Reference solution. Dissolve 10 mg of *carbimazole CRS* in *methylene chloride R* and dilute to 10 ml with the same solvent.

Plate: *TLC silica gel GF_{254} plate R*.

Mobile phase: *acetone R, methylene chloride R* (20:80 *V/V*).

Application: 10 µl.

Development: over a path of 15 cm.

Drying: in air for 30 min.

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.

D. Dissolve about 10 mg in a mixture of 50 ml of *water R* and 0.05 ml of *dilute hydrochloric acid R*. Add 1 ml of *potassium iodobismuthate solution R*. A red precipitate is formed.

TESTS

Impurity A and other related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 5.0 mg of the substance to be examined in 10.0 ml of a mixture of 20 volumes of *acetonitrile R* and 80 volumes of *water R*. Use this solution within 5 min of preparation.

Reference solution (a). Dissolve 5 mg of *thiamazole R* and 0.10 g of *carbimazole CRS* in a mixture of 20 volumes of *acetonitrile R* and 80 volumes of *water R* and dilute to 100.0 ml with the same mixture of solvents. Dilute 1.0 ml of this solution to 10.0 ml with a mixture of 20 volumes of *acetonitrile R* and 80 volumes of *water R*.

Reference solution (b). Dissolve 5.0 mg of *thiamazole R* in a mixture of 20 volumes of *acetonitrile R* and 80 volumes of *water R* and dilute to 10.0 ml with the same mixture of solvents. Dilute 1.0 ml of this solution to 100.0 ml with a mixture of 20 volumes of *acetonitrile R* and 80 volumes of *water R*.

Column:

– *size*: *l* = 0.15 m, Ø = 3.9 mm,
– *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase: *acetonitrile R, water R* (10:90 *V/V*).

Flow rate: 1 ml/min.

Detection: spectrophotometer at 254 nm.

Injection: 10 µl.

Run time: 1.5 times the retention time of carbimazole.

Retention time: carbimazole = about 6 min.

System suitability: reference solution (a):

– *resolution*: minimum 5.0 between the peaks due to impurity A and carbimazole.

Limits:

– *impurity A*: not more than half the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent),
– *any other impurity*: not more than 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent).

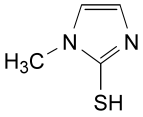
Loss on drying (*2.2.32*): maximum 0.5 per cent, determined on 1.000 g by drying in a desiccator over *diphosphorus pentoxide R* at a pressure not exceeding 0.7 kPa for 24 h.

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

ASSAY

Dissolve 50.0 mg in *water R* and dilute to 500.0 ml with the same solvent. To 10.0 ml add 10 ml of *dilute hydrochloric acid R* and dilute to 100.0 ml with *water R*. Measure the absorbance (*2.2.25*) at the maximum at 291 nm. Calculate the content of $C_7H_{10}N_2O_2S$ taking the specific absorbance to be 557.

IMPURITIES

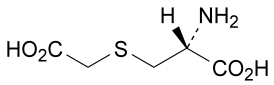


A. 1-methyl-1*H*-imidazole-2-thiol (thiamazole).

01/2008:0885
corrected 6.0

CARBOCISTEINE

Carbocisteinum



$C_5H_9NO_4S$ M_r 179.2
[638-23-3]

DEFINITION

Carbocisteine contains not less than 98.5 per cent and not more than the equivalent of 101.0 per cent of (2*R*)-2-amino-3-[(carboxymethyl)sulphanyl]propanoic acid, calculated with reference to the dried substance.

CHARACTERS

A white or almost white, crystalline powder, practically insoluble in water and in alcohol. It dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides.

IDENTIFICATION

First identification: A, B.

Second identification: A, C, D.

A. It complies with the test for specific optical rotation (see Tests).

B. Examine by infrared absorption spectrophotometry (*2.2.24*), comparing with the spectrum obtained with *carbocisteine CRS*. Examine the substances prepared as discs.

C. Examine the chromatograms obtained in the test for ninhydrin-positive substances. The principal spot in the chromatogram obtained with test solution (b) is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

D. Dissolve 0.1 g in 4.5 ml of *dilute sodium hydroxide solution R*. Heat on a water-bath for 10 min. Cool and add 1 ml of a 25 g/l solution of *sodium nitroprusside R*. A dark red colour is produced, which changes to brown and then to yellow within a few minutes.

TESTS

Solution S. Disperse 5.00 g in 20 ml of *water R* and add dropwise with shaking 2.5 ml of *strong sodium hydroxide solution R*. Adjust to pH 6.3 with *1 M sodium hydroxide* and dilute to 50.0 ml with *water R*.

Appearance of solution. Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

pH (*2.2.3*). Shake 0.2 g with 20 ml of *carbon dioxide-free water R*. The pH of the suspension is 2.8 to 3.0.

Specific optical rotation (*2.2.7*): – 32.5 to – 35.5, determined on solution S and calculated with reference to the dried substance.

Ninhydrin-positive substances. Examine by thin-layer chromatography (*2.2.27*), using a suitable silica gel as the coating substance.

Test solution (a). Dissolve 0.10 g of the substance to be examined in *dilute ammonia R2* and dilute to 10 ml with the same solvent.

Test solution (b). Dilute 1 ml of test solution (a) to 50 ml with *water R*.

Reference solution (a). Dissolve 10 mg of *carbocisteine CRS* in *dilute ammonia R2* and dilute to 50 ml with the same solvent.

Reference solution (b). Dilute 5 ml of test solution (b) to 20 ml with *water R*.

Reference solution (c). Dissolve 10 mg of *carbocisteine CRS* and 10 mg of *arginine hydrochloride CRS* in 5 ml of *dilute ammonia R2* and dilute to 25 ml with *water R*.

Apply separately to the plate 5 µl of each solution. Allow the plate to dry in air. Develop over a path of 15 cm using a mixture of 20 volumes of *glacial acetic acid R*, 20 volumes of *water R* and 60 volumes of *butanol R*. Dry the plate in a current of warm air. Spray with *ninhydrin solution R* and heat at 100 °C to 105 °C for 15 min. Any spot in the chromatogram obtained with test solution (a), apart from the principal spot, is not more intense than the spot in the chromatogram obtained with reference solution (b) (0.5 per cent). The test is not valid unless the chromatogram obtained with reference solution (c) shows two clearly separated principal spots.

Chlorides (*2.4.4*). Dissolve 33 mg in 5 ml of *dilute nitric acid R* and dilute to 15 ml with *water R*. The solution, without further addition of nitric acid, complies with the limit test for chlorides (0.15 per cent).

Sulphates (*2.4.13*). Dissolve 0.5 g in 5 ml of *dilute hydrochloric acid R* and dilute to 15 ml with *distilled water R*. The solution complies with the limit test for sulphates (300 ppm).

Heavy metals (*2.4.8*). 2.0 g complies with limit test D for heavy metals (10 ppm). Prepare the standard using 2 ml of *lead standard solution (10 ppm Pb) R*.

Loss on drying (*2.2.32*). Not more than 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 2 h.

Sulphated ash (*2.4.14*). Not more than 0.3 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.150 g in 10 ml of *anhydrous formic acid R* with slight heating and shake until dissolution is complete. Add 50 ml of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid,* determining the end-point potentiometrically (*2.2.20*).

1 ml of *0.1 M perchloric acid* is equivalent to 17.92 mg of $C_5H_9NO_4S$.

STORAGE

Store protected from light.

01/2008:1299
corrected 6.0

CARBOMERS

Carbomera

DEFINITION

High molecular mass polymers of acrylic acid cross-linked with polyalkenyl ethers of sugars or polyalcohols.

Content: 56.0 per cent to 68.0 per cent of carboxylic acid (-COOH) groups (dried substance).

CHARACTERS

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

Solubility: swells in water and in other polar solvents after dispersion and neutralisation with sodium hydroxide solution.

IDENTIFICATION

First identification: A, E.

Second identification: B, C, D, E.

A. Infrared absorption spectrophotometry (*2.2.24*).
Main bands: at 2960 cm^{-1}, 1720 cm^{-1}, 1455 cm^{-1}, 1415 cm^{-1}, 1250 cm^{-1}, 1175 cm^{-1} and 800 cm^{-1}, with the strongest band at 1720 cm^{-1}.

B. Adjust a 10 g/l dispersion to about pH 7.5 with *1 M sodium hydroxide*. A highly viscous gel is formed.

C. Add 2 ml of a 100 g/l solution of *calcium chloride R* with continuous stirring to 10 ml of the gel from test B. A white precipitate is immediately produced.

D. Add 0.5 ml of *thymol blue solution R* to 10 ml of a 10 g/l dispersion. An orange colour is produced. Add 0.5 ml of *cresol red solution R* to 10 ml of a 10 g/l dispersion. A yellow colour is produced.

E. It complies with the apparent nominal viscosity indicated on the label.

TESTS

Apparent viscosity: the nominal apparent viscosity is in the range 300 mPa·s to 115 000 mPa·s. For a product with a nominal apparent viscosity of 20 000 mPa·s or greater, the apparent viscosity is 70.0 per cent to 130.0 per cent of the value stated on the label; for a product with a nominal apparent viscosity less than 20 000 mPa·s, the apparent viscosity is 50.0 per cent to 150.0 per cent of the value stated on the label.

Dry the substance to be examined *in vacuo* at 80 °C for 1 h. Carefully add 2.50 g of the previously dried substance to be examined to 500 ml of *water R* in a 1000 ml beaker while stirring continuously at 1000 ± 50 r/min, with the stirrer shaft set at an angle of 60° to one side of the beaker. Add the previously dried substance over a period of 45-90 s, at a uniform rate, ensuring that loose aggregates of powder are broken up and continue stirring at 1000 ± 50 r/min for 15 min. Remove the stirrer, and place the beaker containing the dispersion in a water-bath at 25 ± 0.2 °C for 30 min. Insert the stirrer to a depth necessary to ensure that air is not drawn into the dispersion, and while stirring at 300 ± 25 r/min, titrate with a glass-calomel electrode system to pH 7.3-7.8 by adding a 180 g/l solution of *sodium hydroxide R* below the surface, determining the end-point potentiometrically (*2.2.20*). The total volume of the 180 g/l solution of *sodium hydroxide R* used is about 6.2 ml. Allow 2-3 min before the final pH determination. If the final pH exceeds 7.8, discard the preparation, and prepare another