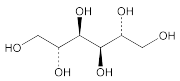
Mannitol

Add the following:

■Portions of the monograph text that are national *USP* text, and are not part of the harmonized text, are marked with symbols (◆◆) to specify this fact.■2S (*USP37*)



$C_6H_{14}O_6$ 182.17
D-Mannitol [69-65-8].

DEFINITION

Change to read:

■Mannitol contains NLT 97.0% and NMT 102.0% of mannitol ($C_6H_{14}O_6$), calculated on the ■dried■1S (*USP38*) basis. ■2S (*USP37*)

IDENTIFICATION

Change to read:

- **A. INFRARED ABSORPTION** ⟨197K⟩
  ■If the spectra shows differences, proceed as directed.
  Standard solution: Dissolve 25 mg of USP Mannitol RS in a glass vial with 0.25 mL of distilled water without heating. The solution is clear. Evaporate to dryness by one of the following methods. Heat in a microwave oven with a power range of 600–700 W for 20 min, or heat in an oven at 100° for 1 h, then gradually apply vacuum until a dry residue is obtained. Non-sticky, white, or slightly yellowish powders are obtained.
  Sample solution: Dissolve 25 mg of Mannitol in a glass vial with 0.25 mL of distilled water without heating. The solution is clear. Evaporate to dryness by one of the following methods. Heat in a microwave oven with a power range of 600–700 W for 20 min, or heat in an oven at 100° for 1 h, then gradually apply vacuum until a dry residue is obtained. Non-sticky, white, or slightly yellowish powders are obtained.
  Analysis: Record new spectra using the residues from the *Standard solution* and the *Sample solution*.■2S (*USP37*)

ASSAY

Change to read:

- **PROCEDURE**
  ■**Mobile phase:** Degassed water
  System suitability solution A: 25.0 mg/mL each of sorbitol and USP Mannitol RS
  System suitability solution B: 1.0 mg/mL each of maltitol and isomalt
  Standard solution A: 50.0 mg/mL of USP Mannitol RS
  Standard solution B: Dilute 2.0 mL of the *Sample solution* with water to 100.0 mL.
  Standard solution C: Dilute 0.5 mL of *Standard solution B* with water to 20.0 mL.
  Sample solution: 50.0 mg/mL of Mannitol
  Chromatographic system
  (See *Chromatography* ⟨621⟩, *System Suitability*.)
  Mode: LC
  Detector: Refractive index
  Column: 7.8-mm × 30-cm; packing L19
  Temperatures
  Column: 85 ± 2°
  Detector: 40° (maintain at a constant temperature)
  Flow rate: 0.5 mL/min
  Injection volume: 20 µL
  Run time: NLT 1.5 times the retention time of the mannitol peak. [NOTE—The retention time for mannitol is about 20 min.]
  System suitability
  Samples: *System suitability solution A*, *System suitability solution B*, *Standard solution B*, and *Standard solution C*
  Suitability requirements
  Resolution: NLT 2.0 between sorbitol and mannitol, *System suitability solution*
  Analysis
  Samples: *Standard solution A* and *Sample solution*
  Calculate the percentage of mannitol ($C_6H_{14}O_6$) in the portion of Mannitol taken:

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

  r_U = peak response from the *Sample solution*
  r_S = peak response from *Standard solution A*
  C_S = concentration of USP Mannitol RS in *Standard solution A* (mg/mL)
  C_U = concentration of the *Sample solution* (mg/mL)
  Acceptance criteria: 97.0%–102.0% on the ■dried■1S (*USP38*) basis■2S (*USP37*)

IMPURITIES

Change to read:

- ■• **RELATED SUBSTANCES**
  Mobile phase, System suitability solution A, System suitability solution B, Standard solution B, Standard solution C, Sample solution, Chromatographic system, and **System suitability:** Proceed as directed in the *Assay*.
  Analysis
  Samples: *Standard solution B*, *Standard solution C*, and *Sample solution*
  Acceptance criteria: See *Table 1* for the relative retention times.

Table 1

Name	Relative Retention Time
Isomalt (1st peak)	0.60
Maltitol	0.69
Isomalt (2nd peak)	0.73
Mannitol	1.0
Sorbitol	1.2

■[NOTE—Impurity A–Sorbitol; Impurity B–Maltitol; Impurity C–Isomalt.]■1S (*USP38*)
[NOTE—Isomalt elutes in two peaks.]
[NOTE—Coelution of impurity B and the second peak of impurity C may be observed.]
Disregard limit: NMT 0.05%; any peak NMT the area of the principal peak obtained with *Standard solution C*
Sorbitol: NMT 2.0%; NMT the area of the principal peak obtained with *Standard solution B*
Sum of isomalt and maltitol: NMT 2.0%; NMT the area of the principal peak obtained with *Standard solution B*

Unspecified impurities: NMT 0.10% for each impurity; NMT twice the area of the principal peak obtained with *Standard solution C*
Total impurities: 2.0%; NMT the area of the principal peak obtained with *Standard solution B* ■2S (*USP37*)

Delete the following:

■• **CHLORIDE AND SULFATE,** *Chloride* ⟨**221**⟩
Control: 0.20 mL of 0.020 N hydrochloric acid
Sample: 2.0 g
Acceptance criteria: 0.007%; the *Sample* shows no more chloride than the *Control*. ■2S (*USP37*)

Delete the following:

■• **CHLORIDE AND SULFATE,** *Sulfate* ⟨**221**⟩
Control: 0.20 mL of 0.020 N sulfuric acid
Sample: 2.0 g
Acceptance criteria: 0.01%; the *Sample* shows no more sulfate than the *Control*. ■2S (*USP37*)

Delete the following:

■• **ARSENIC,** *Method II* ⟨**211**⟩**:** NMT 1 ppm ■2S (*USP37*)

Change to read:

• **REDUCING SUGARS**
■**Copper sulfate solution:** 69.2 mg/mL of copper sulfate ($CuSO_4 \cdot 5H_2O$) ■in water ■1S (*USP38*)
Sodium potassium tartrate solution: Dissolve 173 g of sodium potassium tartrate ($C_4H_4KNaO_6 \cdot 4H_2O$) and 50 g of sodium hydroxide in 400 mL of water. Heat to boiling, allow to cool, and dilute with carbon dioxide-free water to 500 mL. ■ ■1S (*USP38*)
Cupri-tartaric solution: Mix equal volumes of *Copper sulfate solution* ■and *Sodium potassium tartrate solution* ■1S (*USP38*) immediately before use.
Sample: 7.0 g
Analysis: To the *Sample* add 13 mL of water. Boil gently with 40 mL of *Cupri-tartaric solution* for 3 min, and allow to stand for about 2 min. A precipitate is formed. Pass through a sintered-glass filter (10–16 µm) coated with diatomaceous earth or a sintered-glass filter (5–10 µm). Wash the precipitate with hot water (at about 50°–60°) until the washing is no longer alkaline, and pass the washings through the filter described above. Discard all the filtrate at this step. Immediately dissolve the precipitate in 20 mL of ferric sulfate solution, pass through the filter described above in a clean flask, and wash the filter with 15–20 mL of water. Combine the washings and the filtrate, heat to 80°, and titrate with 0.02 M potassium permanganate VS.
Acceptance criteria: NMT 0.1%, expressed as glucose; NMT 3.2 mL of 0.02 M potassium permanganate VS is required to change the color of the solution. The green color turns to pink, and the color persists at least 10 s. ■2S (*USP37*)

Change to read:

■• **NICKEL**
Sample solution: Suspend 10.0 g of Mannitol in 30 mL of dilute acetic acid [115–125 g/L of acetic acid ($C_2H_4O_2$)], add water, and shake to dissolve. Dilute with water to 100.0 mL. Add 2.0 mL of a saturated solution of ammonium pyrrolidinedithiocarbamate ($C_5H_{12}N_2S_2$) (about 10 g/L) and 10.0 mL of water-saturated methyl isobutyl ketone ($C_6H_{12}O$, 4-methyl-2-pentanone), and then shake for 30 s protected from bright light. Allow the layers to separate, and use the methyl isobutyl ketone layer.
Blank solution: Treat water-saturated methyl isobutyl ketone as described for preparation of the *Sample solution*, omitting the mannitol.
Standard solutions: Prepare three reference solutions in the same manner as the *Sample solution* but adding 0.5, 1.0, and 1.5 mL, respectively, of nickel standard solution TS [10 ppm nickel (Ni)] in addition to the 10.0 g of the substance to be examined.
Instrumental conditions
(See *Spectrophotometry and Light-Scattering* ⟨851⟩.)
Mode: Atomic absorption spectrophotometry
Analytical wavelength: 232.0 nm
Lamp: Nickel hollow-cathode
Flame: Air–acetylene
Analysis
Samples: *Standard solutions* and *Sample solution*
Set the zero of the instrument using the blank. Record the average of the steady readings for each of the *Standard solutions* and the *Sample solution*. Between each measurement rinse with water, and ascertain that the reading returns to zero ■with the blank. ■1S (*USP38*) Plot the absorbances of the *Standard solutions* and the *Sample solution* versus the added quantity of nickel. Extrapolate the line joining the points on the graph until it meets the concentration axis. The distance between this point and the intersection of the axes represents the concentration of nickel in the *Sample solution*.
Acceptance criteria: NMT 1 µg/g ■2S (*USP37*)

SPECIFIC TESTS

Change to read:

• **MELTING RANGE OR TEMPERATURE,** ■*Class I* ■2S (*USP37*) ⟨**741**⟩**:** ■165°–170° ■2S (*USP37*)

Delete the following:

■• **OPTICAL ROTATION,** *Specific Rotation* ⟨**781S**⟩
Sample solution: Transfer 1 g of Mannitol to a 100-mL volumetric flask, and add 40 mL of a 1-in-10 ammonium molybdate solution, previously filtered if necessary. Add 20 mL of 1 N sulfuric acid, and dilute with water to volume.
Acceptance criteria: +137° to +145° ■2S (*USP37*)

Add the following:

■• **APPEARANCE OF SOLUTION**
Hydrazine sulfate solution: 10.0 mg/mL of hydrazine sulfate. Allow to stand for 4–6 h.
Methenamine solution: 2.5 g of methenamine in 25 mL of water, in a ground-glass-stoppered flask
Primary opalescent suspension: To the *Methenamine solution*, add 25.0 mL of the *Hydrazine sulfate solution*. Mix, and allow to stand for 24 h. This suspension is stable for two months, provided it is stored in a glass container free from surface defects. The suspension must not adhere to the glass and must be well mixed before use.
Opalescence standard: Dilute 15.0 mL of the *Primary opalescent suspension* with water to 1000.0 mL. This suspension is freshly prepared and may be stored for up to 24 h.
Reference suspension: To 5.0 mL of *Opalescence standard* add 95.0 mL of water. Mix, and shake before use.
Standard solution: Pipet 3.0 mL of ferric chloride CS, 3.0 mL of cobaltous chloride CS, and 2.4 mL of cupric

sulfate CS into a 1-L volumetric flask. Dilute with 1% (w/v) hydrochloric acid to volume.
Sample solution: 100.0 mg/mL of Mannitol
Analysis: Compare the color, clarity, and opalescence of equal volumes of the *Reference suspension*, *Standard solution*, and *Sample solution*.
Acceptance criteria: The *Sample solution* is clear and colorless; its clarity is the same as that of water, or its opalescence is not more pronounced than that of the *Reference suspension*, and it is not more intensely colored than the *Standard solution*.■2S (*USP37*)

Delete the following:

■• **ACIDITY**
Sample solution: 5.0 g in 50 mL of carbon dioxide-free water
Analysis: To the *Sample solution* add 3 drops of phenolphthalein TS, and titrate with 0.020 N sodium hydroxide to a distinct pink endpoint.
Acceptance criteria: NMT 0.30 mL■2S (*USP37*)

Change to read:

• **LOSS ON DRYING** ⟨**731**⟩
Sample: 1.000 g■2S (*USP37*)
Analysis: Dry the *Sample* at 105° for 4 h.
Acceptance criteria: NMT 0.5%■2S (*USP37*)

Add the following:

■• **CONDUCTIVITY**
Sample: 20.0 g
Analysis: Dissolve the *Sample* in carbon dioxide-free water prepared from distilled water by heating to 40°–50°, and dilute with the same solvent to 100 mL. After cooling, measure the conductivity of the solution while gently stirring with a magnetic stirrer.
Acceptance criteria: NMT 20 µS/cm at 25°■2S (*USP37*)

Add the following:

■• **MICROBIAL ENUMERATION TESTS** ⟨**61**⟩ and **TESTS FOR SPECIFIED MICROORGANISMS** ⟨**62**⟩**:** The total aerobic microbial count (TAMC) is NMT 10^3 cfu/g, and the total combined molds and yeasts count is NMT 10^2 cfu/g. It meets the requirements of the test for absence of *Escherichia coli*.
If intended for use in the manufacture of parenteral dosage forms, the TAMC is NMT 10^2 cfu/g.■2S (*USP37*)

Add the following:

■• *Bacterial Endotoxins Test* ⟨85⟩**:** If intended for use in the manufacture of parenteral dosage forms without a further appropriate procedure for the removal of bacterial endotoxins, less than 4 IU/g for parenteral dosage forms with a concentration of 100 g/L or less of mannitol, and less than 2.5 IU/g for parenteral dosage forms with a concentration of more than 100 g/L of mannitol.■2S (*USP37*)

ADDITIONAL REQUIREMENTS

Change to read:

• ■◆■2S (*USP37*)**PACKAGING AND STORAGE:** Preserve in well-closed containers.■◆■2S (*USP37*)

Add the following:

■• **LABELING**
The label states, where applicable, the maximum concentration of bacterial endotoxins.
The label states, where applicable, that the substance is suitable for use in the manufacture of parenteral dosage forms.■2S (*USP37*)

Change to read:

• **USP REFERENCE STANDARDS** ⟨**11**⟩
■USP Endotoxin RS■1S (*USP38*)
USP Mannitol RS