Injection: 20 µL of the test solution and reference solutions (b), (c) and (d).

Run time: twice the retention time of cefapirin.

Relative retention with reference to cefapirin (retention time = about 13 min): impurity B = about 0.3; impurity C = about 0.5; impurity A = about 0.75.

System suitability: reference solution (d):

– *resolution*: minimum 2.0 between the peaks due to cefapirin and impurity A.

Limits:

– *any impurity*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent), and not more than 1 such peak has an area greater than 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent),

– *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (2.0 per cent),

– *disregard limit*: area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

***N,N*-Dimethylaniline** (*2.4.26, Method B*): maximum 20 ppm.

2-Ethylhexanoic acid (*2.4.28*): maximum 0.5 per cent.

Water (*2.5.12*): maximum 2.0 per cent, determined on 0.300 g.

Bacterial endotoxins (*2.6.14*): less than 0.17 IU/mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection: test solution and reference solution (a).

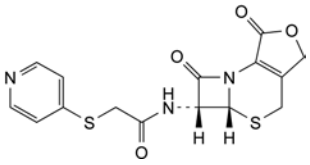
Calculate the percentage content of $C_{17}H_{16}N_3NaO_6S_2$.

STORAGE

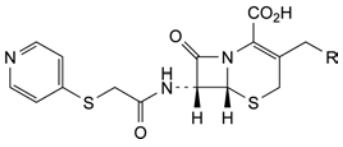
Protected from light. If the substance is sterile, store in a sterile, tamper-proof container.

IMPURITIES

Specified impurities: A, B, C.



A. (5a*R*,6*R*)-6-[[[(pyridin-4-yl)sulfanyl]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 (deacetylcefapirin lactone),



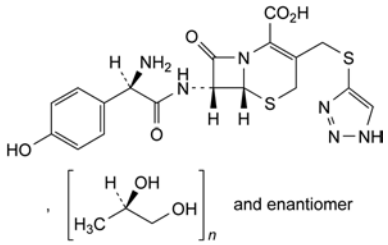
B. R = OH: (6*R*,7*R*)-3-(hydroxymethyl)-8-oxo-7-[[[(pyridin-4-yl)sulfanyl]acetyl]amino]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (deacetylcefapirin),

C. R = H: (6*R*,7*R*)-3-methyl-8-oxo-7-[[[(pyridin-4-yl)sulfanyl]acetyl]amino]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (deacetoxycefapirin).

01/2008:1403

CEFATRIZINE PROPYLENE GLYCOL

Cefatrizinum propylen glycolum



$C_{18}H_{18}N_6O_5S_2,(C_3H_8O_2)_n$ M_r 462.5 (base)

DEFINITION

Mixture of (6*R*,7*R*)-7-[[(2*R*)-2-amino-2-(4-hydroxyphenyl)-acetyl]amino]-8-oxo-3-[[(1*H*-1,2,3-triazol-4-yl)sulfanyl]-methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid and propane-1,2-diol in molecular proportions of about 1:1.

Content: 95.0 per cent to 102.0 per cent of $C_{18}H_{18}N_6O_5S_2$ (anhydrous substance).

CHARACTERS

Appearance: white or almost white powder.

Solubility: slightly soluble in water, practically insoluble in ethanol (96 per cent) and in methylene chloride.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *cefatrizine propylene glycol CRS*.

B. Examine the chromatograms obtained in the test for propylene glycol.

Results: the principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (b).

TESTS

Specific optical rotation (*2.2.7*): + 63 to + 69 (anhydrous substance).

Dissolve 0.400 g in *1 M hydrochloric acid* and dilute to 20.0 mL with the same acid.

Propylene glycol. Gas chromatography (*2.2.28*).

Solvent mixture: *acetone R, water R* (20:80 *V/V*).

Internal standard solution. Dissolve 1.0 g of *dimethylacetamide R* in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Test solution. Introduce 0.40 g of the substance to be examined into a ground-glass-stoppered test-tube. Add 3.0 mL of the internal standard solution, 1.0 mL of the solvent mixture and 2.0 mL of *hydrochloric acid R*. Seal the test-tube and shake.

Reference solution (a). Dissolve 2.0 g of *propylene glycol R* in the solvent mixture and dilute to 100.0 mL with the solvent mixture.

Reference solution (b). Introduce into a ground-glass-stoppered test-tube 1.0 mL of reference solution (a) and 1.0 mL of the internal standard solution.

Column:

– *material*: stainless steel;

– *size*: *l* = 2 m, Ø = 2 mm;

– *stationary phase*: *ethylvinylbenzene-divinylbenzene copolymer R* (150-180 µm).

Carrier gas: *nitrogen for chromatography R*.

Flow rate: 30 mL/min.

Temperature:
– *column*: 200 °C;
– *injection port and detector*: 250 °C.
Detection: flame ionisation.
Injection: 1 µL of the test solution and reference solution (b).
Limit:
– *propylene glycol*: 13.0 per cent to 18.0 per cent.

Related substances. Liquid chromatography (*2.2.29*).
Test solution. Dissolve 60.0 mg of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.
Reference solution (a). Dissolve 60.0 mg of *cefatrizine propylene glycol CRS* in the mobile phase and dilute to 100.0 mL with the mobile phase.
Reference solution (b). Dissolve 30.0 mg of *cefatrizine impurity A CRS* in *buffer solution pH 7.0 R* and dilute to 100.0 mL with the same buffer solution.
Reference solution (c). Dilute 0.6 mL of reference solution (a) to 100.0 mL with the mobile phase.
Reference solution (d). Dilute 1.0 mL of reference solution (b) to 100.0 mL with *buffer solution pH 7.0 R*.
Reference solution (e). To 1.0 mL of reference solution (a) add 1.0 mL of reference solution (b) and dilute to 10.0 mL with the mobile phase.
Column:
– *size*: *l* = 0.25 m, Ø = 4 mm;
– *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).
Mobile phase: mix 5 volumes of *acetonitrile R* and 95 volumes of a 2.72 g/L solution of *potassium dihydrogen phosphate R* in *water R*.
Flow rate: 2 mL/min.
Detection: spectrophotometer at 272 nm.
Injection: 20 µL of the test solution and reference solutions (c), (d) and (e).
Run time: at least twice the retention time of cefatrizine.
System suitability: reference solution (e):
– *resolution*: minimum 5.0 between the peaks due to cefatrizine and impurity A.
Limits:
– *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (d) (0.5 per cent);
– *any other impurity*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.6 per cent);
– *sum of impurities other than A*: not more than 3.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (2.1 per cent);
– *disregard limit*: 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.03 per cent).

Water (*2.5.12*): maximum 1.5 per cent, determined on 0.500 g.

Sulfated ash (*2.4.14*): maximum 0.1 per cent, determined on 1.0 g.

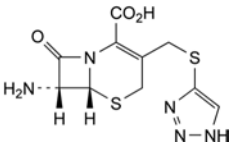
ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.
Injection: test solution and reference solution (a).
System suitability: reference solution (a):
– *repeatability*: maximum relative standard deviation of 1.0 per cent after 6 injections.

Calculate the percentage content of $C_{18}H_{18}N_6O_5S_2$ from the declared content of $C_{18}H_{18}N_6O_5S_2$ in *cefatrizine propylene glycol CRS*.

IMPURITIES

Specified impurities: A.

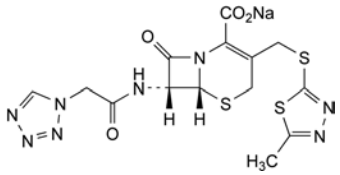


A. (6*R*,7*R*)-7-amino-8-oxo-3-[[(1*H*-1,2,3-triazol-4-yl)sulfanyl]-methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (7-ACA triazole).

01/2008:0988
corrected 6.0

CEFAZOLIN SODIUM

Cefazolinum natricum



$C_{14}H_{13}N_8NaO_4S_3$ M_r 476.5
[27164-46-1]

DEFINITION

Sodium (6*R*,7*R*)-3-[[(5-methyl-1,3,4-thiadiazol-2-yl)sulfanyl]methyl]-8-oxo-7-[(1*H*-tetrazol-1-ylacetyl)amino]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate.

Semi-synthetic product derived from a fermentation product.

Content: 95.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance: white or almost white powder, very hygroscopic.
Solubility: freely soluble in water, very slightly soluble in ethanol (96 per cent).
It shows polymorphism (*5.9*).

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).
Preparation: dissolve 0.150 g in 5 mL of *water R*, add 0.5 mL of *dilute acetic acid R*, swirl and allow to stand for 10 min in iced water. Filter the precipitate and rinse with 1-2 mL of *water R*. Dissolve in a mixture of 1 volume of *water R* and 9 volumes of *acetone R*. Evaporate the solvent almost to dryness, then dry in an oven at 60 °C for 30 min.
Comparison: *cefazolin CRS*.
B. It gives reaction (a) of sodium (*2.3.1*).

TESTS

Solution S. Dissolve 2.50 g in *carbon dioxide-free water R* and dilute to 25.0 mL with the same solvent.

Appearance of solution. Solution S is clear (*2.2.1*) and its absorbance (*2.2.25*) at 430 nm is not greater than 0.15.

pH (*2.2.3*): 4.0 to 6.0 for solution S.

Specific optical rotation (*2.2.7*): – 15 to – 24 (anhydrous substance).
Dissolve 1.25 g in *water R* and dilute to 25.0 mL with the same solvent.

Absorbance (*2.2.25*). Dissolve 0.100 g in *water R* and dilute to 100.0 mL with the same solvent. Dilute 2.0 mL of the solution to 100.0 mL with *sodium hydrogen carbonate solution R*. Examined between 220 nm and 350 nm, the solution shows an absorption maximum at 272 nm. The specific absorbance at the maximum is 260 to 300 (anhydrous substance).