Methylphenidate Hydrochloride Extended-Release Tablets

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In accordance with the Rules and Procedures of the 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 12* to accommodate FDA-approved drug products with different dissolution conditions and/or tolerances than the existing dissolution test(s). The revision also necessitates a change in the table numbering in the test for *Organic Impurities*. In addition, a minor edit of "NLT" has been added to the *Run time* in the *Assay* and in the *Organic Impurities* test for clarity.

- *Dissolution Test 12* was validated using the Acquity UPLC BEH C18 brand of L1 column. The typical retention time for methylphenidate is about 0.9 min.

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: January 1, 2021

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: ▲NLT▲ (RB 1-Jan-2021) 2 times the retention time of methylphenidate

System suitability

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

[NOTE—See ▲*Table 12*▲ (RB 1-Jan-2021) 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 2 N 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 2 N sodium hydroxide or 10% phosphoric acid to 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 1 L 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*.

▲**Test 12:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 12*.

Medium: Acidified water; water adjusted with phosphoric acid to a pH of 3.0; 50 mL, deaerated

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. At the required intervals, the systems are transferred to the next row of new test tubes containing 50 mL of fresh *Medium*.

Times: 0.5, 1, 4, and 8 h

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

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

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

System suitability solution: 0.12 mg/mL of USP Methylphenidate Hydrochloride RS in *Diluent*

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

Standard solutions: 0.003, 0.03, 0.06, 0.12, 0.18, and 0.24 mg/mL of USP Methylphenidate Hydrochloride RS in *Diluent* from the *Standard stock solution*.

Sample solution: Pass a portion of the solution under test through a suitable nylon or PTFE filter of 0.45-µm pore size, discarding the first 2 mL of filtrate. Alternatively, centrifuge a portion of the solution under test and use the clear supernatant.

[NOTE—A centrifuge speed of 4000 rpm for 10 min may be suitable.]

Chromatographic system

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

Mode: LC

Detector: UV 220 nm

Column: 2.1-mm × 5-cm; 1.7-µm packing L1

Flow rate: 0.6 mL/min

Injection volume: 3 µL

Run time: NLT 2 times the retention time of methylphenidate

System suitability

Sample: *System suitability solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard stock solution*, *Standard solutions*, and *Sample solution*

Construct a calibration curve by plotting the peak response versus the concentration of the *Standard stock solution* and the *Standard solutions*. Determine the amount, in milligrams, of methylphenidate hydrochloride ($C_{14}H_{19}NO_2 \cdot HCl$) released at each time point (i) by interpolation from the linear regression analysis of the standard curve.

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

$$\text{Result}_i = Y_i \times (1/L) \times 100$$

Y_i = cumulative amount of methylphenidate hydrochloride dissolved at time point (i) (mg)

L = label claim (mg/Tablet)

Tolerances: See *Table 11*.

Table 11

Time Point (*i*)	Time (h)	Amount Dissolved (%)
1	0.5	NLT 18
2	1	NMT 30
3	4	40–60
4	8	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*. ▲ (RB 1-Jan-2021)

- **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: ▲NLT▲ (RB 1-Jan-2021) 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 12*.

Table 12▲ (RB 1-Jan-2021)

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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Not Applicable

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