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Noncrystallizing Sorbitol Solution

DEFINITION

Noncrystallizing Sorbitol Solution is an aqueous solution containing NLT 45.0% (w/w) of D-sorbitol ($C_6H_{14}O_6$). The amounts of total sugars, other polyhydric alcohols, and any 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: Dissolve 1.4 g of Noncrystallizing Sorbitol 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 gently heat the tube in a flame for 30 s.

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

• **B.** The retention time of the major peak from the *Sample solution* corresponds to that 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 each of USP Diethylene Glycol RS and USP Ethylene Glycol RS in *Diluent*

Sample solution: Transfer 2.0 g of Noncrystallizing Sorbitol Solution to a 25-mL volumetric flask. Add 1.0 mL of *Diluent* to the flask, and mix on a vortex mixer for 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 the 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 Noncrystallizing Sorbitol 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 Noncrystallizing Sorbitol Solution.

ASSAY

• **PROCEDURE**

Mobile phase: Use degassed water.

System suitability solution: 4.8 mg/g each of mannitol and USP Sorbitol RS

Standard solution: 4.8 mg/g of USP Sorbitol RS

Sample solution: Weigh 0.20 g of Noncrystallizing Sorbitol Solution, and dissolve in and dilute with water to 20 g. Record the final solution weight.

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: 0.7 mL/min

Injection volume: 10 µL

System suitability

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

[NOTE—The relative retention times for mannitol and sorbitol are about 0.6 and 1.0, respectively, *System suitability solution*.]

Suitability requirements

Resolution: NLT 2.0 between sorbitol and mannitol, *System suitability solution*

Relative standard deviation: NMT 2.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of D-sorbitol ($C_6H_{14}O_6$) in the portion of Noncrystallizing Sorbitol Solution taken:

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

r_U = peak response of sorbitol from the *Sample solution*

r_S = peak response of sorbitol from the *Standard solution*

C_S = concentration of USP Sorbitol RS in the *Standard solution* (mg/g)

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

Acceptance criteria: NLT 45.0%

IMPURITIES

• **RESIDUE ON IGNITION ⟨281⟩:** NMT 0.1%, calculated on the anhydrous basis, determined 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 each 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 each 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 each flask with *Blank solution* to volume, and mix well. This solution contains 200 ng/mL of nickel.

Sample solution: Transfer a quantity of Noncrystallizing Sorbitol 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 of 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*, *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 nickel.

Similarly, analyze the *Sample solution*. Plot the intensity of the emission of the *Sample solution* on the calibration curve. Determine 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 Noncrystallizing Sorbitol 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 Noncrystallizing Sorbitol 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 Noncrystallizing Sorbitol 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, and the total combined molds and yeasts count is NMT 10^2 cfu/mL.

• **pH ⟨791⟩:** 5.0–7.5, in a 14% (w/w) solution of Noncrystallizing Sorbitol Solution in carbon dioxide-free water

• **Water Determination ⟨921⟩, *Method I*:** 28.5%–31.5%

ADDITIONAL REQUIREMENTS

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

• **USP Reference Standards ⟨11⟩**

USP Diethylene Glycol RS
USP Ethylene Glycol RS
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
NONCRYSTALLIZING SORBITOL SOLUTION	Documentary Standards Support	SE2020 Simple Excipients
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SE2020 Simple Excipients

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