Acetylcysteine

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Please send any comments you may have on this draft document to lab.ipc@gov.in, with a copy to Dr. Gaurav Pratap Singh (email: gpsingh.ipc@gov.in) before the last date for comments.

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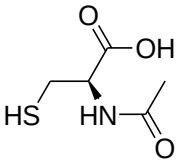
Acetylcysteine



$C_5H_9NO_3S$ Mol. Wt. 163.2

Acetylcysteine is (2R)-2-Acetamido-3-sulfanylpropanoic acid.

Acetylcysteine contains not less than 98.5 per cent and not more than 101.0 per cent of $C_5H_9NO_3S$, calculated on the dried basis.

Category. Antidote to paracetamol poisoning; mucolytic; sulfydryl donor.

Description. A white or almost white, crystalline powder or colourless crystals.

Identification

A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *acetylcysteine IPRS* or with the reference spectrum of acetylcysteine.

B. Specific optical rotation (see Tests).

Tests

Appearance of solution. A 5.0 per cent w/v solution in *water* is clear (2.4.1) and colourless (2.4.1).

Specific optical rotation (2.4.22). +21.0° to +27.0°, determined in a solution prepared by mixing 1.25 g of substance under examination with 1 ml of 1 per cent w/v of solution of *sodium edetate*, add 7.5 ml of *1M sodium hydroxide*, mix and dissolve and dilute 25.0 ml with *phosphate buffer solution pH 7.0*.

Related substances. Determine by liquid chromatography (2.4.14).

NOTE — Prepare the solutions immediately before use.

Solution A. 0.103 per cent w/v solution of *hydrochloric acid*.

Test solution. Dissolve 0.2 g of the substance under examination in solution A with the aid of ultrasound and dilute to 25.0 ml with solution A.

Reference solution (a). A 0.0008 per cent w/v solution of *acetylcysteine IPRS* in solution A.

Reference solution (b). A 0.04 per cent w/v solution of *acetylcysteine impurity A IPRS* in solution A.

Reference solution (c). Dissolve 3 mg of *acetylcysteine impurity B IPRS*, 5 mg of *acetylcysteine impurity C IPRS* and 2.5 mg of *acetylcysteine impurity D IPRS* in solution A, add 4.0 ml of reference solution (b) and dilute to 20 ml with solution A. Dilute 1.0 ml of the solution to 10.0 ml with the test solution.

Reference solution (d). A 0.004 per cent w/v solution of *sodium 2-methyl-2-thiazoline-4-carboxylate* in solution A.

Chromatographic system

– a stainless steel column 25 cm × 4.0 mm, packed with end-capped octadecylsilane bonded to porous silica (5 µm),
– mobile phase: a mixture of 97 volumes of *water*, adjusted to pH 3.0 with *dilute orthophosphoric acid* and 3 volumes of *acetonitrile*,
– flow rate: 1 ml per minute,
– spectrophotometer set at 220 nm,
– injection volume: 20 µl.

Name	Relative retention time	Correction factor
Acetylcysteine impurity A[1]	0.48	---
Acetylcysteine impurity B[2]	0.53	3.4
Sodium 2-methyl-2-thiazoline-4-carboxylate	0.8	---
Acetylcysteine (Retention time: about 5 minutes)	1.0	---
Acetylcysteine impurity C[3]	2.1	0.7
Acetylcysteine impurity D[4]	2.6	0.3

[1]3,3'-disulfanediylbis[(2R)-2-aminopropanoic acid] (L-cystine)
[2](2R)-2-amino-3-sulfanylpropanoic acid (L-cysteine),
[3]3,3'-disulfanediylbis[(2R)-2-acetamidopropanoic acid] (*N, N'*-diacetyl-L-cystine).
[4](2R)-2-acetamido-3-(acetylsulfanyl)propanoic acid (*N,S*-diacetyl-L-cysteine).

Inject reference solution (c) and (d) to identify the peaks due to acetylcysteine impurity A, B, C and D in the chromatogram obtained with reference solution (c) and peak due to 2-methyl-2-thiazoline-4-carboxylic acid in the chromatogram obtained with reference solution (d), respectively.

Inject reference solution (a) and (c). The test is not valid unless the resolution between the peaks due to acetylcysteine impurity A and acetylcysteine impurity B is not less than 1.5, the peak-to-valley ratio (Hp/Hv) is not less than 5.0, where Hp is the height above the baseline of the peak due to 2-methyl-2-thiazoline-4-carboxylic acid and Hv is the height above the baseline of the lowest point of the curve separating the peak due to acetylcysteine in the chromatogram obtained with reference solution (c) and the tailing factor is not more than 2.2, for acetylcysteine peak in the chromatogram obtained with reference solution (a).

Inject reference solution (a) and the test solution. Run the chromatogram 3 times the retention time of the principal peak. In the chromatogram obtained with the test solution, the area of any peak corresponding to acetylcysteine impurity B is not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent), the area of any peak corresponding to acetylcysteine impurity C is not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent), the area of any peak corresponding to acetylcysteine impurity D is not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent),the area of any other secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent) and the sum of the areas of all the secondary peaks is not more than 5 times the area of the principal peak in the chromatogram with reference solution (a) (0.5 per cent). Ignore the peak due to 2-methyl-2-thiazoline-4-carboxyllic acid and any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Sulphated ash (2.3.18). Not more than 0.2 per cent, determined on 1.0 g.

Zinc. Not more than 10 ppm.

Determine by atomic absorption spectrometry (2.4.2).

Test solution. Dissolve 1.0 g of the substance under examination in *0.01 M hydrochloric acid* and dilute to 50.0 ml with *0.01 M hydrochloric acid*.

Reference solution. Prepare the reference solution by diluting *zinc solution AAS* (5 mg per ml Zn) with *0.01 M hydrochloric acid.*

Measure the absorbance at 213.9 nm using a zinc hollow-cathode lamp as source of radiation and an air-acetylene flame. Use a correction procedure for non-specific absorption.

Loss on drying (2.4.19). Not more than 1.0 per cent, determined on 1.0 g by drying in vacuum at 70° for 3 hours.

Assay. Dissolve 0.14 g in 60 ml of *water*, add 10 ml of *dilute hydrochloric acid* and 10 ml of *potassium iodide solution*. Titrate with *0.05 M iodine*, determining the end-point potentiometrically (2.4.25). Carry out a blank titration.

1 ml of *0.05 M iodine* is equivalent to 0.01632 g of $C_5H_9NO_3S$.

Storage. Store protected from light and moisture.

Solubility:
Acetylcysteine. Freely soluble in *water* and in *ethanol (95 per cent)*, practically insoluble in *methylene chloride*.

4.2 General Reagents

Sodium 2-methyl-2-thiazoline-4- carboxylate
$C_5H_6NNa_2S$= 167.2
Sodium 2-methyl-4,5-dihydro-l,3-thiazole-4-carboxylate.
White solid.
Content: minimum 95 per cent.
