Isosorbide Mononitrate Extended-Release Tablets

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Expert Committee	Chemical Medicines Monographs 2
Reason for Revision	Compliance

In accordance with the Rules and Procedures of the 2015–2020 Council of Experts, the Chemical Medicines Monographs 2 Expert Committee has revised the Isosorbide Mononitrate Extended-Release Tablets monograph. The purpose for the revision is to add *Dissolution Test 7* to accommodate FDA-approved drug products with different conditions and tolerances than the existing dissolution tests.

- *Dissolution Test 7* was validated using a Lichrospher RP-18 brand of L1 column from Merck Millipore. The typical retention time for isosorbide mononitrate is about 4 min.

The Isosorbide Mononitrate Extended-Release Tablets Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Edith Chang, Senior Scientific Liaison to the Chemical Medicines Monographs 2 Expert Committee (301-816-8392 or yec@usp.org).

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

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

Standard solution: 0.5 mg/mL of isosorbide mononitrate from USP Diluted Isosorbide Mononitrate RS in absolute alcohol

Sample stock solution: To a portion of the powder from NLT 20 Tablets in a suitable container, nominally equivalent to 120 mg of isosorbide mononitrate, add 50.0 mL of absolute alcohol, sonicate for 10 min, and centrifuge.

Sample solution: Transfer 10 mL of supernatant from the *Sample stock solution* to a 50-mL volumetric flask, and dilute with absolute alcohol to volume.

Chromatographic system

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

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

• **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**

Mobile phase: Methanol and water (200:800)

Standard solution A: 0.15 mg/mL of isosorbide mononitrate related compound A from USP Diluted Isosorbide Mononitrate Related Compound A RS in water

Standard solution B: Equivalent to 0.12 mg/mL of isosorbide mononitrate from USP Diluted Isosorbide Mononitrate RS prepared as follows. Dissolve the sample in water, add methanol equivalent to 20% of the flask volume, then dilute with water to volume.

System suitability solution: Equivalent to 0.12 mg/mL of isosorbide mononitrate and 6 µg/mL of isosorbide mononitrate related compound A prepared as follows. Dissolve a suitable quantity of USP Diluted Isosorbide Mononitrate RS in water in a suitable volumetric flask, add a suitable amount of *Standard solution A* and methanol equivalent to 20% of the flask volume, and dilute with water to volume.

Sample solution: 0.12 mg/mL of isosorbide mononitrate from NLT 20 Tablets finely powdered, prepared as follows. Transfer a portion of the powder, nominally equivalent to 60 mg of isosorbide mononitrate, to a 100-mL volumetric flask. Add 50 mL of methanol, and sonicate for about 30 min with cooling. Warm to ambient temperature, dilute with methanol to volume, and mix. Centrifuge at about 3000 rpm for 10 min. Dilute the supernatant with water, and pass a portion of this solution 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-mm × 12.5-cm; packing L1

Flow rate: 1.5 mL/min

Injection volume: 20 µL

System suitability

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

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 1.5%, *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 (300:700)

Standard solution: (*L*/1000) of USP Diluted Isosorbide Mononitrate RS in *Medium*, where *L* is the label claim in mg/Tablet

Sample solution: Use portions of the solution under test passed 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; packing L1

Flow rate: 1 mL/min

Injection volume: 25 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Relative standard deviation: NMT 1.5%

Analysis

Samples: *Standard solution* and *Sample solution*

Determine the amount, in mg, of isosorbide mononitrate dissolved at each interval:

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

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)
V = volume of *Medium* in the vessel at each time point (mL)

Calculate the amount, in mg, of isosorbide mononitrate removed by sampling at the previous time points:

$$\text{Result} = \Sigma AD \times (V_S/V)$$

AD = amount of isosorbide mononitrate dissolved at each time point (mg)
V_S = volume of the sample taken (mL)
V = volume of *Medium* in the vessel at each time point (mL)

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

$$\text{Result} = (AD + AR) \times (100/L)$$

AD = amount of isosorbide mononitrate dissolved at each time point (mg)
AR = amount of isosorbide mononitrate removed at the previous time point (mg)
L = label claim (mg/Tablet)

Tolerances: See *Table 1*.

Table 1

Time (h)	Amount Dissolved (%)
1	15–35
2	28–48
4	43–68
8	65–90
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 (400:600)
Standard stock solution: 1.2 mg/mL of isosorbide mononitrate from USP Diluted Isosorbide Mononitrate RS diluted in *Medium*
Standard solution: 60 µg/mL of isosorbide mononitrate in *Medium* for Tablets labeled to contain 30 mg, and 120 µg/mL of isosorbide mononitrate in *Medium* for Tablets labeled to contain 60 mg, from the *Standard stock solution*
Sample solution: Pass portions 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
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), in mg/mL, of isosorbide mononitrate removed at each time point (i):

$$\text{Result}_i = (r_{U(i)}/r_S) \times C_S$$

$r_{U(i)}$ = 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 amount of isosorbide mononitrate ($C_6H_9NO_6$) dissolved at each time point (i):

$$\text{Result} = \left\{C_i \times \left[V_0 - \left((i-1) \times V_t\right)\right] + \left(\sum_{j=1}^{i-1} C_j V_t\right)\right\} \times (100/L)$$

C_i = concentration of isosorbide mononitrate at time point i (mg/mL)
V_0 = initial volume of *Medium* (mL)
V_t = volume of sample removed at each sampling time (mL)
C_j = concentration of isosorbide mononitrate at time j (mg/mL)
L = label claim (mg/Tablet)

Tolerances: See *Table 2*.

Table 2

Time (h)	Amount Dissolved (%)
1	25–45
2	35–60
6	65–90
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 acetic acid to a 1-L volumetric flask containing 500 mL of water. Adjust with acetic acid to a pH of 4.7, and dilute with water to volume.

Mobile phase: Methanol, *Buffer*, and water (300:100:600)
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 60 mg, use the *Standard stock solution* with no further dilution (0.12 mg/mL). For Tablets labeled to contain 30 mg, prepare 0.06 mg/mL of isosorbide mononitrate in *Medium* from the *Standard stock solution*.
Sample solution: Pass portions 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
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), in mg/mL, of isosorbide mononitrate at each time point (*i*):

$$\text{Result}_i = (r_{U(i)}/r_S) \times C_S$$

$r_{U(i)}$ = 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 label claim of isosorbide mononitrate ($C_6H_9NO_6$) dissolved at each time point (*i*):

$$\text{Result} = \left\{C_i \times \left[V_0 - \left((i-1) \times V_t\right)\right] + \left(\sum_{j=1}^{i-1} C_j V_t\right)\right\} \times (100/L)$$

C_i = concentration of isosorbide mononitrate at time point *i* (mg/mL)
V_0 = initial volume of *Medium* (mL)
V_t = volume of sample removed at each sampling time (mL)
C_j = concentration of isosorbide mononitrate at time *j* (mg/mL)
L = label claim (mg/Tablet)

Tolerances: See *Table 3*.

Table 3

Time (h)	Amount Dissolved (%)
1	20–40
2	30–50
6	70–90
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 (180:820)
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 portions 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
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 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*):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$
$$\text{Result}_2 = \{[C_2 \times (V - V_S)] + (C_1 \times V_S)\} \times (1/L) \times 100$$
$$\text{Result}_3 = (\{C_3 \times [V - (2 \times V_S)]\} + [(C_2 + C_1) \times V_S]) \times (1/L) \times 100$$
$$\text{Result}_4 = (\{C_4 \times [V - (3 \times V_S)]\} + [(C_3 + C_2 + C_1) \times V_S]) \times (1/L) \times 100$$

C_i = concentration of isosorbide mononitrate in the portion of sample withdrawn at time point *i* (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

Table 4 *(continued)*

Time Point (*i*)	Time (h)	Amount Dissolved (%)
4	12	NLT 85

The percentage of the labeled amount of isosorbide mononitrate dissolved at the times specified conforms 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: 1, 2, 4, 6, and 10 h

Mobile phase: Methanol and water (150:850)

System suitability solution: 0.033 mg/mL of isosorbide mononitrate from USP Diluted Isosorbide Mononitrate RS in *Medium*. Initially add *Medium* to fill 60% of total volume, shake for 30 min, sonicate for 5 min, then dilute with *Medium* to volume.

Standard solution: 0.067 mg/mL of isosorbide mononitrate from USP Diluted Isosorbide Mononitrate RS in *Medium*. Initially add *Medium* to fill 60% of total volume, shake for 30 min, sonicate for 5 min, then dilute with *Medium* to volume.

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

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

System suitability

Sample: *System suitability solution*

Suitability requirements

Relative standard deviation: NMT 2.0%

Tailing factor: 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 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*):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$
$$\text{Result}_2 = [(C_2 \times V) + (C_1 \times V_S)] \times (1/L) \times 100$$
$$\text{Result}_3 = \{(C_3 \times V) + [(C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$
$$\text{Result}_4 = \{(C_4 \times V) + [(C_3 + C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$
$$\text{Result}_5 = \{(C_5 \times V) + [(C_4 + C_3 + C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

C_i = concentration of isosorbide mononitrate in the portion of sample withdrawn at time point *i* (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 5*.

Table 5

Time Point (*i*)	Time (h)	Amount Dissolved (%)
1	1	20–40
2	2	30–50
3	4	50–70
4	6	65–85
5	10	NLT 80

The percentage of the labeled amount of isosorbide mononitrate dissolved at the times specified conforms 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, Sample solution, and **System suitability:** Proceed as directed in *Test 1*.

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

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

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 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*):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$
$$\text{Result}_2 = [(C_2 \times V) + (C_1 \times V_S)] \times (1/L) \times 100$$
$$\text{Result}_3 = \{(C_3 \times V) + [(C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$
$$\text{Result}_4 = \{(C_4 \times V) + [(C_3 + C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$
$$\text{Result}_5 = \{(C_5 \times V) + [(C_4 + C_3 + C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

C_i = concentration of isosorbide mononitrate in the portion of sample withdrawn at time point *i* (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 6*.

Table 6

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 percentage of the labeled amount of isosorbide mononitrate dissolved at the times specified conforms 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 from USP Diluted Isosorbide Mononitrate RS in *Medium*. Initially add *Medium* to fill 60% of total volume, shake for 30 min, sonicate for 5 min, then dilute with *Medium* to volume.

Standard solution 2: 0.067 mg/mL of isosorbide mononitrate from USP Diluted Isosorbide Mononitrate RS in *Medium*. Initially add *Medium* to fill 60% of total volume, shake for 30 min, sonicate for 5 min, then dilute with *Medium* to volume.

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

System suitability

Sample: *Standard solution 1*

Suitability requirements

Relative standard deviation: NMT 2.0%

Tailing factor: NMT 1.5

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 time point *i*:

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

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

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 time point *i* (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 7*.

Table 7

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*.▲ (RB 8-Oct-2018)

• **Uniformity of Dosage Units** ⟨905⟩

Procedure for content uniformity: Proceed as directed in the *Assay*, except use 1 Tablet instead of the portion of powdered Tablets used in the *Sample solution*.

Acceptance criteria: Meet the requirements

IMPURITIES

• **Organic Impurities, Procedure 1**

Standard solution A: 0.0125 mg/mL of USP Isosorbide RS in acetonitrile

Standard solution B: 0.025 mg/mL of USP Isosorbide RS in acetonitrile

Standard solution C: 0.05 mg/mL of USP Isosorbide RS in acetonitrile

Sample solution: Equivalent to 5 mg/mL of isosorbide mononitrate from a portion of powdered Tablets (NLT 20) in acetonitrile. Sonicate for 10 min, then centrifuge. Use the supernatant.

Chromatographic system

(See *Chromatography* ⟨621⟩*, General Procedures, Thin-Layer Chromatography*.)

Mode: TLC

Adsorbent: 0.25-mm layer of chromatographic silica gel mixture

Application volume: 20 µL

Developing solvent system: Toluene, ethyl acetate, and isopropyl alcohol (53:32:15)

Detection solution: Dissolve 1.25 g of potassium permanganate and 10.0 g of sodium hydroxide in 500 mL of water (prepared fresh for each plate), and heat at 105° for 5 min.

Analysis

Samples: *Standard solutions* and *Sample solution*

Proceed as directed in the chapter. After developing, dry the plate with warm air for about 10 min, dip the plate in the *Detection solution*, and heat at 105° for 5 min.

Acceptance criteria: Any spot from the *Sample solution* and corresponding to the R_F value of the spots from the

Standard solutions is not more intense than the spot from *Standard solution C*; NMT 1% of any individual impurity is found.

If the spot from the *Sample solution* is nearly as intense as the spot from *Standard solution C*, further dilute the *Sample solution* with acetonitrile (1:1), repeat the test, and compare the intensity of the isosorbide spot in the diluted *Sample solution* with the intensity of the spots from the *Standard solutions*, correcting the percentage level for the additional dilution of the *Sample solution*.

[NOTE—The R_F values of isosorbide and isosorbide mononitrate are about 0.2 and 0.6, respectively.]

• **ORGANIC IMPURITIES, PROCEDURE 2**

Mobile phase: Methanol and water (250:750)

Isosorbide mononitrate related compound A standard stock solution: 0.3 mg/mL of isosorbide mononitrate related compound A from USP Diluted Isosorbide Mononitrate Related Compound A RS in water

Isosorbide dinitrate standard stock solution: 0.15 mg/mL of isosorbide dinitrate from USP Diluted Isosorbide Dinitrate RS in methanol

Standard stock solution: 6.0 µg/mL each of isosorbide mononitrate related compound A and isosorbide dinitrate from *Isosorbide mononitrate related compound A standard stock solution* and *Isosorbide dinitrate standard stock solution*, respectively, diluted with water

System suitability solution: Transfer a quantity of USP Diluted Isosorbide Mononitrate RS, equivalent to 24 mg of isosorbide mononitrate, to a 100-mL volumetric flask. Add 10.0 mL of the *Standard stock solution* and 20 mL of methanol, and dilute with water to volume.

Standard solution: Transfer 10.0 mL of the *Standard stock solution* and 20 mL of methanol to a 100-mL volumetric flask. Dilute with water to volume.

Sample solution: Transfer a portion of powder from NLT 20 Tablets, equivalent to 60 mg of isosorbide mononitrate, to a 50-mL volumetric flask. Add 40 mL of methanol, and sonicate for about 30 min with cooling. Warm to ambient temperature, dilute with methanol to volume, and mix. Centrifuge at about 3000 rpm for 10 min. Dilute 10 mL of the supernatant with water to 50 mL. Pass a portion of this 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 220 nm

Column: 4.6-mm × 25-cm; packing L1

Flow rate: 1 mL/min

Injection volume: 100 µL

System suitability

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

[NOTE—The relative retention times for isosorbide mononitrate related compound A, isosorbide mononitrate, and isosorbide dinitrate are about 0.9, 1.0, and 5.6, respectively.]

Suitability requirements

Resolution: NLT 1.0 between isosorbide mononitrate related compound A and isosorbide mononitrate, *System suitability solution*

Relative standard deviation: NMT 10% for the isosorbide mononitrate related compound A and isosorbide dinitrate peaks, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of isosorbide mononitrate 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 area of isosorbide mononitrate related compound A or isosorbide dinitrate from the *Sample solution*

r_S = peak area of isosorbide mononitrate related compound A or isosorbide dinitrate from the *Standard solution*

C_S = concentration of USP Diluted Isosorbide Mononitrate Related Compound A RS or USP Diluted Isosorbide Dinitrate RS in the *Standard solution* (mg/mL)

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

Calculate the percentage of each other impurity (other than isosorbide mononitrate related compound A or isosorbide dinitrate) in the portion of Tablets taken:

$$\text{Result} = (r_U/r_T) \times 100$$

r_U = peak area of each impurity from the *Sample solution*

r_T = sum of all the peak areas from the *Sample solution*

Acceptance criteria

Individual impurities: NMT 0.25% each of isosorbide mononitrate related compound A and isosorbide dinitrate

Total other impurities: NMT 0.25%

Total impurities: NMT 0.5% including isosorbide mononitrate related compound A and isosorbide dinitrate

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in tight containers. Store at a temperature of 20°–30°.

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

• **USP REFERENCE STANDARDS** ⟨11⟩

USP Isosorbide RS

The following Reference Standards 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.

$C_6H_9NO_6$ 191.14