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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

• 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 2 times the retention time of methylphenidate

System suitability

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

[NOTE—See [Table 12](#) 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

• [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: $(1.5 \times [L/500])$ 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- μ m 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 \times 25-cm; packing [L10](#)

Flow rate: 1.5 mL/min

Injection volume: 50 μ L

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 $37 \pm 0.5^\circ$

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 \times 5-cm; 5- μ m packing [L1](#)

Column temperature: 30°

Flow rate: 1 mL/min

Injection volume: 25 μ L

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- μ m pore size.

Chromatographic system

(See [Chromatography \(621\), System Suitability](#).)

Mode: LC

Detector: UV 210 nm

Column: 3.0-mm \times 5-cm; 2.5- μ m 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 μ L

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](#):

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

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

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

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- μ m 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 \times 15-cm; 3- μ m packing [L1](#)

Column temperature: 40°

Flow rate: 0.75 mL/min

Injection volume: 10 μ L

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](#):

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

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

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

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

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- μ m pore size, then transfer the filtrate to a suitable container which already contains 10 μ L 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 \times 25-cm; 5- μ m packing [L10](#)

Flow rate: 1.5 mL/min

Injection volume: 50 μ L

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](#):

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

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

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

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

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- μ m 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- μ m 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- μ m pore size.

Chromatographic system

(See [Chromatography \(621\), System Suitability](#).)

Mode: LC

Detector: UV 215 nm

Column: 3.9-mm \times 15-cm; 5- μ m packing [L7](#)

Column temperature: 35 \pm 2°

Flow rate: 1.2 mL/min

Injection volume: 10 μ L

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_1) 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](#):

$$\text{Result}_i = \left(\{r_{U(m)} + [r_{U(a)} \times (1/F)] + r_{U(e)}\} / r_s \right) \times C_s$$

$r_{U(m)}$ = 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 \times 15-cm; 5- μ m packing [L7](#)

Column temperature: 40°

Flow rate: 1.2 mL/min

Injection volume: 10 μ L

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](#):

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

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

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

$$\text{Result}_4 = \text{Result}_3 + \{[C_4 \times (V - V_s)] + [C_3 \times V_s]\} \times (1/L) \times 100$$

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- μ m 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 \times 5-cm; 1.7- μ m packing [L1](#)

Flow rate: 0.6 mL/min

Injection volume: 3 μ L

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>i</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](#).

- **UNIFORMITY OF DOSAGE UNITS (905):** Meet the requirements

IMPURITIES**• 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 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

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*.

Change to read:

- **USP REFERENCE STANDARDS (11):**

[USP Methylphenidate Hydrochloride RS](#)

[USP Methylphenidate Hydrochloride Erythro Isomer Solution RS](#)

[USP Methylphenidate Related Compound A RS](#)

▲(RS)-2-Phenyl-2-[(RS)-piperidin-2-yl]acetic acid hydrochloride.▲ (ERR 1-Jun-2023)

C13H17NO2.HCl 255.74

Auxiliary Information - Please [check for your question in the FAQs](#) before contacting USP.

Topic/Question	Contact	Expert Committee
METHYLPHENIDATE HYDROCHLORIDE EXTENDED-RELEASE TABLETS	Documentary Standards Support	SM42020 Small Molecules 4

Chromatographic Database Information: [Chromatographic Database](#)

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