## Methylphenidate Hydrochloride Extended-Release Tablets

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| **Type of Posting** | Notice of Intent to Revise |
| **Posting Date** | 25–Jan–2019 |
| **Targeted Official Date** | To Be Determined, Revision Bulletin |
| **Expert Committee** | Chemical Medicines Monographs 4 |

In accordance with section 7.04 (c) of the 2015–2020 Rules and Procedures of the Council of Experts and the Pending Monograph Guideline, this is to provide notice that the Chemical Medicines Monographs 4 Expert Committee intends to revise the Methylphenidate Hydrochloride Extended-Release Tablets monograph.

Based on the supporting documentation received from a manufacturer awaiting FDA approval, the Expert Committee proposes to add *Dissolution Test 8*.

- *Dissolution Test 8* was validated using the Acquity BEH C18 brand of L1 column. The typical retention time for methylphenidate is about 0.7 min.

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

The proposed revision is contingent on FDA approval of a product that meets the proposed monograph specifications. The proposed revision will be published as a Revision Bulletin and an official date will be assigned to coincide as closely as possible with the FDA approval of the associated product.

See below for additional information about the proposed text.[1]

Should you have any questions, please contact Mary P. Koleck, Senior Scientific Liaison to the Chemical Medicines Monographs 4 Expert Committee (301-230-7420 or mpk@usp.org).

[1] This text is not the official version of a *USP–NF* monograph and may not reflect the full and accurate contents of the monograph. Please refer to the current edition of the *USP–NF* for official text.

USP provides this text to indicate changes that we anticipate will be made official once the product subject to this proposed revision under the Pending Monograph Program receives FDA approval. Once FDA approval is granted for the associated revision request, a Revision Bulletin will be posted that will include the changes indicated herein, as well as any changes indicated in the product's final approval, combined with the text of the monograph as effective on the date of approval. Any revisions made to a monograph under the Pending Monograph Program that are posted without prior publication for comment in the *Pharmacopeial Forum* must also meet the requirements outlined in the USP Guideline on Use of Accelerated Processes for Revisions to the *USP-NF*.

# 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* ▲9▲ (TBD) 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*.

▲**For products labeled for dosing every 24 h**
**Test 8:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 8*.
**Medium:** Water, degassed; 500 mL
**Apparatus 2:** 50 rpm
**Times:** 1, 4, and 10 h
**Buffer:** Add 2 mL of triethylamine to 1000 mL of water and adjust with phosphoric acid to a pH of 2.5.
**Mobile phase:** Acetonitrile and *Buffer* (20:80)
**Diluent:** Acidified water; adjusted with phosphoric acid to a pH of 3.0
**Standard stock solution:** 0.6 mg/mL of USP Methylphenidate Hydrochloride RS in *Diluent*. Sonicate to dissolve.
**Standard solution:** (*L*/500) mg/mL of USP Methylphenidate Hydrochloride RS in *Diluent* from the *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.
**Chromatographic system**
(See *Chromatography* ⟨621⟩, *System Suitability*.)
**Mode:** LC
**Detector:** UV 210 nm
**Column:** 2.1-mm × 5-cm; 1.7-µm packing L1
**Flow rate:** 0.5 mL/min
**Injection volume:** 1 µL
**Run time:** NLT 2.2 times the retention time of methylphenidate
**System suitability**
**Sample:** *Standard solution*
[NOTE—The relative retention times for methylphenidate related compound A and methylphenidate are 0.65 and 1.0, respectively.]
**Suitability requirements**
**Relative standard deviation:** NMT 2.0%
**Tailing factor:** 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 8*:

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

$r_U$ = 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 8*:

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

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

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

$C_i$ = concentration of methylphenidate hydrochloride in the portion of sample withdrawn at time point (*i*) (mg/mL)
$V$ = volume of *Medium*, 500 mL
$L$ = label claim (mg/Tablet)
$V_S$ = volume of the *Sample solution* withdrawn from the *Medium* (mL)

Calculate the average percentage released from 3.5–7 h:

$$\text{Result} = (Y - X)/3.5$$

$Y$ = cumulative drug released from 0–7 h
$X$ = cumulative drug released from 0–3.5 h

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

**Table 8**

| Time Point (*i*) | Time (h) | Amount Dissolved (%) |
|---|---|---|
| 1 | 1 | 13–33 |
| 2 | 4 | 38–58 |
| 3 | 10 | NLT 80 |
| – | 3.5–7 (avg) | 7.5–16 (%/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*.▲ (TBD)

- **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* ▲9.▲ (TBD)

**Table** ▲9▲ (TBD)

| 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