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Isosorbide Dinitrate Extended-Release Tablets

DEFINITION
Isosorbide Dinitrate Extended-Release Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of isosorbide dinitrate ($C_6H_8N_2O_8$).

IDENTIFICATION

Change to read:

• ▲**A.** **Spectroscopic Identification Tests** ⟨197⟩, *Infrared Spectroscopy*▲ (USP 1-Aug-2023)

Sample solution: Transfer a suitable quantity of finely powdered Tablets to a glass-stoppered centrifuge tube. Add 10 mL of sodium hydroxide solution (1 in 250), shake to wet the powder, add 15 mL of hexane, and shake again. Centrifuge the mixture, and transfer the upper phase to a beaker. Evaporate the solvent, and dry the residue under vacuum over calcium chloride at room temperature for 16 h. Where separation of interferences is required, proceed as follows. Transfer a quantity of finely powdered Tablets, equivalent to 20 mg of isosorbide dinitrate, to a glass-stoppered centrifuge tube. Add 10 mL of sodium hydroxide solution (1 in 250), shake to wet the powder, add 15 mL of solvent hexane, and shake again. Centrifuge the mixture, and transfer the upper phase to a beaker. Place in a freezer, at a temperature of −14°, the beaker and a short-stem funnel fitted with a cotton plug that previously has been chloroform washed and dried. After 30 min, filter the solution while still in the freezer. Evaporate the solvent, and dry the residue in vacuum over calcium chloride for 16 h, dissolved in 0.4 mL of chloroform.

Standard solution: Prepare a solution with USP Diluted Isosorbide Dinitrate RS following a similar preparation as the *Sample solution*.

Acceptance criteria: The IR absorption spectrum of the *Sample solution* exhibits maxima only at the same wavelengths as that of the *Standard solution*. If separation of interference is required, the IR absorption spectrum of the *Sample solution* determined in a 0.1-mm cell shows all of the significant absorption bands present in the spectrum obtained for a similar preparation from the *Standard solution*. The major peaks are at 1650 cm^{-1}, 1284 cm^{-1} and 1275 cm^{-1} (a doublet), 1106 cm^{-1}, and 844 cm^{-1}.

Add the following:

▲• **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.▲ (USP 1-Aug-2023)

ASSAY

Change to read:

• **Procedure**

▲**Solution A:** Methanol and water (6:94)

Solution B: Methanol and water (50:50)

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	100	0
2.5	100	0
18	60	40
18.1	0	100
20.5	0	100
21	100	0
26	100	0

Diluent: Methanol and water (15:85)

Standard solution: 0.25 mg/mL of isosorbide dinitrate prepared as follows. Transfer a portion of USP Diluted Isosorbide Dinitrate RS equivalent to 25 mg of isosorbide dinitrate to a 100-mL volumetric flask. Add 10 mL of methanol and sonicate for NLT 5 min. Add *Diluent* to 60% of the flask volume and sonicate for NLT 15 min with occasional shaking until the solids are dissolved. Dilute with *Diluent* to volume.

Sample solution: Nominally 0.25 mg/mL of isosorbide dinitrate prepared as follows. Transfer a portion of finely powdered Tablets (NLT 20) equivalent to 50 mg of isosorbide dinitrate, to a 200-mL volumetric flask. Add 20 mL of methanol, shake immediately, and sonicate for about 5 min to avoid clumping. Add *Diluent* to 60% of the flask volume and sonicate for about 15 min with occasional shaking. Shake for another 30 min on a shaker and allow the solution to come to room temperature. Dilute with *Diluent* to volume. Centrifuge a portion of the solution and use the clear supernatant.

Chromatographic system

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

Mode: LC

Detector: UV 214 nm

Column: 4.6-mm × 5-cm; 5-µm packing L1

Column temperature: 30°

Flow rate: 2 mL/min

Injection volume: 75 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 1.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of isosorbide dinitrate ($C_6H_8N_2O_8$) in the portion of Tablets taken:

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

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

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

C_S = concentration of isosorbide dinitrate from USP Diluted Isosorbide Dinitrate RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of isosorbide dinitrate in the *Sample solution* (mg/mL)▲ (USP 1-Aug-2023)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

• **Dissolution ⟨711⟩**

Test 1

Medium: Water; 500 mL

Apparatus 2: 50 rpm

Time: 1, 2, 4, and 6 h

Solution A: 13.2 g/L of ammonium sulfate in water. Adjust with 1 N sulfuric acid to a pH of 3.0.

Mobile phase: Methanol and *Solution A* (50:50)

Standard solution: A known concentration of isosorbide dinitrate in *Medium* from USP Diluted Isosorbide Dinitrate RS

Sample solution: Pass a portion of the solution under test through a suitable filter.

Chromatographic system

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

Mode: LC

Column: 5-mm × 25-cm; packing L1

Flow rate: 1 mL/min

Injection volume: 20 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.5

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

▲Calculate the concentration (C_i) of isosorbide dinitrate ($C_6H_8N_2O_8$) in the sample withdrawn from the vessel at each time point (*i*):

$$Result_i = (r_U/r_S) \times C_S$$

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

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

C_S = concentration of isosorbide dinitrate from USP Diluted Isosorbide Dinitrate RS in the *Standard solution* (mg/mL)

Calculate the percentage of the labeled amount of isosorbide dinitrate ($C_6H_8N_2O_8$) dissolved at each time point (*i*):

$$Result_1 = C_1 \times V \times (1/L) \times 100$$

$$Result_2 = \{[C_2 \times (V - V_S)] + (C_1 \times V_S)\} \times (1/L) \times 100$$

$$Result_3 = (\{C_3 \times [V - (2 \times V_S)]\} + [(C_2 + C_1) \times V_S]) \times (1/L) \times 100$$

$$Result_4 = (\{C_4 \times [V - (3 \times V_S)]\} + [(C_3 + C_2 + C_1) \times V_S]) \times (1/L) \times 100$$

C_i = concentration of isosorbide dinitrate in the portion of sample withdrawn at the specified time point (mg/mL)

V = volume of *Medium*, 500 mL

L = label claim (mg/Tablet)

V_S = volume of the *Sample solution* withdrawn at each time point (*i*) (mL)

▲ (USP 1-Aug-2023)

Tolerances: See *Table 2*.

Table 2

Time Point (*i*)	Time (h)	Amount Dissolved (%)
1	1	15–30
2	2	50–70
3	4	65–85
4	6	NLT 75

The percentages of the labeled amount of isosorbide dinitrate ($C_6H_8N_2O_8$) dissolved at the times specified conform to *Dissolution ⟨711⟩, Acceptance Table 2*.

Test 2: If the product complies with this test, the labeling indicates that the product meets USP *Dissolution Test 2*.

Acid stage medium: pH 1.2 simulated gastric fluid (without pepsin); 900 mL

Buffer stage medium: pH 7.5 simulated intestinal fluid (without enzymes); 900 mL

Apparatus 2: 50 rpm, with helix sinkers

Times

Acid stage: 1 h

Buffer stage: 3, 6, and 12 h. The times in the *Buffer stage medium* include the time in the *Acid stage medium*.

Solution A: Dissolve 15.4 g of ammonium acetate in water, add 11.5 mL of glacial acetic acid, dilute with water to 1000 mL, and mix to obtain a solution having a pH of about 4.7.

Mobile phase: Mix 350 mL of water, 100 mL of *Solution A*, and 550 mL of methanol. Dilute with water to 1000 mL.

Standard solution: 40 µg/mL of isosorbide dinitrate in respective medium from USP Diluted Isosorbide Dinitrate RS

Sample solution: ▲Run the test with *Acid stage medium* for 1 h followed by collecting the *Acid stage medium* sample. Continue the test in *Buffer stage medium* by withdrawing samples at the time points specified in *Table 3*.▲ (USP 1-Aug-2023) Withdraw a 5-mL aliquot and pass a portion of the solution under test through a suitable filter of 10-µm pore size. Replace the aliquots withdrawn at the 3 and 6 h timepoints with equal volumes of *Buffer stage medium*.

Chromatographic system

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

Mode: LC

Detector: UV 220 nm

Column: 4-mm × 25-cm; packing L1

Flow rate: 1 mL/min

Injection volume: 20 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

▲Calculate the percentage of the labeled amount of isosorbide dinitrate ($C_6H_8N_2O_8$) dissolved in *Acid stage medium* at time point 1 h (Q_A):

$$\text{Result}_i = (r_U/r_S) \times C_S \times V_A \times (1/L) \times 100$$

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

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

C_S = concentration of isosorbide dinitrate from USP Diluted Isosorbide Dinitrate RS in the *Standard solution* (mg/mL)

V_A = volume of the *Acid stage medium*, 900 mL

L = label claim (mg/Tablet)

Calculate the concentration (C_i) of isosorbide dinitrate ($C_6H_8N_2O_8$) in the sample withdrawn at each *Buffer stage* time point (i):

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

r_U = peak response of isosorbide dinitrate from the *Sample solution* at each time point i

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

C_S = concentration of isosorbide dinitrate from USP Diluted Isosorbide Dinitrate RS in the *Standard solution* (mg/mL)

Calculate the percentage of the labeled amount of isosorbide dinitrate ($C_6H_8N_2O_8$) dissolved at each *Buffer stage* time point (i):

$$\text{Result}_1 = [C_1 \times V_B \times (1/L) \times 100] + Q_A$$

$$\text{Result}_2 = \{[(C_2 \times V_B) + (C_1 \times V_S)] \times (1/L) \times 100\} + Q_A$$

$$\text{Result}_3 = (\{(C_3 \times V_B) + [(C_2 + C_1) \times V_S]\} \times (1/L) \times 100) + Q_A$$

C_i = concentration of isosorbide dinitrate in the *Sample solution* withdrawn at the specified time point (i) (mg/mL)

V_B = volume of the *Buffer stage medium*, 900 mL

L = label claim (mg/Tablet)

Q_A = percentage of the labeled amount of isosorbide dinitrate dissolved in the *Acid stage medium*

V_S = volume of the *Sample solution* withdrawn at each time point (i), 5 mL

▲ (USP 1-Aug-2023)

Tolerances: See *Table 3*.

Table 3

Time Point (*i*)	Time (h)	Amount Dissolved (%)
1	1	5–25
2	3	30–50
3	6	50–80
4	12	NLT 75

The percentages of the labeled amount of isosorbide dinitrate ($C_6H_8N_2O_8$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

• **Uniformity of Dosage Units** ⟨905⟩**:** Meet the requirements

Add the following:

▲**IMPURITIES**

• **Organic Impurities**

Solution A, Solution B, Mobile phase, Diluent, and **Chromatographic system:** Proceed as directed in the *Assay*.

System suitability stock solution: 300 µg/mL of USP Diluted Isosorbide Mononitrate Related Compound A RS and USP Diluted Isosorbide Mononitrate RS prepared as follows. Transfer a portion of USP Diluted Isosorbide Mononitrate Related Compound A RS, equivalent to 30 mg of isosorbide mononitrate related compound A and USP Diluted Isosorbide Mononitrate RS, equivalent to 30 mg of isosorbide mononitrate to a 100-mL volumetric flask. Add 10 mL of methanol and sonicate for NLT 5 min. Add *Diluent* to 60% of the flask volume and sonicate for NLT 15 min with occasional shaking until the solids are dissolved. Dilute with *Diluent* to volume.

System suitability solution: 1.5 µg/mL of isosorbide mononitrate related compound A and isosorbide mononitrate in *Diluent* from *System suitability stock solution*

Standard stock solution: 300 µg/mL of isosorbide dinitrate prepared as follows. Transfer a portion of USP Diluted Isosorbide Dinitrate RS, equivalent to 30 mg of isosorbide dinitrate, to a 100-mL volumetric flask. Add 10 mL of methanol and sonicate for NLT 5 min. Add *Diluent* to 60% of the flask volume and sonicate for NLT 15 min with occasional shaking until the solids are dissolved. Dilute with *Diluent* to volume.

Standard solution: 1.5 µg/mL of isosorbide dinitrate in *Diluent* from *Standard stock solution*

Sensitivity solution: 0.75 µg/mL of isosorbide dinitrate in *Diluent* from *Standard stock solution*

Sample solution: Nominally 750 µg/mL of isosorbide dinitrate prepared as follows. Transfer a portion of finely powdered Tablets (NLT 20) equivalent to 75 mg of isosorbide dinitrate, to a 100-mL volumetric flask. Add 10 mL of methanol and sonicate for 5 min to avoid clumping. Add *Diluent* to 60% of the flask volume and sonicate for 20 min with occasional shaking. Shake for another 30 min on a shaker and allow the solution to come to room temperature. Dilute with *Diluent* to volume. Centrifuge a portion of the solution and use the clear supernatant.

System suitability

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

[Note—The relative retention times for isosorbide mononitrate related compound A and isosorbide mononitrate are about 0.7 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 2 between isosorbide mononitrate related compound A and isosorbide mononitrate, *System suitability solution*

Relative standard deviation: NMT 5.0%, *Standard solution*

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

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each degradation product in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

r_U = peak response of each degradation product from the *Sample solution*

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

C_S = concentration of isosorbide dinitrate from USP Diluted Isosorbide Dinitrate RS in the *Standard solution* (µg/mL)

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

F = relative response factor (see *Table 4*)

Acceptance criteria: See *Table 4*. The reporting threshold is 0.1%.

Table 4

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Isosorbide mononitrate related compound A	0.15	0.70	0.5
Isosorbide mononitrate	0.21	0.60	0.5
Isosorbide dinitrate	1.0	—	—
Any unspecified degradation	—		

product ▲(USP 1-Aug-2023)		1.0	0.2
Total degradation products	—	—	2.0

ADDITIONAL REQUIREMENTS

Change to read:

• **PACKAGING AND STORAGE:** Preserve in well-closed containers. ▲Store at controlled room temperature.▲ (USP 1-Aug-2023)

• **LABELING:** When more than one *Dissolution* test is given, the labeling indicates the *Dissolution* test used only if *Test 1* is not used.

Change to read:

• **USP REFERENCE STANDARDS** ⟨11⟩

▲[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 and suitable excipients to permit safe handling. For quantitative applications, calculate the concentration of the active component based on the content stated on the label.]▲ (USP 1-AUG-2023)

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.

$C_6H_9NO_6$ 191.14▲ (USP 1-Aug-2023)

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

Topic/Question	Contact	Expert Committee
ISOSORBIDE DINITRATE EXTENDED-RELEASE TABLETS	Documentary Standards Support	SM22020 Small Molecules 2

Chromatographic Database Information: Chromatographic Database

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