

Isosorbide Dinitrate Tablets

Type of Posting	Notice of Intent to Revise
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Targeted Official Date	To Be Determined, Revision Bulletin
Expert Committee	Chemical Medicines Monographs 2

In accordance with section 7.04 (c) of the 2015–2020 Rules and Procedures of the Council of Experts and the [Pending Monograph Guideline](#), this is to provide notice that the Chemical Medicines Monographs 2 Expert Committee intends to revise the Isosorbide Dinitrate Tablets monograph.

Based on the supporting data received from a manufacturer awaiting FDA approval, the Expert Committee proposes to add *Test 2* in the *Dissolution* section of the monograph. A *Labeling* section has also been added.

- The analytical procedure in *Dissolution Test 2* was validated using the Supelcosil LC-18 brand of L1 column from Supelco. The typical retention time of the isosorbide dinitrate peak is 2 min.

The proposed revision is contingent on FDA approval of a product that meets the proposed monograph specifications. The proposed revision will be published as a Revision Bulletin and an official date will be assigned to coincide as closely as possible with the FDA approval of the associated product.

See below for additional information about the proposed text.¹

Should you have any questions, please contact Josan Thomas, Scientific Liaison (+91-40-44488948 or josan.thomas@usp.org).

¹ This text is not the official version of a *USP–NF* monograph and may not reflect the full and accurate contents of the currently official monograph. Please refer to the current edition of the *USP–NF* for official text.

USP provides this text to indicate changes that we anticipate will be made official once the product subject to this proposed revision under the Pending Monograph Program receives FDA approval. Once FDA approval is granted for the associated revision request, a Revision Bulletin will be posted that will include the changes indicated herein, as well as any changes indicated in the product's final approval, combined with the text of the monograph as effective on the date of approval. Any revisions made to a monograph under the Pending Monograph Program that are posted without prior publication for comment in the *Pharmacopeial Forum* must also meet the requirements outlined in the [USP Guideline on Use of Accelerated Processes for Revisions to the USP–NF](#).

Isosorbide Dinitrate Tablets

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- μ m pore size and use the filtrate.

Chromatographic system

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

Mode: LC

Detector: UV 214 nm

Column: 4.6-mm \times 5-cm; 5- μ m packing L1

Column temperature: 30°

Flow rate: 3 mL/min

Injection volume: 75 μ L

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▲ (TBD)

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 \times 5-cm; packing L1

Flow rate: 1.0 mL/min

Injection volume: 20 μ L

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: 60 min

Buffer: 13.2 g/L ammonium sulfate solution prepared as follows. Dissolve 13.2 g of ammonium sulfate with 90% of the total volume of water, adjust with sulfuric acid to a pH of 3.0, dilute with water to volume, and mix well.

Mobile phase: Methanol and Buffer (40:60)

Standard stock solution: 0.4 mg/mL of USP Diluted Isosorbide Dinitrate RS prepared as follows. Transfer an appropriate quantity of USP Diluted Isosorbide Dinitrate RS to a suitable volumetric flask. Add 10% of methanol and 10% of Medium of the final flask volume. Sonicate to dissolve. Dilute with Medium to volume and mix well.

Standard solution: 0.16 mg/mL of USP Diluted Isosorbide Dinitrate RS in Medium from Standard stock solution

Sample solutions: Pass a portion of the solution under test through a PVDF filter of 0.45- μ m pore size, discarding the first 4 mL.

Chromatographic system

(See Chromatography <621>, System Suitability.)

Mode: LC

Detector: UV 220 nm

Column: 4.6-mm \times 5-cm; 5- μ m packing L1

Column temperature: 30°

Flow rate: 1 mL/min

Injection volume: 20 μ L

Run time: NLT 2.5 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 USP Diluted Isosorbide Dinitrate RS (mg/mL)

V = volume of Medium, 1000 mL

L = label claim (mg/Tablet)

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

- **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 μ g/mL of isosorbide dinitrate in Diluent from Standard stock solution

Sensitivity solution: 0.375 μ g/mL of isosorbide dinitrate in Diluent from Standard solution

Sample solution: Nominally 750 μ g/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- μ m 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 (μ g/mL)

C_U = nominal concentration of isosorbide dinitrate in the Sample solution (μ g/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	—	—
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.▲ (TBD)

- **USP REFERENCE STANDARDS** <11>
USP Diluted Isosorbide Dinitrate RS