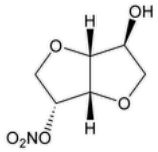
Status: Currently Official on 14-Feb-2025
Official Date: Official as of 01-May-2024
Document Type: USP Monographs
DocId: GUID-DDF4D5F1-9D03-4568-8787-0C5829AFE919_5_en-US
DOI: https://doi.org/10.31003/USPNF_M43610_05_01
DOI Ref: 3t6q4

Diluted Isosorbide Mononitrate



$C_6H_9NO_6$ 191.14

D-Glucitol, 1,4:3,6-dianhydro-, 5-nitrate;

1,4:3,6-Dianhydro-D-glucitol 5-nitrate CAS RN®: 16051-77-7; UNII: LX1OH63030.

DEFINITION

Diluted Isosorbide Mononitrate is a dry mixture of isosorbide mononitrate ($C_6H_9NO_6$) with lactose or other suitable excipients to permit safe handling. It contains NLT 95.0% and NMT 105.0% of the labeled amount of isosorbide mononitrate ($C_6H_9NO_6$).

[CAUTION—Exercise proper precautions in handling undiluted isosorbide mononitrate, which is a powerful explosive and can be exploded by percussion or excessive heat. Only exceedingly small amounts should be isolated.]

IDENTIFICATION

Change to read:

• **A.** ▲**SPECTROSCOPIC IDENTIFICATION TESTS ⟨197⟩, *Infrared Spectroscopy*:** 197A or 197K▲ (USP 1-May-2024)

Sample: Shake a suitable amount of Diluted Isosorbide Mononitrate, equivalent to about 25 mg of isosorbide mononitrate, with 10 mL of acetone for 5 min. Filter, evaporate to dryness at a temperature below 40°, dry the residue in a vacuum over phosphorus pentoxide for 16 h, and use the residue.

Standard: Prepare as directed for the *Sample* using a suitable amount of USP Diluted Isosorbide Mononitrate RS.

Acceptance criteria: Meets the requirements

• **B.** The retention time of the major peak of the *Sample solution* corresponds to that of *Standard solution A*, as obtained in the *Assay*.

ASSAY

Change to read:

• **PROCEDURE**

Mobile phase: Methanol and water (5:95)

Standard solution A: 2.0 mg/mL of isosorbide mononitrate prepared as follows. Transfer a suitable amount of USP Diluted Isosorbide Mononitrate RS to a suitable volumetric flask, dissolve in a suitable volume of water, add a volume of methanol equivalent to 4% of the flask volume, and dilute with water to volume.

▲▲ (USP 1-May-2024)

Standard solution B: 0.05 mg/mL of isosorbide mononitrate related compound A prepared ▲as follows. Transfer a suitable amount of USP Diluted Isosorbide Mononitrate Related Compound A RS to a suitable volumetric flask, dissolve in a suitable volume of water, add a volume of methanol equivalent to 4% of the flask volume, and dilute with water to volume.▲ (USP 1-May-2024)

System suitability solution: 0.02 mg/mL of isosorbide mononitrate and 0.005 mg/mL of isosorbide mononitrate related compound A prepared as follows. Transfer 1.0 mL of *Standard solution A*, 10.0 mL of *Standard solution B*, and 4.0 mL of methanol to a 100-mL volumetric flask, and dilute with water to volume. Filter a portion of the solution, discarding the first few milliliters of the filtrate.

Sample solution: Nominally 2.0 mg/mL of isosorbide mononitrate from Diluted Isosorbide Mononitrate prepared as follows. Transfer a suitable amount of Diluted Isosorbide Mononitrate to a suitable volumetric flask, dissolve in 50% of the flask volume of water, add a volume of methanol equivalent to 4% of the flask volume, and dilute with water to volume. Filter a portion of the solution, discarding the first few milliliters of the filtrate.

Chromatographic system

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

Mode: LC

Detector: UV 220 nm

Column: 4-mm × 12.5-cm; ▲5-µm▲ (USP 1-May-2024) packing L1

Flow rate: 1.5 mL/min, increase to 3.0 mL/min at about 8.5 min. ▲[NOTE—Make sure that the isosorbide mononitrate peak has completely eluted before increasing the flow rate.]▲ (USP 1-May-2024)

Injection volume: 50 µL

▲**Run time:** NLT 5 times the retention time of isosorbide mononitrate▲ (USP 1-May-2024)

System suitability

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

▲[NOTE—The relative retention times for isosorbide mononitrate related compound A and isosorbide mononitrate are 0.8 and 1.0, respectively.]▲ (USP 1-MAY-2024)

Suitability requirements

Resolution: NLT 2.0 between isosorbide mononitrate related compound A and isosorbide mononitrate, *System suitability solution*

Relative standard deviation: NMT ▲0.73%▲ (USP 1-May-2024) *Standard solution A*

Analysis

Samples: *Standard solution A* and *Sample solution*

Calculate the percentage of the labeled amount of isosorbide mononitrate ($C_6H_9NO_6$) in the portion of Diluted Isosorbide Mononitrate taken:

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

r_U = peak response of isosorbide mononitrate from the *Sample solution*

r_S = peak response of isosorbide mononitrate from *Standard solution A*

C_S = concentration of isosorbide mononitrate in *Standard solution A* (mg/mL)

C_U = nominal concentration of isosorbide mononitrate in the *Sample solution* (mg/mL)

Acceptance criteria: 95.0%–105.0%

IMPURITIES

Add the following:

▲• **LIMIT OF NITRATE**

[NOTE—Use water with a resistivity of NLT 18 megohm-cm to prepare the solutions.]

Mobile phase: 20 mM potassium hydroxide in water. [NOTE—*Mobile phase* can be generated electrolytically using an automatic eluant generator.]

Sensitivity solution: 0.5 µg/mL of USP Potassium Nitrate RS in water

Standard solution: 5.0 µg/mL of USP Potassium Nitrate RS in water

Sample solution: Nominally 1000 µg/mL of isosorbide mononitrate from Diluted Isosorbide Mononitrate in water

Chromatographic system

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

Mode: LC

Detector: Conductivity with suppression

Columns

Guard: 4.0-mm × 5-cm; 13-µm packing L120. [NOTE—Alternatively, a 4.0-mm × 0.5-cm column that contains 5.0-µm packing L91 may be used.]

Analytical: 4.0-mm × 25-cm; 7.5-µm packing L113. [NOTE—Alternatively, a 4.0-mm × 15-cm column that contains 5.0-µm packing L91 may be used.]

Column temperature: 30°

Flow rate: 1 mL/min

Injection volume: 100 µL

Run time: NLT 2 times the retention time of nitrate

System suitability

Sample: *Sensitivity solution*

Suitability requirements

Relative standard deviation: NMT 5.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of nitrate as potassium nitrate relative to the labeled amount of isosorbide mononitrate in the portion of Diluted Isosorbide Mononitrate taken:

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

r_U = peak response of the nitrate ion from the *Sample solution*

r_S = peak response of the nitrate ion from the *Standard solution*

C_S = concentration of USP Potassium Nitrate RS in the *Standard solution* (µg/mL)

C_U = nominal concentration of isosorbide mononitrate in the *Sample solution* (µg/mL)

Acceptance criteria: NMT 0.5%, calculated as potassium nitrate▲ (USP 1-May-2024)

Change to read:

• **Organic Impurities**

▲[Note—It is recommended to use GC-grade methanol to prepare the solutions.]

Sensitivity solution: 1.5 µg/mL of isosorbide mononitrate in methanol prepared as follows. Transfer a suitable amount of USP Diluted Isosorbide Mononitrate RS to a suitable volumetric flask. Add methanol to about 80% of the final volume and sonicate for 30 min with intermittent shaking. Dilute with methanol to volume. Centrifuge a portion of the solution and use the clear supernatant.

Standard solution: 3 µg/mL of isosorbide mononitrate, 15 µg/mL of isosorbide, and 7.5 µg/mL each of ▲isosorbide mononitrate related compound A▲ (ERR 1-May-2024) and isosorbide dinitrate in methanol prepared as follows. Transfer a suitable amount of USP Diluted Isosorbide Mononitrate RS, USP Diluted Isosorbide Mononitrate Related Compound A RS, and USP Diluted Isosorbide Dinitrate RS to a suitable volumetric flask. Add methanol to about 80% of the final volume and sonicate for 30 min with intermittent shaking. Add an appropriate amount of USP Isosorbide RS to the volumetric flask, and dilute with methanol to volume. Centrifuge a portion of the solution and use the clear supernatant.

Sample solution: Nominally 3 mg/mL of isosorbide mononitrate in methanol prepared as follows. Transfer a suitable amount of Diluted Isosorbide Mononitrate to a suitable volumetric flask. Add methanol to about 80% of the final volume, sonicate for 30 min with intermittent shaking, and dilute with methanol to volume. Centrifuge a portion of the solution and use the clear supernatant.

Chromatographic system

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

Mode: GC

Detector: Flame ionization

Column: 0.53-mm × 30-m fused-silica capillary; coated with a 1.5-µm film of phase G2

Temperatures

Injection port: 150°

Column: 125°

Detector: 275°

Carrier gas: Hydrogen

Flow rate: 180 cm/s (linear velocity)

Injection volume: 1 µL

Injection type: Split, split ratio 1:6

Run time: NLT 3 times the retention time of isosorbide mononitrate

System suitability

Samples: *Sensitivity solution* and *Standard solution*

[Note—See *Table 1* for the relative retention times.]

Suitability requirements

Relative standard deviation: NMT 5.0% each for isosorbide mononitrate, isosorbide, ▲isosorbide mononitrate related compound A▲ (ERR 1-May-2024), and isosorbide dinitrate, *Standard solution*

Signal-to-noise ratio: NLT 10, *Sensitivity solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of isosorbide, ▲isosorbide mononitrate related compound A▲ (ERR 1-May-2024), and isosorbide dinitrate relative to the labeled amount of isosorbide mononitrate in the portion of Diluted Isosorbide Mononitrate taken:

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

r_U = peak response of isosorbide, ▲isosorbide mononitrate related compound A▲ (ERR 1-May-2024), or isosorbide dinitrate from the *Sample solution*

r_S = peak response of isosorbide, ▲isosorbide mononitrate related compound A▲ (ERR 1-May-2024), or isosorbide dinitrate from the *Standard solution*

C_S = concentration of isosorbide, ▲isosorbide mononitrate related compound A▲ (ERR 1-May-2024), or isosorbide dinitrate in the *Standard solution* (mg/mL)

C_U = nominal concentration of isosorbide mononitrate in the *Sample solution* (mg/mL)

Calculate the percentage of any unspecified impurity relative to the labeled amount of isosorbide mononitrate in the portion of Diluted Isosorbide Mononitrate taken:

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

r_U = peak response of each unspecified impurity from the *Sample solution*

r_S = peak response of isosorbide mononitrate from the *Standard solution*

C_S = concentration of isosorbide mononitrate in the *Standard solution* (mg/mL)

C_U = nominal concentration of isosorbide mononitrate in the *Sample solution* (mg/mL)

Acceptance criteria: See *Table 1*. The reporting threshold is 0.05%.

Table 1

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Isosorbide	0.4	0.5
▲Isosorbide mononitrate related compound A▲ (ERR 1-May-2024)	0.6	0.25
Isosorbide mononitrate	1.0	—
Isosorbide dinitrate	1.6	0.25
Any unspecified impurity	—	0.10
Total impurities	—	0.5

▲ (USP 1-May-2024)

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight containers. Store at a temperature of 20°–30°.

Change to read:

• **USP Reference Standards** ⟨11⟩

USP Isosorbide RS

[Note—USP Diluted Isosorbide Dinitrate RS, USP Diluted Isosorbide Mononitrate RS, and USP Diluted Isosorbide Mononitrate Related Compound A RS are dry mixtures of an active component with suitable excipients to permit safe handling. For quantitative applications, calculate the concentration of the active component on the basis of the content stated on the label.]

USP Diluted Isosorbide Dinitrate RS

USP Diluted Isosorbide Mononitrate RS

USP Diluted Isosorbide Mononitrate Related Compound A RS

1,4:3,6-Dianhydro-D-glucitol 2-nitrate ▲in lactose.▲ (USP 1-May-2024)

$C_6H_9NO_6$ 191.14

▲ USP Potassium Nitrate RS▲ (USP 1-May-2024)

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

Topic/Question	Contact	Expert Committee
DILUTED ISOSORBIDE MONONITRATE	Documentary Standards Support	SM22020 Small Molecules 2

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
Pharmacopeial Forum: Volume No. 47(3)

Current DocID: GUID-DDF4D5F1-9D03-4568-8787-0C5829AFE919_5_en-US

DOI: https://doi.org/10.31003/USPNF_M43610_05_01

DOI ref: 3t6q4