Edition: BP 2025 (Ph. Eur. 11.6 update)

Lactulose Oral Powder

General Notices

Action and use

Osmotic laxative.

DEFINITION

Lactulose Oral Powder consists of Lactulose with or without lesser amounts of other sugars including lactose and galactose.

The oral powder complies with the requirements stated under Oral Powders and with the following requirements.

Content of lactulose, $C_{12}H_{22}O_{11}$

95.0 to 102.0%.

Dissolve 3 g in carbon dioxide-free water and dilute to 50 mL with the same solvent (solution S).

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using *silica gel G* as the coating substance and a mixture of 10 volumes of *glacial acetic acid*, 15 volumes of a 5% w/v solution of *boric acid*, 20 volumes of *methanol* and 55 volumes of *ethyl acetate* as the mobile phase. Apply separately to the plate 2 µL of each of the following solutions. For solution (1) dissolve 50 mg of the oral powder in *water* and dilute to 10 mL with the same solvent. For solution (2) dissolve 50 mg of *lactulose BPCRS* in *water* and dilute to 10 mL with the same solvent. After removal of the plate, dry it at 100° to 105° for 5 minutes and allow to cool. Spray the plate with a 0.1% w/v solution of *1,3-dihydroxynaphthalene* in a mixture of 10 volumes of *sulfuric acid* and 90 volumes of *methanol*. Heat the plate at 110° for 5 minutes. The principal spot in the chromatogram obtained with solution (1) is similar in position, colour and size to the principal spot in the chromatogram obtained with solution (2).
B. In the Assay, the principal peak in the chromatogram obtained with solution (1) is similar in position and size to the principal peak in the chromatogram obtained with solution (3).
C. Dissolve 0.05 g in 10 mL of *water*. Add 3 mL of *cupri-tartaric solution* and heat. A red precipitate is formed.
D. Dissolve 0.125 g in 5 mL of *water*. Add 5 mL of *ammonia*. Heat on a water bath at 80° for 10 minutes. A red colour develops.
E. Complies with the test for Specific optical rotation.

TESTS

Clarity and colour of solution

Solution S is *clear*, Appendix IV A, and not more intensely coloured than *reference solution* BY_5, Appendix IV B, Method II.

pH

To 10 mL of solution S add 0.1 mL of a saturated solution of *potassium chloride*. The pH of the solution is 3.0 to 7.0, Appendix V L.

Specific optical rotation

Dissolve 1.25 g in *water*, add 0.2 mL of 13. 5M *ammonia* and dilute to 25 mL with *water*. The *specific optical rotation* is –46.0° to –50.0°, Appendix V G.

Related substances

In the Assay, in the chromatogram obtained with solution (1), the sum of the areas of any peaks corresponding to the principal peaks in the chromatograms obtained with solutions 5, 6, 7, 8 and 9 respectively (galactose, lactose, epilactose, tagatose and fructose) is not greater than the area of the peak corresponding to lactulose in the chromatogram obtained with solution (2) (3%).

Methanol

Carry out the method for *head-space gas chromatography*, Appendix III B, Method II. Mix 0.5 mL of *propan-1-ol* with 100 mL of *water*. Dilute 1 mL to 100 mL with *water*. Dilute 5 mL to 50 mL with *water* (internal standard solution). For solution (1) add 1 mL of the internal standard solution and 5 µL of a 0.1% v/v solution of *methanol* to 79 mg of the oral powder in a 20 mL vial. For solution (2) add 5 µL of a 0.1% v/v solution of *methanol* to 1 mL of the internal standard solution in a 20 mL vial.

The chromatographic procedure may be carried out using (a) a column (2 m × 2 mm) packed with *ethylvinylbenzene–divinylbenzene co-polymer* (180 µm), (b) *helium for chromatography* as the carrier gas at a flow rate of 30 mL per minute and (c) a flame-ionisation detector, maintaining the temperature of the column at 140°, that of the injection port at 200° and that of the detector at 220°. Maintain each solution at 60° for 1 hour, pressurise for 1 minute and transfer onto the column 1 mL of the gaseous phase.

In the chromatogram obtained with solution (1), the ratio of the area of the methanol peak to that of the internal standard peak is not greater than twice the corresponding ratio for the chromatogram obtained with solution (2) (50 ppm, calculated assuming the density of methanol to be 0.79 g/mL at 20°).

Boron

Avoid where possible the use of glassware. Prepare a reference solution as follows. Dissolve 50 mg of *boric acid* in *water* and dilute to 100 mL with the same solvent. Dilute 5 mL of this solution to 100 mL with *water*. Keep in a well-closed polyethylene container. In four polyethylene 25 mL flasks, place 0.50 g of the oral powder dissolved in 2 mL of *water* (solution A), 0.50 g of the oral powder dissolved in 1 mL of the reference solution and 1 mL of *water* (solution B), 1 mL of the reference solution and 1 mL of *water* (solution C) and 2 mL of *water* (solution D). To each flask, add 4 mL of *acetate-edetate buffer solution pH 5.5*. Mix and add 4 mL of freshly prepared *azomethine H solution*. Mix and allow to stand for 1 hour. Measure the *absorbance*, Appendix II B, of solutions A, B and C at 420 nm, using solution D as the compensation liquid. The test is not valid unless the absorbance of solution C is at least 0.25. The absorbance of solution B is not less than twice that of solution A (9 ppm of boron).

Lead

Complies with the *limit test for lead in sugars*, Appendix VII (0.5 ppm).

Water

Not more than 2.5%, Appendix IX C, Method I. Use 0.5 g.

Sulfated ash

Not more than 0.1%, Appendix IX A, Method II. Use 1 g.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1) dissolve 1 g of the oral powder in 10 mL of *water*, add 12.5 mL of *acetonitrile* with gentle heating and dilute to 25 mL with *water*. For solution (2) add 47.5 mL of *acetonitrile* to 3 mL of solution (1) with gentle heating and dilute to 100 mL with *water*. For solution (3) dissolve 1 g of *lactulose BPCRS* in 10 mL of *water*, add 12.5 mL of *acetonitrile* with gentle heating and dilute to 25 mL with *water*. For solution (4) dissolve 20 mg of *lactulose BPCRS* and 20 mg of *epilactose EPCRS* in 2 mL of *water*, add 2.5 mL of *acetonitrile* with gentle heating and dilute to 5 mL with *water*. For solution (5) dissolve 0.2 g of *galactose* in 20 mL of *water*, add 25 mL of *acetonitrile* with gentle heating and dilute to 50 mL with *water*. For solution (6) dissolve 0.2 g of *lactose* in 20 mL of *water*, add 25 mL of *acetonitrile* with gentle heating and dilute to 50 mL with *water*. For solution (7) dissolve 20 mg of *epilactose EPCRS* in 2 mL of *water*, add 2.5 mL of *acetonitrile* with gentle heating and dilute to 5 mL with *water*. For solution (8) dissolve 0.2 g of *tagatose* in 20 mL of *water*, add 25 mL of *acetonitrile* with gentle heating and dilute to 50 mL with *water*. For solution (9) dissolve 0.2 g of *fructose* in 20 mL of *water*, add 25 mL of *acetonitrile* with gentle heating and dilute to 50 mL with *water*.

The chromatographic procedure may be carried out using (a) a stainless steel column (5 cm × 4.6 mm) followed by a stainless steel column (15 cm × 4.6 mm), both packed with *aminopropylsilyl silica gel for chromatography* (3 µm) and maintained at 37° to 39°, (b) as mobile phase with a flow rate of 1.0 mL per minute a mixture prepared as follows: dissolve 0.253 g of *sodium dihydrogen orthophosphate* in 220 mL of *water* and add 780 mL of *acetonitrile*, and (c) as detector a refractometer maintained at a constant temperature.

When the chromatograms are recorded in the prescribed conditions, the retention time of lactulose is about 18.3 minutes and retention times relative to lactulose are about 0.38 for tagatose, 0.42 for fructose, 0.57 for galactose, 0.90 for epilactose and 1.17 for lactose.

Inject 20 µL of solution (4). The test is not valid unless the *resolution factor* between the peaks corresponding to lactulose and epilactose is at least 1.3. If necessary, adjust the concentration of *acetonitrile* in the mobile phase to between 75.0% and 82.0% v/v to achieve the prescribed resolution.

Inject separately 20 µL of solution (1) and 20 µL of solution (3) and continue the chromatography for 2.5 times the retention time of lactulose. Calculate the percentage content of $C_{12}H_{22}O_{11}$ (lactulose) from the areas of the peaks and from the declared content of $C_{12}H_{22}O_{11}$ in *lactulose BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed in the monograph for Lactulose.