System suitability: reference solution (c):

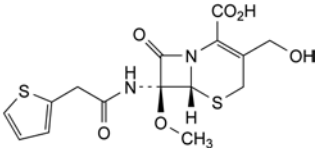
– *resolution*: minimum 3.5 between the 2 principal peaks.

Calculate the percentage content of cefoxitin sodium.

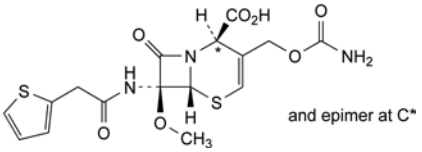
STORAGE

In an airtight container. If the substance is sterile, store in a sterile, airtight, tamper-proof container.

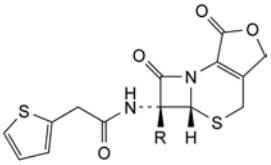
IMPURITIES



A. (6*R*,7*S*)-3-(hydroxymethyl)-7-methoxy-8-oxo-7-[[(thiophen-2-yl)acetyl]amino]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (decarbamoylcefoxitin),



B. (2*RS*,6*R*,7*S*)-3-[(carbamoyloxy)methyl]-7-methoxy-8-oxo-7-[[(thiophen-2-yl)acetyl]amino]-5-thia-1-azabicyclo[4.2.0]oct-3-ene-2-carboxylic acid (delta-3-cefoxitin),



C. R = H: (5a*R*,6*R*)-6-[[(thiophen-2-yl)acetyl]amino]-5a,6-dihydro-3*H*,7*H*-azeto[2,1-*b*]furo[3,4-*d*][1,3]thiazine-1,7(4*H*)-dione (cefalotin lactone),

D. R = OCH_3: (5a*R*,6*S*)-6-methoxy-6-[[(thiophen-2-yl)acetyl]amino]-5a,6-dihydro-3*H*,7*H*-azeto[2,1-*b*]furo[3,4-*d*][1,3]thiazine-1,7(4*H*)-dione (cefoxitin lactone).

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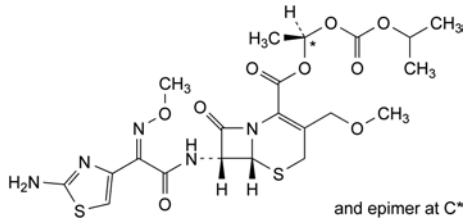
CEFPODOXIME PROXETIL

Cefpodoximum proxetili



$C_{21}H_{27}N_5O_9S_2$ M_r 557.6
[87239-81-4]

DEFINITION

(1*RS*)-1-[[(1-Methylethoxy)carbonyl]oxy]ethyl (6*R*,7*R*)-7-[[(2*Z*)-2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetyl]amino]-3-(methoxymethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate.

Semi-synthetic product derived from a fermentation product.

Content: 94.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance: white or pale yellow or light brown, amorphous powder.

Solubility: very slightly soluble or practically insoluble in water, very soluble in acetonitrile and in methanol, freely soluble in anhydrous ethanol.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *cefpodoxime proxetil CRS*.

TESTS

Diastereoisomer ratio. Liquid chromatography (*2.2.29*) as described under Assay. Use the normalisation procedure.

Limit: test solution:

– the ratio of the area of the peak due to cefpodoxime proxetil diastereoisomer II to the sum of the areas of the peaks due to cefpodoxime proxetil diastereoisomers I and II is between 0.5 and 0.6.

Related substances. Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use or store them at 2-8 °C.*

Solvent mixture: *glacial acetic acid R, acetonitrile R, water R* (2:99:99 *V/V/V*).

Test solution. Dissolve 50 mg of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (a). Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture.

Reference solution (b). Dissolve 5 mg of *cefpodoxime proxetil for peak identification CRS* (containing impurities B, C and D) in 5.0 mL of the solvent mixture.

Reference solution (c). Dissolve 5 mg of *cefpodoxime proxetil for impurity H identification CRS* in 5.0 mL of the solvent mixture.

Column:

– *size*: *l* = 0.15 m, Ø = 4.6 mm;

– *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

– *temperature*: maintain at a constant temperature of 20 °C.

Mobile phase:

– *mobile phase A*: *anhydrous formic acid R, methanol R, water R* (1:400:600 *V/V/V*);

– *mobile phase B*: *anhydrous formic acid R, water R, methanol R* (1:50:950 *V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 65	95	5
65 - 145	95 → 15	5 → 85
145 - 155	15	85

Flow rate: 0.6 mL/min.

Detection: spectrophotometer at 254 nm.

Injection: 20 µL.

Identification of impurities: use the chromatogram supplied with *cefpodoxime proxetil for peak identification CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities B, C and D; use the chromatogram supplied with *cefpodoxime proxetil for impurity H identification CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurity H.

Relative retention with reference to cefpodoxime proxetil diastereoisomer II (retention time = about 58 min): diastereoisomer I of impurity B = about 0.68; diastereoisomer I of cefpodoxime proxetil = about 0.74; impurity C = about 0.82; diastereoisomer II of impurity B = about 0.85; impurity D (2 peaks) = about 0.88 and 1.13; peaks due to diastereoisomers of impurity H: between about 1.9 and 2.3.

System suitability:

- the chromatogram obtained with reference solution (b) is similar to the chromatogram supplied with *cefpodoxime proxetil for peak identification CRS*;
- *resolution*: minimum 6.0 between the peaks due to cefpodoxime proxetil diastereoisomers I and II in the chromatogram obtained with reference solution (a);
- *peak-to-valley ratio*: minimum 1.1, where H_p = height above the baseline of the peak due to diastereoisomer II of impurity B and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity C in the chromatogram obtained with reference solution (b).

Limits:

- *impurity C*: not more than twice the sum of the areas of the 2 principal peaks in the chromatogram obtained with reference solution (a) (2.0 per cent);
- *impurity D (sum of the 2 diastereoisomers)*: not more than the sum of the areas of the 2 principal peaks in the chromatogram obtained with reference solution (a) (1.0 per cent);
- *impurity H (sum of the diastereoisomers)*: not more than the sum of the areas of the 2 principal peaks in the chromatogram obtained with reference solution (a) (1.0 per cent);
- *impurity B (sum of the 2 diastereoisomers)*: not more than 0.5 times the sum of the areas of the 2 principal peaks in the chromatogram obtained with reference solution (a) (0.5 per cent);
- *any other impurity*: for each impurity, not more than 0.2 times the sum of the areas of the 2 principal peaks in the chromatogram obtained with reference solution (a) (0.2 per cent);
- *total*: not more than 4 times the sum of the areas of the 2 principal peaks in the chromatogram obtained with reference solution (a) (4.0 per cent);
- *disregard limit*: 0.05 times the sum of the areas of the 2 principal peaks in the chromatogram obtained with reference solution (a) (0.05 per cent).

Water (*2.5.12*): maximum 2.5 per cent, determined on 0.500 g.

ASSAY

Liquid chromatography (*2.2.29*).

Solution A: 20 mg/L solution of *anhydrous citric acid R* in *acetonitrile R*.

Test solution. Dissolve 30.0 mg of the substance to be examined in solution A and dilute to 50.0 mL with solution A.

Reference solution. Dissolve 30.0 mg of *cefpodoxime proxetil CRS* in solution A and dilute to 50.0 mL with solution A.

Column:

- *size*: *l* = 0.15 m, Ø = 4.6 mm;
- *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);
- *temperature*: 40 °C.

Mobile phase: *methanol R, water R* (9:11 *V/V*).

Flow rate: 0.8 mL/min.

Detection: spectrophotometer at 240 nm.

Injection: 10 µL.

Run time: 1.2 times the retention time of cefpodoxime proxetil diastereoisomer II.

Retention time: cefpodoxime proxetil diastereoisomer II = about 30 min.

System suitability: reference solution:

- *resolution*: minimum 4.0 between the peaks due to cefpodoxime proxetil diastereoisomers I and II.

Calculate the percentage content of $C_{21}H_{27}N_5O_9S_2$ from the sum of the areas of the 2 peaks due to the diastereoisomers and using the declared content of *cefpodoxime proxetil CRS*.

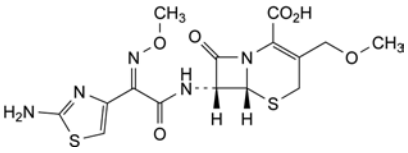
STORAGE

Protected from light.

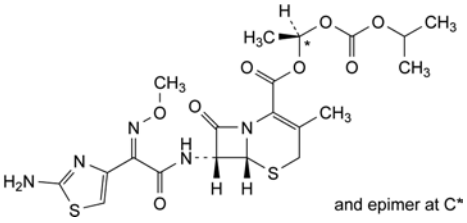
IMPURITIES

Specified impurities: B, C, D, H.

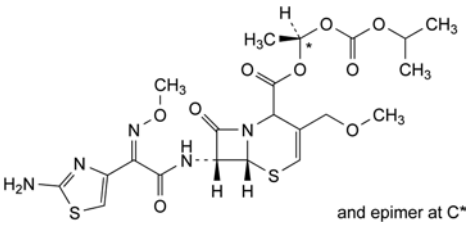
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical use (2034)*. It is therefore not necessary to identify these impurities for demonstration of compliance. See also *5.10. Control of impurities in substances for pharmaceutical use*): *A, E, F, G.*



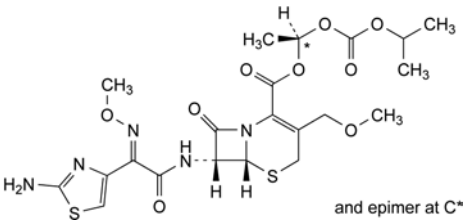
A. (6*R*,7*R*)-7-[[(2*Z*)-2-(2-aminothiazol-4-yl)-2-(methoxyimino)-acetyl]amino]-3-(methoxymethyl)-8-oxo-5-thia-1-azabicyclo-[4.2.0]oct-2-ene-2-carboxylic acid (cefpodoxime),



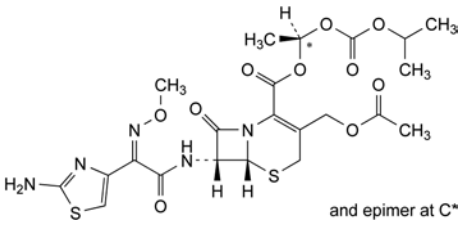
B. (1*RS*)-1-[[(1-methylethoxy)carbonyl]oxy]ethyl (6*R*,7*R*)-7-[[(2*Z*)-2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetyl]amino]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate (ADCA-analogue of cefpodoxime proxetil),



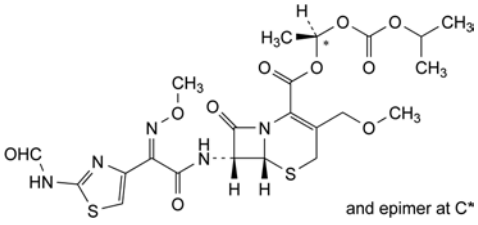
C. (1*RS*)-1-[[(1-methylethoxy)carbonyl]oxy]ethyl (6*R*,7*R*)-7-[[(2*Z*)-2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetyl]amino]-3-(methoxymethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-3-ene-2-carboxylate (delta-2-cefpodoxime proxetil),



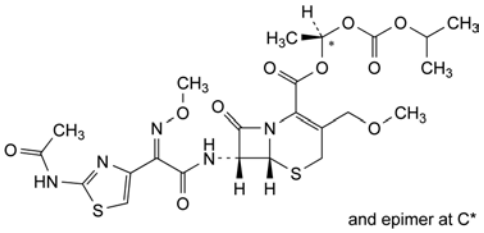
D. (1*RS*)-1-[[(1-methylethoxy)carbonyl]oxy]ethyl (6*R*,7*R*)-7-[[(2*E*)-2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetyl]amino]-3-(methoxymethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate (anti-cefpodoxime proxetil),



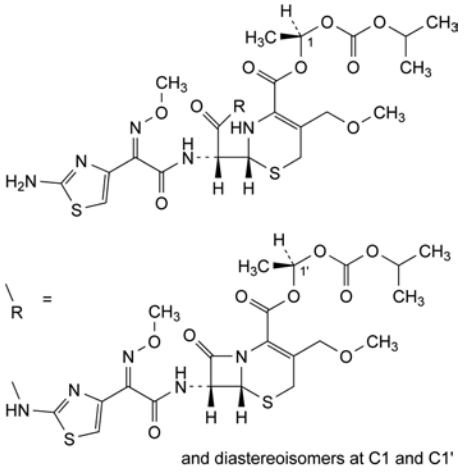
E. (1*RS*)-1-[[(1-methylethoxy)carbonyl]oxy]ethyl (6*R*,7*R*)-3-(acetoxymethyl)-7-[[(2*Z*)-2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetyl]amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate (ACA-analogue of cefpodoxime proxetil),



F. (1*RS*)-1-[[(1-methylethoxy)carbonyl]oxy]ethyl (6*R*,7*R*)-7-[[(2*Z*)-2-[(2-formylamino)thiazol-4-yl)-2-(methoxyimino)acetyl]amino]-3-(methoxymethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate (*N*-formyl cefpodoxime proxetil),



G. (1*RS*)-1-[[(1-methylethoxy)carbonyl]oxy]ethyl (6*R*,7*R*)-7-[[(2*Z*)-[2-(2-acetylamino)thiazol-4-yl]-2-(methoxyimino)acetyl]amino]-3-(methoxymethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate (*N*-acetyl-cefpodoxime proxetil),

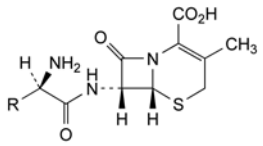


H. mixture of the diastereoisomers of 1-[[(1-methylethoxy)carbonyl]oxy]ethyl (6*R*,7*R*)-7-[[(2*Z*)-2-[2-[[(2*R*)-2-[[(2*Z*)-2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetyl]amino]-2-[(2*R*)-5-(methoxymethyl)-4-[[1-[[(1-methylethoxy)carbonyl]oxy]ethoxy]carbonyl]-3,6-dihydro-2*H*-1,3-thiazin-2-yl]acetyl]amino]thiazol-4-yl]-2-(methoxyimino)acetyl]amino]-3-(methoxymethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate (cefpodoxime proxetil dimer).

07/2010:0814

CEFRADINE

Cefradinum



Compound	R	Mol. Formula	M_r
cefradine		$C_{16}H_{19}N_3O_4S$	349.4
cefalexin		$C_{16}H_{17}N_3O_4S$	347.4
4',5'-dihydrocefradine		$C_{16}H_{21}N_3O_4S$	351.4

Cefradine: [38821-53-3]

DEFINITION

Main component: (6*R*,7*R*)-7-[[(2*R*)-amino(cyclohexa-1,4-dienyl)acetyl]amino]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (cefradine).

Semi-synthetic product derived from a fermentation product.

Content:

– *cefradine*: minimum 90.0 per cent (anhydrous substance);
– *cefalexin*: maximum 5.0 per cent (anhydrous substance);
– *4',5'-dihydrocefradine*: maximum 2.0 per cent (anhydrous substance);
– *sum of the percentage contents of cefradine, cefalexin and 4',5'-dihydrocefradine*: 96.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance: white or slightly yellow, hygroscopic powder.

Solubility: sparingly soluble in water, practically insoluble in ethanol 96 per cent and in hexane.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *cefradine CRS*.

If the spectra obtained in the solid state show differences, dissolve 30 mg of the substance to be examined and of the reference substance separately in 10 mL of *methanol R*, evaporate to dryness at 40 °C at a pressure less than 2 kPa and record new spectra using the residues.

TESTS

Solution S. Dissolve 2.50 g in *sodium carbonate solution R* and dilute to 25.0 mL with the same solvent.

Appearance of solution. Solution S is not more opalescent than reference suspension II (*2.2.1*). Allow solution S to stand for 5 min. The absorbance (*2.2.25*) of solution S measured at 450 nm is not greater than 0.60.

pH (*2.2.3*): 3.5 to 6.0.

Dissolve 0.100 g in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent.

Specific optical rotation (*2.2.7*): + 80.0 to + 90.0 (anhydrous substance).

Dissolve 0.250 g in *acetate buffer solution pH 4.6 R* and dilute to 25.0 mL with the same solution.