefixime Capsule 200mg & 400mg Specifications.**

I am directed to refer to the subject captioned above. Registration Board in its 313rd meeting held on 16th – 18th November, 2021 deliberated the subject matter in detail and after thoroughly reviewing the product documents of innovator drug product Suprax 400mg capsule and the monograph of cefixime capsule in Japanese Pharmacopeia 17th Edition, decided to approve the monograph for cefixime capsule attached as **Annexure-I**.

2. The Board further advised the manufacturer's / importers having registration of the subject products to revise their specifications in the light of instant approved monograph within 6 months after its notification and shall mention "Manufacturer's Specifications" on the label.

3. Accordingly, above decision of Registration Board is hereby circulated for information and compliance for all relevant stakeholders, and directed to apply for approval of change of specifications in relevant section of PE&R Division.

(ABDULLAH) 14/03/22
Additional Director (PE&R)/
Secretary, Registration Board

Distribution:

i. Director (MIS), DRAP for uploading on DRAP's website.
ii. Director, Central Drugs Laboratory, Karachi.
iii. Chief, Drug Control and Traditional Medicine Division, National Institute of Health, Islamabad.
iv. Director, Drug Testing Laboratories of the Punjab (Lahore, Faisalabad, Multan, Bahawalpur, Rawalpindi), Sindh, Khyber Pakhtunkhwa, Balochistan, AJ&K and Gilgit Baltistan.
v. The Chief Drugs Controller/Inspector, Punjab / KPK / Sindh / Balochistan / ICT / AJ&K / Gilgit Baltistan.
vi. Additional Director / Officer In-charge DRAP Karachi, Lahore, Islamabad, Peshawar, Quetta for circulation to pharmaceutical units located in their respective area of jurisdiction
vii. Chairman, Pakistan Pharmaceutical Manufacturer's Association, Islamabad.
viii. Executive Director, Pharma Bureau, Karachi.
ix. Executive Director, PCDA, Karachi.

MONOGRAPH FOR CEFIXIME CAPSULE

CEFIXIME CAPSULES

Cefixime Capsules contain not less than 90.0% and not more than 105.0% of the labeled potency of cefixime ($C_{16}H_{15}N_5O_7S_2$: 453.45).

1. IDENTIFICATION:

Take out the contents of Cefixime Capsules, to a quantity of the contents of Cefixime Capsules, equivalent to 70 mg (potency) of Cefixime Hydrate, add 100 mL of 0.1 mol/L phosphate buffer solution (pH 7.0), shake for 30 minutes, and filter. To 1 mL of the filtrate add 0.1 mol/L phosphate buffer solution (pH 7.0) to make 50 mL. Determine the absorption spectrum of this solution using Ultraviolet-visible Spectrophotometry: it exhibits a maximum between 286 nm and 290 nm.

2. PURITY: Related substances—

Take out the contents of Cefixime Capsules, to a quantity of the contents of Cefixime Capsules, equivalent to 0.1 g (potency) of Cefixime Hydrate, add 100 mL of 0.1 mol/L phosphate buffer solution (pH 7.0), shake for 30 minutes, filter, and use the filtrate as the sample solution. Perform the test with 10 µL of the sample solution using Liquid Chromatography according to the following conditions.

Determine each peak area from the sample solution by the automatic integration method, and calculate the amount of them by the area percentage method: the amount of each peak other than cefixime is not more than 1.0%, and the total amount of the peaks other than cefixime is not more than 2.5%.

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column 4 mm in inside diameter and 125 mm in length, packed with octadecylsilanized silica gel for liquid chromatography (4 µm in particle diameter).

Column temperature: A constant temperature of about 40°C.

Mobile phase: To 25 mL of a solution of tetrabutylammonium hydroxide TS (10 in 13) add water to make 1000 mL, adjust to pH 6.5 with diluted phosphoric acid (1 in 10). To 300 mL of this solution add 100 mL of acetonitrile.

Flow rate: Adjust so that the retention time of cefixime is about 10 minutes.

Time span for measurement: About 3 times as long as the retention time of cefixime beginning after the solvent peak.

System suitability—

Test for required detectability:

Pipet 1 mL of the sample solution, and add 0.1 mol/L phosphate buffer solution (pH 7.0) to make exactly 100 mL, and use this solution as the solution for system suitability test. Pipet 1 mL of the solution for system suitability test, and add 0.1 mol/L phosphate buffer solution (pH 7.0) to make exactly 10 mL. Confirm that the peak area of cefixime obtained from 10 µL of this solution is equivalent to 7 to 13% of that obtained from 10 µL of the solution for system suitability test.

System performance: When the procedure is run with 10µL of the solution for system suitability test under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of cefixime are not less than 4000 and not more than 2.0, respectively.

System repeatability: When the test is repeated 6 times with 10 µL of the solution for system suitability test under the above operating conditions, the relative standard deviation of the peak area of cefixime is not more than 2.0%.

3. WATER:

Not more than 12.0% (0.1 g of the contents, volumetric titration, direct titration).

4. UNIFORMITY OF DOSAGE UNITS:

Perform the Mass variation test, or the Content uniformity test according to the following method

Sample solution:

Take out the contents of 1 capsule of Cefixime Capsules, and to the contents and the capsule shells add 7V/10 mL of 0.1 mol/L phosphate buffer solution (pH 7.0), shake for 30minutes, and add 0.1 mol/L phosphate buffer solution (pH 7.0) to make exactly V mL so that each mL contains about 1 mg (potency) of Cefixime Hydrate. Centrifuge this solution, pipet 10 mL of the supernatant liquid, add 0.1 mol/L phosphate buffer solution (pH 7.0) to make exactly 50 mL, and use this solution as the sample solution.

Standard solution

Separately, weigh accurately an amount of Cefixime RS, equivalent to about 20 mg (potency), dissolve in 0.1 mol/L phosphate buffer solution (pH 7.0) to make exactly 100 mL, and use this solution as the standard solution.

Procedure

Perform the test with exactly 10 µL each of the sample solution and standard solution using Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of cefixime in each solution.

Amount [mg (potency)] of Cefixime ($C_{16}H_{15}N_5O_7S_2$)

$$= MS \times A_T/A_S \times V/20$$

MS: Amount [mg (potency)] of Cefixime RS taken

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column 4 mm in inside diameter and 125 mm in length, packed with octadecylsilanized silica gel for liquid chromatography (4 µm in particle diameter).

Column temperature: A constant temperature of about 40°C.

Mobile phase: To 25 mL of a solution of tetrabutylammonium hydroxide TS (10 in 13) add water to make 1000 mL, adjust to pH 6.5 with diluted phosphoric acid (1 in 10). To 300 mL of this solution add 100 mL of acetonitrile.

Flow rate: Adjust so that the retention time of cefixime is about 10 minutes.

System suitability—

System performance:

When the procedure is run with 10 µL of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of cefixime are not less than 4000 and not more than 2.0, respectively.

System repeatability:

When the test is repeated 6 times with 10 µL of the standard solution under the above operating conditions, the relative standard deviation of peak areas of cefixime is not more than 2.0%.

5. DISSOLUTION:

Apparatus:	Basket (I)
RPM:	100
Medium:	0.05 M Phosphate Buffer, pH 7.2
Volume:	900ml
Time:	45 minutes

Sample solution:
Start the test with 1 capsule of Cefixime Capsules, withdraw not less than 20 mL of the medium 45 minutes after starting the test, and filter through a membrane filter with a pore size not exceeding 0.5 μm. Discard the first 10 mL of the filtrate, pipet V mL of the subsequent filtrate, add the dissolution medium to make exactly *V'* mL so that each mL contains about 56 μg (potency) of Cefixime Hydrate, and use this solution as the sample solution.
Standard solution:
Separately, weigh accurately an amount of Cefixime RS, equivalent to about 28 mg (potency), and dissolve in the dissolution medium to make exactly 100 mL. Pipet 4 mL of this solution, add the dissolution medium to make exactly 20 mL, and use this solution as the standard solution.
Procedure:
Perform the test with exactly 20 μL each of the sample solution and standard solution as directed under Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of cefixime in each solution.
Dissolution rate (%) with respect to the labeled amount of cefixime ($C_{16}H_{15}N_5O_7S_2$)
$= M_S \times A_T/A_S \times V'/V \times 1/C \times 180$
MS: Amount [mg (potency)] of Cefixime RS taken
C: Labeled amount [mg (potency)] of Cefixime Hydrate in 1 capsule
Acceptance criteria: Not Less than 80% in 45 minutes
Operating conditions—
Detector: An ultraviolet absorption photometer (wavelength: 254 nm).
Column: A stainless steel column 4 mm in inside diameter and 125 mm in length, packed with octadecylsilanized silica gel for liquid chromatography (4 μm in particle diameter).
Column temperature: A constant temperature of about 40°C.
Mobile phase: To 25 mL of a solution of tetrabutylammonium hydroxide TS (10 in 13) add water to make 1000 mL, adjust to pH 6.5 with diluted phosphoric acid (1 in 10). To 300 mL of this solution add 100 mL of acetonitrile.
Flow rate: Adjust so that the retention time of cefixime is about 10 minutes.
System suitability—
System performance:
When the procedure is run with 20 μL of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of cefixime are not less than 4000 and not more than 2.0, respectively.
System repeatability:
When the test is repeated 6 times with 20 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of cefixime is not more than 2.0%.

6. ASSAY:
Operating conditions—
Detector: An ultraviolet absorption photometer (wavelength: 254 nm).
Column: A stainless steel column 4 mm in inside diameter and 125 mm in length, packed with octadecylsilanized silica gel for liquid chromatography (4 μm in particle diameter).
Column temperature: A constant temperature of about 40°C.
Mobile phase: To 25 mL of a solution of tetrabutylammonium hydroxide TS (10 in 13) add water to make 1000 mL, adjust to pH 6.5 with diluted phosphoric acid (1 in 10). To 300 mL of this solution add 100 mL of acetonitrile.
Flow rate: Adjust so that the retention time of cefixime is about 10 minutes.

Sample solution:

Take out the contents of not less than 20 Cefixime Capsules, weigh accurately the mass of the contents, and powder. Weigh accurately a portion of the powder, equivalent to about 0.1 g (potency) of Cefixime Hydrate, add 70 mL of 0.1 mol/L phosphate buffer solution (pH 7.0) and shake for 30 minutes, add 0.1 mol/L phosphate buffer solution (pH 7.0) to make exactly 100 mL. Centrifuge this solution, pipet 10 mL of the supernatant liquid, add 0.1 mol/L phosphate buffer solution (pH 7.0) to make exactly 50 mL, and use this solution as the sample solution.

Standard solution:

Separately, weigh accurately an amount of Cefixime RS, equivalent to about 20 mg (potency), dissolve in 0.1 mol/L phosphate buffer solution (pH 7.0) to make exactly 100 mL, and use this solution as the standard solution.

Procedure:

Perform the test with exactly 10 μL each of the sample solution and standard solution using Liquid Chromatography and determine the peak areas, A_T and A_S, of cefixime in each solution.

Amount [mg (potency)] of cefixime ($C_{16}H_{15}N_5O_7S_2$)

$= M_S \times A_T/A_S \times 5$

M_S: Amount [mg (potency)] of Cefixime RS taken

System suitability—

System performance: When the procedure is run with 10 μL of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of cefixime are not less than 4000 and not more than 2.0, respectively.

System repeatability: When the test is repeated 6 times with 10 μL of the standard solution under the above operating conditions, the relative standard deviation of peak areas of cefixime is not more than 2.0%.

Containers and storage Containers—Tight containers.