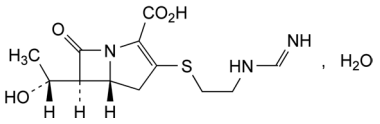
04/2013:1226

IMIPENEM MONOHYDRATE

Imipenemum monohydricum



$C_{12}H_{17}N_3O_4S,H_2O$ M_r 317.4
[74431-23-5]

DEFINITION

(5*R*,6*S*)-6-[(*R*)-1-Hydroxyethyl]-3-[[2-[(iminomethyl)amino]-ethyl]sulfanyl]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid monohydrate.

Semi-synthetic product derived from a fermentation product or obtained by any other means.

Content: 98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance: white or almost white or pale yellow powder, slightly hygroscopic.

Solubility: slightly soluble in water and in methanol.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *imipenem CRS*.

TESTS

Appearance of solution. The solution is not more opalescent than reference suspension II (*2.2.1*) and not more intensely coloured than intensity 6 of the range of the reference solutions of the most appropriate colour (*2.2.2, Method II*).

Dissolve 0.500 g in *phosphate buffer solution pH 7.0 R3* and dilute to 50 mL with the same solution.

pH (*2.2.3*): 4.5 to 7.5.

Dissolve 0.500 g in *carbon dioxide-free water R* and dilute to 100.0 mL with the same solvent.

Specific optical rotation (*2.2.7*): + 90 to + 95 (anhydrous substance), measured at 25 °C. *Prepare the solutions immediately before use.*

Dissolve 0.125 g in *phosphate buffer solution pH 7.0 R3* and dilute to 25.0 mL with the same solution.

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

Buffer solution A. Dissolve 0.32 g of *anhydrous sodium dihydrogen phosphate R* and 1.04 g of *anhydrous disodium hydrogen phosphate R* in 900 mL of *water R*. Adjust to pH 7.3 with *dilute phosphoric acid R* and dilute to 1000 mL with *water R*.

Buffer solution B. Dissolve 0.11 g of *anhydrous disodium hydrogen phosphate R* in 900 mL of *water R*. Adjust to pH 6.8 with *dilute phosphoric acid R* and dilute to 1000 mL with *water R*.

Solvent mixture: *acetonitrile R*, buffer solution B (0.7:99.3 *V/V*).

Test solution. Dissolve 25.0 mg of the substance to be examined in the solvent mixture and dilute to 25.0 mL with the solvent mixture.

Reference solution (a). Dissolve 25.0 mg of *imipenem CRS* in the solvent mixture and dilute to 25.0 mL with the solvent mixture.

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

Reference solution (c). Dissolve 5 mg of the substance to be examined in 8 mL of a mixture of 1 volume of *dilute sulfuric acid R* and 200 volumes of *water R*. After 5 min, add 10 mg of *sodium carbonate R* and dilute to 10.0 mL with *water R*.

Column:

- *size*: *l* = 0.15 m, Ø = 4.6 mm;
- *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3 µm);
- *temperature*: 30 °C.

Mobile phase:

- *mobile phase A*: *acetonitrile R1*, buffer solution A (0.7:99.3 *V/V*);
- *mobile phase B*: *acetonitrile R1*, buffer solution A (25:75 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 9	100	0
9 - 24	100 → 68	0 → 32
24 - 24.5	68 → 50	32 → 50
24.5 - 29	50	50

Flow rate: 1.0 mL/min.

Detection: spectrophotometer at 210 nm.

Injection: 10 µL of the test solution and reference solutions (b) and (c).

Identification of impurities: use the chromatogram obtained with reference solution (c) to identify the peaks due to the epimers of impurity B.

Relative retention with reference to imipenem (retention time = about 8 min): epimer I of impurity B = about 0.33; epimer II of impurity B = about 0.35; impurity A = about 0.8.

System suitability: reference solution (c):

- *peak-to-valley ratio*: minimum 2.0, where H_p = height above the baseline of the peak due to epimer I 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 epimer II of impurity B.

Calculation of percentage contents:

- for impurity A, multiply the peak area by the correction factor 2.4;
- for each impurity, use the concentration of imipenem in reference solution (b).

Limits:

- *impurity A*: maximum 1.0 per cent;
- *impurity B*: for each epimer, maximum 0.3 per cent;
- *unspecified impurities*: for each impurity, maximum 0.10 per cent;
- *total*: maximum 1.5 per cent;
- *reporting threshold*: 0.05 per cent.

Water (*2.5.12*): 5.0 per cent to 8.0 per cent, determined on 0.100 g. Use an iodosulfurous reagent containing imidazole instead of pyridine and a clean container for each determination.

Sulfated ash (*2.4.14*): maximum 0.2 per cent, determined on 1.0 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 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).

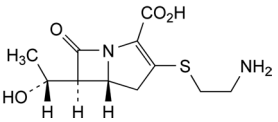
Calculate the percentage content of $C_{12}H_{17}N_3O_4S$ taking into account the assigned content of *imipenem CRS*.

STORAGE

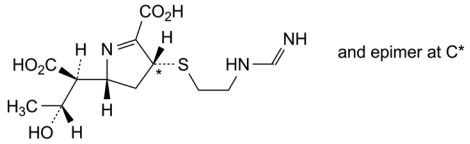
In an airtight container, at a temperature of 2 °C to 8 °C. If the substance is sterile, store in a sterile, airtight, tamper-proof container.

IMPURITIES

Specified impurities: A, B.



A. (5*R*,6*S*)-3-[(2-aminoethyl)sulfanyl]-6-[(*R*)-1-hydroxyethyl]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid (thienamycin),

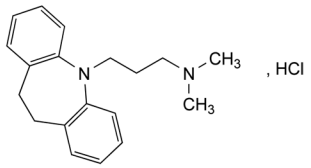


B. (2*R*,4*RS*)-2-[(1*S*,2*R*)-1-carboxy-2-hydroxypropyl]-4-[[2-[(iminomethyl)amino]ethyl]sulfanyl]-3,4-dihydro-2*H*-pyrrole-5-carboxylic acid (imipenemoic acid).

01/2017:0029

IMIPRAMINE HYDROCHLORIDE

Imipramini hydrochloridum



$C_{19}H_{25}ClN_2$ M_r 316.9

[113-52-0]

DEFINITION

3-(10,11-Dihydro-5*H*-dibenzo[*b*,*f*]azepin-5-yl)-*N*,*N*-dimethylpropan-1-amine hydrochloride.

Content: 98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance: white or slightly yellow, crystalline powder.

Solubility: freely soluble in water and in ethanol (96 per cent).

IDENTIFICATION

First identification: B, D.

Second identification: A, C, D.

A. Melting point (*2.2.14*): 170 °C to 174 °C.

B. Infrared absorption spectrophotometry (*2.2.24*).
Comparison: *imipramine hydrochloride CRS*.

C. Dissolve about 5 mg in 2 mL of *nitric acid R*. An intense blue colour develops.

D. About 20 mg gives reaction (a) of chlorides (*2.3.1*).

TESTS

Solution S. To 3.0 g add 20 mL of *carbon dioxide-free water R*, dissolve rapidly by shaking and triturating with a glass rod and dilute to 30 mL with the same solvent.

Appearance of solution. Solution S is clear (*2.2.1*). Immediately after preparation, dilute solution S with an equal volume of *water R*. This solution is not more intensely coloured than reference solution BY_6 (*2.2.2, Method II*).

pH (*2.2.3*): 3.6 to 5.0 for solution S, measured immediately after preparation.

Related substances. Liquid chromatography (*2.2.29*).

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

Reference solution (a). Dissolve 5.0 mg of *imipramine for system suitability CRS* (containing impurity B) in the mobile phase and dilute to 5.0 mL with the mobile phase.

Reference solution (b). Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Column:

– *size*: *l* = 0.15 m, Ø = 4.6 mm;
– *stationary phase*: *end-capped polar-embedded octadecylsilyl amorphous organosilica polymer R* (5 µm);
– *temperature*: 40 °C.

Mobile phase: mix 40 volumes of *acetonitrile R1* with 60 volumes of a 5.2 g/L solution of *dipotassium hydrogen phosphate R* previously adjusted to pH 7.0 with *phosphoric acid R*.

Flow rate: 1.0 mL/min.

Detection: spectrophotometer at 220 nm.

Injection: 10 µL.

Run time: 2.5 times the retention time of imipramine.

Relative retention with reference to imipramine (retention time = about 7 min): impurity B = about 0.7.

System suitability: reference solution (a):

– *resolution*: minimum 5.0 between the peaks due to impurity B and imipramine.

Limits:

– *impurity B*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (a) (0.1 per cent);
– *unspecified impurities*: for each impurity, not more than the area of the peak due to imipramine in the chromatogram obtained with reference solution (b) (0.10 per cent);
– *total*: not more than 3 times the area of the peak due to imipramine in the chromatogram obtained with reference solution (b) (0.3 per cent);
– *disregard limit*: 0.5 times the area of the peak due to imipramine in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (*2.2.32*): maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

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

ASSAY

Dissolve 0.250 g in 50 mL of *ethanol (96 per cent) R* and add 5.0 mL of *0.01 M hydrochloric acid*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 31.69 mg of $C_{19}H_{25}ClN_2$.

STORAGE

Protected from light.

IMPURITIES

Specified impurities: B.

Monographs I