

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. 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 anhydrous lactose 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 (2.9.15). 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.

α -Lactose and β -lactose. Gas chromatography (2.2.28).

Silylation reagent. Mix 28 volumes of *N*-trimethylsilyl-imidazole R and 72 volumes of pyridine R.

Test solution. Dissolve about 1 mg of the substance to be examined in 0.45 ml of *dimethyl sulphoxide* R. Add 1.8 ml of the silylation reagent. Mix gently and allow to stand for 20 min.

Reference solution. Prepare a mixture of α -lactose monohydrate R and β -lactose R having an anomeric ratio of about 1:1 based on the labelled anomeric contents of the α -lactose monohydrate and β -lactose. Dissolve about 1 mg of this mixture in 0.45 ml of *dimethyl sulphoxide* R. Add 1.8 ml of the silylation reagent. Mix gently and allow to stand for 20 min.

Column:

- **material:** glass;
- **size:** $l = 0.9$ m, $\varnothing = 4$ mm;
- **stationary phase:** silanised diatomaceous earth for gas chromatography R impregnated with 3 per cent *m/m* of poly[(cyanopropyl)(methyl)][(phenyl)(methyl)] siloxane R.

Carrier gas: helium for chromatography R.

Flow rate: 40 ml/min.

Temperature:

- **column:** 215 °C;
- **injection port and detector:** 275 °C.

Detection: flame ionisation.

Injection: 2 μ l.

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:

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

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

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

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

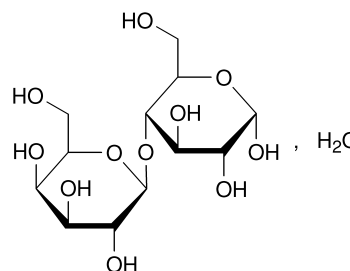
S_b = area of the peak due to β -lactose.

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

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corrected 6.0

LACTOSE MONOHYDRATE

Lactosum monohydricum



$C_{12}H_{22}O_{11} \cdot H_2O$

M_r 360.3

DEFINITION

O- β -D-Galactopyranosyl-(1 \rightarrow 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 starting points.

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 sulphuric 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 BY₇ (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 R. 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.

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.

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

Microbial contamination. Total viable aerobic count (2.6.12) not more than 10² micro-organisms per gram, determined by plate-count. It complies with the test for *Escherichia coli* (2.6.13).

STORAGE

In an airtight container.

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

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

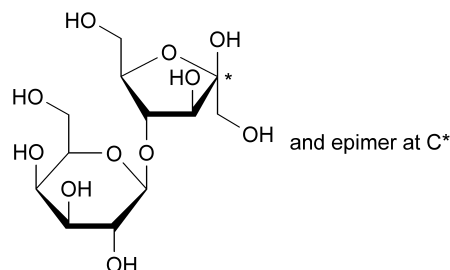
V_0 = volume of bulk substance;

V_f = volume of tapped substance.

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LACTULOSE

Lactulosum



C₁₂H₂₂O₁₁
[4618-18-2]

M_r 342.3

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.