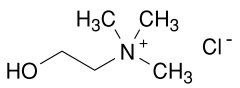
IMPURITIES



A. 2-hydroxy-*N,N,N*-trimethylethanaminium chloride (choline chloride).

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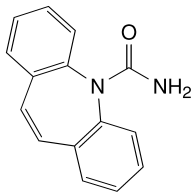
corrected 6.0

CARBAMAZEPINE

Carbamazepinum



$C_{15}H_{12}N_2O$ M_r 236.3
[298-46-4]

DEFINITION

5*H*-Dibenzo[*b,f*]azepine-5-carboxamide.

Content: 98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance: white or almost white, crystalline powder.

Solubility: very slightly soluble in water, freely soluble in methylene chloride, sparingly soluble in acetone and in ethanol (96 per cent).

It shows polymorphism (*5.9*). The acceptable crystalline form corresponds to *carbamazepine CRS*.

IDENTIFICATION

A. Melting point (*2.2.14*): 189 °C to 193 °C.

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *carbamazepine CRS*.

Preparation: examine the substances as discs without prior treatment.

TESTS

Acidity or alkalinity. To 1.0 g add 20 ml of *carbon dioxide-free water R*, shake for 15 min and filter. To 10 ml of the filtrate add 0.05 ml of *phenolphthalein solution R1* and 0.5 ml of *0.01 M sodium hydroxide*; the solution is red. Add 1.0 ml of *0.01 M hydrochloric acid*; the solution is colourless. Add 0.15 ml of *methyl red solution R*; the solution is red.

Related substances. Liquid chromatography (*2.2.29*).

Test solution (a). Dissolve 60.0 mg of the substance to be examined in *methanol R2* and dilute to 20.0 ml with the same solvent. Sonicate. Dilute 10.0 ml of this solution to 20.0 ml with *water R*.

Test solution (b). Dilute 10.0 ml of test solution (a) to 50.0 ml with a mixture of equal volumes of *methanol R2* and *water R*.

Reference solution (a). Dissolve 7.5 mg of *carbamazepine CRS*, 7.5 mg of *carbamazepine impurity A CRS* and 7.5 mg of *iminodibenzyl R* (impurity E) in *methanol R2* and dilute to 100.0 ml with the same solvent. Dilute 1.0 ml of this solution to 50.0 ml with a mixture of equal volumes of *methanol R2* and *water R*.

Reference solution (b). Dissolve 60.0 mg of *carbamazepine CRS* in *methanol R2* and dilute to 20.0 ml with the same solvent. Sonicate. Dilute 5.0 ml of this solution to 50.0 ml with a mixture of equal volumes of *methanol R2* and *water R*.

Column:

– *size*: *l* = 0.25 m, Ø = 4.6 mm;
– *stationary phase*: *nitrile silica gel for chromatography R1* (10 µm).

Mobile phase: *tetrahydrofuran R, methanol R2, water R* (3:12:85 *V/V/V*); to 1000 ml of this solution add 0.2 ml of *anhydrous formic acid R* and 0.5 ml of *triethylamine R*.

Flow rate: 2.0 ml/min.

Detection: a spectrophotometer at 230 nm.

Injection: 20 µl of test solution (a) and reference solution (a).

Run time: 6 times the retention time of carbamazepine.

Relative retention with reference to carbamazepine (retention time = about 10 min): impurity A = about 0.9; impurity E = about 5.1.

System suitability:

– *resolution*: minimum 1.7 between the peaks due to carbamazepine and impurity A in the chromatogram obtained with reference solution (a).

Limits:

– *impurities A, E*: for each impurity, not more than the area of the corresponding peak in the chromatogram obtained with reference solution (a) (0.1 per cent);
– *unspecified impurities*: not more than the area of the peak due to carbamazepine in the chromatogram obtained with reference solution (a) (0.10 per cent);
– *total*: not more than 5 times the area of the peak due to carbamazepine in the chromatogram obtained with reference solution (a) (0.5 per cent);
– *disregard limit*: 0.5 times the area of the peak due to carbamazepine in the chromatogram obtained with reference solution (a) (0.05 per cent).

Chlorides (*2.4.4*): maximum 140 ppm.

Suspend 0.715 g in 20 ml of *water R* and boil for 10 min. Cool and dilute to 20 ml with *water R*. Filter through a membrane filter (nominal pore size: 0.8 µm). Dilute 10 ml of the filtrate to 15 ml with *water R*. This solution complies with the limit test for chlorides.

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

1.0 g complies with test C. Prepare the reference solution using 2 ml of *lead standard solution (10 ppm Pb) R*.

Loss on drying (*2.2.32*): maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 2h.

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

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances.

Injection: test solution (b) and reference solution (b).

System suitability:

– *repeatability*: reference solution (b).

Calculate the percentage content *m/m* of dried substance.

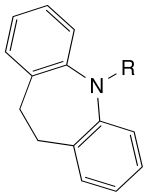
STORAGE

In an airtight container.

IMPURITIES

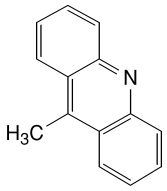
Specified impurities: *A, E.*

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*): *B, C, D, F.*

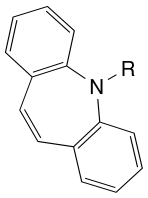


A. R = CO-NH_2: 10,11-dihydro-5*H*-dibenzo[*b,f*]azepine-5-carboxamide (10,11-dihydrocarbamazepine),

E. R = H: 10,11-dihydro-5*H*-dibenzo[*b,f*]azepine (iminodibenzyl),



B. 9-methylacridine,



C. R = CO-NH-CO-NH_2: (5*H*-dibenzo[*b,f*]azepin-5-ylcarbonyl)urea (*N*-carbamoylcarbamazepine),

D. R = H: 5*H*-dibenzo[*b,f*]azepine (iminostilbene),

F. R = CO-Cl: 5*H*-dibenzo[*b,f*]azepine-5-carbonyl chloride (5-chlorocarbonyliminostilbene).

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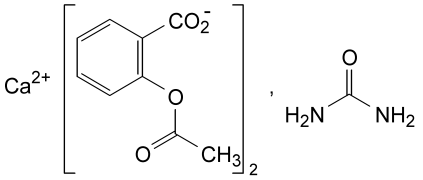
corrected 6.0

CARBASALATE CALCIUM

Carbasalatum calcicum



$C_{19}H_{18}CaN_2O_9$ M_r 458.4
[5749-67-7]

DEFINITION

Equimolecular compound of calcium di[2-(acetyloxy)benzoate] and urea.

Content: 99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance: white or almost white, crystalline powder.

Solubility: freely soluble in water and in dimethylformamide, practically insoluble in acetone and in anhydrous methanol.

Protect the substance from moisture during handling. Examination in aqueous solutions has to be performed immediately after preparation.

IDENTIFICATION

First identification: B, E.

Second identification: A, C, D, E.

A. Ultraviolet and visible absorption spectrophotometry (*2.2.25*).

Test solution. Dissolve 0.250 g in *water R* and dilute to 100.0 ml with the same solvent. To 1.0 ml of the solution add 75 ml of *water R* and 5 ml of *dilute hydrochloric acid R*, mix and dilute to 100.0 ml with *water R*. Examine immediately.

Spectral range: 220-350 nm.

Absorption maxima: at 228 nm and 276 nm.

Specific absorbances at the absorption maxima:

– at 228 nm: 363 to 379,

– at 276 nm: 49 to 53.

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *Ph. Eur. reference spectrum of carbasalate calcium.*

C. Dissolve 0.1 g in 10 ml of *water R*, boil for 2 min and cool. The solution gives reaction (a) of salicylates (*2.3.1*).

D. Heat 0.2 g with 0.2 g of *sodium hydroxide R*; a yellow or yellowish-brown colour is produced and the vapour turns *red litmus paper R* blue.

E. It gives reaction (a) of calcium (*2.3.1*).

TESTS

Appearance of solution. The solution is not more opalescent than reference suspension II (*2.2.1*) and is colourless (*2.2.2, Method II*).

Dissolve 2.5 g in 50 ml of *water R*.

Related substances: maximum 0.1 per cent, expressed as acetylsalicylsalicylic acid.

In a 100 ml volumetric flask, dissolve 0.150 g in 10 ml of *0.1 M tetrabutylammonium hydroxide in 2-propanol*. Allow to stand for 10 min shaking occasionally. Add 8.0 ml of *0.1 M hydrochloric acid* and 20.0 ml of a 19 g/l solution of *disodium tetraborate R* and mix. While swirling continuously, add 2.0 ml of a 10 g/l solution of *aminopyrazolone R* and 2.0 ml of a 10 g/l solution of *potassium ferricyanide R*. Allow to stand for 2 min, dilute to 100.0 ml with *water R*, mix and allow to stand for 20 min. Measure the absorbance (*2.2.25*) of the solution at the absorption maximum at 505 nm using *water R* as the compensation liquid. The absorbance is not greater than 0.125.

Impurity C: maximum 0.5 per cent.

In a 100 ml volumetric flask, dissolve 0.200 g in 80 ml of *water R* and add 10 ml of a 10 g/l solution of *ferric nitrate R* in a 80 g/l solution of *dilute nitric acid R*. Dilute to 100.0 ml with *water R*. Immediately after preparation, measure the absorbance (*2.2.25*) of the solution at the absorption