Cefdinir Capsules

Cefdinir Capsules contain not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of cefdinir ,$C_{14}H_{13}N_5O_5S_2$.

Usual strength. 300 mg.

Identification

A. When examined in the range 200 nm to 400 nm (2.4.7), a 0.001 per cent w/v solution of capsule powder containing cefdinir in the buffer solution prepared by dissolving 10.7 g of *dibasic sodium phosphate* and 3.4 g of *monobasic potassium phosphate* in 1000 ml of *water*, adjusted to pH 7.0 ± 0.05 with *orthophosphoric acid* or *sodium hydroxide*, shows an absorption maxima and minima at the same wavelength as the reference solution.

B. In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with reference solution (b).

Tests

Dissolution (2.5.2).

Apparatus No. 1,
Medium. 900 ml of *0.05 M phosphate buffer pH 6.8*,
Speed and time. 50 rpm and 30 minutes.

Withdraw a suitable volume of the medium and filter through a membrane filter having an average pore size not greater than 0.45 µm, rejecting the first few ml of the filtrate. Measure the absorbance of the resulting solution, suitably diluted if necessary with the medium, at the maximum at about 290 nm (2.4.7).

Calculate the content of $C_{14}H_{13}N_5O_5S_2$ in the medium from the absorbance obtained from a solution of known concentration of *cefdinir RS* in dissolution medium.

D. Not less than 80 per cent of the stated amount of $C_{14}H_{13}N_5O_5S_2$.

Related substances. Determine by liquid chromatography (2.4.14).

Buffer solution. A mixture of solutions containing 2:1 ratio of a solution prepared by dissolving 14.2 g of *anhydrous dibasic sodium phosphate* in 1000 ml of *water* and 13.6 g of *monobasic potassium phosphate* in 1000 ml of *water*, is maintained, adjusted to pH 7.0 ± 0.1.

Solution A. A 0.1 per cent v/v solution of *tetramethylammonium hydroxide solution (10 per cent)* in *water*, adjusted to pH 5.5 ± 0.1 with *dilute phosphoric acid*.

Solution B. A 3.72 per cent w/v solution of *sodium edetate* in *water*.

Test solution. Weigh a quantity of the mixed contents of 20 capsules containing 300 mg of cefdinir and transfer to a 200.0 ml volumetric flask. Dissolve in 30 ml of the buffer solution, and dilute to volume with solution A to obtain 0.15 per cent w/v solution of cefdinir.

Reference solution (a). A 0.004 per cent w/v solution of *cefdinir related compound A RS (2R)-2-[(Z)-2-(2-Aminothiazol-4-yl)-2-(hydroxyimino)acetamido]-2-[(2RS, 5RS)-5-methyl-7-oxo-2,4,5,7-tetrahydro-1H -furo[3,4-d][1,3]thiazin-2-yl]acetic acid* in solution A.

Reference solution (b). A 0.004 per cent w/v solution of *cefdinir related compound B RS (6R, 7R)-7-[2-(2-Amino-4-thiazolyl)acetamido]-8-oxo-3-vinyl-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid* in solution A.

Reference solution (c).Transfer 37.5 mg of *cefdinir RS* to a 25.0 ml of volumetric flask. Add about 10 ml of the buffer solution. Add 5.0 ml each of reference solution (a) and reference solution (b), and dilute with solution A to volume.

Reference solution (d). A 0.075 per cent w/v solution of *cefdinir RS* in the buffer solution.

Reference solution (e). Dilute reference solution (d) to obtain a solution containing 0.0015 per cent w/v of *cefdinir RS* in solution A.

Chromatographic system

- a stainless steel column 15 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm),
- column. temperature 40º,
- sample temperature: 4°,
- mobile phase: A. a mixture of 1000 volumes of solution A and 0.4 volumes of solution B,
  B. a mixture of 150 volumes of *acetonitrile,* 100 volumes of *methanol,* 250 volumes of solution A and 0.2 volumes of solution B,
- a gradient programme using the conditions given below,
- flow rate: 1 ml per minute,
- spectrophotometer set at 254 nm,
- injection volume: 10 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	95	5
2	95	5
22	75	25
32	50	50
37	50	50
38	95	5
58	95	5

Name	Relative retention time	Correction factor
Thiazolylacetyl glycine oxime[1]	1.0	1.0
Thiazolylacetyl glycine oxime acetal[2]	0.13	1.0
Cefdinir sulfoxide[3]	0.36	1.0
Cefdinir thiazine analog[4]	0.46	1.47
3-Methyl cefdinir[5]	0.75	1.0
Cefdinir impurity 1[6]	0.77	1.0
Cefdinir related compound A (cefdinir open ring lactone a) [7, 8]	0.85	1.54
Cefdinir related compound A (cefdinir open ring lactone b) [7, 8]	0.94	1.54
Cefdinir related compound A (cefdinir open ring lactone c) [7, 8]	1.11	1.54
Cefdinir related compound A (cefdinir open ring lactone d) [7, 8]	1.14	1.54
7*S* -Cefdinir [9]	1.18	1.0
Cefdinir lactone[10]	1.23	1.0
Cefdinir related compound B[11]	1.28	1.0
Cefdinir isoxazole analog[12]	1.37	1.39
Cefdinir impurity 2[6]	1.44	1.0

Cefdinir glyoxalic analog[13]	1.49	1.0
E-Cefdinir [14]	1.51	1.0
Cefdinir decarboxy open ring lactone a[15, 16]	1.62	1.0
Cefdinir decarboxy open ring lactone b[15, 16]	1.64	1.0
Cefdinir impurity 3[6]	1.82	1.0
Individual unidentified impurities	---	1.0
Total impurities	---	---

[1]*N*-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-(hydroxyimino)acetyl]glycine,

[2](Z)-2-(2-Aminothiazol-4-yl)-N-(2,2-dihydroxyethyl)-2-(hydroxyimino)acetamide,

[3](6*R* ,7*R*)-7-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-(hydroxyimino)acetamido]-5,8-dioxo-3-vinyl-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,

[4](*R*,*Z*)-2-{(*R*)-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-(hydroxyimino)acetamido](carboxy)methyl}-5-ethylidene-5,6-dihydro-2*H* -1,3-thiazine-4-carboxylic acid,

[5](6*R* ,7*R*)-7-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-(hydroxyimino)acetamido]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,

[6]Cefdinir impurity 1, cefdinir impurity 2, and cefdinir impurity 3 are unidentified impurities,

[7]Cefdinir related compound A is a mixture of four isomers labeled cefdinir open ring lactones a, b, c, and d. The sum of the values is reported. The limit for the sum of the four isomers is 2.5%,

[8]2(*R*)-2-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-(hydroxyimino)acetamido]-2-[(2*RS* ,5*RS*)-5-methyl-7-oxo-2,4,5,7-tetrahydro-1*H* -furo[3,4-*d*][1,3]thiazin-2-yl]acetic acid,

[9](6*R* ,7*S*)-7-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-(hydroxyimino)acetamido]-8-oxo-3-vinyl-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,

[10](*Z*)-2-(2-Aminothiazol-4-yl)-2-(hydroxyimino)-*N*-((3*RS* ,5a*R* ,6*R*)-3-methyl-1,7-dioxo-1,3,4,5a,6,7-hexahydroazeto[2,1-*b*]furo[3,4-*d*][1,3]thiazin-6-yl)acetamide,

[11](6*R* ,7*R*)-7-[2-(2-Amino-4-thiazolyl)acetamido]-8-oxo-3-vinyl-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,

[12](6*R* ,7*R*)-7-(4-Hydroxyisoxazole-3-carboxamido)-8-oxo-3-vinyl-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,

[13](6*R* ,7*R*)-7-[2-(2-Aminothiazol-4-yl)-2-oxoacetamido]-8-oxo-3-vinyl-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,

[14](6*R* ,7*R*)-7-[(*E*)-2-(2-Aminothiazol-4-yl)-2-(hydroxyimino)acetamido]-8-oxo-3-vinyl-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,

[15]Cefdinir decarboxy open ring lactone is a mixture of two isomers labeled cefdinir decarboxy open ring lactone a and b. The sum of the values is reported. The limit for the sum of the two isomers is 1.0%,

[16](*Z*)-2-(2-Aminothiazol-4-yl)-2-(hydroxyimino)-*N*-{[(2*RS* ,5*RS*)-5-methyl-7-oxo-2,4,5,7-tetrahydro-1*H* -furo[3,4-*d*][1,3]thiazin-2-yl]methyl}acetamide

Inject reference solution (c) and (e). The test is not valid unless the resolution between the peaks due to cefdinir and *cefdinir related compound A RS* is not less than 1.5 in the chromatogram obtained with reference solution (c), the tailing factor is not more than 1.5 in the chromatogram obtained with reference solution (c) and the relative standard deviation for replicate injections is not more than 2.0 per cent in the chromatogram obtained with reference solution (e).

Inject reference solution (e) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to thiazolylacetyl glycine oxime, thiazolylacetyl glycine oxime acetal, cefdinir isoxazole analog and cefdinir impurity 2 is not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (e) (0.5 per cent), cefdinir sulfoxide, 7*S*–cefdinir, cefdinir related compound B, cefdinir glyoxalic analog and cefdinir impurity 3 is not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (e)(0.2 per cent), cefdinir thiazine analog and 3- methyl cefdinir is not more than 0.7 times the area of the principal peak in the chromatogram obtained with reference solution (e) (0.7 per cent), cefdinir lactone, cefdinir decarboxy open ring lactone a, cefdinir decarboxy open ring lactone b is not more than the area of the principal peak in the chromatogram obtained with reference solution (e) (1.0 per cent),E-cefdinir is not more than 1.2 times the area of the principal peak in the chromatogram obtained with reference solution (e) (1.2 per cent), cefdinir impurity 1 is not more than 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (e) (0.3 per cent), cefdinir related compound A (cefdinir open ring lactone a), cefdinir related com

pound A (cefdinir open ring lactone b),cefdinir related compound A (cefdinir open ring lactone c) and cefdinir relate d compound A (cefdinir open ring lactone d) is not more than 2.5 times the area of the principal peak in the chromatogram obtained with the reference solution (e) (2.5 per cent) and the area of any other secondary peak is not more than 0.2 times the area of the principal peak in the chromatogram obtained with the reference solution (e) (0.2 per cent) and the sum of areas of all the secondary peaks is not more than 5.0 times the area of the principal peak in the chromatogram obtained with reference solution (e) (5.0 per cent).

Other tests. Comply with the tests stated under Capsules.

Assay. Determine by liquid chromatography (2.4.14).

Buffer solution. A mixture prepared by dissolving 10.7 g of *dibasic sodium phosphate* and 3.4 g of *monobasic potassium phosphate* in 1000 ml of *water,* adjusted to pH 7.0 ± 0.05 with *orthophosphoric acid* or *sodium hydroxide* before final dilution.

Solution A. A 0.7 per cent w/v solution of *citric acid monohydrate* in *water,* adjusted to pH 2.0 ± 0.05 with *orthophosphoric acid.*

Test solution. Weigh a quantity of the mixed contents of 20 capsules containing about 100 mg of Cefdinir, dissolve in the buffer solution by shaking mechanically, dilute to 100.0 ml with the buffer solution and filter. Dilute 5.0 ml of this solution to 100.0 ml with the buffer solution.

Reference solution (a). A solution containing 0.005 per cent w/v of *cefdinir RS* and 0.0175 per cent w/v of *m-hydroxybenzoic acid* in the buffer solution.

Reference solution (b). A 0.005 per cent w/v solution of *cefdinir RS* in the buffer solution.

Chromatographic system

- a stainless steel column 15 cm x 3.9 mm, packed with octadecylsilane bonded to porous silica (4 µm),
- mobile phase: a mixture of 111 volumes of *methanol* and 28 volumes of *tetrahydrofuran* and 1000 volumes of solution A,
- flow rate: 1.4 ml per minute,
- spectrophotometer set at 254 nm,
- injection volume: 15 µl.

Inject reference solution (a) and (b). The test is not valid unless the resolution between the peaks due to cefdinir and *m*-hydroxybenzoic acid in the chromatogram obtained with reference solution (a) is not less than 3.0, the tailing factor for the peak due to cefdinir in the chromatogram obtained with reference solution (a) is not more than 2.0 and the relative standard deviation for replicate injections is not more than 1.0 per cent for the peak due to cefdinir in the chromatogram obtained with reference solution (b).

Inject reference solution (b) and the test solution.

Calculate the content of $C_{14}H_{13}N_5O_5S_2$ in the capsules.

Storage. Store protected from light, moisture and at a temperature not exceeding 25°.