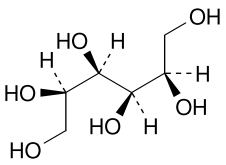
01/2008:0559

MANNITOL

Mannitolum



$C_6H_{14}O_6$ M_r 182.2
[69-65-8]

DEFINITION

D-Mannitol.

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

CHARACTERS

Appearance: white or almost white, crystalline powder or free-flowing granules.

Solubility: freely soluble in water, very slightly soluble in ethanol (96 per cent).

It shows polymorphism (*5.9*).

IDENTIFICATION

First identification: C.

Second identification: A, B, D.

A. Specific optical rotation (*2.2.7*): + 23 to + 25 (anhydrous substance).

Dissolve 2.00 g of the substance to be examined and 2.6 g of *disodium tetraborate R* in about 20 ml of *water R* at 30 °C; shake continuously for 15-30 min without further heating. Dilute the resulting clear solution to 25.0 ml with *water R*.

B. Melting point (*2.2.14*): 165 °C to 170 °C.

C. Infrared absorption spectrophotometry (*2.2.24*).

Preparation: discs.

Comparison: *mannitol CRS*.

If the spectra obtained in the solid state show differences, dissolve separately in 2 glass vials 25 mg of the substance to be examined and 25 mg of the reference substance in 0.25 ml of *distilled water R* without heating. The solutions obtained are clear. Evaporate to dryness by heating in a microwave oven with a power range of 1000-1300 W for 15-30 min or by heating in an oven *in vacuo* at 100 °C. Non-sticky, white or slightly yellowish powders are obtained. Record new spectra using the residues.

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

Test solution. Dissolve 25 mg of the substance to be examined in *water R* and dilute to 10 ml with the same solvent.

Reference solution (a). Dissolve 25 mg of *mannitol CRS* in *water R* and dilute to 10 ml with the same solvent.

Reference solution (b). Dissolve 25 mg of *mannitol R* and 25 mg of *sorbitol R* in *water R* and dilute to 10 ml with the same solvent.

Plate: *TLC silica gel G plate R*.

Mobile phase: *water R, ethyl acetate R, propanol R* (10:20:70 *V/V/V*).

Application: 2 µl.

Development: over 2/3 of the plate.

Drying: in air.

Detection: spray with *4-aminobenzoic acid solution R*. Dry in a current of cold air until the acetone is removed. Heat at 100 °C for 15 min. Allow to cool and spray with a 2 g/l solution of *sodium periodate R*. Dry in a current of cold air. Heat at 100 °C for 15 min.

System suitability: reference solution (b):

– the chromatogram shows 2 clearly separated spots.

Results: the principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

TESTS

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

Dissolve 5.0 g in *water R* and dilute to 50 ml with the same solvent.

Conductivity (*2.2.38*): maximum 20 µS·cm^{-1}.

Dissolve 20.0 g in *carbon dioxide-free water R* prepared from *distilled water R* by heating at 40-50 °C and dilute to 100.0 ml with the same solvent. After cooling, measure the conductivity of the solution while gently stirring with a magnetic stirrer.

Reducing sugars: maximum 0.2 per cent (calculated as glucose equivalent).

Dissolve 5.0 g in 25 ml of *water R* with the aid of gentle heating. Cool and add 20 ml of *cupri-citric solution R* and a few glass beads. Heat so that boiling begins after 4 min and maintain boiling for 3 min. Cool rapidly and add 100 ml of a 2.4 per cent *V/V* solution of *glacial acetic acid R* and 20.0 ml of *0.025 M iodine*. With continuous shaking, add 25 ml of a mixture of 6 volumes of *hydrochloric acid R* and 94 volumes of *water R* and, when the precipitate has dissolved, titrate the excess of iodine with *0.05 M sodium thiosulphate* using 1 ml of *starch solution R*, added towards the end of the titration, as indicator. Not less than 12.8 ml of *0.05 M sodium thiosulphate* is required.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 5.0 g of the substance to be examined in 25 ml of *water R* and dilute to 100.0 ml with the same solvent.

Reference solution (a). Dissolve 0.50 g of *mannitol CRS* in 2.5 ml of *water R* and dilute to 10.0 ml with the same solvent.

Reference solution (b). Dilute 2.0 ml of the test solution to 100.0 ml with *water R*.

Reference solution (c). Dilute 0.5 ml of reference solution (b) to 20.0 ml with *water R*.

Reference solution (d). Dissolve 0.5 g of *mannitol R* and 0.5 g of *sorbitol R* (impurity A) in 5 ml of *water R* and dilute to 10.0 ml with the same solvent.

Reference solution (e). Dissolve 0.1 g of *maltitol R* (impurity B) and 0.1 g of *isomalt R* (impurity C) in 5 ml of *water R* and dilute to 100 ml with the same solvent.

Column:

– *size*: *l* = 0.3 m, Ø = 7.8 mm;

– *stationary phase*: *strong cation-exchange resin (calcium form) R* (9 µm);

– *temperature*: 85 ± 1 °C.

Mobile phase: degassed *water R*.

Flow rate: 0.5 ml/min.

Detection: refractometer maintained at a constant temperature.

Injection: 20 µl of the test solution and reference solutions (b), (c), (d) and (e).

Run time: twice the retention time of mannitol.

Relative retention with reference to mannitol (retention time = about 22 min): impurity C (eluted in 2 peaks) = about 0.7; impurity B = about 0.8; impurity A = about 1.2.

System suitability: reference solution (d):

– *resolution*: minimum 2 between the peaks due to mannitol and impurity A.

Limits:

– *impurities A, B*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (2.0 per cent);

– *impurity C*: for the sum of the areas of the 2 peaks, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (2.0 per cent);

– *unspecified impurities*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (c) (0.10 per cent);

– *total*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (2.0 per cent);

– *disregard limit*: the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

Lead (*2.4.10*): maximum 0.5 ppm.

Dissolve the substance to be examined in 150.0 ml of the prescribed mixture of solvents.

Nickel (*2.4.15*): maximum 1 ppm.

Dissolve the substance to be examined in 150.0 ml of the prescribed mixture of solvents.

Water (*2.5.12*): maximum 0.5 per cent, determined on 1.00 g. Use as solvent 40 ml of a mixture of equal volumes of *anhydrous methanol R* and *formamide R* at about 50 °C.

Microbial contamination: if intended for use in the manufacture of parenteral dosage forms: the total viable aerobic count (*2.6.12*) is not more than 10^2 bacteria and 10^2 fungi per gram, determined by plate count; it complies with the tests for *Escherichia coli* and *Salmonella* (*2.6.13*).

Bacterial endotoxins (*2.6.14*): if intended for use in the manufacture of parenteral dosage forms without a further appropriate procedure for the removal of bacterial endotoxins: less than 4 IU/g for parenteral dosage forms having a concentration of 100 g/l or less of mannitol, and less than 2.5 IU/g for parenteral dosage forms having a concentration of more than 100 g/l of mannitol.

ASSAY

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

Injection: test solution and reference solution (a).

Calculate the percentage content of D-mannitol from the areas of the peaks and the declared content of *mannitol CRS*.

LABELLING

The label states:

– where applicable, the maximum concentration of bacterial endotoxins;

– where applicable, that the substance is suitable for use in the manufacture of parenteral dosage forms.

IMPURITIES

Specified impurities: A, B, C.

A. sorbitol,

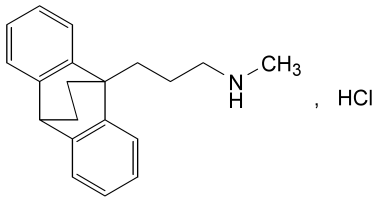
B. maltitol,

C. isomalt.

01/2008:1237

MAPROTILINE HYDROCHLORIDE

Maprotilini hydrochloridum



$C_{20}H_{24}ClN$ M_r 313.9

[10347-81-6]

DEFINITION

3-(9,10-Ethanoanthracen-9(10*H*)-yl)-*N*-methylpropan-1-amine hydrochloride.

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

CHARACTERS

Appearance: white or almost white, crystalline powder.

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

It shows polymorphism (*5.9*).

IDENTIFICATION

First identification: B, D.

Second identification: A, C, D.

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

Test solution. Dissolve 10 mg in *1 M hydrochloric acid* and dilute to 100 ml with the same acid.

Spectral range: 250-300 nm.

Absorption maxima: at 265 nm and 272 nm.

Absorption minimum: at 268 nm.

Absorbance ratio: A_{272}/A_{265} = 1.1 to 1.3.

B. Infrared absorption spectrophotometry (*2.2.24*).

Preparation: discs.

Comparison: *maprotiline hydrochloride CRS*.

If the spectra obtained show differences, dissolve the substance to be examined and the reference substance separately in *methanol R*, evaporate to dryness and record new spectra using the residues.

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

Test solution. Dissolve 25 mg of the substance to be examined in *methanol R* and dilute to 5 ml with the same solvent.

Reference solution (a). Dissolve 25 mg of *maprotiline hydrochloride CRS* in *methanol R* and dilute to 5 ml with the same solvent.

Reference solution (b). Dissolve 10 mg of *maprotiline impurity D CRS* in reference solution (a) and dilute to 2 ml with reference solution (a).

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