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Carbocisteine Capsules

Details for the public consultation of this monograph are as follows:

EAG/Panel/Working Party	Medicinal Chemicals 2
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Notes	New monograph If limits are too restrictive, please provide batch/stability data to demonstrate that an increase is required.

Action and use

Mucolytic

DEFINITION

Carbocisteine Capsules contain Carbocisteine.

The capsules complies with the requirements stated under Capsules and with the following requirements.

Content of carbocisteine, $C_5H_9NO_4S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the contents of the capsules containing 0.375g of Carbocisteine with 5 mL of water, filter and dry the filtrate at 105° . The infrared absorption spectrum of the dried residue, Appendix II A, is concordant with the reference spectrum of carbocisteine *(RS XXX)*.

TESTS

Dissolution

Comply with the dissolution test for tablets and capsules, Appendix XII B1.

Solution A 2.72% w/v of *potassium dihydrogen phosphate* adjusted to pH 6.8 using a solution of 0.2M *sodium hydroxide*.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 75 revolutions per minute.

(b) Use 900 mL of solution A, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes withdraw a sample of the medium and filter. Use the filtered medium, diluted with solution A, if necessary, to produce a solution expected to contain 0.0075% w/v of Carbocisteine.

(2) 0.0075% w/v of *carbocisteine BPCRS* in solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm x 4.6 mm) packed with *acidic-embedded cation-exchange resin for chromatography* (5 µm) (Primesep 100 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 0.5 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 210 nm.

(f) Use an autosampler temperature of 5°.

(g) Inject 20 µL of each solution.

MOBILE PHASE

8 volumes of *acetonitrile R1* and 92 volumes of a 0.27% w/v solution of *potassium dihydrogen orthophosphate*.

DETERMINATION OF CONTENT

Calculate the total content of carbocisteine, $C_5H_9NO_4S$, in the medium from the chromatograms obtained and using the declared content of $C_5H_9NO_4S$, in *carbocisteine BPCRS*.

LIMITS

The amount of carbocisteine released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. *Prepare the solutions immediately before use.*

Solution B 1 volume of 1M *sodium hydroxide* and 5 volumes of *water*

(1) Dissolve a quantity of the capsule contents containing 75 mg of Carbocisteine in 6 mL of solution B, immediately add 8 mL of *acetonitrile R1* and dilute to 100 mL with *water*, mix and filter.

(2) To 1 volume of solution (1) add 8 volumes of *acetonitrile R1* and dilute to 100 volumes with *water*.

(3) Dissolve 7.5 mg of *carbocisteine BPCRS* and 7.5 mg of *carbocisteine impurity C EPCRS* in 0.5 mL of solution B and immediately dilute to 100 mL with *water*.

(4) Dissolve 7.5 mg of *carbocisteine impurity B EPCRS* and 7.5 mg of *cystine* in 0.5 mL solution B, immediately dilute to 10 mL with *water*. Mix 1 volume of this solution with 1 volume of solution (3) and dilute to 10 volumes with *water*.

(5) Dilute 1 volume of solution (2) to 10 volumes with *water*

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column 25 cm × 4.6 mm packed with *acidic-embedded cation-exchange resin for chromatography* (5µm) (Primesep 100 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use the flow rate gradient described below.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 210 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

8 volumes of acetonitrile and 92 volumes of a 0.27% w/v solution of *potassium dihydrogen orthophosphate*.

Time (Minutes)	Flow rate (mL/min)
0-40	0.5
40-42	0.5→0.8
42-47	0.8
47-50	0.8→0.5
50-60	0.5

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to carbocisteine (retention time about 7 minutes) are: impurity B, about 0.5; impurity C, about 0.7 and impurity D, about 2.1.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the resolution between carbocisteine and carbocisteine impurity C is at least 5.0.

LIMITS

Use the chromatogram obtained with solution (4) to identify the peaks due to impurities B, C and D in the chromatogram obtained with solution (1). Multiply the area of the peak due to impurity C by a correction factor of 0.2.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity B, C or D is not greater than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (5) (0.1%);

the sum of the areas of all secondary peaks is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.1%).

ASSAY

Weigh the contents of 20 capsules, mix and powder if necessary. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use.

Solution B Use solution B from the related substances procedure

(1) Dissolve a quantity of the mixed capsule contents containing 375 mg of Carbocisteine in 6 mL solution B, add 8 mL of acetonitrile and immediately dilute to 100 mL with *water*. Dilute 1 volume of this solution to 50 volumes with *water*.
(2) 0.0075% w/v of *carbocisteine BPCRS* in a mixture of 1 volume solution B and 9 volumes of *water* (dissolve in solution B before diluting to volume with water).

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under dissolution may be used.

DETERMINATION OF CONTENT

Calculate the content of carbocisteine, $C_5H_9NO_4S$, in the capsules from the chromatograms obtained and using the declared content of $C_5H_9NO_4S$, in *carbocisteine BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities B, C, D and E listed under *Carbocisteine*.