adapted to the pulse angle in order to have sufficient relaxation of the protons concerned between 2 pulses (for example: 10 s for a 90° pulse).

Record the FID, with at least 8 scans, so as to obtain a spectral window comprised, at least, between 0 ppm and 6.2 ppm, referring to the signal of exchangeable protons (solvent) at 4.8 ppm (25 °C).

Make a zero filling of at least 3-fold in size relative to the acquisition data file and transform the FID to the spectrum without any correction of Gaussian broadening factor (GB = 0) and with a line broadening factor not greater than 0.2 (LB ≤ 0.2). Call the integration sub-routine after phase corrections and baseline correction between 0.5 ppm and 6.2 ppm.

Measure the peak areas of the doublet from the methyl groups at 1.2 ppm (A_1), and of the signals of the glycosidic protons between 5 ppm and 5.4 ppm (A_2).

The molar substitution is obtained using the following equation:

$$MS = \frac{A_1}{(3 \times A_2)}$$

A_1 = area of the signal due to the 3 protons of the methyl groups that are part of the hydroxypropyl groups;

A_2 = area of the signals due to the glycosidic protons.

The degree of substitution is the number of hydroxypropyl groups per molecule of β-cyclodextrin and is obtained by multiplying the *MS* by 7.

Microbial contamination

If intended for use in the manufacture of parenteral preparations:

– TAMC: acceptance criterion 10^2 CFU/g (*2.6.12*).

If not intended for use in the manufacture of parenteral preparations:

– TAMC: acceptance criterion 10^3 CFU/g (*2.6.12*);
– TYMC: acceptance criterion 10^2 CFU/g (*2.6.12*);
– absence of *Escherichia coli* (*2.6.13*);
– absence of Salmonella (*2.6.13*).

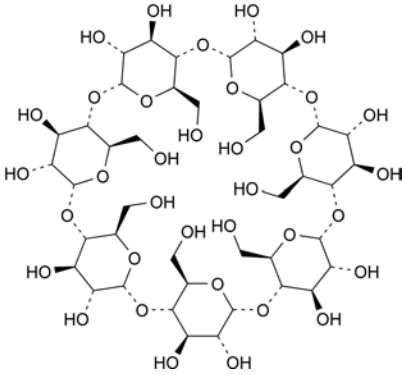
Bacterial endotoxins (*2.6.14*): less than 10 IU/g, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

LABELLING

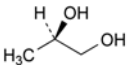
The label states:

– the molar substitution (*MS*);
– where applicable, that the substance is suitable for use in the manufacture of parenteral preparations.

IMPURITIES



A. cycloheptakis-(1→4)-(α-D-glucopyranosyl) (betadex or cyclomaltoheptaose or β-cyclodextrin),



and enantiomer

B. (*RS*)-propane-1,2-diol (propylene glycol).

01/2008:0337
corrected 6.0

HYDROXYPROPYLCELLULOSE

Hydroxypropylcellulosum

[9004-64-2]

DEFINITION

Partly *O*-(2-hydroxypropylated) cellulose.

It may contain maximum 0.6 per cent of silica (SiO_2).

CHARACTERS

Appearance: white or yellowish-white powder or granules, hygroscopic after drying.

Solubility: soluble in cold water, in glacial acetic acid, in anhydrous ethanol, in methanol and in propylene glycol and in a mixture of 10 parts of methanol and 90 parts of methylene chloride giving colloidal solutions, sparingly soluble or slightly soluble in acetone depending on the degree of substitution, practically insoluble in hot water, in ethylene glycol and in toluene.

IDENTIFICATION

A. Heat 10 mL of solution S (see Tests) in a water-bath while stirring. At a temperature above 40 °C the solution becomes cloudy or a flocculent precipitate is formed. The solution becomes clear again on cooling.

B. To 10 mL of solution S add 0.3 mL of *dilute acetic acid R* and 2.5 mL of a 100 g/L solution of *tannic acid R*. A yellowish-white flocculent precipitate is formed which dissolves in *dilute ammonia R1*.

C. In a test-tube about 160 mm long, thoroughly mix 1 g with 2 g of finely powdered *manganese sulfate R*. Introduce to a depth of 2 cm into the upper part of the tube a strip of filter paper impregnated with a freshly prepared mixture of 1 volume of a 20 per cent *V/V* solution of *diethanolamine R* and 11 volumes of a 50 g/L solution of *sodium nitroprusside R*, adjusted to about pH 9.8 with *1 M hydrochloric acid*. Insert the tube 8 cm into a silicone-oil bath at 190-200 °C. The filter paper becomes blue within 10 min. Carry out a blank test.

D. Dissolve completely 0.2 g without heating in 15 mL of a 70 per cent *m/m* solution of *sulfuric acid R*. Pour the solution with stirring into 100 mL of iced *water R* and dilute to 250 mL with iced *water R*. In a test-tube, mix thoroughly while cooling in iced water 1 mL of this solution with 8 mL of *sulfuric acid R* added dropwise. Heat in a water-bath for exactly 3 min and immediately cool in iced water. While the mixture is cold, carefully add 0.6 mL of *ninhydrin solution R2* and mix well. Allow to stand at 25 °C. A pink colour is produced immediately and becomes violet within 100 min.

E. Place 1 mL of solution S on a glass plate. After evaporation of the water a thin film is formed.

F. 0.2 g does not dissolve in 10 mL of *toluene R* but dissolves completely in 10 mL of *anhydrous ethanol R*.

TESTS

Solution S. While stirring, introduce a quantity of the substance to be examined equivalent to 1.0 g of the dried substance into 50 g of *carbon dioxide-free water R* heated to 90 °C. Allow to cool, adjust the mass of the solution to 100 g with *carbon dioxide-free water R* and stir until dissolution is complete.

Appearance of solution. Solution S is not more opalescent than reference suspension III (*2.2.1*) and not more intensely coloured than reference solution Y_6 (*2.2.2, Method II*).

pH (*2.2.3*): 5.0 to 8.5 for solution S.

Apparent viscosity (*2.2.10*): 75 per cent to 140 per cent of the value stated on the label.

While stirring, introduce a quantity of the substance to be examined equivalent to 6.00 g of the dried substance into 150 g of *water R* heated to 90 °C. Stir with a propeller-type stirrer for 10 min, place the flask in a bath of iced water, continue the stirring and allow to remain in the bath of iced water for 40 min to ensure that dissolution is complete. Adjust the mass of the solution to 300 g and centrifuge the solution to expel any entrapped air. Adjust the temperature of the solution to 20 ± 0.1 °C. Determine the viscosity with a rotating viscometer at 20 °C and a shear rate of 10 s^{-1}.

For a product of low viscosity, use a quantity of the substance to be examined sufficient to prepare a solution of the concentration stated on the label.

Silica: maximum 0.6 per cent.

To the residue obtained in the test for sulfated ash add sufficient *ethanol (96 per cent) R* to moisten the residue completely. Add 6 mL of *hydrofluoric acid R* in small portions. Evaporate to dryness at 95-105 °C, taking care to avoid loss from sputtering. Cool and rinse the wall of the platinum crucible with 6 mL of *hydrofluoric acid R*. Add 0.5 mL of *sulfuric acid R* and evaporate to dryness. Progressively increase the temperature, ignite at 900 ± 50 °C, allow to cool in a desiccator and weigh. The difference between the mass of the residue obtained in the test for sulfated ash and the mass of the final residue is equal to the amount of silica in the substance to be examined.

Chlorides (*2.4.4*): maximum 0.5 per cent.

Dilute 1 mL of solution S to 15 mL with *water R*.

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 7.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*): maximum 1.6 per cent, determined on 1.0 g using a platinum crucible.

LABELLING

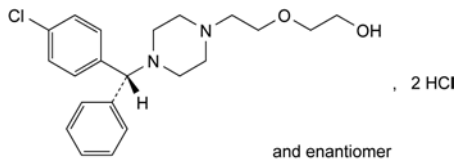
The label states:

- the apparent viscosity in millipascal seconds for a 2 per cent *m/m* solution,
- for a product of low viscosity, the concentration of the solution to be used and the apparent viscosity in millipascal seconds,
- where applicable, that the substance contains silica.

01/2008:0916
corrected 6.0

HYDROXYZINE HYDROCHLORIDE

Hydroxyzini hydrochloridum



$C_{21}H_{29}Cl_3N_2O_2$ M_r 447.8
[2192-20-3]

DEFINITION

(*RS*)-2-[2-[4-[(4-Chlorophenyl)phenylmethyl]piperazin-1-yl]ethoxy]ethanol dihydrochloride.

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

CHARACTERS

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

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

mp: about 200 °C, with decomposition.

IDENTIFICATION

First identification: A, D.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (*2.2.24*).

Preparation: discs.

Comparison: *hydroxyzine hydrochloride CRS*.

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

Solvent mixture: *methanol R, methylene chloride R* (50:50 *V/V*).

Test solution. Dissolve 0.50 g of the substance to be examined in the solvent mixture and dilute to 10 mL with the solvent mixture.

Reference solution (a). Dissolve 0.50 g of *hydroxyzine hydrochloride CRS* in the solvent mixture and dilute to 10 mL with the solvent mixture.

Reference solution (b). Dissolve 0.50 g of *meclozine dihydrochloride R* in the solvent mixture and dilute to 10 mL with the solvent mixture. Dilute 1 mL of this solution to 2 mL with reference solution (a).

Plate: *TLC silica gel G plate R*.

Mobile phase: *concentrated ammonia R, ethanol (96 per cent) R, toluene R* (1:24:75 *V/V/V*).

Application: 2 µL.

Development: over a path of 15 cm.

Drying: in air.

Detection: spray with *potassium iodobismuthate solution R2*.

System suitability: reference solution (b):

- the chromatogram shows 2 clearly separated principal 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).

C. Dissolve 0.1 g in *ethanol (96 per cent) R* and dilute to 15 mL with the same solvent. Add 15 mL of a saturated solution of *picric acid R* in *ethanol (96 per cent) R*. Allow to stand for 15 min. A precipitate is formed. Filter. Recrystallise from *ethanol (96 per cent) R*. Initiate crystallisation, if necessary, by scratching the wall of the tube with a glass rod. The crystals melt (*2.2.14*) at 189 °C to 192 °C.

D. It gives reaction (a) of chlorides (*2.3.1*).

TESTS

Solution S. Dissolve 2.0 g in *water R* and dilute to 20.0 mL with the same solvent.

Appearance of solution. Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution Y_7 (*2.2.2, Method II*).

Optical rotation (*2.2.7*): – 0.10° to + 0.10°, determined on solution S.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 10.0 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.