Methylphenidate Hydrochloride Extended-Release Tablets

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Reason for Revision	Compliance

In accordance with the Rules and Procedures of the 2020–2025 Council of Experts, the Small Molecules 4 Expert Committee has revised the Methylphenidate Hydrochloride Extended-Release Tablets monograph. The purpose for the revision is to add *Dissolution Test 11* to accommodate FDA-approved drug products with different tolerances than the existing dissolution tests.

- *Dissolution Test 11* was validated using a Waters Symmetry C8 brand of column with L7 packing. The typical retention time for methylphenidate is about 3.4 min.

The revision also necessitates a change in the table numbering in the test for *Organic Impurities*.

The Methylphenidate Hydrochloride Extended-Release Tablets Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Mary P. Koleck, Senior Scientific Liaison (301-230-7420 or mpk@usp.org).

Revision Bulletin
Official: October 1, 2020

Methylphenidate Hydrochloride Extended-Release Tablets

DEFINITION

Methylphenidate Hydrochloride Extended-Release Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of methylphenidate hydrochloride ($C_{14}H_{19}NO_2 \cdot HCl$).

IDENTIFICATION

● **A. Infrared Absorption**

Sample: Place a portion of powdered Tablets, equivalent to 100 mg of methylphenidate hydrochloride, in a 100-mL beaker. Add 20 mL of chloroform, stir for 5 min, and filter, collecting the filtrate. Evaporate the filtrate to about 5 mL. Add ethyl ether slowly, with stirring, until crystals form. Filter the crystals, wash with ethyl ether, and dry at 80° for 30 min.

Acceptance criteria: The IR absorption spectrum of a mineral oil dispersion of the crystals so obtained exhibits maxima only at the same wavelengths as those of a similar preparation of USP Methylphenidate Hydrochloride 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

Change to read:

● **Procedure**

Mobile phase: Dissolve 2 g of octanesulfonic acid sodium salt in 730 mL of water. Adjust with phosphoric acid to a pH of 2.7. Mix with 270 mL of acetonitrile.

Solution A: Acidified water; adjusted with phosphoric acid to a pH of 3

Diluent A: Acetonitrile and *Solution A* (25:75)

Diluent B: Acetonitrile and methanol (50:50)

System suitability solution: 80 µg/mL of USP Methylphenidate Hydrochloride RS, 1 µg/mL of methylphenidate hydrochloride erythro isomer from USP Methylphenidate Hydrochloride Erythro Isomer Solution RS, and 2 µg/mL of USP Methylphenidate Related Compound A RS in *Diluent A*

Standard solution: 0.1 mg/mL of USP Methylphenidate Hydrochloride RS in *Diluent A*

Sample stock solution: Nominally 1 mg/mL of methylphenidate hydrochloride prepared as follows. Dissolve NLT 10 Tablets in a suitable volumetric flask with 20% of the total flask volume of *Diluent B*. [Note—Alternatively, a portion of powder from NLT 10 Tablets may be transferred to a suitable volumetric flask and suspended in 20% of the total flask volume of *Diluent B*.] Stir for 4 h. Dilute with *Solution A* to volume.

Sample solution: Nominally 0.1 mg/mL of methylphenidate hydrochloride in *Solution A* from the *Sample stock solution*. [Note—Centrifuge before chromatographic analysis.]

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

Column: 3.9-mm × 15-cm; 5-µm packing L1

Column temperature: 30°

Flow rate: 1 mL/min

Injection volume: 25 µL

Run time: 2 times the retention time of methylphenidate

System suitability

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

[NOTE—See ▲*Table 11*▲ (RB 1-Oct-2020) for relative retention times.]

Suitability requirements

Resolution: NLT 4.0 between methylphenidate related compound A and methylphenidate hydrochloride erythro isomer; NLT 6.0 between the methylphenidate and erythro isomer peaks, *System suitability solution*

Tailing factor: NMT 2.0 for the methylphenidate peak, *Standard solution*

Relative standard deviation: NMT 2.0% for the methylphenidate peak, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of methylphenidate hydrochloride ($C_{14}H_{19}NO_2 \cdot HCl$) in the portion of Tablets taken:

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

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of USP Methylphenidate Hydrochloride RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of methylphenidate hydrochloride in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

- **DISSOLUTION** ⟨711⟩

Test 1

Medium: Water; 500 mL

Apparatus 2: 50 rpm

Times: 1, 2, 3.5, 5, and 7 h

Buffer: Dissolve 1.6 g of anhydrous sodium acetate in 900 mL of water. Adjust with acetic acid to a pH of 4.0 and dilute with water to 1000 mL.

Mobile phase: Methanol, acetonitrile, and *Buffer* (40:30:30)

Internal standard solution: 0.4 mg/mL of phenylephrine hydrochloride in *Mobile phase*

Standard stock solution: (1.5 × [*L*/500]) mg/mL of USP Methylphenidate Hydrochloride RS in *Mobile phase* where *L* is the label claim of methylphenidate hydrochloride in mg/Tablet

Standard solution: Transfer 10.0 mL of the *Standard stock solution* to a glass-stoppered, 25-mL conical flask, add 5.0 mL of the *Internal standard solution*, and mix.

Sample stock solution: Use portions of the solution under test passed through a suitable filter of 0.45-µm pore size. Do not use glass fiber filters.

Sample solution: Transfer 10.0 mL of the *Sample stock solution* to a glass-stoppered, 25-mL conical flask, add 5.0 mL of the *Internal standard solution*, and mix.

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

Column: 4.6-mm × 25-cm; packing L10

Flow rate: 1.5 mL/min

Injection volume: 50 µL

System suitability

Sample: *Standard solution*

[NOTE—The relative retention times for phenylephrine hydrochloride and methylphenidate hydrochloride are 0.8 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 2.0 between the analyte and internal standard peaks

Relative standard deviation: NMT 2.0% for the peak response ratios of the analyte to the internal standard

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of methylphenidate hydrochloride ($C_{14}H_{19}NO_2 \cdot HCl$) dissolved by using the procedure in the *Assay*, making any necessary volumetric adjustments.

Tolerances: See *Table 1*.

Table 1

Time (h)	Amount Dissolved (%)
1	25–45
2	40–65
3.5	55–80
5	70–90
7	NLT 80

The percentages of the labeled amount of methylphenidate hydrochloride ($C_{14}H_{19}NO_2 \cdot HCl$) dissolved at the times specified conform to *Dissolution ⟨711⟩, Acceptance Table 2*.

For products labeled for dosing every 24 h

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

Medium: Acidified water; adjusted with phosphoric acid to a pH of 3; 50 mL at 37 ± 0.5°

Apparatus 7: 30 cycles/min; 2–3 cm amplitude. Follow *Drug Release ⟨724⟩, General Drug Release Standards, Apparatus 7, Sample preparation A* using a metal spring sample holder (*Drug Release ⟨724⟩, Figure 5d*). Place one Tablet in the holder with the Tablet orifice facing down, and cover the top of the holder with Parafilm™. At the end of each specified test interval, the systems are transferred to the next row of new test tubes containing 50 mL of fresh *Medium*.

Times: 1-h intervals for a duration of 10 h

Calculate the percentage of the labeled amount of methylphenidate hydrochloride ($C_{14}H_{19}NO_2 \cdot HCl$) dissolved by using the following method.

Solution A: Dissolve 2.0 g of sodium 1-octanesulfonate in 700 mL of water, mix well, and adjust with phosphoric acid to a pH of 3.0.

Mobile phase: Acetonitrile and *Solution A* (30:70)

Diluent: Acetonitrile and *Medium* (25:75)

Standard stock solution: 0.3 mg/mL of USP Methylphenidate Hydrochloride RS in *Diluent*

Standard solutions: Prepare at least six solutions by making serial dilutions of the *Standard stock solution* in *Diluent* to bracket the expected drug concentration range.

Chromatographic system

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

Mode: LC

Detector: UV 220 nm

Column: 3.2-mm × 5-cm; 5-µm packing L1

Column temperature: 30°

Flow rate: 1 mL/min

Injection volume: 25 µL

System suitability

Sample: Middle range concentration of the *Standard solutions*

Suitability requirements

Tailing factor: NMT 2

Relative standard deviation: NMT 2% for the peak response of the analyte; NMT 2% for the retention time of the analyte

Analysis

Samples: *Standard solutions* and the solution under test

Construct a calibration curve by plotting the peak response versus the concentration of the *Standard solutions*. Determine the amount of methylphenidate hydrochloride ($C_{14}H_{19}NO_2 \cdot HCl$) in each interval by linear regression analysis of the standard curve.

Tolerances: See *Table 2*.

Table 2

Time (h)	Amount Dissolved (%)
1	12–32
4	40–60
10	NLT 85
3–6 (avg)	9–15 (/h)

The percentages of the labeled amount of methylphenidate hydrochloride ($C_{14}H_{19}NO_2 \cdot HCl$) dissolved at the times specified conform to *Dissolution ⟨711⟩*, *Acceptance Table 2*.

Calculate the average percentage released from 3–6 h:

$$\text{Result} = (Y - X)/3$$

Y = cumulative drug released from 0–6 h

X = cumulative drug released from 0–3 h

For products labeled for dosing every 24 h

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

Medium: pH 6.8 phosphate buffer (6.8 g/L of monobasic potassium phosphate in water; adjusted with 2N sodium hydroxide or 10% phosphoric acid to a pH of 6.80); 900 mL

Apparatus 1: 100 rpm

Times: 0.75, 4, and 10 h

Buffer: pH 4.0 phosphate buffer (2.72 g/L of monobasic potassium phosphate in water; adjusted with 2N sodium hydroxide or 10% phosphoric acidto a pH of 4.00)

Mobile phase: Acetonitrile and *Buffer* (17.5: 82.5)

Standard solution: 0.06 mg/mL of USP Methylphenidate Hydrochloride RS in 0.1 N hydrochloric acid

Sample solution: Pass a portion of the solution under test through a suitable polytetrafluoroethylene (PTFE) filter of 0.45-µm pore size.

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

Column: 3.0-mm × 5-cm; 2.5-µm packing L1
Column temperature: 50°
Flow rate: See *Table 3*.

Table 3

Time (min)	Flow Rate (mL/min)
0.0	0.75
2.5	0.75
3.0	2.00
6.0	2.00
6.5	0.75
7.0	0.75

Injection volume: 10 µL

System suitability

Sample: *Standard solution*

[NOTE—The relative retention times for methylphenidate related compound A, the erythro isomer, and methylphenidate are 0.47, 0.65, and 1.0, respectively.]

Suitability requirements

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the concentration (C_i) of methylphenidate hydrochloride ($C_{14}H_{19}NO_2 \cdot HCl$) in the sample withdrawn from the vessel at each time point (i) shown in *Table 4*:

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

r_U = sum of the peak responses of methylphenidate and methylphenidate related compound A from the *Sample solution*

r_S = peak response of methylphenidate from the *Standard solution*

C_S = concentration of USP Methylphenidate Hydrochloride RS in the *Standard solution* (mg/mL)

Calculate the percentage of the labeled amount of methylphenidate hydrochloride ($C_{14}H_{19}NO_2 \cdot HCl$) dissolved at each time point (i) shown in *Table 4*:

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

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

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

C_i = concentration of methylphenidate hydrochloride 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 the *Medium* (mL)

Tolerances: See *Table 4*.

Table 4

Time Point (*i*)	Time (h)	Amount Dissolved (%)
1	0.75	12–30
2	4	55–80
3	10	NLT 80

The percentages of the labeled amount of methylphenidate hydrochloride ($C_{14}H_{19}NO_2 \cdot HCl$) 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: 0.001 N hydrochloric acid; 500 mL

Apparatus 2: 50 rpm

Times: 1, 2, 6, and 10 h

Mobile phase: Acetonitrile and water (20:80). For every L of *Mobile phase* add 1.0 mL of formic acid and 0.2 mL of trifluoroacetic acid.

Standard solution: 0.02 mg/mL of USP Methylphenidate Hydrochloride RS in *Mobile phase*

Sample solution: Pass a portion of the solution under test through a suitable PTFE filter of 0.45-µm pore size. Do not use glass fiber filters.

Chromatographic system

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

Mode: LC

Detector: UV 220 nm

Column: 3.0-mm × 15-cm; 3-µm packing L1

Column temperature: 40°

Flow rate: 0.75 mL/min

Injection volume: 10 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Relative standard deviation: NMT 5.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the concentration (C_i) of methylphenidate hydrochloride ($C_{14}H_{19}NO_2 \cdot HCl$) in the sample withdrawn from the vessel at each time point (*i*) shown in *Table 5*:

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

r_U = peak response of methylphenidate from the *Sample solution*

r_S = peak response of methylphenidate from the *Standard solution*

C_S = concentration of USP Methylphenidate Hydrochloride RS in the *Standard solution* (mg/mL)

Calculate the percentage of the labeled amount of methylphenidate hydrochloride ($C_{14}H_{19}NO_2 \cdot HCl$) dissolved at each time point (*i*) shown in *Table 5*:

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

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

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

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

C_i = concentration of methylphenidate hydrochloride 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 the *Sample solution* withdrawn from the *Medium* (mL)

Tolerances: See *Table 5*.

Table 5

Time Point (i)	Time (h)	Amount Dissolved (%)
1	1	20–40
2	2	35–55
3	6	65–85
4	10	NLT 80

The percentages of the labeled amount of methylphenidate hydrochloride ($C_{14}H_{19}NO_2 \cdot HCl$) 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: Water; 500 mL

Apparatus 2: 50 rpm

Times: 1, 2, 3.5, and 5 h

Buffer: 1.6 g/L of anhydrous sodium acetate in water. Adjust with acetic acid to a pH of 4.0.

Mobile phase: Methanol, acetonitrile, and *Buffer* (40:30:30)

Standard stock solution: 0.2 mg/mL of USP Methylphenidate Hydrochloride RS in 0.1 N hydrochloric acid VS

Standard solution: [L/500] mg/mL of USP Methylphenidate Hydrochloride RS in 0.1 N hydrochloric acid VS from *Standard stock solution*, where L is the label claim of methylphenidate hydrochloride in mg/Tablet

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size, then transfer the filtrate to a suitable container which already contains 10 µL of 2 N hydrochloric acid TS for every 1 mL of solution transferred.

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

Column: 4.6-mm × 25-cm; 5-µm packing L10

Flow rate: 1.5 mL/min

Injection volume: 50 µL

Run time: NLT 1.6 times the retention time of methylphenidate

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 methylphenidate hydrochloride ($C_{14}H_{19}NO_2 \cdot HCl$) in the sample withdrawn from the vessel at each time point (i) shown in *Table 6*:

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

r_U = peak response of methylphenidate from the *Sample solution*

r_S = peak response of methylphenidate from the *Standard solution*

C_S = concentration of USP Methylphenidate Hydrochloride RS in the *Standard solution* (mg/mL)

Calculate the percentage of the labeled amount of methylphenidate hydrochloride ($C_{14}H_{19}NO_2 \cdot HCl$) dissolved at each time point (i) shown in *Table 6*:

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

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

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

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

C_i = concentration of methylphenidate hydrochloride 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 the *Sample solution* withdrawn from the *Medium* (mL)

Tolerances: See *Table 6*.

Table 6

Time Point (*i*)	Time (h)	Amount Dissolved (%)
1	1	40–60
2	2	55–80
3	3.5	75–95
4	5	NLT 80

The percentages of the labeled amount of methylphenidate hydrochloride ($C_{14}H_{19}NO_2 \cdot HCl$) dissolved at the times specified conform to *Dissolution ⟨711⟩*, *Acceptance Table 2*.

For products labeled for dosing every 24 h

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

Medium: Acidified water adjusted with phosphoric acid to a pH of 3; 50 mL

Apparatus 7: 30 cycles/min; 2–3 cm amplitude. Follow *Drug Release ⟨724⟩, General Drug Release Standards, Apparatus 7, Sample preparation A* using a metal spring sample holder (*Drug Release ⟨724⟩, Figure 5d*). Place 1 Tablet in the holder with the Tablet orifice facing down, and cover the top of the holder with Parafilm™. At the end of each specified test interval, the systems are transferred to the next row of new vessels containing 50 mL of fresh *Medium*.

Times: 1-h intervals for a duration of 10 h

Calculate the percentage of the labeled amount of methylphenidate hydrochloride ($C_{14}H_{19}NO_2 \cdot HCl$) dissolved by using the following method.

Buffer: Dissolve 2.0 g of sodium 1-octanesulfonate in 700 mL of water, mix well, and adjust with phosphoric acid to a pH of 3.0.

Mobile phase: Acetonitrile and *Buffer* (30:70)

Diluent A: Acetonitrile and *Medium* (25:75)

Diluent B: Acetonitrile and *Medium* (50:50)

Standard stock solution: 0.3 mg/mL of USP Methylphenidate Hydrochloride RS in *Diluent A*

Standard solution: (*L*/1000) mg/mL of USP Methylphenidate Hydrochloride RS in *Diluent A* from the *Standard stock solution*, where *L* is the label claim of methylphenidate hydrochloride in mg/Tablet

Sample solutions: Following the dissolution, transfer the contents of each vessel to a separate 100-mL volumetric flask. Rinse each vessel three times, using about 15 mL of *Diluent B* each time, and transfer the rinsates to the volumetric flask. Allow to cool and dilute with *Diluent B* to volume. Centrifuge and use the supernatant.

Chromatographic system

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

Mode: LC

Detector: UV 220 nm

Column: 3.2-mm × 5-cm; 5-µm packing L1

Column temperature: 30°

Flow rate: 1 mL/min

Injection volume: 25 µL

Run time: NLT 2 times the retention time of methylphenidate

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2

Relative standard deviation: NMT 2.0% for the peak response of methylphenidate; NMT 2% for the retention time of methylphenidate

Analysis

Samples: *Standard solution* and *Sample solutions*

Calculate the concentration (C_i) of methylphenidate hydrochloride ($C_{14}H_{19}NO_2 \cdot HCl$) in the sample withdrawn from the vessel at each time point (i) shown in *Table 7*:

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

r_U = peak response of methylphenidate from the *Sample solution*

r_S = peak response of methylphenidate from the *Standard solution*

C_S = concentration of USP Methylphenidate Hydrochloride RS in the *Standard solution* (mg/mL)

Calculate the percentage of the labeled amount of methylphenidate hydrochloride ($C_{14}H_{19}NO_2 \cdot HCl$) dissolved at each time point (i) shown in *Table 7*:

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

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

$$\text{Result}_i = (C_i + C_{i-1} + C_{i-2} + C_{i-3} + C_{i-x}) \times V \times D \times (1/L) \times 100$$

C_i = concentration of methylphenidate hydrochloride in the portion of sample withdrawn at time point *i* (mg/mL)

V = volume of *Medium*, 50 mL

D = dilution factor, 2

L = label claim (mg/Tablet)

Calculate the average percentage released from 3–6 h:

$$\text{Result} = (Y - X)/3$$

Y = cumulative drug released from 0–6 h

X = cumulative drug released from 0–3 h

Tolerances: See *Table 7*.

Table 7

Time (h)	Amount Dissolved (%)
1	12–32
4	50–75
10	NLT 80
3–6 (avg)	8–13 (%/h)

The percentages of the labeled amount of methylphenidate hydrochloride ($C_{14}H_{19}NO_2 \cdot HCl$) dissolved at the times specified conform to *Dissolution ⟨711⟩*, *Acceptance Table 2*.

Test 9: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 9*.

Medium: 0.001 N hydrochloric acid TS; 500 mL, deaerated

Apparatus 2: 50 rpm

Times: 0.5, 2, 6, and 10 h

Buffer: 2.93 g/L of sodium 1-heptanesulfonate in water. Adjust with 50% phosphoric acid to a pH of 3.2.

Mobile phase: *Buffer* and acetonitrile (70:30)

Standard solution: 0.072 mg/mL of USP Methylphenidate Hydrochloride RS in *Medium*. Sonicate to dissolve as needed.

Sample solution: Pass a portion 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 210 nm

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

Column temperature: 30°

Flow rate: 1.5 mL/min

Injection volume: 20 µL

Run time: NLT 1.5 times the retention time of methylphenidate

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the concentration (C_i) of methylphenidate hydrochloride ($C_{14}H_{19}NO_2 \cdot HCl$) 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 methylphenidate from the *Sample solution*

r_S = peak response of methylphenidate from the *Standard solution*

C_S = concentration of USP Methylphenidate Hydrochloride RS in the *Standard solution* (mg/mL)

Calculate the percentage of the labeled amount of methylphenidate hydrochloride ($C_{14}H_{19}NO_2 \cdot HCl$) 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 methylphenidate hydrochloride 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 the *Sample solution* withdrawn from the *Medium* (mL)

Tolerances: See *Table 8*.

Table 8

Time Point (*i*)	Time (h)	Amount Dissolved (%)
1	0.5	10–30
2	2	28–48
3	6	70–90
4	10	NLT 85

The percentages of the labeled amount of methylphenidate hydrochloride ($C_{14}H_{19}NO_2 \cdot HCl$) dissolved at the times specified conform to *Dissolution ⟨711⟩*, *Acceptance Table 2*.

Test 10: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 10*.

Acid stage medium: 0.1 N hydrochloric acid; 900 mL

Buffer stage medium: 6 g/L of monobasic sodium phosphate in water. Add 1 mL/L of 50% sodium hydroxide. Adjust with diluted phosphoric acid or sodium hydroxide, if necessary, to a pH of 6.6; 900 mL.

Apparatus 1: 100 rpm

Times

Acid stage: 0.5 and 2 h

Buffer stage: 4, 6, and 10 h. The time in the *Buffer stage medium* includes the time in the *Acid stage medium*.

Buffer: 6.8 g/L of monobasic potassium phosphate in water, adjusted with phosphoric acid to a pH of 3.2

Mobile phase: Acetonitrile and *Buffer* (20:80)

Standard stock solution: 0.30 mg/mL of USP Methylphenidate Hydrochloride RS in *Mobile phase*

Standard solution: 0.06 mg/mL of USP Methylphenidate Hydrochloride RS in *Mobile phase* from the *Standard stock solution*

System suitability solution: 0.06 mg/mL of USP Methylphenidate Hydrochloride RS and 0.01 mg/mL of USP Methylphenidate Related Compound A RS in *Mobile phase* prepared as follows. Transfer a suitable amount of USP Methylphenidate Related Compound A RS to a suitable volumetric flask, add *Standard stock solution* equivalent to 20% of the flask volume, and dilute with *Mobile phase* to volume.

Sample solution: At the times specified in the *Acid stage medium*, pass a portion of the solution under test through a suitable filter of 10-µm pore size. Carefully transfer the Tablet to a dissolution vessel containing the *Buffer stage medium*. At the times specified in the *Buffer stage medium*, pass a portion of the solution under test through a suitable filter of 10-µm pore size.

Chromatographic system

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

Mode: LC

Detector: UV 215 nm

Column: 3.9-mm × 15-cm; 5-µm packing L7

Column temperature: 35 ± 2°

Flow rate: 1.2 mL/min

Injection volume: 10 µL

Run time: NLT 1.5 times the retention time of methylphenidate

System suitability

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

[Note—The relative retention times for methylphenidate related compound A, the erythro isomer, and methylphenidate are 0.57, 0.66, and 1.0, respectively.]

Suitability requirements

Resolution: NLT 2.0 between methylphenidate related compound A and methylphenidate, *System suitability solution*

Tailing factor: NMT 2.0, *Standard solution*

Relative standard deviation: NMT 2.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the concentration (C_i) of methylphenidate hydrochloride ($C_{14}H_{19}NO_2 \cdot HCl$) in the sample withdrawn from the vessel at each time point (i) shown in *Table 9*:

$$\text{Result}_i = (\{r_{U(m)} + [r_{U(a)} \times (1/F)] + r_{U(e)}\}/r_S) \times C_S$$

$r_{U(m)}$ = peak response of methylphenidate from the *Sample solution*

$r_{U(a)}$ = peak response of methylphenidate related compound A from the *Sample solution*

F = relative response factor of methylphenidate related compound A, 1.2

$r_{U(e)}$ = peak response of the erythro isomer from the *Sample solution*

r_S = peak response of methylphenidate from the *Standard solution*

C_S = concentration of USP Methylphenidate Hydrochloride RS in the *Standard solution* (mg/mL)

Calculate the percentage of the labeled amount of methylphenidate hydrochloride ($C_{14}H_{19}NO_2 \cdot HCl$) dissolved at each time point (*i*) shown in *Table 9*:

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

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

$$\text{Result}_3 = \text{Result}_2 + C_3 \times V \times (1/L) \times 100$$

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

$$\text{Result}_5 = \text{Result}_2 + (\{C_5 \times [V - (2 \times V_S)]\} + [(C_3 + C_4) \times V_S]) \times (1/L) \times 100$$

C_i = concentration of methylphenidate hydrochloride in the portion of sample withdrawn at time point (*i*) (mg/mL)

V = volume of *Acid stage medium* or *Buffer stage medium*, 900 mL

L = label claim (mg/Tablet)

V_S = volume of the *Sample solution* withdrawn from either the *Acid stage medium* or *Buffer stage medium* (mL)

Tolerances: See *Table 9*.

Table 9

Time Point (*i*)	Time (h)	Amount Dissolved (%)
1	0.5	NLT 20
2	2	NMT 37
3	4	38–58
4	6	59–79
5	10	NLT 80

The percentages of the labeled amount of methylphenidate hydrochloride ($C_{14}H_{19}NO_2 \cdot HCl$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

▲**Test 11:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 11*.

Buffer stage medium 1: Acetate buffer pH 4.50 ± 0.05. Dissolve 26.3 g of anhydrous sodium acetate in 1 L of water in a suitable container. Transfer to a 6 L container containing 4 L of water. Add 30 mL of glacial acetic acid and dilute with water to 6 L. Adjust with glacial acetic acid or 0.2 M anhydrous sodium acetate to a pH of 4.50 ± 0.05; 500 mL, deaerated.

Buffer stage medium 2: Sodium phosphate buffer pH 6.60 ± 0.05. Dissolve 114.9 g of tribasic sodium phosphate in 1L of water. Transfer to a 6 L container containing 4.7 L of water. Add 37.5 mL of hydrochloric acid and adjust with 0.2 M hydrochloric acid to a pH of 6.60 ± 0.05. Dilute with water to 6 L and adjust with 0.2 M hydrochloric acid to a pH of 6.60 ± 0.05, if necessary; 500 mL, deaerated.

Apparatus 1: 100 rpm

Times

Buffer stage medium 1: 0.5 and 2 h

Buffer stage medium 2: 4 and 8 h. The time in *Buffer stage medium 2* includes the time in *Buffer stage medium 1*.

Buffer: 6.8 g/L of monobasic potassium phosphate in water; adjusted with phosphoric acid to a pH of 3.20 ± 0.05

Mobile phase: Acetonitrile and *Buffer* (20:80)

Standard stock solution 1: 0.72 mg/mL of USP Methylphenidate Hydrochloride RS in *Mobile phase*

Standard stock solution 2: 0.36 mg/mL of USP Methylphenidate Related Compound A RS in *Mobile phase*

Standard solution: 0.072 mg/mL of USP Methylphenidate Hydrochloride RS and 0.036 mg/mL of USP Methylphenidate Related Compound A RS in *Mobile phase* from *Standard stock solution 1* and *Standard stock solution 2*, respectively

Sample solution: At the times specified in the *Buffer stage medium 1*, use a portion of the solution under test. If cloudy, centrifuge a portion of the solution and use the supernatant. After 2 h in *Buffer stage medium 1*, carefully transfer the basket containing the Tablet to a vessel containing the *Buffer stage medium 2*. At the times specified in the *Buffer stage 2 medium*, use a portion of the solution under test. If cloudy, centrifuge a portion of the solution, and use the supernatant. [NOTE—A centrifuge speed of 2500 rpm for 10 min may be suitable.]

Chromatographic system

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

Mode: LC

Detector: UV 220 nm

Column: 3.9-mm × 15-cm; 5-µm packing L7

Column temperature: 40°

Flow rate: 1.2 mL/min

Injection volume: 10 µL

Run time: NLT 1.5 times the retention time of methylphenidate

System suitability

Sample: *Standard solution*

[NOTE—The relative retention times for methylphenidate related compound A, the erythro isomer, and methylphenidate are 0.55, 0.65, and 1.0, respectively.]

Suitability requirements

Tailing factor: NMT 2.0 for methylphenidate

Relative standard deviation: NMT 2.0% for both methylphenidate and methylphenidate related compound A

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the concentration (C_i) of methylphenidate hydrochloride ($C_{14}H_{19}NO_2 \cdot HCl$) in the sample withdrawn from the vessel at each time point (i) shown in *Table 10*:

$$\text{Result}_i = \{[(r_{U(m)} + r_{U(e)})/r_{S(m)}] \times C_{S1}\} + [(r_{U(a)}/r_{S(a)}) \times C_{S2} \times (M_{r1}/M_{r2})]$$

$r_{U(m)}$ = peak response of methylphenidate from the *Sample solution*

$r_{U(e)}$ = peak response of the erythro isomer from the *Sample solution*

$r_{S(m)}$ = peak response of methylphenidate from the *Standard solution*

C_{S1} = concentration of USP Methylphenidate Hydrochloride RS in the *Standard solution* (mg/mL)

$r_{U(a)}$ = peak response of methylphenidate related compound A from the *Sample solution*

$r_{S(a)}$ = peak response of methylphenidate related compound A from the *Standard solution*

C_{S2} = concentration of USP Methylphenidate Related Compound A RS in the *Standard solution* (mg/mL)

M_{r1} = molecular weight of methyphenidate hydrochloride, 269.77

M_{r2} = molecular weight of methylphenidate related compound A, 255.74

Calculate the percentage of the labeled amount of methylphenidate hydrochloride ($C_{14}H_{19}NO_2 \cdot HCl$) dissolved at each time point (*i*) shown in *Table 10*:

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

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

$$\text{Result}_3 = \text{Result}_2 + C_3 \times V \times (1/L) \times 100$$

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

C_i = concentration of methylphenidate hydrochloride in the portion of sample withdrawn at time point (*i*) (mg/mL)

V = volume of *Buffer stage medium 1* or *Buffer stage medium 2*, 500 mL

L = label claim (mg/Tablet)

V_S = volume of the *Sample solution* withdrawn from either the *Buffer stage 1 medium* or *Buffer stage 2 medium* (mL)

Tolerances: See *Table 10*.

Table 10

Time Point (*i*)	Time (h)	Amount Dissolved (%)
1	0.5	17–32
2	2	20–40
3	4	40–65
4	8	NLT 85

The percentages of the labeled amount of methylphenidate hydrochloride ($C_{14}H_{19}NO_2 \cdot HCl$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.▲ (RB 1-Oct-2020)

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

IMPURITIES

Change to read:

- **Organic Impurities**

Mobile phase: Dissolve 2 g of sodium 1-octanesulfonate in 730 mL of water. Adjust with phosphoric acid to a pH of 2.7. Mix with 270 mL of acetonitrile.

Solution A: Acidified water; adjusted with phosphoric acid to a pH of 3

Diluent A: Acetonitrile and *Solution A* (25:75)

Diluent B: Acetonitrile and methanol (50:50)

System suitability solution: 80 µg/mL of USP Methylphenidate Hydrochloride RS, 1 µg/mL of methylphenidate hydrochloride erythro isomer from USP Methylphenidate Hydrochloride Erythro Isomer

Solution RS, and 2 µg/mL of USP Methylphenidate Related Compound A RS in *Diluent A*

Standard solution: 0.2 µg/mL of USP Methylphenidate Hydrochloride RS, 0.5 µg/mL of methylphenidate hydrochloride erythro isomer from USP Methylphenidate Hydrochloride Erythro Isomer Solution RS, and 1.5 µg/mL of USP Methylphenidate Related Compound A RS in *Diluent A*

Sample stock solution: Nominally 1 mg/mL of methylphenidate hydrochloride prepared as follows. Dissolve NLT 10 Tablets in a suitable volumetric flask with 20% of the total flask volume of *Diluent B*. [NOTE—Alternatively, a portion of powder from NLT 10 Tablets may be transferred to a suitable volumetric flask and suspended in 20% of the total flask volume of *Diluent B*.] Stir for 4 h. Dilute with *Solution A* to volume.

Sample solution: 0.1 mg/mL of methylphenidate hydrochloride in *Solution A* from the *Sample stock solution*. [NOTE—Centrifuge before chromatographic analysis.]

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

Column: 3.9-mm × 15-cm; 5-µm packing L1

Column temperature: 30°

Flow rate: 1 mL/min

Injection volume: 25 µL

Run time: 2 times the retention time of methylphenidate

System suitability

Sample: *System suitability solution*

Suitability requirements

Resolution: NLT 6.0 between the methylphenidate and erythro isomer peaks

Tailing factor: NMT 2.0 for the methylphenidate peak

Relative standard deviation: NMT 2.0% for the methylphenidate peak; NMT 4.0% each for the methylphenidate related compound A and erythro isomer peaks

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of methylphenidate related compound A or erythro isomer in the portion of Tablets taken:

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

r_U = peak response of methylphenidate related compound A or erythro isomer from the *Sample solution*

r_S = peak response of methylphenidate related compound A or erythro isomer from the *Standard solution*

C_S = concentration of USP Methylphenidate Related Compound A RS or methylphenidate hydrochloride erythro isomer in the *Standard solution* (mg/mL)

C_U = nominal concentration of methylphenidate hydrochloride 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 USP Methylphenidate Hydrochloride RS from the *Standard solution*

C_S = concentration of USP Methylphenidate Hydrochloride RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of methylphenidate hydrochloride in the *Sample solution* (mg/mL)

Acceptance criteria: See ▲*Table 11*.

Table 11▲ (RB 1-Oct-2020)

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Methylphenidate related compound A	0.47	1.5
Erythro isomer[a]	0.65	0.5
Methylphenidate	1.0	—
Any unspecified degradation product	—	0.2
Total degradation products	—	2.5

[a] Methyl (*RS,SR*)-2-phenyl-2-(piperidin-2-yl)acetate.

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight containers. Store at controlled room temperature.
- **Labeling:** The labeling states the *Dissolution* test with which the product complies if other than *Test 1*.
- **USP Reference Standards** ⟨11⟩
  USP Methylphenidate Hydrochloride RS
  USP Methylphenidate Hydrochloride Erythro Isomer Solution RS
  USP Methylphenidate Related Compound A RS
  α-Phenyl-2-piperidineacetic acid hydrochloride.
  $C_{13}H_{17}NO_2 \cdot HCl$ 255.74

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