STORAGE

In an airtight container, at a temperature of 2 °C to 8 °C. If the substance is sterile, store in a sterile, airtight, tamper-proof container.

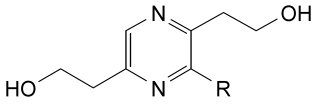
IMPURITIES

Specified impurities: A, B, C, D, G, H, I, J, K, L, M.

Other detectable impurities: E, F.

By liquid chromatography: A, B, C, D, E, F, G.

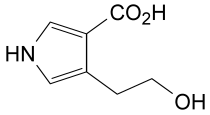
By gas chromatography: H, I, J, K, L, M.



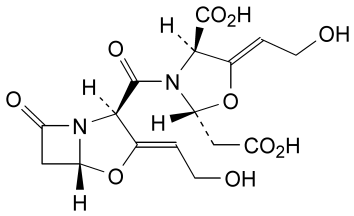
A. R = H: 2,2′-(pyrazine-2,5-diyl)diethanol,

B. R = CH_2-CH_2-CO_2H: 3-[3,6-bis(2-hydroxyethyl)pyrazin-2-yl]propanoic acid,

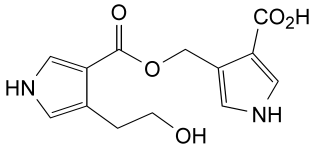
C. R = CH_2-CH_3: 2,2′-(3-ethylpyrazine-2,5-diyl)diethanol,



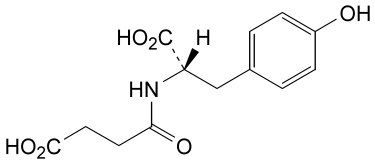
D. 4-(2-hydroxyethyl)pyrrole-3-carboxylic acid,



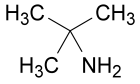
E. (2*R*,4*R*,5*Z*)-2-(carboxymethyl)-5-(2-hydroxyethylidene)-3-[[(2*R*,3*Z*,5*R*)-3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-azabibyclo[3.2.0]hept-2-yl]carbonyl]oxazolidine-4-carboxylic acid,



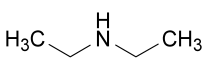
F. 4-[[[[4-(2-hydroxyethyl)-1*H*-pyrrol-3-yl]carbonyl]oxy]methyl]-1*H*-pyrrole-3-carboxylic acid,



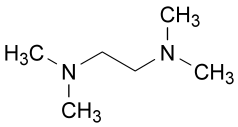
G. 4-[[(1*S*)-1-carboxy-2-(4-hydroxyphenyl)ethyl]amino]-4-oxobutanoic acid (*N*-succinyltyrosine),



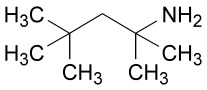
H. 2-amino-2-methylpropane (1,1-dimethylethylamine),



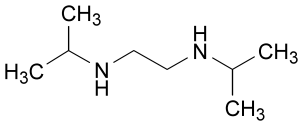
I. diethylamine,



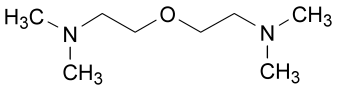
J. 1,2-bis(dimethylamino)ethane (*N*,*N*,*N*′,*N*′-tetramethylethylenediamine),



K. 2-amino-2,4,4-trimethylpentane (1,1,3,3-tetramethylbutylamine),



L. *N*,*N*′-bis(1-methylethyl)-1,2-ethanediamine (*N*,*N*′-diisopropylethylenediamine),

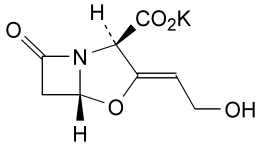


M. bis(2-dimethylamino)ethyl ether [2,2′-oxybis(*N*,*N*-dimethylethylamine)].

01/2008:1653

POTASSIUM CLAVULANATE, DILUTED

Kalii clavulanas dilutus



$C_8H_8KNO_5$ M_r 237.3

DEFINITION

Dry mixture of *Potassium clavulanate (1140)* and *Cellulose, microcrystalline (0316)* or *Silica, colloidal anhydrous (0434)* or *Silica, colloidal hydrated (0738)*.

Content: 91.2 per cent to 107.1 per cent of the content of potassium clavulanate stated on the label.

CHARACTERS

Appearance of diluted potassium clavulanate: white or almost white powder, hygroscopic.

Solubility of potassium clavulanate: freely soluble in water, slightly soluble in alcohol, very slightly soluble in acetone.

The solubility of the diluted product depends on the diluent and its concentration.

IDENTIFICATION

A. Examine the chromatograms obtained in the assay.

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

B. It gives reaction (b) of potassium (*2.3.1*).

C. Depending on the diluent used, carry out the corresponding identification test (a) or (b).

(a) A quantity of the substance to be examined, corresponding to 20 mg of cellulose, when placed on a watch-glass and dispersed in 4 ml of *iodinated zinc chloride solution R*, becomes violet-blue.

(b) It gives the reaction of silicates (*2.3.1*).

TESTS

pH (*2.2.3*): 4.8 to 8.0.

Suspend a quantity of the substance to be examined corresponding to 0.200 g of potassium clavulanate in 20 ml of *carbon dioxide-free water R*.

Absorbance (*2.2.25*): maximum 0.40 measured immediately at 278 nm.

Disperse a quantity of the substance to be examined corresponding to 50.0 mg of potassium clavulanate in 10 ml of *0.1 M phosphate buffer solution pH 7.0 R*, dilute to 50.0 ml with the same buffer solution and filter.

Related substances. Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use.*

Test solution. Disperse a quantity of the substance to be examined corresponding to 0.250 g of potassium clavulanate in 5 ml of mobile phase A, dilute to 25.0 ml with mobile phase A and filter.

Reference solution (a). Dilute 1.0 ml of the test solution to 100.0 ml with mobile phase A.

Reference solution (b). Dissolve 10 mg of *amoxicillin trihydrate CRS* in 1 ml of the test solution and dilute to 100 ml with mobile phase A.

Column:

– *size*: *l* = 0.10 m, Ø = 4.6 mm,
– *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm),
– *temperature*: 40 °C.

Mobile phase:

– *mobile phase A*: 7.8 g/l solution of *sodium dihydrogen phosphate R* adjusted to pH 4.0 with *dilute phosphoric acid R*,
– *mobile phase B*: mixture of equal volumes of mobile phase A and *methanol R*,

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 4	100	0
4 - 15	100 → 50	0 → 50
15 - 18	50	50
18 - 24	50 → 100	50 → 0
24 - 39	100	0

Flow rate: 1 ml/min.

Detection: spectrophotometer at 230 nm.

Injection: 20 µl.

System suitability: reference solution (b):

– *resolution*: minimum of 13 between the peak due to clavulanate (1st peak) and the peak due to amoxicillin (2nd peak).

Limits:

– *any impurity*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent),
– *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (2.0 per cent),
– *disregard limit*: 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Water (*2.5.12*): maximum 2.5 per cent, determined on 1.000 g.

ASSAY

Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use.*

Test solution. Disperse a quantity of the substance to be examined corresponding to 50.0 mg of potassium clavulanate in a 4.1 g/l solution of *sodium acetate R* previously adjusted to pH 6.0 with *glacial acetic acid R*, dilute to 50.0 ml with the same solution and filter.

Reference solution (a). Dissolve 50.0 mg of *lithium clavulanate CRS* in a 4.1 g/l solution of *sodium acetate R* previously adjusted to pH 6.0 with *glacial acetic acid R* and dilute to 50.0 ml with the same solution.

Reference solution (b). Dissolve 10 mg of *amoxicillin trihydrate CRS* in 10 ml of reference solution (a).

Column:

– *size*: *l* = 0.3 m, Ø = 4.6 mm,
– *stationary phase*: *octadecylsilyl silica gel for chromatography R* (10 µm).

Mobile phase: mix 5 volumes of *methanol R1* and 95 volumes of a 15 g/l solution of *sodium dihydrogen phosphate R* previously adjusted to pH 4.0 with *dilute phosphoric acid R*.

Flow rate: 1 ml/min.

Detection: spectrophotometer at 230 nm.

Injection: 10 µl.

System suitability: reference solution (b):

– *resolution*: minimum 3.5 between the peak due to clavulanate (1st peak) and the peak due to amoxicillin (2nd peak).

1 mg of $C_8H_9NO_5$ is equivalent to 1.191 mg of $C_8H_8KNO_5$.

STORAGE

In an airtight container.

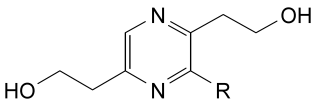
LABELLING

The label states the *m/m* percentage content of potassium clavulanate and the diluent used to prepare the mixture.

IMPURITIES

Specified impurities: A, B, C, D, G.

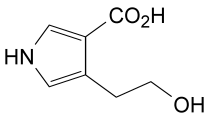
Other detectable impurities: E, F.



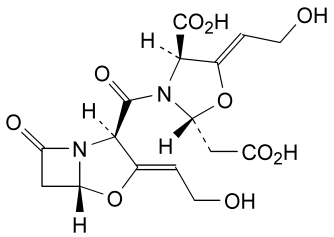
A. R = H: 2,2′-(pyrazine-2,5-diyl)diethanol,

B. R = CH_2-CH_2-CO_2H: 3-[3,6-bis(2-hydroxyethyl)pyrazin-2-yl]propanoic acid,

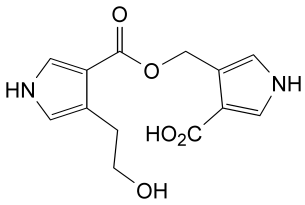
C. R = CH_2-CH_3: 2,2′-(3-ethylpyrazine-2,5-diyl)diethanol,



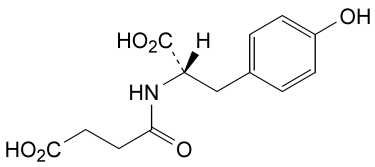
D. 4-(2-hydroxyethyl)-1*H*-pyrrole-3-carboxylic acid,



E. (2*R*,4*R*,5*Z*)-2-(carboxymethyl)-5-(2-hydroxyethylidene)-3-[[(2*R*,3*Z*,5*R*)-3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[3.2.0]hept-2-yl]carbonyl]oxazolidine-4-carboxylic acid,



F. 4-[[[[4-(2-hydroxyethyl)-1*H*-pyrrol-3-yl]carbonyl]oxy]methyl]-1*H*-pyrrole-3-carboxylic acid,



G. 4-[[(1*S*)-1-carboxy-2-(4-hydroxyphenyl)ethyl]amino]-4-oxobutanoic acid (*N*-succinyltyrosine).

01/2008:0920
corrected 6.0

POTASSIUM DIHYDROGEN PHOSPHATE

Kalii dihydrogenophosphas

KH_2PO_4 M_r 136.1
[7778-77-0]

DEFINITION

Content: 98.0 per cent to 100.5 per cent (dried substance).

CHARACTERS

Appearance: white or almost white, crystalline powder or colourless crystals.

Solubility: freely soluble in water, practically insoluble in ethanol (96 per cent).

IDENTIFICATION

A. Solution S (see Tests) is slightly acid (*2.2.4*).

B. Solution S gives reaction (b) of phosphates (*2.3.1*).

C. 0.5 ml of solution S gives reaction (b) of potassium (*2.3.1*).

TESTS

Solution S. Dissolve 10.0 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 100 ml with the same solvent.

Appearance of solution. Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

pH (*2.2.3*): 4.2 to 4.5.

To 5 ml of solution S add 5 ml of *carbon dioxide-free water R*.

Reducing substances. To 5 ml of solution S add 5 ml of *dilute sulphuric acid R* and 0.25 ml of *0.02 M potassium permanganate*. Heat on a water-bath for 5 min. The colour of the permanganate is not completely discharged.

Chlorides (*2.4.4*): maximum 200 ppm.

Dilute 2.5 ml of solution S to 15 ml with *water R*.

Sulphates (*2.4.13*): maximum 300 ppm.

To 5 ml of solution S add 0.5 ml of *hydrochloric acid R* and dilute to 15 ml with *distilled water R*.

Arsenic (*2.4.2, Method A*): maximum 2 ppm, determined on 0.5 g.

Iron (*2.4.9*): maximum 10 ppm, determined on solution S.

Sodium: maximum 0.10 per cent, if intended for use in the manufacture of parenteral dosage forms.

Atomic emission spectrometry (*2.2.22, Method I*).

Test solution. Dissolve 1.00 g of the substance to be examined in *water R* and dilute to 100.0 ml with the same solvent.

Reference solutions. Prepare the reference solutions using the following solution, diluted as necessary with *water R*: dissolve 0.5084 g of *sodium chloride R*, previously dried at 100-105 °C for 3 h, in *water R* and dilute to 1000.0 ml with the same solvent (200 µg of Na per millilitre).

Wavelength: 589 nm.

Heavy metals (*2.4.8*): maximum 10 ppm.

12 ml of solution S complies with test A. Prepare the reference solution using *lead standard solution (1 ppm Pb) R*.

Loss on drying (*2.2.32*): maximum 2.0 per cent, determined on 1.000 g by drying in an oven at 125-130 °C.

ASSAY

Dissolve 1.000 g in 50 ml of *carbon dioxide-free water R*. Titrate with carbonate-free *1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*).

1 ml of *1 M sodium hydroxide* is equivalent to 0.1361 g of KH_2PO_4.

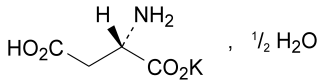
LABELLING

The label states, where applicable, that the substance is suitable for use in the manufacture of parenteral dosage forms.

01/2008:2076
corrected 6.0

POTASSIUM HYDROGEN ASPARTATE HEMIHYDRATE

Kalii hydrogenoaspartas hemihydricus



$C_4H_6KNO_4,{}^1/_2H_2O$ M_r 180.2

DEFINITION

Potassium hydrogen (2*S*)-2-aminobutanedioate hemihydrate.

Content: 99.0 per cent to 101.0 per cent (anhydrous substance).

ERRATA

In the following monographs, after the heading ‘Other detectable impurities’ in the Impurities section, read:

‘(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*)’

Articaine hydrochloride (1688)
Biperiden hydrochloride (1074)
Caffeine (0267)
Caffeine monohydrate (0268)
Ibuprofen (0721)
Ifosfamide (1529)
Metformin hydrochloride (0931)
Naphazoline hydrochloride (0730)
Norethisterone acetate (0850)
Oxaliplatin (2017)
Potassium clavulanate (1140)
Potassium clavulanate, diluted (1653)
Testosterone propionate (0297)
Thiamine hydrochloride (0303)
Thiamine nitrate (0531)
Tranexamic acid (0875)