- *sum of impurities other than A and B*: not more than 0.5 times the area of the peak due to betadex in the chromatogram obtained with reference solution (b) (0.5 per cent).

Residual solvents. Head-space gas chromatography (*2.2.28*): use the standard additions method.

Internal standard: *ethylene chloride R*.

Test solutions. In each of 4 identical 20 ml flasks, dissolve 0.5 g of the substance to be examined in *water R* and add 0.10 g of *calcium chloride R* and 30 µl of *α-amylase solution R*. Add 1 ml of reference solutions (a), (b), (c) and (d), adding a different solution to each flask. Dilute to 10 ml with *water R*.

Reference solutions. Prepare a 10 µl/l solution of *ethylene chloride R* (reference solution (a)). Prepare reference solutions (b), (c) and (d) from reference solution (a) to contain respectively, per litre, 5 µl, 10 µl and 15 µl of both *trichloroethylene R* and *toluene R*.

Column:

- *material*: fused silica;
- *size*: *l* = 25 m, Ø = 0.32 mm;
- *stationary phase*: *macrogol 20 000 R* (film thickness 1 µm).

Carrier gas: *helium for chromatography R*.

Static head-space conditions which may be used:

- *equilibration temperature*: 45 °C;
- *equilibration time*: 2 h.

Temperature:

- *column*: 50 °C;
- *injection port*: 140 °C;
- *detector*: 280 °C.

Detection: flame ionisation.

Injection: 200 µl of the head space, at least 3 times.

Retention time: toluene = about 10 min.

System suitability:

- *resolution*: minimum 1.1 between the peaks due to trichloroethylene and toluene; minimum 1.1 between the peaks due to toluene and ethylene chloride;
- *repeatability*: maximum relative standard deviations of the ratios of the areas of the peaks due to trichloroethylene and toluene to that of the peak due to ethylene chloride of 5 per cent.

Calculate the content of trichloroethylene and of toluene taking their relative densities to be 1.46 and 0.87, respectively.

Limits:

- *trichloroethylene*: maximum 10 ppm;
- *toluene*: maximum 10 ppm.

Heavy metals (*2.4.8*): maximum 10 ppm.

1.0 g complies with test C. Prepare the reference solution using 1 ml of *lead standard solution (10 ppm Pb) R*.

Loss on drying (*2.2.32*): maximum 16.0 per cent, determined on 1.000 g by drying in an oven at 120 °C for 2 h.

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 with the following modifications.

Injection: test solution (b) and reference solutions (a) and (c).

System suitability: reference solution (a):

- *repeatability*: maximum relative standard deviation of the area of the peak due to betadex of 2.0 per cent.

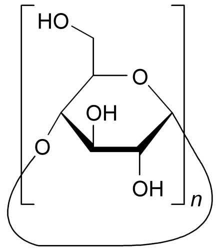
Calculate the percentage content of $[C_6H_{10}O_5]_7$ from the declared content of *betadex CRS*.

STORAGE

In an airtight container.

IMPURITIES

Specified impurities: A, B.



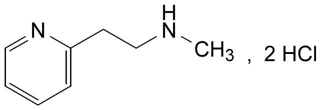
A. *n* = 6: alfadex,

B. *n* = 8: gammacyclodextrin.

01/2008:1665
corrected 6.0

BETAHISTINE DIHYDROCHLORIDE

Betahistini dihydrochloridum



$C_8H_{14}Cl_2N_2$ M_r 209.1
[5579-84-0]

DEFINITION

N-Methyl-2-(pyridin-2-yl)ethanamine dihydrochloride.

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

CHARACTERS

Appearance: white to slightly yellow powder, very hygroscopic.

Solubility: very soluble in water, soluble in ethanol (96 per cent), practically insoluble in 2-propanol.

IDENTIFICATION

First identification: B, D.

Second identification: A, C, D.

A. Melting point (*2.2.14*): 150 °C to 154 °C.

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *betahistine dihydrochloride CRS*.

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

Test solution. Dissolve 10 mg of the substance to be examined in 2 ml of *ethanol (96 per cent) R*.

Reference solution. Dissolve 10 mg of *betahistine dihydrochloride CRS* in 2 ml of *ethanol (96 per cent) R*.

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

Mobile phase: *concentrated ammonia R, ethyl acetate R, methanol R* (0.75:15:30 *V/V/V*).

Application: 2 μl.

Development: over 2/3 of the plate.

Drying: at 110 °C for 10 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. It gives reaction (a) of chlorides (*2.3.1*).

TESTS

Solution S. Dissolve 5.0 g in *carbon dioxide-free water R,* and dilute to 50 ml with the same solvent.

Appearance of solution. Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution B_8 (*2.2.2, Method II*).

pH (*2.2.3*): 2.0 to 3.0 for solution S.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 25 mg of the substance to be examined in the mobile phase and dilute to 25.0 ml with the mobile phase.

Reference solution (a). Dissolve 10 mg of *betahistine dihydrochloride CRS* and 10 mg of *2-vinylpyridine R* in the mobile phase and dilute to 50.0 ml with the mobile phase. Dilute 2.0 ml of the solution to 50.0 ml with the mobile phase.

Reference solution (b). Dilute 1.0 ml of the test solution to 100.0 ml with the mobile phase.

Reference solution (c). Dilute 2.0 ml of reference solution (b) to 10.0 ml with the mobile phase.

Column:

- *size*: l = 0.15 m, Ø = 3.0 mm,
- *stationary phase*: *end-capped octadecylsilyl base deactivated silica gel for chromatography R* (5 μm).

Mobile phase: dissolve 2.0 g of *sodium dodecyl sulphate R* in a mixture of 15 ml of a 10 per cent *V/V* solution of *sulphuric acid R,* 35 ml of a 17 g/l solution of *tetrabutylammonium hydrogen sulphate R* and 650 ml of *water R*; adjust to pH 3.3 using *dilute sodium hydroxide solution R* and mix with 300 ml of *acetonitrile R.*

Flow rate: 1 ml/min.

Detection: spectrophotometer at 260 nm.

Injection: 20 μl.

Run time: 4 times the retention time of betahistine.

Relative retention with reference to betahistine (retention time = about 7 min): impurity B = about 0.2; impurity A = about 0.3; impurity C = about 3.

System suitability: reference solution (a):

- *resolution*: minimum 3.5 between the peaks due to 2-vinylpyridine and betahistine.

Limits:

- *correction factor*: for the calculation of content, multiply the peak area of impurity B by 0.4;
- *impurities A, B, C*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.2 per cent);
- *any other impurity*: for each impurity, not more than 0.5 times of the area of the principal peak in the chromatogram obtained with reference solution (c) (0.1 per cent);
- *total*: not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);
- *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

Loss on drying (*2.2.32*): maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

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

ASSAY

Dissolve 80.0 mg in 50 ml of *ethanol (96 per cent) R.* Titrate with *0.1 M sodium hydroxide,* determining the end-point potentiometrically (*2.2.20*). Read the volume added to reach the second point of inflexion.

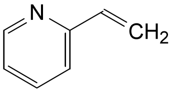
1 ml of *0.1 M sodium hydroxide* is equivalent to 10.46 mg of $C_8H_{14}Cl_2N_2$.

STORAGE

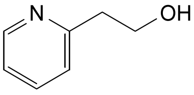
In an airtight container.

IMPURITIES

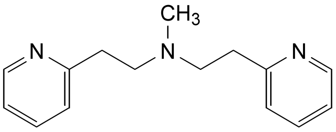
Specified impurities: A, B, C.



A. 2-ethenylpyridine (2-vinylpyridine),



B. 2-(pyridin-2-yl)ethanol,

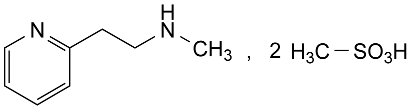


C. *N*-methyl-2-(pyridin-2-yl)-*N*-[2-(pyridin-2-yl)ethyl]ethanamine.

01/2008:1071
corrected 6.0

BETAHISTINE MESILATE

Betahistini mesilas



$C_{10}H_{20}N_2O_6S_2$ M_r 328.4
[54856-23-4]

DEFINITION

N-Methyl-2-(pyridin-2-yl)ethanamine bis(methanesulphonate).

Content: 98.0 per cent to 101.0 per cent (anhydrous substance).

PRODUCTION

The production method must be evaluated to determine the potential for formation of alkyl mesilates, which is particularly likely to occur if the reaction medium contains