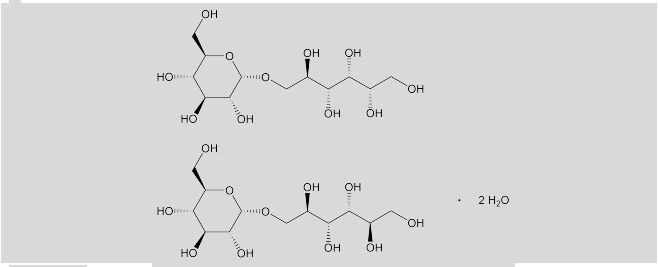
Isomalt

Add the following:

■Portions of this monograph that are national *USP* text, and are not part of the harmonized text, are marked with symbols (◆) to specify this fact.■1S (*NF34*)

Change to read:

■



■1S (*NF34*)

$C_{12}H_{24}O_{11}$ 344.31

$C_{12}H_{24}O_{11} \cdot 2H_2O$ 380.32

■6-*O*-α-Glucopyranosyl-D-sorbitol and 1-*O*-α-D-glucopyranosyl-D-mannitol dihydrate;
6-*O*-α-D-Glucopyranosyl-D-glucitol and 1-*O*-α-D-glucopyranosyl-D-mannitol dihydrate■1S (*NF34*) [64519-82-0].

DEFINITION

Isomalt contains NLT 98.0% and NMT 102.0% of a mixture of 6-*O*-α-D-glucopyranosyl-D-sorbitol (1,6-GPS) and 1-*O*-α-D-glucopyranosyl-D-mannitol (1,1-GPM), and neither of the two components is less than 3.0% of the mixture, calculated on the anhydrous basis.

IDENTIFICATION

Change to read:

- ■◆■1S (*NF34*)**A. Thin-Layer Chromatographic Identification Test** ⟨**201**⟩
  Standard solution: 5 mg/mL of USP Isomalt RS
  Sample solution: 5 mg/mL
  Chromatographic system
  Adsorbent: 0.25-mm layer of chromatographic silica gel mixture containing a fluorescent indicator having optimal intensity at 254 nm
  Application volume: 1 µL
  Developing solvent system: *Ethyl acetate*, *pyridine*, water, *acetic acid*, and *propionic acid* (10:10:2:1:1)
  Analysis
  Samples: *Standard solution* and *Sample solution*
  Proceed as directed in the chapter. Thoroughly dry the starting points in warm air. Develop over 10 cm using the *Developing solvent system*, dry the plate in a current of hot air, and dip for 3 s in a 1-mg/mL solution of *sodium periodate*. Dip the plate for 3 s in a mixture of *dehydrated alcohol*, *sulfuric acid*, *acetic acid*, and *anisaldehyde* (90:5:1:1). Dry the plate in a current of hot air until colored spots become visible. The background color may be brightened by exposure to warm steam. Examine in daylight.
  Acceptance criteria: The principal spots of the *Sample solution* are similar in position and color to those of the *Standard solution*.■◆■1S (*NF34*)

- **B.** The retention times of the two principal peaks of the *Sample solution* correspond to those of the *Standard solution*, as obtained in the *Assay*.

ASSAY

Change to read:

- **Procedure**
  Mobile phase: Water
  Standard solution: 20 mg/mL of USP Isomalt RS
  Sample solution: 20 mg/mL of Isomalt
  Chromatographic system
  (See *Chromatography* ⟨621⟩, *System Suitability*.)
  Mode: LC
  Detector: Refractive index, ■maintained at a constant temperature (40° for example)■1S (*NF34*)
  Columns
  Guard: 4.6-mm × 3-cm; packing L19
  Analytical: 7.8-mm × 30-cm; packing L19
  Column temperature: 80 ± ■3°■1S (*NF34*)
  Flow rate: 0.5 mL/min
  Injection volume: 20 µL
  System suitability
  Sample: *Standard solution*
  [NOTE—The relative retention times for 1,1-GPM and 1,6-GPS are about 1.0 and 1.2, respectively.]
  Suitability requirements
  Resolution: NLT 2.0 between 1,1-GPM and 1,6-GPS
  Relative standard deviation: NMT 2.0% for the 1,6-GPS and 1,1-GPM peaks
  Analysis
  Samples: *Standard solution* and *Sample solution*
  Calculate the percentage of 1,6-GPS in the portion of Isomalt taken:

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

r_U = peak response of 1,6-GPS from the *Sample solution*
r_S = peak response of 1,6-GPS from the *Standard solution*
C_S = concentration of 1,6-GPS in the *Standard solution*, with calculation based on the declared 1,6-GPS content of USP Isomalt RS (mg/mL)
C_U = concentration of Isomalt in the *Sample solution* (mg/mL)

  Calculate the percentage of 1,1-GPM in the portion of Isomalt taken:

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

r_U = peak response of 1,1-GPM from the *Sample solution*
r_S = peak response of 1,1-GPM from the *Standard solution*
C_S = concentration of 1,1-GPM in the *Standard solution*, with calculation based on the declared 1,1-GPM content of USP Isomalt RS (mg/mL)
C_U = concentration of Isomalt in the *Sample solution* (mg/mL)

  Acceptance criteria: 98.0%–102.0% of a mixture of 6-*O*-α-D-glucopyranosyl-D-sorbitol (1,6-GPS) and 1-*O*-α-D-glucopyranosyl-D-mannitol (1,1-GPM), and neither of the two components is less than 3.0% of the mixture, calculated on the anhydrous basis

IMPURITIES

Delete the following:

•• **HEAVY METALS,** *Method I* ⟨**231**⟩**:** NMT 10 µg/g •• (Official 1-Jan-2018)

Delete the following:

■• **LIMIT OF NICKEL**

[NOTE—The purity of the reagents and the water used must be suitable for trace analysis, and the reagents and water must be free of nickel.]

Nickel standard solution: Transfer 1 mL of nickel standard solution TS to a 100-mL volumetric flask, add 1 mL of nitric acid, and dilute with water to volume. This solution contains the equivalent of 0.1 µg/mL of nickel.

Standard solutions: Into seven identical 10-mL volumetric flasks, introduce respectively 0, 0.5, 1.0, 1.5, 2.0, 2.5, and 3.0 mL of *Nickel standard solution* equivalent to 0, 0.05, 0.1, 0.15, 0.2, 0.25, and 0.3 µg of nickel. To each flask add a 2.0-mL portion of the *Sample solution*, and dilute with water to volume.

Sample solution: Weigh 8 g of Isomalt in a 50-mL volumetric flask, add 8 mL of water and 3 mL of 65% nitric acid solution, and incubate at 95° for 1 h. Allow the solution to cool to room temperature, add another 3 mL of 65% nitric acid solution, and incubate at 95° until all brown vapors have dissipated (1–1.5 h). Allow the solution to cool to room temperature, carefully add 3 mL of 30% hydrogen peroxide, and keep the solution at 95° until the evolution of gas has ceased (1–2 h). Allow the solution to cool to room temperature. Repeat the procedure two more times, i.e., adding 30% hydrogen peroxide, heating to 95°, and cooling to room temperature. Dilute the resulting solution with water to 50 mL.

Blank: Prepare as directed for the *Sample solution*, except omit the addition of Isomalt.

Blank solutions: Prepare as directed for the *Standard solutions*, except replace 2 mL of the *Sample solution* with 2 mL of the *Blank*.

Instrumental conditions

(See *Spectrophotometry and Light-Scattering* ⟨851⟩.)

Mode: Atomic absorption spectrophotometry, using an instrument equipped with a graphite furnace

Analytical wavelength: 232.0 nm

Lamp: Nickel hollow-cathode

Analysis: Concomitantly determine the absorbances of the *Standard solutions* and the *Blank solutions*. Record the average of the steady readings for each of the *Standard solutions* and the *Blank solutions*. Plot the absorbances of the *Standard solutions* versus the quantity of nickel, in µg, in the portion of *Nickel standard solution* added to each *Standard solution* flask. 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 amount of nickel (A_T), in µg, in the portion of the *Sample solution* that was added to each of the *Standard solution* flasks. Similarly, plot the absorbances of the *Blank solutions* versus the quantity of nickel, in µg, in the portion of *Nickel standard solution* added to each of the *Blank solutions* flasks to determine the quantity of nickel (A_B) in the portion of *Blank* added to each of the *Blank solutions* flasks.

Calculate the quantity, in µg/g, of nickel in the portion of Isomalt taken:

$$\text{Result} = (A_T - A_B) \times (D/W)$$

A_T = amount of nickel in the portion of the *Sample solution* that was added to each of the *Standard solutions* flasks (µg)

A_B = quantity of nickel in the portion of *Blank* added to each of the *Blank solutions* flasks (µg)

D = volume of the *Sample solution* prepared per volume of the *Sample solution* used for analysis, 50/2

W = weight of Isomalt used to prepare the *Sample solution* (g)

Acceptance criteria: NMT 1 µg/g, calculated on the anhydrous basis ■1S (*NF34*)

Add the following:

■• **LIMIT OF NICKEL**

[NOTE—The purity of the reagents and the water used must be suitable for trace analysis, and the reagents and water must be free of nickel.]

Sample solution: Dissolve 10.0 g of Isomalt in 30 mL of dilute acetic acid (115–125 g/L), add water, and shake to dissolve. Dilute with water to 100.0 mL. Add 2.0 mL of *saturated ammonium pyrrolidinedithiocarbamate TS* 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.

Standard solutions: Prepare three reference solutions in the same manner as the *Sample solution* except add 0.5 mL, 1.0 mL, and 1.5 mL, respectively, of *nickel standard solution TS* (10 ppm Ni) in addition to the 10.0 g of the substance to be examined.

Blank solution: Treat water-saturated *methyl isobutyl ketone* as described for preparation of the *Sample solution* omitting the Isomalt.

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: *Sample solution*, *Standard solutions*, and *Blank solution*

Set the zero of the instrument using the *Blank solution*. 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 solution*. 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, calculated on the anhydrous basis ■1S (*NF34*)

• **ORGANIC IMPURITIES**

Mobile phase, **Sample solution**, and **Chromatographic system:** Proceed as directed in the *Assay*.

System suitability solution: 20 mg/mL of USP Isomalt RS and 0.1 mg/mL each of USP Mannitol RS and USP Sorbitol RS in water

Standard solution: 0.1 mg/mL each of USP Sorbitol RS and USP Mannitol RS
System suitability
Sample: *System suitability solution*
[NOTE—The relative retention times for 1,1-GPM, 1,6-GPS, mannitol, and sorbitol are about 1.0, 1.2, 1.6, and 2.0, respectively. The typical retention time for 1,1-GPM is about 12.3 min.]
Suitability requirements
Resolution: NLT 2.0 between 1,1-GPM and 1,6-GPS
Analysis
Samples: *Sample solution* and *Standard solution*
Calculate the percentage of mannitol or sorbitol in the portion of Isomalt taken:

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

r_U = peak response of mannitol or sorbitol from the *Sample solution*
r_S = peak response of mannitol or sorbitol from the *Standard solution*
C_S = concentration of USP Mannitol RS or USP Sorbitol RS in the *Standard solution* (mg/mL)
C_U = concentration of Isomalt in the *Sample solution* (mg/mL)

Calculate the percentage of any unknown impurity in the portion of Isomalt taken:

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

r_U = peak response of each unknown impurity 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/mL)
C_U = concentration of Isomalt in the *Sample solution* (mg/mL)

Acceptance criteria: See *Table 1*. [NOTE—Disregard any impurity peak that is less than 0.1%.]

Table 1

Name	Acceptance Criteria, NMT (%)
Mannitol	0.5
Sorbitol	0.5
Any unknown impurity	0.5
Total impurities	2.0

Change to read:

- **REDUCING SUGARS**
Sample solution: Dissolve 3.3 g in 10 mL of Purified Water with the aid of gentle heat. Cool and add 20 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 ■100 mL of a 2.4% (v/v) solution of glacial acetic acid■1S (*NF34*) and 20 mL of 0.025 M iodine VS. With continuous shaking, add 25 mL of a mixture of ■hydrochloric acid and water (6:94).■1S (*NF34*)
Analysis: After the precipitate has dissolved, titrate the excess iodine with 0.05 N sodium thiosulfate VS, using 1 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, determined on the anhydrous basis as glucose.

SPECIFIC TESTS

Change to read:

- **WATER DETERMINATION ⟨921⟩,** *Method I*
Sample: 0.3 g
Analysis: Add the *Sample* to a mixture of *anhydrous methanol* and *formamide* (1:1) at 50 ± 5°.
Acceptance criteria: NMT ■7.0%■1S (*NF34*)

Change to read:

- **CONDUCTIVITY**
Sample solution: Dissolve 20 g in carbon dioxide-free water ■with gentle heating (40°–50°), cool,■1S (*NF34*) and dilute with the same solvent to 100 mL.
Analysis: Using an appropriate conductivity meter that has been standardized with a potassium chloride conductivity calibration standard, measure the conductivity of the *Sample solution* while gently stirring with a magnetic stirrer.
Acceptance criteria: NMT 20 µS/cm

ADDITIONAL REQUIREMENTS

Change to read:

- ■◆■1S (*NF34*)**PACKAGING AND STORAGE:** Preserve in well-closed containers. No storage requirements are specified. ■◆■1S (*NF34*)
- **LABELING:** Label it to indicate the percentage content of 1,6-GPS and 1,1-GPM.
- **USP REFERENCE STANDARDS ⟨11⟩**
USP Isomalt RS
USP Mannitol RS
USP Sorbitol RS