B. Iodine value (see Tests).

C. Composition of fatty acids (see Tests).

Margaric acid: maximum 0.2 per cent for oleic acid of vegetable origin and maximum 4.0 per cent for oleic acid of animal origin.

TESTS

Acid value (*2.5.1*): maximum 16.0, determined on 5.0 g.

Hydroxyl value (*2.5.3, Method A*): 55 to 75.

Iodine value (*2.5.4*): 76 to 90.

Peroxide value (*2.5.5*): maximum 10.0.

Saponification value (*2.5.6*): 170 to 190.

Carry out the saponification for 1 h.

Composition of fatty acids. Gas chromatography (*2.4.22, Method C*).

Composition of the fatty acid fraction of the substance:

- *myristic acid*: maximum 5.0 per cent;
- *palmitic acid*: maximum 16.0 per cent;
- *palmitoleic acid*: maximum 8.0 per cent;
- *stearic acid*: maximum 6.0 per cent;
- *oleic acid*: 65.0 per cent to 88.0 per cent;
- *linoleic acid*: maximum 18.0 per cent;
- *linolenic acid*: maximum 4.0 per cent;
- *fatty acids with chain length greater than C_{18}*: maximum 4.0 per cent.

Water (*2.5.12*): maximum 1.5 per cent, determined on 1.00 g.

Total ash (*2.4.16*): maximum 0.5 per cent, determined on 1.5 g.

STORAGE

Protected from light.

LABELLING

The label states the origin of the oleic acid used (animal or vegetable).

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). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can 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 sorbitan trioleate used as emulsifier and co-solubiliser in creams.

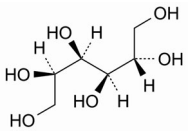
Composition of fatty acids (see Tests).

Hydroxyl value (see Tests).

07/2019:0435

SORBITOL

Sorbitolum



$C_6H_{14}O_6$ M_r 182.2

[50-70-4]

DEFINITION

D-Glucitol (D-sorbitol).

Content: 97.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance: white or almost white, crystalline powder.

Solubility: very soluble in water, practically insoluble in ethanol (96 per cent).

It shows polymorphism (*5.9*).

IDENTIFICATION

First identification: A.

Second identification: B, C, D.

A. 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 (a).

B. Dissolve 0.5 g with heating in a mixture of 0.5 mL of *pyridine R* and 5 mL of *acetic anhydride R*. After 10 min, pour the solution into 25 mL of *water R* and allow to stand in iced water for 2 h. The precipitate, recrystallised from a small volume of *ethanol (96 per cent) R* and dried *in vacuo*, melts (*2.2.14*) at 98 °C to 104 °C.

C. 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 *sorbitol CRS* in *water R* and dilute to 10 mL with the same solvent.

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

Plate: *TLC silica gel 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).

D. Specific optical rotation (*2.2.7*): + 4.0 to + 7.0 (anhydrous substance).

Dissolve 5.00 g of the substance to be examined and 6.4 g of *disodium tetraborate R* in 40 mL of *water R*. Allow to stand for 1 h, shaking occasionally, and dilute to 50.0 mL with *water R*. Filter if necessary.

TESTS

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

Dissolve 5 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* and dilute to 100.0 mL with the same solvent. Measure the conductivity of the solution while gently stirring with a magnetic stirrer.

Reducing sugars: maximum 0.2 per cent, expressed as glucose equivalent.

Dissolve 5.0 g in 6 mL of *water R* with the aid of gentle heat. 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 thiosulfate* 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 thiosulfate* is required.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 5.0 g of the substance to be examined in 20 mL of *water R* and dilute to 100.0 mL with the same solvent.

Reference solution (a). Dissolve 0.50 g of *sorbitol CRS* in 2 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 5.0 mL of reference solution (b) to 100.0 mL with *water R*.

Reference solution (d). Dissolve 0.5 g of *sorbitol R* and 0.5 g of *mannitol R* (impurity A) in 5 mL of *water R* and dilute to 10 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 for chromatography R*.

Flow rate: 0.5 mL/min.

Detection: differential refractometer maintained at a constant temperature (e.g. 35 °C).

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

Run time: twice the retention time of sorbitol.

Relative retention with reference to sorbitol (retention time = about 27 min): impurity C = about 0.6; impurity A = about 0.8; impurity B = about 1.1.

System suitability: reference solution (d):

- *resolution*: minimum 2.0 between the peaks due to impurity A and sorbitol.

Limits:

- *any impurity*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (2.0 per cent);
- *total*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (3.0 per cent);
- *disregard limit*: the area of the principal peak in the chromatogram obtained with reference solution (c) (0.1 per cent).

Water (*2.5.12*): maximum 1.5 per cent, determined on 1.00 g. Use a mixture of 1 volume of *formamide R1* and 2 volumes of *anhydrous methanol R* as solvent.

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*). If intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins:

- less than 4 IU/g for parenteral preparations having a concentration of less than 100 g/L of sorbitol;
- less than 2.5 IU/g for parenteral preparations having a concentration of 100 g/L or more of sorbitol.

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).

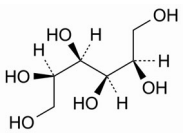
Calculate the percentage content of $C_6H_{14}O_6$ taking into account the assigned content of *sorbitol CRS*.

LABELLING

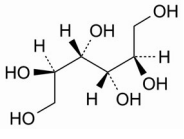
The label states:

- where applicable, the maximum concentration of bacterial endotoxins;
- where applicable, that the substance is suitable for use in the manufacture of parenteral preparations.

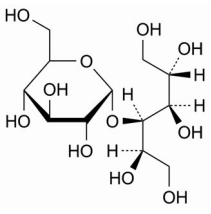
IMPURITIES



A. D-mannitol,



B. D-iditol,



C. 4-*O*-α-D-glucopyranosyl-D-glucitol (D-maltitol).

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). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can 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 sorbitol used as filler and binder in tablets.

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

Powder flow (*2.9.36*).

07/2019:0436

SORBITOL, LIQUID (CRYSTALLISING)

Sorbitolum liquidum cristallisabile

DEFINITION

Aqueous solution of a hydrogenated, partly hydrolysed starch.

Content:

- anhydrous substance: 68.0 per cent *m/m* to 72.0 per cent *m/m*,
- D-glucitol (D-sorbitol, $C_6H_{14}O_6$): 92.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance: clear, colourless, syrupy liquid, miscible with water.

IDENTIFICATION

A. Examine the chromatograms obtained in the assay.

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

B. To 7.0 g add 40 mL of *water R* and 6.4 g of *disodium tetraborate R*, allow to stand for 1 h, shaking occasionally, and dilute to 50.0 mL with *water R*. Filter if necessary. The angle of rotation (*2.2.7*) is 0° to + 1.5°.

C. It is a clear, syrupy liquid at a temperature of 25 °C.

TESTS

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

Dilute 7.0 g to 50 mL with *water R*.

Conductivity (*2.2.38*): maximum 10 µS·cm^{-1} measured on the undiluted liquid sorbitol (crystallising) while gently stirring with a magnetic stirrer.

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

To 5.0 g add 6 mL of *water R*, 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 thiosulfate* 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 thiosulfate* is required.

Water (*2.5.12*): 28.0 per cent to 32.0 per cent *m/m*, determined on 0.100 g.

ASSAY

Liquid chromatography (*2.2.29*).

Test solution. Mix 1.00 g of the substance to be examined with 20 mL of *water R* and dilute to 50.0 mL with the same solvent.

Reference solution (a). Dissolve 65.0 mg of *sorbitol CRS* in 2 mL of *water R* and dilute to 5.0 mL with the same solvent.

Reference solution (b). Dissolve 65 mg of *mannitol R* and 65 mg of *sorbitol R* in 2 mL of *water R* and dilute to 5 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 for chromatography R*.

Flow rate: 0.5 mL/min.

Detection: differential refractometer maintained at a constant temperature (e.g. 35 °C).

Injection: 20 µL.

Run time: twice the retention time of sorbitol.

Relative retention with reference to sorbitol (retention time = about 27 min): mannitol = about 0.8.

System suitability: reference solution (b):

- *resolution*: minimum 2.0 between the peaks due to mannitol and to sorbitol.

Calculate the percentage content of $C_6H_{14}O_6$ taking into account the assigned content of *sorbitol CRS*.

07/2019:0437

SORBITOL, LIQUID (NON-CRYSTALLISING)

Sorbitolum liquidum non cristallisabile

DEFINITION

Aqueous solution of a hydrogenated, partly hydrolysed starch.

Content:

- anhydrous substance: 68.0 per cent *m/m* to 72.0 per cent *m/m*,
- D-glucitol (D-sorbitol, $C_6H_{14}O_6$): 72.0 per cent to 92.0 per cent (anhydrous substance).

CHARACTERS

Appearance: clear, colourless, syrupy liquid, miscible with water.

IDENTIFICATION

A. Examine the chromatograms obtained in the assay.

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