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# Isosorbide Mononitrate Extended-Release Tablets

## DEFINITION

Isosorbide Mononitrate Extended-Release Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of isosorbide mononitrate ($C_6H_9NO_6$).

## IDENTIFICATION

***Change to read:***

• **A. Thin-Layer Chromatographic Identification Test ⟨201⟩**

**Standard solution:** 0.5 mg/mL of isosorbide mononitrate ▲in absolute alcohol▲ (USP 1-Dec-2024) from USP Diluted Isosorbide Mononitrate RS▲▲ (USP 1-Dec-2024)

**Sample stock solution:** ▲Nominally 2.4 mg/mL of isosorbide mononitrate prepared as follows. Finely powder NLT 20 Tablets and transfer a suitable portion of the powder to a suitable container. Add a suitable volume of absolute alcohol, sonicate for 10 min, and centrifuge. Use the supernatant.▲ (USP 1-Dec-2024)

**Sample solution:** Nominally 0.48 mg/mL of isosorbide mononitrate in absolute alcohol, from ▲*Sample stock solution*▲ (USP 1-Dec-2024)

**Chromatographic system**

▲**Adsorbent:** 0.25-mm layer of chromatographic silica gel mixture▲ (USP 1-Dec-2024)

**Application volume:** 20 µL

**Developing solvent system:** Chloroform and methanol (95:5)

**Spray reagent:** Dissolve 1 g of soluble starch in 100 mL of boiling water. Cool, and add 0.5 g of potassium iodide.

**Analysis**

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

Examine the plate under short-wave UV light, marking any observed spots. Visualize nitrates on the plate by spraying with *Spray reagent* and illuminating with short-wave UV light for 10 min.

**Acceptance criteria:** Isosorbide mononitrate and other nitrates appear as a violet spot on a white-to-light-violet background.

***Change to read:***

• **B.** The retention time of the major peak of the *Sample solution* corresponds to that of *Standard solution* ▲*B*,▲ (USP 1-Dec-2024) as obtained in the *Assay*.

## ASSAY

***Change to read:***

• **Procedure**

**Mobile phase:** Methanol and water▲(20:80)▲ (USP 1-Dec-2024)

**Standard solution A:** 0.15 mg/mL of isosorbide mononitrate related compound A ▲in water,▲ (USP 1-Dec-2024) from USP Diluted Isosorbide Mononitrate Related Compound A RS▲▲ (USP 1-Dec-2024)

**Standard solution B:** ▲0.12 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 methanol to 20% of the final volume, and dilute with water to volume.▲ (USP 1-Dec-2024)

**System suitability solution:** ▲▲ (USP 1-Dec-2024) 0.12 mg/mL of isosorbide mononitrate and 6 µg/mL of isosorbide mononitrate related compound A 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 suitable amount of *Standard solution A*, add methanol to 20% of the final volume,▲ (USP 1-Dec-2024) and dilute with water to volume.

▲**Sample stock solution:** Nominally 0.6 mg/mL of isosorbide mononitrate prepared as follows. Finely powder NLT 20 Tablets and transfer a suitable portion of the powder to a suitable volumetric flask. Add methanol to 50% of the final volume, and sonicate for about 30 min with cooling. Warm to ambient temperature, and dilute with methanol to volume. Centrifuge a portion of the solution and use the clear supernatant.▲ (USP 1-Dec-2024)

**Sample solution:** ▲Nominally 0.12 mg/mL of isosorbide mononitrate prepared as follows. Dilute the *Sample stock solution* with water and pass a portion of the solution through a suitable filter of 0.45-µm pore size.▲ (USP 1-Dec-2024)

**Chromatographic system**

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

**Mode:** LC

**Detector:** UV 220 nm

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

**Flow rate:** 1.5 mL/min

**Injection volume:** 20 µL

▲**Run time:** NLT 2 times the retention time of isosorbide mononitrate▲ (USP 1-Dec-2024)

**System suitability**

**Samples:** *Standard solution B* 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-DEC-2024)

**Suitability requirements**

**Resolution:** NLT 1.5 between isosorbide mononitrate related compound A and isosorbide mononitrate, *System suitability solution*

**Tailing factor:** NMT 1.5, *Standard solution B*

**Relative standard deviation:** NMT ▲1.0%,▲ (USP 1-Dec-2024) *Standard solution B*

**Analysis**

**Samples:** *Standard solution B* and *Sample solution*

Calculate the percentage of the labeled amount of isosorbide mononitrate ($C_6H_9NO_6$) 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 mononitrate from the *Sample solution*

$r_S$ = peak response of isosorbide mononitrate from *Standard solution B*

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

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

**Acceptance criteria:** 90.0%–110.0%

**PERFORMANCE TESTS**

***Change to read:***

• **DISSOLUTION ⟨711⟩**

**Test 1**

**Medium:** Water; 900 mL

**Apparatus 2:** 50 rpm; Tablets are placed in a metal helix prepared by winding 10 in of a 0.8-mm stainless steel wire around a 9/32-in shaft and pulling the coils to form a helix 1 in long.

**Times:** 1, 2, 4, 8, and 12 h

**Mobile phase:** Methanol and water▲(30:70)▲ (USP 1-Dec-2024)

**Standard solution:** (*L*/1000) ▲mg/mL of isosorbide mononitrate from▲ (USP 1-Dec-2024) USP Diluted Isosorbide Mononitrate RS in *Medium*, where *L* is the label claim in mg/Tablet

**Sample solution:** ▲Pass a portion of the solution under test▲ (USP 1-Dec-2024) through a suitable nylon filter of 0.45-µm pore size, discarding the first 4–6 mL of the filtrate.

**Chromatographic system**

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

**Mode:** LC

**Detector:** UV 220 nm

**Column:** 4.6-mm × 25-cm; ▲5-µm▲ (USP 1-Dec-2024) packing L1

**Flow rate:** 1 mL/min

**Injection volume:** 25 µL

▲**Run time:** NLT 1.8 times the retention time of isosorbide mononitrate▲ (USP 1-Dec-2024)

**System suitability**

**Sample:** *Standard solution*

**Suitability requirements**

**Relative standard deviation:** NMT 1.5%

**Analysis**

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

▲Calculate the concentration ($C_i$) of isosorbide mononitrate ($C_6H_9NO_6$) in the sample withdrawn from the vessel at each time point (*i*):

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

$r_U$ = peak response of isosorbide mononitrate 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)

Calculate the percentage of the labeled amounts of isosorbide mononitrate ($C_6H_9NO_6$) dissolved at each time point (*i*):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$

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

$$\text{Result}_3 = (\{C_3 \times [V - (2 \times V_S)]\} + [(C_2 + C_1) \times V_S]) \times (1/L) \times 100$$

$$\text{Result}_4 = (\{C_4 \times [V - (3 \times V_S)]\} + [(C_3 + C_2 + C_1) \times V_S]) \times (1/L) \times 100$$

$$\text{Result}_5 = (\{C_5 \times [V - (4 \times V_S)]\} + [(C_4 + C_3 + C_2 + C_1) \times V_S]) \times (1/L) \times 100$$

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

$V$ = volume of *Medium*, 900 mL

$L$ = label claim (mg/Tablet)

$V_S$ = volume of *Sample solution* withdrawn at each time point (mL)▲ (USP 1-Dec-2024)

**Tolerances:** See *Table 1*.

**Table 1**

| ▲Time Point (*i*)▲ (USP 1-Dec-2024) | Time (h) | Amount Dissolved (%) |
|---|---|---|
| ▲1▲ (USP 1-Dec-2024) | 1 | 15–35 |
| ▲2▲ (USP 1-Dec-2024) | 2 | 28–48 |
| ▲3▲ (USP 1-Dec-2024) | 4 | 43–68 |
| ▲4▲ (USP 1-Dec-2024) | 8 | 65–90 |
| ▲5▲ (USP 1-Dec-2024) | 12 | NLT 80 |

The percentages of the labeled amount of isosorbide mononitrate ($C_6H_9NO_6$) 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*.

**Medium:** Simulated gastric fluid (without enzymes); 500 mL

**Apparatus 2:** 50 rpm

**Times:** 1, 2, 6, and 12 h

**Mobile phase:** Methanol and water▲(40:60)▲ (USP 1-Dec-2024)

**Standard stock solution:** 1.2 mg/mL of isosorbide mononitrate from USP Diluted Isosorbide Mononitrate RS▲ (USP 1-Dec-2024) in *Medium*

**Standard solution**

**For Tablets labeled to contain 30 mg:** 60 µg/mL of isosorbide mononitrate in *Medium*, from the *Standard stock solution*

**For Tablets labeled to contain 60 mg:** 120 µg/mL of isosorbide mononitrate in *Medium*, from the *Standard stock solution*

**Sample solution:** Pass ▲a portion▲ (USP 1-Dec-2024) of the solution under test through a suitable filter of 0.45-µm pore size.

**Chromatographic system**

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

**Mode:** LC

**Detector:** UV 220 nm

**Column:** 4.6-mm × 25-cm; 10-µm packing L1

**Flow rate:** 1 mL/min

**Injection volume:** 20 µL

▲**Run time:** NLT 1.6 times the retention time of isosorbide mononitrate▲ (USP 1-Dec-2024)

**System suitability**

**Sample:** *Standard solution*

**Suitability requirements**

**Relative standard deviation:** NMT 2.0%

**Analysis**

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

Calculate the concentration ($C_i$) ▲▲ (USP 1-Dec-2024) of isosorbide mononitrate ▲($C_6H_9NO_6$) in the sample withdrawn from the vessel▲ (USP 1-Dec-2024) at each time point (*i*):

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

$r_U$▲ (USP 1-Dec-2024) = peak response of isosorbide mononitrate from the *Sample solution*▲▲ (USP 1-Dec-2024)

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

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

Calculate the percentage of the labeled amount of isosorbide mononitrate ($C_6H_9NO_6$) dissolved at each time point (*i*):

$$▲\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$

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

$$\text{Result}_3 = (\{C_3 \times [V - (2 \times V_S)]\} + [(C_2 + C_1) \times V_S]) \times (1/L) \times 100$$

$$\text{Result}_4 = (\{C_4 \times [V - (3 \times V_S)]\} + [(C_3 + C_2 + C_1) \times V_S]) \times (1/L) \times 100$$

$C_i$ = concentration of isosorbide mononitrate 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 *Sample solution* withdrawn at each time point (mL)▲ (USP 1-Dec-2024)

**Tolerances:** See *Table 2*.

**Table 2**

| ▲Time Point (*i*)▲ (USP 1-Dec-2024) | Time (h) | Amount Dissolved (%) |
|---|---|---|
| ▲1▲ (USP 1-Dec-2024) | 1 | 25–45 |
| ▲2▲ (USP 1-Dec-2024) | 2 | 35–60 |
| ▲3▲ (USP 1-Dec-2024) | 6 | 65–90 |
| ▲4▲ (USP 1-Dec-2024) | 12 | NLT 80 |

The percentages of the labeled amount of isosorbide mononitrate ($C_6H_9NO_6$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

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

**Medium:** Simulated gastric fluid (without enzymes); 500 mL

**Apparatus 2:** 50 rpm

**Times:** 1, 2, 6, and 12 h

**Buffer:** Transfer 15.4 g of ammonium acetate and 11.5 mL of ▲glacial acetic acid▲ (USP 1-Dec-2024) to a 1-L volumetric flask containing 500 mL of water. Adjust with ▲glacial acetic acid▲ (USP 1-Dec-2024) to a pH of 4.7, and dilute with water to volume.

**Mobile phase:** Methanol, *Buffer*, and water▲(30:10:60)▲ (USP 1-Dec-2024)

**Standard stock solution:** 0.12 mg/mL of isosorbide mononitrate from USP Diluted Isosorbide Mononitrate RS in *Medium*

**Standard solution**

**For Tablets labeled to contain 30 mg:** 0.06 mg/mL of isosorbide mononitrate in *Medium*, from the *Standard stock solution*

**For Tablets labeled to contain 60 mg:** Use the *Standard stock solution* with no further dilution.

**Sample solution:** Pass ▲a portion▲ (USP 1-Dec-2024) of the solution under test through a suitable filter of 0.45-µm pore size.

**Chromatographic system**

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

**Mode:** LC

**Detector:** UV 220 nm

**Column:** 4.6-mm × 15-cm; 5-µm packing L1

**Flow rate:** 1 mL/min

**Injection volume:** 100 µL

▲**Run time:** NLT 1.8 times the retention time of isosorbide mononitrate▲ (USP 1-Dec-2024)

**System suitability**

**Sample:** *Standard solution*

**Suitability requirements**

**Relative standard deviation:** NMT 2.0%

**Analysis**

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

Calculate the concentration ($C_i$) ▲▲ (USP 1-Dec-2024) of isosorbide mononitrate ▲($C_6H_9NO_6$) in the sample withdrawn from the vessel▲ (USP 1-Dec-2024) at each time point ($i$):

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

$r_U$▲ (USP 1-Dec-2024) = peak response of isosorbide mononitrate from the *Sample solution*▲▲ (USP 1-Dec-2024)

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

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

Calculate the percentage of the labeled amount of isosorbide mononitrate ($C_6H_9NO_6$) dissolved at each time point ($i$):

$$▲\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$

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

$$\text{Result}_3 = (\{C_3 \times [V - (2 \times V_S)]\} + [(C_2 + C_1) \times V_S]) \times (1/L) \times 100$$

$$\text{Result}_4 = (\{C_4 \times [V - (3 \times V_S)]\} + [(C_3 + C_2 + C_1) \times V_S]) \times (1/L) \times 100$$

$C_i$ = concentration of isosorbide mononitrate 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 *Sample solution* withdrawn at each time point (mL)▲ (USP 1-Dec-2024)

**Tolerances:** See *Table 3*.

**Table 3**

| ▲Time Point ($i$)▲ (USP 1-Dec-2024) | Time (h) | Amount Dissolved (%) |
|---|---|---|
| ▲1▲ (USP 1-Dec-2024) | 1 | 20–40 |

| ▲Time Point (*i*)▲ (USP 1-Dec-2024) | Time (h) | Amount Dissolved (%) |
|---|---|---|
| ▲2▲ (USP 1-Dec-2024) | 2 | 30–50 |
| ▲3▲ (USP 1-Dec-2024) | 6 | 70–90 |
| ▲4▲ (USP 1-Dec-2024) | 12 | NLT 85 |

The percentages of the labeled amount of isosorbide mononitrate dissolved at the times specified conform to *Dissolution* ⟨711⟩ , *Acceptance Table 2*.

**Test 4:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 4*.

**Medium:** 0.2% sodium chloride in 0.1 N hydrochloric acid; 500 mL

**Apparatus 2:** 50 rpm; sinker baskets (see *Dissolution ⟨711⟩, Figure 2a*)

**Times:** 1, 2, 6, and 12 h

**Mobile phase:** Methanol and water▲(18:82)▲ (USP 1-Dec-2024)

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

**Sample solution:** Pass ▲a portion▲ (USP 1-Dec-2024) 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 × 15-cm; 5-µm packing L1

**Column temperature:** 30°

**Flow rate:** 1 mL/min

**Injection volume:** 20 µL

▲**Run time:** NLT 2 times the retention time of isosorbide mononitrate▲ (USP 1-Dec-2024)

**System suitability**

**Sample:** *Standard solution*

**Suitability requirements**

**Relative standard deviation:** NMT 2.0%

**Analysis**

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

Calculate the concentration ($C_i$) of isosorbide mononitrate ($C_6H_9NO_6$) in the sample withdrawn from the vessel at each time point (*i*):

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

$r_i$ = peak response of isosorbide mononitrate from the *Sample solution* at the specified time point

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

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

Calculate the percentage of the labeled amount of isosorbide mononitrate ($C_6H_9NO_6$) dissolved at each time point (*i*):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$

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

$$\text{Result}_3 = (\{C_3 \times [V - (2 \times V_S)]\} + [(C_2 + C_1) \times V_S]) \times (1/L) \times 100$$

$$\text{Result}_4 = (\{C_4 \times [V - (3 \times V_S)]\} + [(C_3 + C_2 + C_1) \times V_S]) \times (1/L) \times 100$$

$C_i$ = concentration of isosorbide mononitrate 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 *Sample solution* withdrawn from the *Medium* (mL)

**Tolerances:** See *Table 4*.

**Table 4**

| Time Point (*i*) | Time (h) | Amount Dissolved (%) |
|---|---|---|
| 1 | 1 | 20–40 |
| 2 | 2 | 30–55 |
| 3 | 6 | 60–90 |
| 4 | 12 | NLT 85 |

The percentages of the labeled amount of isosorbide mononitrate dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

**Test 5:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 5*.

**Medium:** 0.1 N hydrochloric acid; 900 mL

**Apparatus 2:** 50 rpm; helix sinkers

**Times**

**For 60 mg and 60 mg half-Tablets:** 1, 2, 4, 6, and 10 h

**For 30 mg Tablets:** 1, 2, 4, and 10 h

**Mobile phase:** Methanol and water (15:85)

**System suitability solution**

**For 60 mg Tablets:** 0.033 mg/mL of isosorbide mononitrate from USP Diluted Isosorbide Mononitrate RS in *Medium* prepared as follows. Transfer a quantity of USP Diluted Isosorbide Mononitrate RS to an appropriate volumetric flask and add 60% of the flask volume of *Medium*. Shake for 30 min, sonicate for 5 min, and dilute with *Medium* to volume.

**For 30 mg and 60 mg half-Tablets:** 0.017 mg/mL of isosorbide mononitrate from USP Diluted Isosorbide Mononitrate RS in *Medium* prepared as follows. Transfer a quantity of USP Diluted Isosorbide Mononitrate RS to an appropriate volumetric flask and add 60% of the flask volume of *Medium*. Shake for 30 min, sonicate for 5 min, and dilute with *Medium* to volume.

**Standard solution:**

**For 60 mg Tablets:** 0.067 mg/mL of isosorbide mononitrate from USP Diluted Isosorbide Mononitrate RS in *Medium* prepared as follows. Transfer a quantity of USP Diluted Isosorbide Mononitrate RS to an appropriate volumetric flask and add 60% of the flask volume of *Medium*. Shake for 30 min, sonicate for 5 min, and dilute with *Medium* to volume.

**For 30 mg and 60 mg half-Tablets:** 0.033 mg/mL of isosorbide mononitrate from USP Diluted Isosorbide Mononitrate RS in *Medium* prepared as follows. Transfer a quantity of USP Diluted Isosorbide Mononitrate RS to an appropriate volumetric flask and add 60% of the flask volume of *Medium*. Shake for 30 min, sonicate for 5 min, and dilute with *Medium* to volume.

**Sample solution:** At the times specified, pass a portion of the solution under test through a suitable filter. Replace the portion removed with an equal volume of fresh *Medium* at 37°.

**Chromatographic system**

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

**Mode:** LC

**Detector:** UV 230 nm

**Column:** 4-mm × 12.5-cm; 5-µm packing L1

**Flow rate:** 1 mL/min

**Injection volume:** 50 µL

▲**Run time:** NLT 1.5 times the retention time of isosorbide mononitrate▲ (USP 1-Dec-2024)

**System suitability**

**Sample:** *System suitability solution*

**Suitability requirements**

**Tailing factor:** NMT 1.5

**Relative standard deviation:** NMT 2.0%

**Analysis**

**For 60 mg Tablets and 60 mg half-Tablets:**

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

Calculate the concentration ($C_i$) of isosorbide mononitrate ($C_6H_9NO_6$) in the sample withdrawn from the vessel at each time point (*i*):

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

$r_i$ = peak response of isosorbide mononitrate from the *Sample solution* at the specified time point

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

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

Calculate the percentage of the labeled amounts of isosorbide mononitrate ($C_6H_9NO_6$) dissolved at each time point (*i*):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$

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

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

$$\text{Result}_4 = \{(C_4 \times V) + [(C_3 + C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

$$\text{Result}_5 = \{(C_5 \times V) + [(C_4 + C_3 + C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

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

$V$ = volume of *Medium*, 900 mL

$L$ = label claim (mg/Tablet) or label claim (mg/half-Tablet)

$V_S$ = volume of the *Sample solution* withdrawn at each time point and replaced with*Medium* (mL)

**For 30 mg Tablets:**

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

Calculate the concentration ($C_i$) of isosorbide mononitrate ($C_6H_9NO_6$) in the sample withdrawn from the vessel at time point *i*:

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

$r_i$ = peak response of isosorbide mononitrate from the *Sample solution* at time point *i*

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

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

Calculate the percentage of the labeled amounts of isosorbide mononitrate ($C_6H_9NO_6$) dissolved at each time point (*i*):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$

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

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

$$\text{Result}_4 = \{(C_4 \times V) + [(C_3 + C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

$C_i$ = concentration of isosorbide mononitrate in the portion of sample withdrawn at time point *i* (mg/mL)

$V$ = volume of *Medium*, 900 mL

$L$ = label claim (mg/Tablet)

$V_S$ = volume of the *Sample solution* withdrawn at each time point and replaced with *Medium* (mL)

**Tolerances:** See *Table 5* and *Table 6*.

**Table 5**

| Time Point (*i*) | Time (h) | Amount Dissolved (for 60 mg Tablets) (%) | Amount Dissolved (for 60 mg half-Tablets) (%) |
|---|---|---|---|
| 1 | 1 | 20–40 | 30–50 |
| 2 | 2 | 30–50 | 45–65 |
| 3 | 4 | 50–70 | 65–85 |

| Time Point (*i*) | Time (h) | Amount Dissolved (for 60 mg Tablets) (%) | Amount Dissolved (for 60 mg half-Tablets) (%) |
|---|---|---|---|
| 4 | 6 | 65–85 | 75–95 |
| 5 | 10 | NLT 80 | NLT 80 |

**Table 6**

| Time Point (*i*) | Time (h) | Amount Dissolved (for 30 mg Tablets) (%) |
|---|---|---|
| 1 | 1 | 25–45 |
| 2 | 2 | 40–60 |
| 3 | 4 | 65–85 |
| 4 | 10 | NLT 80 |

The percentages of the labeled amount of isosorbide mononitrate dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

**Test 6:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 6*.

**Medium, Apparatus 2, Times, Mobile phase, Standard solution,** ▲▲ (USP 1-Dec-2024) and **System suitability:** Proceed as directed in *Test 1*.

▲**Sample solution:** Pass a portion of the solution under test through a suitable filter. Replace the amount of solution withdrawn at each time point with the same volume of *Medium*.▲ (USP 1-Dec-2024)

**Chromatographic system:** Proceed as directed in *Test 1* except for the *Injection volume*.

**Injection volume:** 50 µL

**Analysis**

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

Calculate the concentration ($C_i$) of isosorbide mononitrate ($C_6H_9NO_6$) in the sample withdrawn from the vessel at each time point (*i*):

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

$r_i$ = peak response of isosorbide mononitrate from the *Sample solution* at the specified time point

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

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

Calculate the percentage of the labeled amounts of isosorbide mononitrate ($C_6H_9NO_6$) dissolved at each time point (*i*):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$

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

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

$$\text{Result}_4 = \{(C_4 \times V) + [(C_3 + C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

$$\text{Result}_5 = \{(C_5 \times V) + [(C_4 + C_3 + C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

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

$V$ = volume of *Medium*, 900 mL

$L$ = label claim (mg/Tablet)

$V_S$ = volume of the *Sample solution* withdrawn ▲at each time point and replaced with▲ (USP 1-Dec-2024) *Medium* (mL)

**Tolerances:** See *Table 7*.

**Table 7**

| Time Point (*i*) | Time (h) | Amount Dissolved (%) |
|---|---|---|
| 1 | 1 | 15–35 |
| 2 | 2 | 30–50 |
| 3 | 4 | 50–70 |
| 4 | 8 | 75–95 |
| 5 | 12 | NLT 80 |

The percentages of the labeled amount of isosorbide mononitrate dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

**Test 7:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 7*.

**Medium, Apparatus 2, Mobile phase,** and **Chromatographic system:** Proceed as directed in *Test 5*.

**Times:** 1, 4, 8, and 12 h

**Standard solution 1:** 0.133 mg/mL of isosorbide mononitrate ▲▲ (USP 1-Dec-2024) in *Medium*

▲prepared as follows. Transfer an appropriate amount of USP Diluted Isosorbide Mononitrate RS to a suitable volumetric flask,▲ (USP 1-Dec-2024) add *Medium* to 60% of the total volume, shake for 30 min, sonicate for 5 min, and then dilute with *Medium* to volume.

**Standard solution 2:** 0.067 mg/mL of isosorbide mononitrate ▲▲ (USP 1-Dec-2024) in *Medium*

▲prepared as follows. Transfer an appropriate amount of USP Diluted Isosorbide Mononitrate RS to a suitable volumetric flask,▲ (USP 1-Dec-2024) add *Medium* to 60% of the total volume, shake for 30 min, sonicate for 5 min, and then dilute with *Medium* to volume.

**Sample solution:** Pass ▲a portion▲ (USP 1-Dec-2024) of the solution under test through a suitable filter.

**System suitability**

**Sample:** *Standard solution 1*

**Suitability requirements**

**Tailing factor:** NMT 1.5

**Relative standard deviation:** NMT 2.0%

**Analysis**

**Samples:** *Standard solution 1*, *Standard solution 2*, and *Sample solution*

Calculate the response factor for *Standard solution 1* and *Standard solution 2*:

$$\text{Result} = C_S / r_S$$

$C_S$ = concentration of isosorbide mononitrate in *Standard solution 1* or *Standard solution 2* (mg/mL)

$r_S$ = peak response of isosorbide mononitrate from *Standard solution 1* or *Standard solution 2*

Calculate the concentration ($C_i$) of isosorbide mononitrate ($C_6H_9NO_6$) in the sample withdrawn from the vessel at each time point (*i*):

$$\text{Result}_i = r_i \times F_R$$

$r_i$ = peak response of isosorbide mononitrate from the *Sample solution* at the specified time point

$F_R$ = average response factor from *Standard solution 1* and *Standard solution 2*

Calculate the percentage of the labeled amount of isosorbide mononitrate ($C_6H_9NO_6$) dissolved at each time point (*i*):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$

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

$$\text{Result}_3 = (\{C_3 \times [V - (2 \times V_S)]\} + [(C_2 + C_1) \times V_S]) \times (1/L) \times 100$$

$$\text{Result}_4 = (\{C_4 \times [V - (3 \times V_S)]\} + [(C_3 + C_2 + C_1) \times V_S]) \times (1/L) \times 100$$

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

$V$ = volume of *Medium*, 900 mL

$L$ = label claim (mg/Tablet)

$V_S$ = volume of the *Sample solution* withdrawn from *Medium* (mL)

**Tolerances:** See *Table 8*.

**Table 8**

| Time Point (*i*) | Time (h) | Amount Dissolved (%) |
|---|---|---|
| 1 | 1 | 15–35 |
| 2 | 4 | 40–60 |
| 3 | 8 | 60–80 |
| 4 | 12 | NLT 80 |

The percentages of the labeled amount of isosorbide mononitrate dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

**Test 8:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 8*.

**Medium:** Water, deaerated; 900 mL

**Apparatus 2:** 50 rpm with suitable sinkers

**Times**

**For Tablets labeled to contain 30 and 60 mg:** 1, 2, 4, 8, and 10 h

**For Tablets labeled to contain 120 mg:** 1, 2, 4, 8, and 12 h

**Mobile phase:** Prepare as directed in *Test 1*.

**Standard stock solution:** 0.67 mg/mL of isosorbide mononitrate from USP Diluted Isosorbide Mononitrate RS in *Medium* prepared as follows. Transfer an appropriate portion of USP Diluted Isosorbide Mononitrate RS to a suitable volumetric flask. Add *Medium* to about 70% of the final volume, and sonicate to dissolve. Dilute with *Medium* to volume.

**Standard solution:** (*L*/900) mg/mL of isosorbide mononitrate in *Medium*, from the *Standard stock solution*, where *L* is the label claim in mg/Tablet

**Sample solution:** At the times specified, withdraw 10 mL of the solution under test. Replace the aliquots withdrawn for analysis with equal volumes of *Medium* maintained at 37°. Pass the solution through a suitable PVDF filter of 0.45-µm pore size. Discard the first 3 mL of the filtrate.

**Chromatographic system**

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

**Mode:** LC

**Detector:** UV 220 nm

**Column:** 4.6-mm × 25-cm; 5-µm packing L1

**Column temperature:** 35°

**Flow rate:** 1 mL/min

**Injection volume:** 25 µL

**Run time:** NLT 2 times the retention time of isosorbide mononitrate

**System suitability**

**Sample:** *Standard solution*

**Suitability requirements**

**Tailing factor:** NMT 2.0

**Relative standard deviation:** NMT 1.5%

**Analysis**

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

Calculate the concentration ($C_i$) of isosorbide mononitrate ($C_6H_9NO_6$) in the sample withdrawn from the vessel at each time point (*i*):

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

$r_i$ = peak response of isosorbide mononitrate from the *Sample solution* at the specified time point

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

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

Calculate the percentage of the labeled amount of isosorbide mononitrate ($C_6H_9NO_6$) dissolved at each time point (*i*):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$

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

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

$$\text{Result}_4 = \{(C_4 \times V) + [(C_3 + C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

$$\text{Result}_5 = \{(C_5 \times V) + [(C_4 + C_3 + C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

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

$V$ = volume of *Medium*, 900 mL

$L$ = label claim (mg/Tablet)

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

**Tolerances:** See *Table 9* and *Table 10*.

**Table 9**

| Time Point (*i*) | Time (h) | Amount Dissolved (for Tablets labeled to contain 30 or 60 mg) (%) |
|---|---|---|
| 1 | 1 | 15–35 |
| 2 | 2 | 30–50 |
| 3 | 4 | 50–70 |
| 4 | 8 | 73–93 |
| 5 | 10 | NLT 80 |

**Table 10**

| Time Point (*i*) | Time (h) | Amount Dissolved (for Tablets labeled to contain 120 mg) (%) |
|---|---|---|
| 1 | 1 | 15–35 |
| 2 | 2 | 28–48 |
| 3 | 4 | 43–63 |
| 4 | 8 | 65–85 |
| 5 | 12 | NLT 80 |

The percentages of the labeled amount of isosorbide mononitrate dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

***Change to read:***

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

▲▲ (USP 1-Dec-2024)

**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—The *Mobile phase* can be generated electrolytically by using an automatic eluant generator.]

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

**Standard solution:** 1.0 µg/mL of USP Potassium Nitrate RS in water

**Sample solution:** Nominally 200 µg/mL of isosorbide mononitrate prepared as follows. Transfer a suitable portion of finely powdered Tablets (NLT 20) to a suitable flask. Add water to about 40% of the final volume and sonicate for about 10 min with intermittent shaking. Cool to ambient temperature, and add additional water to 10% of the final volume. Agitate vigorously using a mechanical shaker for about 30 min. Centrifuge a portion of the solution and use the clear supernatant.

**Chromatographic system**

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

**Mode:** LC

**Detector:** Conductivity with suppression

**Columns**

**Guard:** 4.0-mm × 0.5-cm; 5.0-µm packing L91

**Analytical:** 4.0-mm × 15-cm; 5.0-µm packing L91

**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 in the portion of Tablets 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%▲ (USP 1-Dec-2024)

***Delete the following:***

▲• **Organic Impurities, Procedure 1**▲ (USP 1-Dec-2024)

***Delete the following:***

▲• **Organic Impurities, Procedure 2**▲ (USP 1-Dec-2024)

***Add the following:***

▲• **Organic Impurities**

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

**Sensitivity solution:** 3 µg/mL of isosorbide mononitrate 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:** 30 µg/mL of isosorbide and 7.5 µg/mL each of isosorbide mononitrate, isosorbide related compound A, 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 prepared as follows. Transfer a suitable portion of finely powdered Tablets (NLT 20) to a suitable volumetric flask. Add methanol to about 80% of the final volume and sonicate for 30 min with intermittent shaking, cool to ambient temperature, 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°, isothermal

**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 11* for the relative retention times.]

**Suitability requirements**

**Relative standard deviation:** NMT 5.0% each for isosorbide mononitrate, isosorbide, isosorbide related compound A, 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 related compound A, and isosorbide dinitrate 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, isosorbide related compound A, or isosorbide dinitrate from the *Sample solution*

$r_S$ = peak response of isosorbide, isosorbide related compound A, or isosorbide dinitrate from the *Standard solution*

$C_S$ = concentration of isosorbide, isosorbide related compound A, 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 degradation product in the portion of Tablets taken:

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

$r_U$ = peak response of each unspecified degradation product 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 11*. The reporting threshold is 0.1%.

**Table 11**

| Name | Relative Retention Time | Acceptance Criteria, NMT (%) |
|---|---|---|
| Isosorbide | 0.4 | 1 |
| Isosorbide related compound A | 0.6 | 0.25 |
| Isosorbide mononitrate | 1.0 | — |
| Isosorbide dinitrate | 1.6 | 0.25 |
| Any unspecified degradation product | — | 0.2 |
| Total degradation products[a] | — | 0.5▲ (USP 1-Dec-2024) |

[a] Total degradation products excluding isosorbide.

**ADDITIONAL REQUIREMENTS**

***Change to read:***

• **PACKAGING AND STORAGE:** Preserve in tight containers. Store at a temperature of 20°–30°, ▲with excursions permitted between 15° and 30°.▲ (USP 1-Dec-2024)

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

***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▲ (USP 1-Dec-2024) 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 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-Dec-2024)

$C_6H_9NO_6$ 191.14

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

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

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

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