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Sorbitol Sorbitan Solution

Former Title: Anhydrized Liquid Sorbitol

DEFINITION

Sorbitol Sorbitan Solution is a water solution containing NLT 25.0% of D-sorbitol ($C_6H_{14}O_6$) and NLT 15.0% of 1,4-sorbitan ($C_6H_{12}O_5$) on the anhydrous basis. The amounts of total sugars, other polyhydric alcohols, and any other hexitol anhydrides, if detected, are not included in the requirements nor in the calculated amount as stated in *General Notices, 5.60.10 Other Impurities in USP and NF Articles*.

IDENTIFICATION

• **A.**

Sample solution: 1.4 g of Sorbitol Sorbitan Solution in 75 mL of water

Analysis: Transfer 3 mL of *Sample solution* to a 15-cm test tube. Add 3 mL of a freshly prepared solution of catechol (1 in 10), and mix. Add 6 mL of sulfuric acid, mix again, and then gently heat the tube in a flame for about 30 s.

Acceptance criteria: A deep pink or wine-red color appears.

• **B.** The retention times of the *Sample solution* correspond to those of the *Standard solution,* as obtained in the *Assay*.

• **C. Limit of Diethylene Glycol and Ethylene Glycol**

Diluent: Acetone and water (96:4)

Standard solution: 0.08 mg/mL of USP Diethylene Glycol RS and 0.08 mg/mL of USP Ethylene Glycol RS in *Diluent*

Sample solution: Transfer 2.0 g of Sorbitol Sorbitan Solution to a 25-mL volumetric flask. Add 1.0 mL of *Diluent* to the flask, and mix on a vortex mixer for about 3 min. Add the remaining *Diluent* to the flask to volume in 3 equal portions. Mix on a vortex mixer for about 3 min after each addition of *Diluent*. Pass a portion of the supernatant layer obtained through a 0.45-µm nylon filter. Discard the first 2 mL of the filtrate, and collect the rest of the filtrate for analysis. [Note—Acetone is used to precipitate sorbitol.]

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: GC

Detector: Flame ionization

Column: 0.32-mm × 15-m fused-silica capillary column; 0.25-µm layer of phase G46

Temperatures

Detector: 300°

Injection port: 240°

Column: See *Table 1*.

Table 1

Initial Temperature (°)	Temperature Ramp (°/min)	Final Temperature (°)	Hold Time at Final Temperature (min)
70	—	70	2
70	50	300	5

Carrier gas: Helium

Flow rate: 3.0 mL/min

Injection volume: 1.0 µL

Injection type: Split, split ratio 10:1. [NOTE—A split liner, deactivated with glass wool, is used.]

System suitability

Sample: *Standard solution*

[NOTE—Diethylene glycol elutes after ethylene glycol.]

Suitability requirements

Resolution: NLT 30 between ethylene glycol and diethylene glycol

Analysis

Samples: *Standard solution* and *Sample solution*

Based on the *Standard solution*, identify the peaks of ethylene glycol and diethylene glycol. Compare peak areas of ethylene glycol and diethylene glycol in the *Standard solution* and the *Sample solution.*

Acceptance criteria

Diethylene glycol: The peak area of diethylene glycol in the *Sample solution* is NMT the peak area of diethylene glycol in the *Standard solution*, corresponding to NMT 0.10% of diethylene glycol in Sorbitol Sorbitan Solution.

Ethylene glycol: The peak area of ethylene glycol in the *Sample solution* is NMT the peak area of ethylene glycol in the *Standard solution*, corresponding to NMT 0.10% of ethylene glycol in Sorbitol Sorbitan Solution.

ASSAY

• **PROCEDURE**

Mobile phase: Water

System suitability solution: 10 mg/g of sorbitol, 4 mg/g of 1,4-sorbitan, 4 mg/g of isosorbide, and 1 mg/g of mannitol in water

Standard solution: 10 mg/g of USP Sorbitol RS and 4 mg/g of USP 1,4-Sorbitan RS in water

Sample solution: Dissolve 0.40 g of Sorbitol Sorbitan Solution in water, and dilute with water to about 20 g. Record the weight of the final solution, and mix thoroughly.

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: Refractive index

Column: 7.8-mm × 10-cm; packing L34

Temperatures

Detector: 35°

Column: 50 ± 2°

Flow rate: 0.6 mL/min

Injection volume: 10 µL

System suitability

Samples: *System suitability solution* and *Standard solution*

[NOTE—The relative retention times for 1,4-sorbitan, isosorbide, mannitol, and sorbitol are about 0.35, 0.43, 0.7, and 1.0, respectively.]

Suitability requirements

Resolution: NLT 2.0 between 1,4-sorbitan and isosorbide, *System suitability solution*

Relative standard deviation: NMT 2.0% for each analyte, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Separately calculate the percentages, on the anhydrous basis, of 1,4-sorbitan ($C_6H_{12}O_5$) and D-sorbitol ($C_6H_{14}O_6$) in the portion of Sorbitol Sorbitan Solution taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times [100/(100 - W)] \times 100$$

r_U = peak responses of the corresponding analyte from the *Sample solution*

r_S = peak responses of the corresponding analyte from the *Standard solution*

C_S = concentration of the appropriate USP Reference Standard in the *Standard solution* (mg/g)

C_U = concentration of Sorbitol Sorbitan Solution in the *Sample solution* (mg/g)

W = percentage from the test for *Water Determination* (%)

Acceptance criteria: NLT 25.0% of D-sorbitol and NLT 15.0% of 1,4-sorbitan on the anhydrous basis

IMPURITIES

• **Residue on Ignition ⟨281⟩:** NMT 0.20%, calculated on the anhydrous basis on a 2-g portion

Change to read:

• **Limit of Nickel**

▲[Note—When water is specified as the diluent, use deionized ultra-filtered water. Use of glass volumetric flasks is discouraged.]

Digest solution: Add 360 mL of hydrochloric acid, ultratrace, and 240 mL of nitric acid, ultratrace, to 1200 mL of water.

Blank solution: Add 40 mL of nitric acid, ultratrace, to a 2000-mL volumetric flask, dilute with water to volume, and mix well.

Internal standard solution: Transfer 2.0 mL of solution containing 1000 mg/L of yttrium[1] to a 1000-mL volumetric flask, dilute with *Blank solution* to volume, and mix well. The *Internal standard solution* contains 2 µg/mL of yttrium. [Note—The concentration of the *Internal standard solution* can be adjusted if a high number of signal counts from the *Internal standard solution* causes an artifact.]

Standard stock solution: [Note—Prepare this solution fresh every 2 months.] Quantitatively dilute an accurately measured volume of the solution containing 1000 mg/L of nickel[2] with *Blank solution* to obtain a solution containing 10 µg/mL of nickel.

Standard nickel solution A: [Note—Prepare this solution fresh weekly.] Pipet 1.0 mL of *Standard stock solution* into a 200-mL volumetric flask. Dilute the content in the flask with *Blank solution* to volume, and mix well. This solution contains 50 ng/mL of nickel.

Standard nickel solution B: [Note—Prepare this solution fresh weekly.] Pipet 2.0 mL of *Standard stock solution* into a 200-mL volumetric flask. Dilute the content in the flask with *Blank solution* to volume, and mix well. This solution contains 100 ng/mL of nickel.

Standard nickel solution C: [Note—Prepare this solution fresh weekly.] Pipet 4.0 mL of *Standard stock solution* into a 200-mL volumetric flask. Dilute the content in the flask with *Blank solution* to volume, and mix well. This solution contains 200 ng/mL of nickel.

Sample solution: Transfer a quantity of Sorbitol Sorbitan Solution, equivalent to 10.0 g on the anhydrous basis, into a 125-mL conical flask. Add 40 mL of *Digest solution*, and place on a hot plate. Heat the solution for about 20 min, being careful to prevent the solution from boiling over. Pull the sample off the hot plate just before it turns a dark caramel color. [Note—Do not overburn the sample.] Transfer the flask's contents into a clean, dry, 50-mL volumetric flask with washings of *Blank solution*. Dilute with *Blank solution* to volume. Filter the sample into a 15-mL centrifuge tube, using a 10-mL disposable syringe fitted with a syringe filter of 0.45-µm pore size.

Instrumental conditions

(See *Plasma Spectrochemistry ⟨730⟩*.)

Mode: ICP–OES

Emission wavelengths: 232.005 nm for nickel and 371.029 nm for yttrium. Set the sample read time and other instrument parameters as appropriate or as recommended by the instrument manufacturer.

System suitability

Samples: *Blank solution*, *Standard nickel solution A*, *Standard nickel solution B*, and *Standard nickel solution C*

Suitability requirements

[Note—Instrument performance must be verified to conform to the manufacturer's specifications for resolution and sensitivity. Before analyzing samples, the instrument must pass a suitable performance check.]

Correlation coefficient: NLT 0.999, determined from the *Calibration curve* constructed in the *Analysis*

Analysis

Samples: *Blank solution*, *Standard nickel solution A*, *Standard nickel solution B*, and *Standard nickel solution C*, and *Sample solution*

[Note—The following analysis is described for one type of ICP–OES instruments. If a different ICP–OES instrument is used, follow the instrument manufacturer's recommendations for operation.]

Take 3 replicate scans with the integration set as recommended by the instrument manufacturer. Follow the instrument manufacturer's recommendations for delivering the sample. Add the *Internal standard solution* in-line via a mixing block between the sample probe and the spray chamber. Flush the samples through the system before analysis. Program a read delay into the sampling routine to allow for fluid flow equilibration after the high-speed flush, before the first analytical read of the sample. Between samples, wash the pumping system by flushing the *Blank solution*.

Calibration curve: Generate the calibration curve using the *Blank solution*, *Standard nickel solution A*, *Standard nickel solution B*, and *Standard nickel solution C* as follows. Scan the *Internal standard solution* while running the *Blank solution* to measure the intensity of the yttrium emission. Hold this value constant throughout the remainder of the test. Separately scan the *Blank solution*, *Standard nickel solution A*, *Standard nickel solution B*, and *Standard nickel solution C* for nickel and yttrium. [Note—Add the *Internal standard solution* via an in-line mixing chamber.] Normalize the yttrium intensity to the value of the *Internal standard solution*. Apply this normalization factor to the nickel intensity, which is then referred to as the corrected nickel intensity. Construct a calibration curve by plotting the corrected nickel intensity versus the known concentrations, in ng/mL, of the nickel.

Similarly, analyze the *Sample solution*. Plot the intensity of the emission of the *Sample solution* on the calibration curve. Obtain the concentration of nickel (*C*), in ng/mL, in the *Sample solution* through the calibration curve.

Calculate the content, in µg/g, of nickel in the solid portion of Sorbitol Sorbitan Solution taken:

$$\text{Result} = (F \times V \times C)/W$$

F = conversion factor, 10^{-3} µg/ng (ng to µg)

V = volume of the *Sample solution*, 50 mL

C = concentration of nickel in the *Sample solution* (ng/mL)

W = weight of Sorbitol Sorbitan Solution calculated on the anhydrous basis (g)

Acceptance criteria: NMT 1 µg/g▲ (NF 1-May-2021)

• **Reducing Sugars**

[Note—The amount determined in this test is not included in the calculated amount as requested in *General Notices, 5.60.10 Other Impurities in USP and NF Articles*.]

Sample: An amount of Solution equivalent to 3.3 g, on the anhydrous basis

Analysis: To the *Sample*, add 3 mL of water, 20.0 mL of cupric citrate TS, and a few glass beads. Heat so that boiling begins after 4 min, and maintain boiling for 3 min. Cool rapidly and add 40 mL of diluted acetic acid, 60 mL of water, and 20.0 mL of 0.05 N iodine VS. With continuous shaking add 25 mL of a mixture of 6 mL of hydrochloric acid and 94 mL of water. When the precipitate has dissolved, titrate the excess of iodine with 0.05 N sodium thiosulfate VS, using 2 mL of starch TS, added toward the end of the titration, as an indicator.

Acceptance criteria: NLT 12.8 mL of 0.05 N sodium thiosulfate VS is required, corresponding to NMT 0.3% of reducing sugars, on the anhydrous basis, as glucose.

SPECIFIC TESTS

• **Microbial Enumeration Tests ⟨61⟩** and **Tests for Specified Microorganisms ⟨62⟩:** The total aerobic microbial count using the *Plate Method* is NMT 10^3 cfu/mL. The total combined molds and yeasts count is NMT 10^2 cfu/mL.

• **pH ⟨791⟩:** 4.0–7.0, in a 14% (w/w) solution of Sorbitol Sorbitan Solution in carbon dioxide-free water

• **Water Determination ⟨921⟩, *Method I*:** NMT 31.5%

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in well-closed containers. No storage requirements are specified.

• **Labeling:** The labeling indicates the percentage content, on the anhydrous basis, of D-sorbitol and 1,4-sorbitan.

• **USP Reference Standards ⟨11⟩**

USP Diethylene Glycol RS
USP Ethylene Glycol RS
USP 1,4-Sorbitan RS $C_6H_{12}O_5$ 164.16
USP Sorbitol RS

[1] Yttrium ICP standard solutions are commercially available. A suitable yttrium ICP standard is available from LGC (www.lgcstandards.com) or Millipore Sigma (www.sigmaaldrich.com).

[2] Nickel ICP standard solutions are commercially available. A suitable nickel ICP standard is available from LGC (www.lgcstandards.com) or Millipore Sigma (www.sigmaaldrich.com).

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
SORBITOL SORBITAN SOLUTION	Documentary Standards Support	SE2020 Simple Excipients
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SE2020 Simple Excipients

Chromatographic Database Information: Chromatographic Database

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