Sulfated ash (*2.4.14*): maximum 0.2 per cent, determined on 1.0 g, moistened with a mixture of 2 mL of *dilute sulfuric acid R* and 5 mL of *ethanol (96 per cent) R*.

ASSAY

Measure the absorbance (*2.2.25*) of test solution (b) used in Identification at the absorption maximum at 455 nm, using *cyclohexane R* as the compensation liquid.

Calculate the content of $C_{40}H_{56}$ taking the specific absorbance to be 2500.

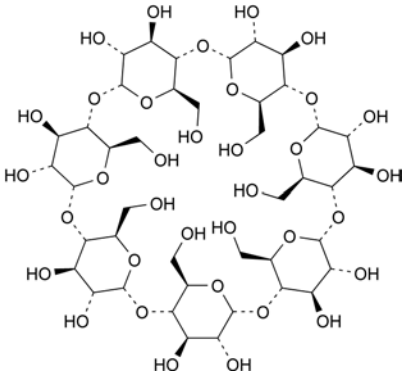
STORAGE

In an airtight container, protected from light, at a temperature not exceeding 25 °C.

01/2008:1070
corrected 7.0

BETADEX

Betadexum



$[C_6H_{10}O_5]_7$ M_r 1135
[7585-39-9]

DEFINITION

Cycloheptakis-(1→4)-(α-D-glucopyranosyl) (cyclomaltoheptaose or β-cyclodextrin).

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

CHARACTERS

Appearance: white or almost white, amorphous or crystalline powder.

Solubility: sparingly soluble in water, freely soluble in propylene glycol, practically insoluble in anhydrous ethanol and in methylene chloride.

IDENTIFICATION

A. Specific optical rotation (see Tests).

B. Examine the chromatograms obtained in the assay.
Results: the principal peak in the chromatogram obtained with test solution (b) is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (c).

C. Dissolve 0.2 g in 2 mL of *iodine solution R4* by warming on a water-bath, and allow to stand at room temperature. A yellowish-brown precipitate is formed.

TESTS

Solution S. Dissolve 1.000 g in *carbon dioxide-free water R* with heating, allow to cool and dilute to 100.0 mL with the same solvent.

Appearance of solution. Solution S is clear (*2.2.1*).

pH (*2.2.3*): 5.0 to 8.0.

To 10 mL of solution S add 0.1 mL of a saturated solution of *potassium chloride R*.

Specific optical rotation (*2.2.7*): + 160 to + 164 (dried substance), determined on solution S.

Reducing sugars: maximum 0.2 per cent.

Test solution. To 1 mL of solution S add 1 mL of *cupri-tartaric solution R4*. Heat on a water-bath for 10 min, cool to room temperature. Add 10 mL of *ammonium molybdate reagent R1* and allow to stand for 15 min.

Reference solution. Prepare a reference solution at the same time and in the same manner as the test solution, using 1 mL of a 0.02 g/L solution of *glucose R*.

Measure the absorbance (*2.2.25*) of the test solution and the reference solution at the absorption maximum at 740 nm using *water R* as the compensation liquid. The absorbance of the test solution is not greater than that of the reference solution.

Light-absorbing impurities. Examine solution S between 230 nm and 750 nm. Between 230 nm and 350 nm, the absorbance (*2.2.25*) is not greater than 0.10. Between 350 nm and 750 nm, the absorbance (*2.2.25*) is not greater than 0.05.

Related substances. Liquid chromatography (*2.2.29*).

Test solution (a). Dissolve 0.25 g of the substance to be examined in *water R* with heating, cool and dilute to 25.0 mL with the same solvent.

Test solution (b). Dilute 5.0 mL of test solution (a) to 50.0 mL with *water R*.

Reference solution (a). Dissolve 25.0 mg of *alfadex CRS* (impurity A), 25.0 mg of *gammacyclodextrin CRS* (impurity B) and 50.0 mg of *betadex CRS* in *water R*, then dilute to 50.0 mL with the same solvent.

Reference solution (b). Dilute 5.0 mL of reference solution (a) to 50.0 mL with *water R*.

Reference solution (c). Dissolve 25.0 mg of *betadex CRS* in *water R* and dilute to 25.0 mL with the same solvent.

Column:
- *size*: *l* = 0.25 m, Ø = 4.6 mm;
- *stationary phase*: *octadecylsilyl silica gel for chromatography R* (10 μm).

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

Flow rate: 1.5 mL/min.

Detection: differential refractometer.

Equilibration: with the mobile phase for about 3 h.

Injection: 50 μL of test solution (a) and reference solutions (a) and (b).

Run time: 1.5 times the retention time of betadex.

Relative retention with reference to betadex (retention time = about 10 min): impurity B = about 0.3; impurity A = about 0.45.

System suitability: reference solution (a):
- *resolution*: minimum 1.5 between the peaks due to impurities B and A; if necessary, adjust the concentration of methanol in the mobile phase.

Limits:
- *impurities A, B*: for each impurity, not more than 0.5 times the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.25 per cent);
- *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.

Sulfated 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.

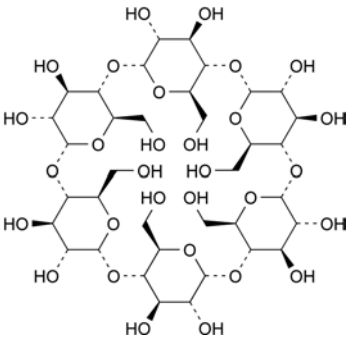
Calculate the percentage content of $[C_6H_{10}O_5]_7$ from the declared content of *betadex CRS*.

STORAGE

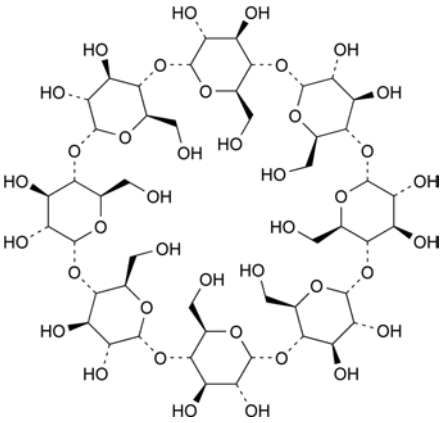
In an airtight container.

IMPURITIES

Specified impurities: A, B.



A. cyclohexakis-(1→4)-(α-D-glucopyranosyl) (alfadex or cyclomaltohexaose or α-cyclodextrin),

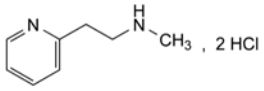


B. cyclooctakis-(1→4)-(α-D-glucopyranosyl) (cyclomaltooctaose or γ-cyclodextrin).

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 or 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*.