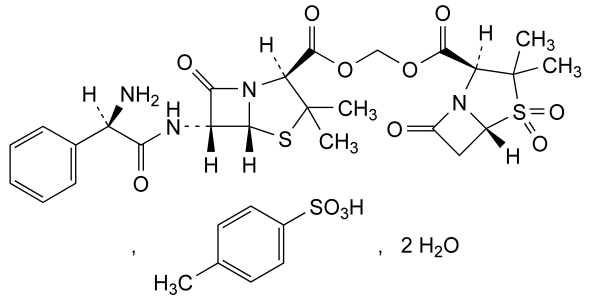
01/2008:2212

SULTAMICILLIN TOSILATE DIHYDRATE

Sultamicillini tosilas dihydricus



$C_{32}H_{38}N_4O_{12}S_3,2H_2O$ M_r 803

DEFINITION

4-Methylbenzenesulphonate of methylene (2*S*,5*R*,6*R*)-6-[[(2*R*)-aminophenylacetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (2*S*,5*R*)-3,3-dimethyl-4,4,7-trioxo-4λ⁶-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate dihydrate.

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, crystalline powder.

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

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *sultamicillin tosilate CRS*.

TESTS

Specific optical rotation (*2.2.7*): + 178 to + 195 (anhydrous substance).

Dissolve 1.000 g in *dimethylformamide R* and dilute to 50.0 ml with the same solvent.

Related substances. Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use or keep at 2-8 °C for not more than 6 h.*

Solution A: *methanol R1, acetonitrile R1* (20:80 *V/V*).

Solution B. Dissolve 1.56 g of *sodium dihydrogen phosphate R* in 900 ml of *water R*. Add 7.0 ml of *phosphoric acid R* and dilute to 1000 ml with *water R*.

Blank solution: solution B, solution A (30:70 *V/V*).

Test solution. Dissolve 70.0 mg of the substance to be examined in 35 ml of solution A and sonicate for about 1 min. Add 13 ml of solution B, mix and sonicate for about 1 min. Dilute to 50.0 ml with solution B and mix.

Reference solution (a). Dissolve 70.0 mg of *sultamicillin tosilate CRS* in 35 ml of solution A and sonicate for about 1 min. Add 13 ml of solution B, mix and sonicate for about 1 min. Dilute to 50.0 ml with solution B and mix.

Reference solution (b). Suspend 15 mg of the substance to be examined in 20 ml of a 0.4 g/l solution of *sodium hydroxide R* and sonicate in an ultrasonic bath for about 5 min. Add 20 ml of a 0.36 g/l solution of *hydrochloric acid R* and dilute to 100.0 ml with *water R*.

Reference solution (c). Dissolve 0.200 g of the substance to be examined in 70.0 ml of solution A and sonicate for about 1 min. Add 25.0 ml of solution B, mix and sonicate for about 1 min. Dilute to 100.0 ml with solution B and mix. Dilute 1.0 ml of this solution to 100.0 ml with the blank solution.

Reference solution (d). Dissolve 32.3 mg of *ampicillin trihydrate CRS* (impurity B) and 7.0 mg of *sulbactam CRS* (impurity A) in *water R* and dilute to 1000 ml with the same solvent.

Column:

- *size*: *l* = 0.10 m, Ø = 4.6 mm;
- *stationary phase*: *octadecylsilyl silica gel for chromatography R* (3.5 µm);
- *temperature*: 25 °C.

Mobile phase:

- *mobile phase A*: 4.68 g/l solution of *sodium dihydrogen phosphate R* adjusted to pH 3.0 with *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 - 15	95 → 30	5 → 70
15 - 16	30	70
16 - 16.5	30 → 95	70 → 5
16.5 - 20	95	5

Flow rate: 1.0 ml/min.

Detection: spectrophotometer at 215 nm.

Injection: 5 µl of the blank solution, the test solution and reference solutions (b), (c) and (d).

Relative retention with reference to sultamicillin (retention time = about 9.3 min): impurity A = about 0.41; ampicillin penicilloic acid = about 0.47; tosilate = about 0.50; impurity B = about 0.55; impurity C = about 0.94; impurity D = about 1.09; impurity E = about 1.23; impurity F = about 1.26; impurity G = about 1.42.

System suitability: reference solution (b):

- *resolution*: minimum 2.5 between the peaks due to ampicillin penicilloic acid and tosilate and minimum 2.5 between the peaks due to tosilate and impurity B.

Limits:

- *impurity B*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (d) (2.0 per cent);
- *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (d) (0.5 per cent);
- *impurities C, D, E, F, G*: for each impurity, not more than 0.5 times the area of the peak due to sultamicillin in the chromatogram obtained with reference solution (c) (0.5 per cent);
- *any other impurity*: for each impurity, not more than 0.5 times the area of the peak due to sultamicillin in the chromatogram obtained with reference solution (c) (0.5 per cent);
- *total*: not more than 4 times the area of the peak due to sultamicillin in the chromatogram obtained with reference solution (c) (4.0 per cent);
- *disregard limit*: 0.1 times the area of the peak due to sultamicillin in the chromatogram obtained with reference solution (c) (0.1 per cent).

Ethyl acetate. Head space gas chromatography (*2.2.28*).

Test solution. Dissolve 0.200 g in 7.0 ml of a mixture of 1 volume of *water R* and 99 volumes of *dimethylformamide R*.

Reference solution. Dissolve 0.200 g of *ethyl acetate R* in 240 ml of a mixture of 1 volume of *water R* and 99 volumes of *dimethylformamide R* and dilute to 250.0 ml with the same mixture of solvents. Dilute 5.0 ml of this solution to 7.0 ml with a mixture of 1 volume of *water R* and 99 volumes of *dimethylformamide R*.

Immediately close the vials with a tight rubber membrane stopper coated with polytetrafluoroethylene and secure with an aluminium crimped cap. Shake to obtain a homogeneous solution.

Column:

– *material*: fused silica;
– *size*: *l* = 50 m, Ø = 0.32 mm;
– *stationary phase*: *poly(dimethyl)siloxane R* (film thickness: 1.8 µm or 3 µm).

Carrier gas: *helium for chromatography R.*

Linear velocity: 35 cm/s.

Split ratio: 1:5.

Static head-space conditions that may be used:

– *equilibration temperature*: 105 °C;
– *equilibration time*: 45 min;
– *transfer-line temperature*: 110 °C;
– *pressurisation time*: 30 s.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 6	70
	6 - 16	70 → 220
	16 - 18	220
Injection port		140
Detector		250

Detection: flame ionisation.

Injection: 1 ml.

Relative retention with reference to dimethylformamide (retention time = about 14 min): ethyl acetate = about 0.7.

Limit:

– *ethyl acetate*: maximum 2.0 per cent.

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

Dissolve 2.0 g in a mixture of 40 volumes of *methanol R* and 60 volumes of *acetonitrile R* and dilute to 20.0 ml with the same mixture of solvents. 12 ml of the solution complies with test B. Prepare the reference solution using lead standard solution (2 ppm Pb) obtained by diluting *lead standard solution (100 ppm Pb) R* with a mixture of 40 volumes of *methanol R* and 60 volumes of *acetonitrile R*.

Water (*2.5.12*): 4.0 per cent to 6.0 per cent, determined on 0.200 g.

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

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 sultamicillin tosilate ($C_{32}H_{38}N_4O_{12}S_3$) from the declared content of sultamicillin ($C_{25}H_{30}N_4O_9S_2$) in *sultamicillin tosilate CRS* and by multiplying the sultamicillin content by 1.3502.

STORAGE

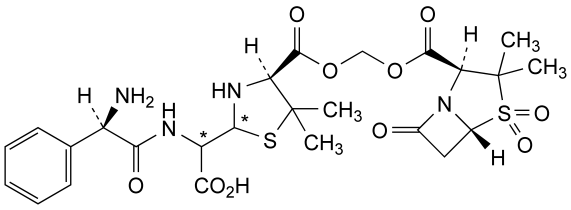
In an airtight container.

IMPURITIES

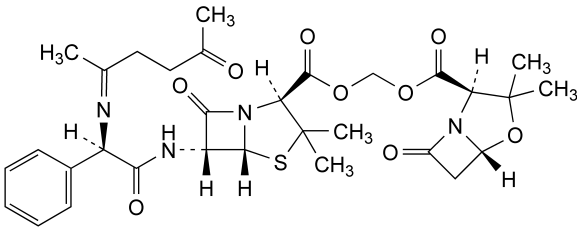
Specified impurities: A, B, C, D, E, F, G.

A. sulbactam,

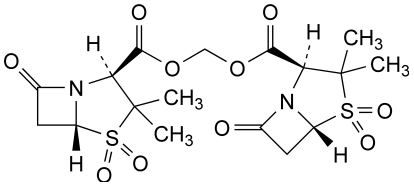
B. ampicillin,



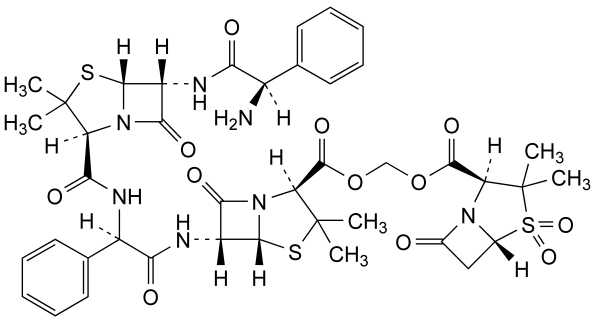
C. [[(2*R*)-aminophenylacetyl]amino][(4*S*)-4-[[[[[(2*S*,5*R*)-3,3-dimethyl-4,4,7-trioxo-4λ⁶-thia-1-azabicyclo[3.2.0]hept-2-yl]carbonyl]oxy]methoxy]carbonyl]-5,5-dimethylthiazolidin-2-yl]acetic acid (penicilloic acids of sultamicillin),



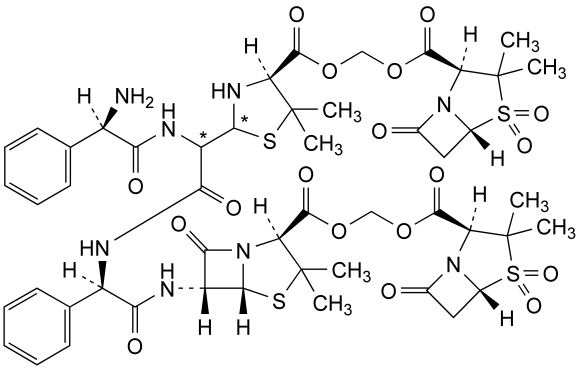
D. methylene (2*S*,5*R*,6*R*)-3,3-dimethyl-6-[[(2*R*)-[(1-methyl-4-oxopentylidene)amino]phenylacetyl]amino]-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (2*S*,5*R*)-3,3-dimethyl-7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane-2-carboxylate,



E. methylene bis[(2*S*,5*R*)-3,3-dimethyl-4,4,7-trioxo-4λ⁶-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate] (sulbactam methylene ester),



F. methylene (2*S*,5*R*,6*R*)-6-[[(2*R*)-[[[(2*S*,5*R*,6*R*)-6-[[(2*R*)-aminophenylacetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-yl]carbonyl]amino]phenylacetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (2*S*,5*R*)-3,3-dimethyl-4,4,7-trioxo-4λ⁶-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (ampicillin sultamicillin amide),

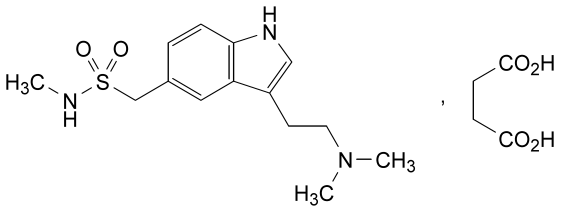


G. methylene (2*S*,5*R*,6*R*)-6-[[(2*R*)-[[[[(2*R*)-amino-phenylacetyl]amino][(4*S*)-4-[[[[[(2*S*,5*R*)-3,3-dimethyl-4,4,7-trioxo-4λ⁶-thia-1-azabicyclo[3.2.0]hept-2-yl] carbonyl]oxy]methoxy]carbonyl]-5,5-dimethylthiazolidin-2-yl]acetyl]amino]phenylacetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (2*S*,5*R*)-3,3-dimethyl-4,4,7-trioxo-4λ⁶-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate (sultamicillin dimer).

01/2008:1573

SUMATRIPTAN SUCCINATE

Sumatriptani succinas



$C_{18}H_{27}N_3O_6S$ M_r 413.5
[103628-48-4]

DEFINITION

[3-[2-(Dimethylamino)ethyl]-1*H*-indol-5-yl]-*N*-methylmethanesulphonamide hydrogen butanedioate.

Content: 97.5 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance: white or almost white powder.

Solubility: freely soluble in water, sparingly soluble in methanol, practically insoluble in methylene chloride.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Preparation: discs.

Comparison: *sumatriptan succinate CRS*.

TESTS

Solution S. Dissolve 1.0 g in *carbon dioxide-free water R* and dilute to 25.0 ml with the same solvent.

pH (*2.2.3*): 4.5 to 5.3.

Dilute 2.5 ml of solution S to 10 ml with *carbon dioxide-free water R*.

Absorbance (*2.2.25*): maximum 0.10, measured at 440 nm on solution S.

Impurities A and H. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 30.0 mg of the substance to be examined in the mobile phase and dilute to 10.0 ml with the mobile phase.

Reference solution (a). 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.

Reference solution (b). Dissolve the contents of a vial of *sumatriptan for system suitability CRS* (containing impurities A and H) in the mobile phase and dilute to 1 ml with the mobile phase.

Column:

– *size*: *l* = 0.25 m, Ø = 4.6 mm;
– *stationary phase*: *silica gel for chromatography R* (5 µm).

Mobile phase: mix 10 volumes of a 771 g/l solution of *ammonium acetate R* and 90 volumes of *methanol R*.

Flow rate: 2.0 ml/min.

Detection: spectrophotometer at 282 nm.

Injection: 20 µl.

Run time: 5 times the retention time of sumatriptan.

System suitability: reference solution (b):

– *resolution*: minimum 1.5 between the peaks due to sumatriptan and impurity A;
– the chromatogram is similar to the chromatogram supplied with *sumatriptan for system suitability CRS*.

Limits:

– *impurity A*: not more than 6 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.6 per cent);
– *impurity H*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent).

Related substances. Liquid chromatography (*2.2.29*).

Solution A. Dissolve 2.925 g of *sodium dihydrogen phosphate R* in 600 ml of *water R*, adjust to pH 6.5 with *strong sodium hydroxide solution R*, dilute to 750 ml with *water R*, add 250 ml of *acetonitrile R* and mix.

Test solution (a). Dissolve 30.0 mg of the substance to be examined in the mobile phase and dilute to 10.0 ml with the mobile phase.

Test solution (b). Dissolve 15.0 mg of the substance to be examined in solution A and dilute to 100.0 ml with solution A.

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

Reference solution (b). Dissolve the contents of a vial of *sumatriptan impurity mixture CRS* (containing impurities B, C, D and E) in the mobile phase and dilute to 1 ml with the mobile phase.

Reference solution (c). Dissolve 15.0 mg of *sumatriptan succinate CRS* in solution A and dilute to 100.0 ml with solution A.

Column:

– *size*: *l* = 0.25 m, Ø = 4 mm;
– *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase: mix 25 volumes of *acetonitrile R* with 75 volumes of a solution prepared as follows: dissolve 0.970 g of *dibutylamine R*, 0.735 g of *phosphoric acid R*