Flow rate: 40 mL/min.

Temperature:

– *column*: 215 °C;

– *injection port and detector*: 275 °C.

Detection: flame ionisation.

Injection: 2 µL.

System suitability: reference solution:

– *relative retention* with reference to β-lactose: α-lactose = about 0.7;

– *resolution*: minimum 3.0 between the peaks due to α-lactose and β-lactose.

Calculate the percentage content of α-lactose from the following expression:

$$\frac{100 S_a}{S_a + S_b}$$

Calculate the percentage content of β-lactose from the following expression:

$$\frac{100 S_b}{S_a + S_b}$$

S_a = area of the peak due to α-lactose;

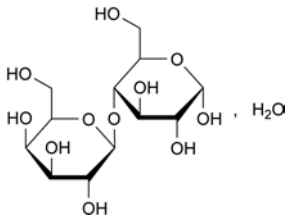
S_b = area of the peak due to β-lactose.

Loss on drying (*2.2.32*). Determine on 1.000 g by drying in an oven at 80 °C for 2 h.

07/2009:0187

LACTOSE MONOHYDRATE

Lactosum monohydricum



$C_{12}H_{22}O_{11},H_2O$ M_r 360.3

DEFINITION

O-β-D-Galactopyranosyl-(1→4)-α-D-glucopyranose monohydrate.

CHARACTERS

Appearance: white or almost white, crystalline powder.

Solubility: freely but slowly soluble in water, practically insoluble in ethanol (96 per cent).

IDENTIFICATION

First identification: *A, D.*

Second identification: *B, C, D.*

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *lactose CRS.*

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

Solvent mixture: *water R, methanol R* (2:3 *V/V*).

Test solution. Dissolve 10 mg of the substance to be examined in the solvent mixture and dilute to 20 mL with the solvent mixture.

Reference solution (a). Dissolve 10 mg of *lactose CRS* in the solvent mixture and dilute to 20 mL with the solvent mixture.

Reference solution (b). Dissolve 10 mg of *fructose CRS*, 10 mg of *glucose CRS*, 10 mg of *lactose CRS* and 10 mg of *sucrose CRS* in the solvent mixture and dilute to 20 mL with the solvent mixture.

Plate: *TLC silica gel G plate R.*

Mobile phase: *water R, methanol R, glacial acetic acid R, ethylene chloride R* (10:15:25:50 *V/V/V/V*); measure the volumes accurately, as a slight excess of water produces cloudiness.

Application: 2 µL; thoroughly dry the points of application.

Development A: over a path of 15 cm.

Drying A: in a current of warm air.

Development B: immediately, over a path of 15 cm, after renewing the mobile phase.

Drying B: in a current of warm air.

Detection: spray with a solution of 0.5 g of *thymol R* in a mixture of 5 mL of *sulfuric acid R* and 95 mL of *ethanol (96 per cent) R*; heat at 130 °C for 10 min.

System suitability: reference solution (b):

– the chromatogram shows 4 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).

C. Dissolve 0.25 g in 5 mL of *water R*. Add 5 mL of *ammonia R* and heat in a water-bath at 80 °C for 10 min. A red colour develops.

D. Water (see Tests).

TESTS

Appearance of solution. The solution is clear (*2.2.1*) and not more intensely coloured than reference solution BY_7 (*2.2.2, Method II*).

Dissolve 1.0 g in boiling *water R* and dilute to 10 mL with the same solvent.

Acidity or alkalinity. Dissolve 6.0 g by heating in 25 mL of *carbon dioxide-free water R*, cool and add 0.3 mL of *phenolphthalein solution R1*. The solution is colourless. Not more than 0.4 mL of *0.1 M sodium hydroxide* is required to change the colour of the indicator to pink or red.

Specific optical rotation (*2.2.7*): + 54.4 to + 55.9 (anhydrous substance).

Dissolve 10.0 g in 80 mL of *water R*, heating to 50 °C. Allow to cool and add 0.2 mL of *dilute ammonia R1*. Allow to stand for 30 min and dilute to 100.0 mL with *water R*.

Absorbance (*2.2.25*).

Test solution (a). Dissolve 1.0 g in boiling *water R* and dilute to 10.0 mL with the same solvent.

Test solution (b). Dilute 1.0 mL of test solution (a) to 10.0 mL with *water R*.

Spectral range: 400 nm for test solution (a) and 210-300 nm for test solution (b).

Results:

– at 400 nm: maximum 0.04 for test solution (a);

– from 210 nm to 220 nm: maximum 0.25 for test solution (b);

– from 270 nm to 300 nm: maximum 0.07 for test solution (b).

Heavy metals (*2.4.8*): maximum 5 ppm.

Dissolve 4.0 g in *water R* with warming, add 1 mL of *0.1 M hydrochloric acid* and dilute to 20 mL with *water R*. 12 mL of the solution complies with test A. Prepare the reference solution using *lead standard solution (1 ppm Pb) R*.

Water (*2.5.12*): 4.5 per cent to 5.5 per cent, determined on 0.50 g, using a mixture of 1 volume of *formamide R* and 2 volumes of *methanol R* as the solvent.

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

Microbial contamination

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

Absence of *Escherichia coli* (*2.6.13*).

STORAGE

In an airtight container.

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). This section is a non-mandatory part of the monograph and it is not necessary to verify the characteristics to demonstrate compliance. Control of these characteristics can however contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for lactose monohydrate used as a filler/diluent in solid dosage forms (compressed and powder).

Particle size distribution (*2.9.31* or *2.9.38*).

Bulk and tapped density (*2.9.34*). Determine the bulk density and the tapped density. Calculate the Hausner Index using the following expression:

$$\frac{V_0}{V_f}$$

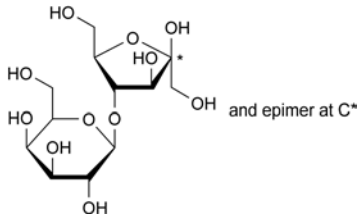
V_0 = volume of bulk substance;

V_f = volume of tapped substance.

01/2009:1230

LACTULOSE

Lactulosum



$C_{12}H_{22}O_{11}$ M_r 342.3

[4618-18-2]

DEFINITION

4-*O*-(β-D-Galactopyranosyl)-D-*arabino*-hex-2-ulofuranose.

Content: 95.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance: white or almost white, crystalline powder.

Solubility: freely soluble in water, sparingly soluble in methanol, practically insoluble in toluene.

mp: about 168 °C.

IDENTIFICATION

First identification: B, C, D, E.

Second identification: A, C, D, E.

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

Test solution. Dissolve 50.0 mg of the substance to be examined in *water R* and dilute to 10.0 mL with the same solvent.

Reference solution. Dissolve 50.0 mg of *lactulose CRS* in *water R* and dilute to 10.0 mL with the same solvent.

Plate: *TLC silica gel G plate R.*

Mobile phase: *glacial acetic acid R*, 50 g/L solution of *boric acid R, methanol R, ethyl acetate R* (10:15:20:55 *V/V/V/V*).

Application: 2 µL.

Development: over a path of 15 cm.

Drying: at 100-105 °C for 5 min and allow to cool.

Detection: spray with a 1.0 g/L solution of *1,3-dihydroxynaphthalene R* in a mixture of 10 volumes of *sulfuric acid R* and 90 volumes of *methanol R*; heat at 110 °C for 5 min.

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 the reference solution.

B. Examine the chromatograms obtained in the assay.

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

C. Dissolve 50 mg in 10 mL of *water R*. Add 3 mL of *cupri-tartaric solution R* and heat. A red precipitate is formed.

D. Dissolve 0.125 g in 5 mL of *water R*. Add 5 mL of *ammonia R*. Heat on a water-bath at 80 °C for 10 min. A red colour develops.

E. Specific optical rotation (see Tests).

TESTS

Solution S. Dissolve 3.0 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 BY_5 (*2.2.2, Method II*).

pH (*2.2.3*): 3.0 to 7.0.

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

Specific optical rotation (*2.2.7*): +46.0 to +50.0 (anhydrous substance).

Dissolve 1.25 g in *water R*, add 0.2 mL of *concentrated ammonia R* and dilute to 25.0 mL with *water R*.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 1.00 g of the substance to be examined in 10 mL of *water R*. Add 12.5 mL of *acetonitrile R* with gentle heating and dilute to 25.0 mL with *water R*.

Reference solution (a). To 3 mL of the test solution add 47.5 mL of *acetonitrile R* with gentle heating and dilute to 100.0 mL with *water R*.

Reference solution (b). Dissolve 1.00 g of *lactulose CRS* in 10 mL of *water R*. Add 12.5 mL of *acetonitrile R* with gentle heating and dilute to 25.0 mL with *water R*.

Reference solution (c). Dissolve the contents of a vial of *lactulose for system suitability CRS* in 1 mL of a mixture of equal volumes of *acetonitrile R* and *water R*.

Precolumn:

– *size*: *l* = 0.05 m, Ø = 4.6 mm;
– *stationary phase*: *aminopropylsilyl silica gel for chromatography R* (3 µm);
– *temperature*: 38 ± 1 °C.

Column:

– *size*: *l* = 0.15 m, Ø = 4.6 mm;
– *stationary phase*: *aminopropylsilyl silica gel for chromatography R* (3 µm);
– *temperature*: 38 ± 1 °C.

Mobile phase: dissolve 0.253 g of *sodium dihydrogen phosphate R* in 220 mL of *water R* and add 780 mL of *acetonitrile R*.

Flow rate: 1.0 mL/min.