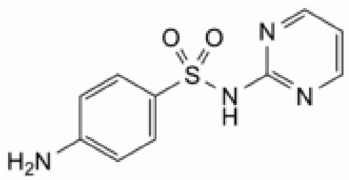
Edition: BP 2025 (Ph. Eur. 11.6 update)

Sulfadiazine

General Notices

(Ph. Eur. monograph 0294)



$C_{10}H_{10}N_4O_2S$ 250.3 *68-35-9*

Action and use

Sulfonamide antibacterial.

Preparation

Sulfadiazine Injection

Ph Eur

DEFINITION

4-Amino-*N*-(pyrimidin-2-yl)benzenesulfonamide.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White, yellowish-white or pinkish-white, crystalline powder or crystals.

Solubility

Practically insoluble in water, slightly soluble in acetone, very slightly soluble in ethanol (96 per cent). It dissolves in solutions of alkali hydroxides and in dilute mineral acids.

IDENTIFICATION

First identification: A.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *sulfadiazine CRS*.

B. Thin-layer chromatography (*2.2.27*).

Solvent mixture *concentrated ammonia R*, *methanol R* (4:96 *V/V*)

Test solution Dissolve 20 mg of the substance to be examined in 3 mL of the solvent mixture and dilute to 5.0 mL with the solvent mixture.

Reference solution Dissolve 20 mg of *sulfadiazine CRS* in 3 mL of the solvent mixture and dilute to 5.0 mL with the solvent mixture.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *dilute ammonia R1*, *water R*, *nitromethane R*, *dioxan R* (3:5:40:50 *V/V/V/V*).

Application 5 µL.

Development Over 3/4 of the plate.

Drying At 105 °C.

Detection Examine in ultraviolet light at 254 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

C. Place 3 g in a dry tube. Immerse the lower part of the tube, inclined at 45°, in a silicone oil bath and heat to about 270 °C. The substance to be examined decomposes and a white or yellowish-white sublimate is formed, which, after recrystallisation from *toluene R* and drying at 100 °C, melts (*2.2.14*) at 123 °C to 127 °C.

D. Dissolve about 5 mg in 10 mL of a 103 g/L solution of *hydrochloric acid R*. Dilute 1 mL of the solution to 10 mL with *water R*. The solution, without further acidification, gives the reaction of primary aromatic amines (*2.3.1*).

TESTS

Appearance of solution

The solution is not more intensely coloured than reference solution Y_5, BY_5 or GY_5 (2.2.2, Method II).

Dissolve 0.8 g in a mixture of 5 mL of dilute sodium hydroxide solution R and 5 mL of water R.

Acidity

To 1.25 g, finely powdered, add 25 mL of carbon dioxide-free water R. Heat at about 70 °C for 5 min. Cool in iced water for about 15 min and filter. To 20 mL of the filtrate add 0.1 mL of bromothymol blue solution R1. Not more than 0.2 mL of 0.1 M sodium hydroxide is required to change the colour of the indicator.

Related substances

Liquid chromatography (2.2.29).

Solvent mixture 40 g/L solution of sodium hydroxide R, acetonitrile R, water R (2:20:60 *V/V/V*).

Test solution Dissolve 50.0 mg of the substance to be examined in the solvent mixture and dilute to 100.0 mL with water R.

Reference solution (a) Dissolve 5.0 mg of sulfadiazine impurity A CRS and 5.0 mg of sulfanilic acid RV (impurity B) in the solvent mixture and dilute to 10.0 mL with water R. Dilute 1.0 mL of the solution to 100.0 mL with the mobile phase. Dilute 3.0 mL of this solution to 10.0 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.

Reference solution (c) Dissolve the contents of a vial of acetylsulfadiazine CRS (impurity E) in 1 mL of the mobile phase.

Reference solution (d) Dissolve 5 mg of sulfadiazine for identification of impurity F CRS in the solvent mixture and dilute to 10.0 mL with water R.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: octadecylsilyl silica gel for chromatography R (5 µm).

Mobile phase acetonitrile R, 2.8 g/L solution of phosphoric acid R (10:90 *V/V*).

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 260 nm.

Injection 20 µL.

Run time 7 times the retention time of sulfadiazine.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A and B; use the chromatogram obtained with reference solution (c) to identify the peak due to impurity E; use the chromatogram obtained with reference solution (d) to identify the peak due to impurity F.

Relative retention With reference to sulfadiazine (retention time = about 8.5 min): impurity A = about 0.26; impurity B = about 0.30; impurity E = about 2.1; impurity F = about 6.0.

System suitability Reference solution (a):

— *resolution*: minimum 2.0 between the peaks due to impurities A and B.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity E by 0.7;

— *impurities A, B*: for each impurity, not more than the area of the corresponding peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *impurity E*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *impurity F*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent);

— *total*: maximum 0.5 per cent;

— *disregard limit*: 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.03 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 0.200 g in a mixture of 20 mL of *dilute hydrochloric acid R* and 50 mL of *water R*. Cool the solution in iced water. Carry out the determination of primary aromatic amino-nitrogen (*2.5.8*), determining the end-point electrometrically.

1 mL of *0.1 M sodium nitrite* is equivalent to 25.03 mg of $C_{10}H_{10}N_4O_2S$.

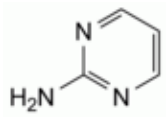
STORAGE

Protected from light.

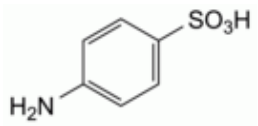
IMPURITIES

Specified impurities *A, B, E, F.*

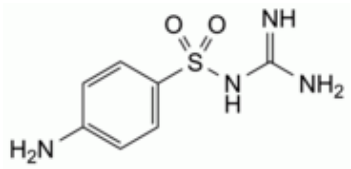
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical 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) C, D.



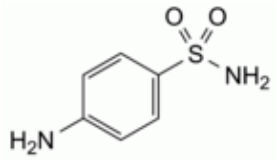
A. pyrimidin-2-amine,



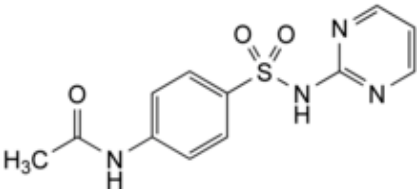
B. 4-aminobenzenesulfonic acid (sulfanilic acid),



C. [(4-aminophenyl)sulfonyl]guanidine (sulfaguanidine),



D. 4-aminobenzenesulfonamide (sulfanilamide),



E. *N*-[4-(pyrimidin-2-ylsulfamoyl)phenyl]acetamide (acetylsulfadiazine),

F. unknown structure.

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