colour additives. The diameter of sugar spheres varies usually from 200 µm to 2000 µm and the upper and lower limits of the size of the sugar spheres are stated on the label.

IDENTIFICATION

A. Examine by thin-layer chromatography (*2.2.27*), using a *TLC silica gel G plate R*.

Test solution. Mix 2 ml of solution S (see Tests) with 3 ml of *methanol R*. Dilute to 20 ml with a mixture of 2 volumes of *water R* and 3 volumes of *methanol R*.

Reference solution (a). Dissolve 10 mg of *sucrose CRS* in a mixture of 2 volumes of *water R* and 3 volumes of *methanol R* and dilute to 20 ml with the same mixture of solvents.

Reference solution (b). Dissolve 10 mg of *fructose CRS*, 10 mg of *glucose CRS*, 10 mg of *lactose CRS* and 10 mg of *sucrose CRS* in a mixture of 2 volumes of *water R* and 3 volumes of *methanol R* and dilute to 20 ml with the same mixture of solvents.

Apply to the plate 2 µl of each solution and thoroughly dry the starting points. Develop over a path of 15 cm using a mixture of 10 volumes of *water R*, 15 volumes of *methanol R*, 25 volumes of *anhydrous acetic acid R* and 50 volumes of *ethylene chloride R*, measured accurately as a slight excess of water causes cloudiness of the solution. Dry the plate in a current of warm air. Repeat the development immediately after renewing the mobile phase. Dry the plate in a current of warm air and spray evenly with a 5 g/l solution of *thymol R* in a mixture of 5 volumes of *sulphuric acid R* and 95 volumes of *alcohol R*. Heat at 130 °C for 10 min. The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a). The test is not valid unless the chromatogram obtained with reference solution (b) shows 4 clearly separated spots.

B. To water slurry of the insoluble portion obtained (see Assay), add 0.05 ml of *iodine solution R1*. A dark-blue is produced which disappears on heating.

C. To 5 ml of solution S add 0.15 ml of freshly prepared *copper sulphate solution R* and 2 ml of freshly prepared *dilute sodium hydroxide solution R*. The solution is blue and clear and remains so after boiling. To the hot solution add 4 ml of *dilute hydrochloric acid R* and boil for 1 min. Add 4 ml of *dilute sodium hydroxide solution R*. An orange precipitate is formed immediately.

TESTS

Solution S. To 0.5 g in a 100 ml volumetric flask add 80 ml of *water R* and shake until the sucrose is dissolved. Dilute to 100.0 ml with *water R*. Filter under vacuum to obtain a clear solution.

Fineness (*2.9.12*). Minimum of 90 per cent (*m/m*) of the sugar spheres are between the lower and the upper limits of the size of the sugar spheres stated on the label.

Heavy metals (*2.4.8*). 2.0 g complies with limit test C for heavy metals (5 ppm). Prepare the standard using 1.0 ml of *lead standard solution (10 ppm Pb) R*.

Loss on drying (*2.2.32*). Not more than 5.0 per cent, determined on 1.000 g by drying in an oven at 105 °C for 4 h.

Sulphated ash (*2.4.14*). Not more than 0.2 per cent, determined on 2 g.

Microbial contamination. Total viable aerobic count (*2.6.12*) not more than 10^3 bacteria and 10^2 fungi per gram, determined by plate count. It complies with the tests for *Escherichia coli* and *Salmonella* (*2.6.13*).

ASSAY

Sucrose content

Weigh 10.000 g of ground sugar spheres in a 100 ml graduated flask and complete to 100.0 ml with *water R*. Stir and decant. Filter under vacuum to obtain a clear solution (the insoluble portion is used for the identification test B). Measure the angle of optical rotation (*2.2.7*) and calculate the sucrose percentage content as follows:

$$\frac{10^6 \times \alpha}{66.5 \times l \times m \times (100 - H)}$$

α = angle of rotation,

l = length of the polarimeter tube, in decimetres,

m = exact weight of the granules sample, in grams,

H = loss on drying.

LABELLING

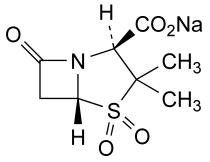
The label states:

- the upper and the lower limits of the size of the sugar spheres,
- any added colour additives,
- any added starch hydrolysates.

01/2008:2209

SULBACTAM SODIUM

Sulbactamum natricum



$C_8H_{10}NNaO_5S$ M_r 255.2

[69388-84-7]

DEFINITION

Sodium (2*S*,5*R*)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate 4,4-dioxide.

Semi-synthetic product derived from a fermentation product.

Content: 97.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance: white or almost white, hygroscopic, crystalline powder.

Solubility: freely soluble in water, sparingly soluble in ethyl acetate, very slightly soluble in ethanol (96 per cent). It is freely soluble in dilute acids.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *sulbactam sodium CRS*.

B. It gives reaction (a) of sodium (*2.3.1*).

TESTS

Appearance of solution. The solution is clear (*2.2.1*).

Dissolve 2.0 g in *water R* and dilute to 20 ml with the same solvent.

Absorbance (*2.2.25*): maximum 0.10 at 430 nm.

Dissolve 1.0 g in *water R* and dilute to 100.0 ml with the same solvent.

pH (*2.2.3*): 4.5 to 7.2; if the substance is sterile: 5.2 to 7.2.

Dissolve 1.0 g in *carbon dioxide-free water R* and dilute to 20 ml with the same solvent.

Specific optical rotation (*2.2.7*): + 219 to + 233 (anhydrous substance).

Dissolve 0.500 g in *water R* and dilute to 50.0 ml with the same solvent.

Related substances. Liquid chromatography (*2.2.29*).

Solution A. 2.72 g/l solution of *potassium dihydrogen phosphate R* adjusted to pH 4.0 with *dilute phosphoric acid R*.

Solution B. Dilute 2 ml of *acetonitrile R1* to 100.0 ml with solution A.

Test solution. Suspend 77.0 mg of the substance to be examined in 2 ml of *acetonitrile R1* and sonicate for about 5 min. Dilute to 100.0 ml with solution A.

Reference solution (a). Suspend 70.0 mg of *sulbactam CRS* in 2 ml of *acetonitrile R1* and sonicate for about 5 min. Dilute to 100.0 ml with solution A.

Reference solution (b). Dilute 1.0 ml of reference solution (a) to 100.0 ml with solution B. Dilute 1.0 ml of this solution to 10.0 ml with solution B.

Reference solution (c). Dissolve 15.0 mg of *6-aminopenicillanic acid R* in solution A and dilute to 50.0 ml with solution A.

Reference solution (d). Mix 1 ml of reference solution (a) and 1 ml of reference solution (c) and dilute to 25.0 ml with solution B.

Reference solution (e). Dissolve 8 mg of *sulbactam for peak identification CRS* (containing impurities A, C, D, E and F) in 1 ml of *acetonitrile R1*, sonicate for about 5 min and dilute to 10 ml with solution B.

Column:

- *size*: *l* = 0.10 m, Ø = 4.0 mm;
- *stationary phase*: *octadecylsilyl silica gel for chromatography R* (3.0 µm);
- *temperature*: 40 °C.

Mobile phase:

- *mobile phase A*: 5.44 g/l solution of *potassium dihydrogen phosphate R* adjusted to pH 4.0 with *dilute phosphoric acid R*;
- *mobile phase B*: *acetonitrile R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 7.5	98 → 50	2 → 50
7.5 - 8.5	50	50
8.5 - 9.0	50 → 98	50 → 2
9.0 - 12.5	98	2

Flow rate: 1.0 ml/min.

Detection: spectrophotometer at 215 nm.

Injection: 20 µl of the test solution, solution B and reference solutions (b), (d) and (e).

Relative retention with reference to sulbactam (retention time = about 2.5 min): impurity A = about 0.4; impurity B = about 0.6; impurity C = about 1.6; impurity D = about 2.0; impurity E = about 2.1; impurity F = about 2.5.

Identification of impurities: use the chromatogram supplied with *sulbactam for peak identification CRS* and the chromatogram obtained with reference solution (e) to identify the peaks due to impurities A, C, D, E and F.

System suitability: reference solution (d):

- *resolution*: minimum 7.0 between the peaks due to impurity B and sulbactam.

Limits:

- *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 0.6; impurity B = 0.5; impurity D = 0.5; impurity F = 0.6;
- *impurity A*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);
- *impurities B, D, F*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent);
- *impurities C, E*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);
- *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);
- *total*: not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent);
- *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

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

Heavy metals (*2.4.8*): maximum 20 ppm.

1.0 g complies with test A. Prepare the reference solution using 10.0 ml of *lead standard solution (2 ppm Pb) R*.

Water (*2.5.12*): maximum 1.0 per cent, determined on 1.00 g.

Bacterial endotoxins (*2.6.14, Method A*): less than 0.17 IU/mg, if intended for use in the manufacture of parenteral dosage forms 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 sulbactam sodium by multiplying the percentage content of sulbactam by 1.094 and using the declared content of *sulbactam CRS*.

STORAGE

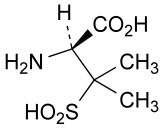
In an airtight container. If the substance is sterile, store in a sterile, airtight, tamper-proof container.

IMPURITIES

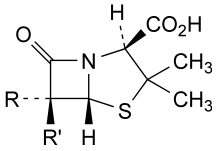
Specified impurities: A, B, C, D, E, F.

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*): G.



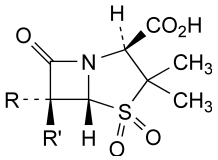
A. (2*S*)-2-amino-3-methyl-3-sulphinobutanoic acid,



B. R = NH_2, R′ = H: (2*S*,5*R*,6*R*)-6-amino-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (6-aminopenicillanic acid),

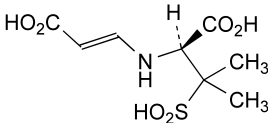
D. R = Br, R′ = H: (2*S*,5*R*,6*R*)-6-bromo-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (6-bromopenicillanic acid),

F. R = R′ = Br: (2*S*,5*R*)-6,6-dibromo-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (6,6-dibromopenicillanic acid),



C. R = Br, R′ = H: (2*S*,5*R*,6*R*)-6-bromo-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid 4,4-dioxide (6-bromopenicillanic acid sulphone),

E. R = R′ = Br: (2*S*,5*R*)-6,6-dibromo-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid 4,4-dioxide (6,6-dibromopenicillanic acid sulphone),

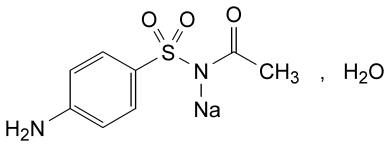


G. (2*E*)-3-[[(1*S*)-1-carboxy-2-methyl-2-sulphinopropyl]amino]prop-2-enoic acid.

01/2008:0107

SULFACETAMIDE SODIUM

Sulfacetamidum natricum



$C_8H_9N_2NaO_3S,H_2O$ M_r 254.2

DEFINITION

Sulfacetamide sodium contains not less than 99.0 per cent and not more than the equivalent of 101.0 per cent of the sodium derivative of *N*-[(4-aminophenyl)sulphonyl]acetamide, calculated with reference to the anhydrous substance.

CHARACTERS

A white or yellowish-white, crystalline powder, freely soluble in water, slightly soluble in ethanol.

IDENTIFICATION

First identification: B, F.

Second identification: A, C, D, E, F.

A. Dissolve 0.1 g in *phosphate buffer solution pH 7.0 R* and dilute to 100.0 ml with the same buffer solution. Dilute 1.0 ml of the solution to 100.0 ml with *phosphate buffer solution pH 7.0 R*. Examined between 230 nm and 350 nm (*2.2.25*), the solution shows an absorption maximum at 255 nm. The specific absorbance at the maximum is 660 to 720, calculated with reference to the anhydrous substance.

B. Examine by infrared absorption spectrophotometry (*2.2.24*), comparing with the spectrum obtained with *sulfacetamide sodium CRS*.

C. Dissolve 1 g in 10 ml of *water R*, add 6 ml of *dilute acetic acid R* and filter. The precipitate, washed with a small quantity of *water R* and dried at 100 °C to 105 °C for 4 h, melts (*2.2.14*) at 181 °C to 185 °C.

D. Dissolve 0.1 g of the precipitate obtained in identification test C in 5 ml of *alcohol R*. Add 0.2 ml of *sulphuric acid R* and heat. The odour of ethyl acetate is perceptible.

E. Dissolve about 1 mg of the precipitate obtained in identification test C, with heating, in 1 ml of *water R*. The solution gives the reaction of primary aromatic amines (*2.3.1*) with formation of an orange-red precipitate.

F. Solution S (see Tests) gives the reactions of sodium (*2.3.1*).

TESTS

Solution S. Dissolve 1.25 g in *carbon dioxide-free water R* and dilute to 25 ml with the same solvent.

Appearance of solution. Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution GY_4 (*2.2.2, Method II*).

pH (*2.2.3*). The pH of solution S is 8.0 to 9.5.

Related substances. Examine by thin-layer chromatography (*2.2.27*), using *silica gel* HF_{254} *R* as the coating substance.

Test solution. Dissolve 1.5 g of the substance to be examined in *water R* and dilute to 15 ml with the same solvent.

Reference solution (a). Dissolve 5 mg of *sulfanilamide R* in *water R* and dilute to 10 ml with the same solvent.

Reference solution (b). Dilute 5 ml of reference solution (a) to 10 ml with *water R*.

Reference solution (c). Dissolve 5 mg of *sulfanilamide R* in 10 ml of the test solution.

Apply to the plate 5 µl of each solution. Develop over a path of 15 cm using a mixture of 10 volumes of *concentrated ammonia R*, 25 volumes of *ethanol R*, 25 volumes of *water R* and 50 volumes of *butanol R*. Allow the plate to dry in air and spray with *dimethylaminobenzaldehyde solution R2*. Any spot in the chromatogram obtained with the test solution, apart from the principal spot, is not more intense than the spot in the chromatogram obtained with reference solution (a) (0.5 per cent), and not more than one such spot is more intense than the spot in the chromatogram obtained with reference solution (b) (0.25 per cent). The test is not valid unless the chromatogram obtained with reference solution (c) shows two clearly separated spots.

Sulphates (*2.4.13*). Dissolve 2.5 g in *distilled water R* and dilute to 25 ml with the same solvent. Add 25 ml of *dilute acetic acid R*, shake for 30 min and filter. 15 ml of the filtrate complies with the limit test for sulphates (200 ppm).