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Isosorbide Dinitrate Tablets

To view the Notice from the Expert Committee that posted in conjunction with this accelerated revision, please click https://www.uspnf.com/rb-isosorbide-dinitrate-tabs-20230526.

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

IDENTIFICATION

• **A.**

Sample: 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 again shake. 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.

Acceptance criteria: The IR absorption spectrum of a suitable solution in chloroform of the *Sample* exhibits maxima only at the same wavelengths as that of a similar preparation from the residue obtained from USP Diluted Isosorbide Dinitrate RS.

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

ASSAY

• **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
18.0	60	40
18.1	0	100
20.5	0	100
21.0	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 suitable portion of USP Diluted Isosorbide Dinitrate RS, equivalent to an appropriate amount of isosorbide dinitrate, to a suitable volumetric flask. Add methanol to 10% of the flask volume and sonicate. Dilute with *Diluent* to 60% of the flask volume, and sonicate with occasional shaking until the solids are dissolved. Cool to room temperature and dilute with *Diluent* to volume.

Sample solution: Nominally 0.25 mg/mL of isosorbide dinitrate prepared as follows. Transfer a suitable portion of finely powdered Tablets (NLT 10), equivalent to 50 mg of isosorbide dinitrate, to a 200-mL volumetric flask. Add 10 mL of methanol and sonicate. Dilute with *Diluent* to 60% of the flask volume and sonicate with occasional shaking until solids are dissolved. Cool to room temperature and dilute with *Diluent* to volume. Pass the solution through a suitable filter of 0.45-µm pore size and use the filtrate.

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: 3 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)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

• **Dissolution** ⟨711⟩

▲**Test 1**▲ (RB 1-Jun-2023)

Medium: Water; 1000 mL

Apparatus 2: 75 rpm

Time: 45 min

Mobile phase: Methanol and pH 3.0, 0.1 M ammonium sulfate (1:1). [Note—Make adjustments, if necessary (see *Chromatography* ⟨621⟩, *System Suitability*), using sulfuric acid for any necessary pH adjustment.]

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

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

Chromatographic system

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

Mode: LC

Detector: UV 220 nm

Column: 4.6-mm × 5-cm; packing L1

Flow rate: 1.0 mL/min

Injection volume: 20 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.5

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.

Tolerances: NLT 70% (*Q*) of the labeled amount of isosorbide dinitrate ($C_6H_8N_2O_8$) is dissolved.

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

Medium: 0.1 N hydrochloric acid; 1000 mL

Apparatus 2: 75 rpm

Time: 20 min

Buffer: 13.2 g/L ammonium sulfate in water prepared as follows. Dissolve 13.2 g of ammonium sulfate in 900 mL of water, adjust with sulfuric acid to a pH of 3.0, and dilute with water to 1000 mL.

Mobile phase: Methanol and *Buffer* (40:60)

Standard stock solution: 0.1 mg/mL of isosorbide dinitrate from USP Diluted Isosorbide Dinitrate RS prepared as follows. Transfer an appropriate quantity of USP Diluted Isosorbide Dinitrate RS, equivalent to an appropriate amount of isosorbide dinitrate, to a suitable

volumetric flask. Add separately methanol and *Medium*, each to 10% of the final flask volume. Sonicate to dissolve. Dilute with *Medium* to volume.

Standard solution: (*L*/1000) mg/mL of isosorbide dinitrate from USP Diluted Isosorbide Dinitrate RS from the *Standard stock solution* in *Medium*, where *L* is the label claim in mg/Tablet

Sample solutions: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size, discarding the first 4 mL of filtrate.

Chromatographic system

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

Mode: LC

Detector: UV 220 nm

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

Column temperature: 30°

Flow rate: 1 mL/min

Injection volume: 20 µL

Run time: NLT 2.3 times the retention time of isosorbide dinitrate

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.5

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:

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

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 = volume of *Medium*, 1000 mL

L = label claim (mg/Tablet)

Tolerances: NLT 80% (*Q*) of the labeled amount of isosorbide dinitrate ($C_6H_8N_2O_8$) is dissolved.

Test 3: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 3*.

Medium: 0.1 N hydrochloric acid; 500 mL

Apparatus 2: 75 rpm

Time: 15 min

Mobile phase: Methanol and water (20:80)

Standard stock solution: 0.2 mg/mL isosorbide dinitrate from USP Diluted Isosorbide Dinitrate RS in *Medium* prepared as follows. Transfer an appropriate quantity of USP Diluted Isosorbide Dinitrate RS, equivalent to an appropriate amount of isosorbide dinitrate, to a suitable volumetric flask. Add *Medium* to 70% of the final flask volume. Sonicate with intermittent shaking to dissolve. Cool to room temperature. Dilute with *Medium* to volume.

Standard solution: (*L*/500) mg/mL of isosorbide dinitrate from USP Diluted Isosorbide Dinitrate RS from the *Standard stock solution* in *Medium*, where *L* is the label claim in mg/Tablet.

Sample solutions: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size, discarding the first 3 mL of filtrate.

Chromatographic system

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

Mode: LC

Detector: UV 220 nm

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

Flow rate: 1.2 mL/min

Injection volume: 20 µL

Run time: NLT 1.8 times the retention time of isosorbide dinitrate

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.5

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:

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

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 = volume of *Medium*, 500 mL

L = label claim (mg/Tablet)

Tolerances: NLT 80% (Q) of the labeled amount of isosorbide dinitrate ($C_6H_8N_2O_8$) is dissolved.▲ (RB 1-Jun-2023)

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

IMPURITIES

• **Organic Impurities**

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

Standard stock solution: 0.3 mg/mL of isosorbide dinitrate prepared as follows. Transfer a suitable portion of USP Diluted Isosorbide Dinitrate RS, equivalent to an appropriate amount of isosorbide dinitrate, to a suitable volumetric flask. Add methanol to 10% of the flask volume and sonicate. Dilute with *Diluent* to 60% of the flask volume and sonicate with occasional shaking until the solids are dissolved. Cool to room temperature and dilute with *Diluent* to volume.

Standard solution: 7.5 µg/mL of isosorbide dinitrate in *Diluent* from *Standard stock solution*

Sensitivity solution: 0.375 µg/mL of isosorbide dinitrate in *Diluent* from *Standard solution*

Sample solution: Nominally 750 µg/mL of isosorbide dinitrate prepared as follows. Transfer a suitable 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. Dilute with *Diluent* to 60% of the flask volume and sonicate with occasional shaking. Cool to room temperature and dilute with *Diluent* to volume. Pass the solution through a suitable filter of 0.45-µm pore size and use the filtrate.

System suitability

Samples: *Standard solution* and *Sensitivity solution*

[Note—See *Table 2* for relative retention times.]

Suitability requirements

Relative standard deviation: NMT 2.0%, *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 2*)

Acceptance criteria: See *Table 2*. The reporting threshold is 0.1%.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Isosorbide mononitrate related compound A[a]	0.15	0.61	0.2
Isosorbide mononitrate[b]	0.21	0.61	0.2
Isosorbide dinitrate	1.0	—	—

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Any unspecified degradation product	—	1.0	0.2
Total degradation products	—	—	2.0

[a] 1,4:3,6-Dianhydro-D-glucitol 2-nitrate.

[b] 1,4:3,6-Dianhydro-D-glucitol 5-nitrate.

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in well-closed containers. Store at controlled room temperature.

Add the following:

▲• **Labeling:** When more than one *Dissolution* test is given, the labeling states the test used only if *Test 1* is not used.▲ (RB 1-Jun-2023)

• **USP Reference Standards** ⟨11⟩

USP Diluted Isosorbide Dinitrate RS

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

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

Chromatographic Database Information: Chromatographic Database

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