Methylphenidate Hydrochloride Extended-Release Tablets

Type of Posting         Revision Bulletin  
Posting Date           25–Sep–2020  
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Expert Committee       Small Molecules 4  
Reason for Revision    Compliance  

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

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

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

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

Should you have any questions, please contact Mary P. Koleck, Senior Scientific Liaison (301-230-7420 or mpk@usp.org).
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 ($\text{C}_{14}\text{H}_{19}\text{NO}_2 \cdot \text{HCl}$).

**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 x 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
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 ($\text{C}_{14}\text{H}_{19}\text{NO}_2 \cdot \text{HCl}$) in the portion of Tablets taken:

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_S}{C_U} \right) \times 100
\]

\(r_U\) = 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: $(1.5 \times \frac{L}{500})$ 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
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>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25–45</td>
</tr>
<tr>
<td>2</td>
<td>40–65</td>
</tr>
<tr>
<td>3.5</td>
<td>55–80</td>
</tr>
<tr>
<td>5</td>
<td>70–90</td>
</tr>
<tr>
<td>7</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

*Table 1*

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 (C₁₄H₁₉NO₂·HCl) in each interval by linear regression analysis of the standard curve.

Tolerances: See Table 2.

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12–32</td>
</tr>
<tr>
<td>4</td>
<td>40–60</td>
</tr>
<tr>
<td>10</td>
<td>NLT 85</td>
</tr>
<tr>
<td>3–6 (avg)</td>
<td>9–15 (/h)</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of methylphenidate hydrochloride (C₁₄H₁₉NO₂·HCl) dissolved at the times specified conform to Dissolution (711), Acceptance Table 2.

Calculate the average percentage released from 3–6 h:

Result = (Y − X)/3

Y = cumulative drug released from 0–6 h
X = cumulative drug released from 0–3 h

For products labeled for dosing every 24 h
Test 3: If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 3.
Medium: pH 6.8 phosphate buffer (6.8 g/L of monobasic potassium phosphate in water; adjusted with 2N sodium hydroxide or 10% phosphoric acid to a pH of 6.80); 900 mL
Apparatus 1: 100 rpm
Times: 0.75, 4, and 10 h
Buffer: pH 4.0 phosphate buffer (2.72 g/L of monobasic potassium phosphate in water; adjusted with 2N sodium hydroxide or 10% phosphoric 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
Column temperature: 50°
Flow rate: See *Table 3*.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Flow Rate (mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>0.75</td>
</tr>
<tr>
<td>2.5</td>
<td>0.75</td>
</tr>
<tr>
<td>3.0</td>
<td>2.00</td>
</tr>
<tr>
<td>6.0</td>
<td>2.00</td>
</tr>
<tr>
<td>6.5</td>
<td>0.75</td>
</tr>
<tr>
<td>7.0</td>
<td>0.75</td>
</tr>
</tbody>
</table>

**Table 3**

**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*:

\[
\text{Result}_i = \left( \frac{r_i}{r_S} \right) \times C_S
\]

\( r_U = \) 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*:

\[
\text{Result}_1 = C_i \times V \times \frac{1}{L} \times 100
\]

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

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

\( C_i = \) 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)
\( V_S = \text{volume of the Sample solution withdrawn from the Medium (mL)} \)

**Tolerances:** See Table 4.

<table>
<thead>
<tr>
<th>Time Point ((i))</th>
<th>Time ((h))</th>
<th>Amount Dissolved ((%))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.75</td>
<td>12–30</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>55–80</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

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:

\[ \text{Result}_i = \left( \frac{r_U}{r_S} \right) \times C_S \]

- \(r_U\) = 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:
Result$_1 = C_i \times V \times (1/L) \times 100$

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

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

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**

<table>
<thead>
<tr>
<th>Time Point $(i)$</th>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>20–40</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>35–55</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>65–85</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

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) of methylphenidate hydrochloride (C\textsubscript{14}H\textsubscript{19}NO\textsubscript{2} · HCl) in the sample withdrawn from the vessel at each time point (i) shown in Table 6:

\[
\text{Result}_i = \left( \frac{r_U}{r_S} \right) \times C_S
\]

\( r_U \) = 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\textsubscript{14}H\textsubscript{19}NO\textsubscript{2} · 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**

<table>
<thead>
<tr>
<th>Time Point (i)</th>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>40–60</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>55–80</td>
</tr>
<tr>
<td>3</td>
<td>3.5</td>
<td>75–95</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of methylphenidate hydrochloride (C\textsubscript{14}H\textsubscript{19}NO\textsubscript{2} · 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 \((\text{C}_{14}\text{H}_{19}\text{NO}_2 \cdot \text{HCl})\) 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 \(L_1\)

**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 \((\text{C}_{14}\text{H}_{19}\text{NO}_2 \cdot \text{HCl})\) in the sample withdrawn from the vessel at each time point \((i)\) shown in *Table 7*:

\[
\text{Result}_i = \frac{r_U}{r_S} \times C_S
\]

- \(r_U\) = 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 \((\text{C}_{14}\text{H}_{19}\text{NO}_2 \cdot \text{HCl})\) dissolved at each time point \((i)\) shown in *Table 7*:
Result_1 = \( C_1 \times V \times D \times \left(1/L\right) \times 100 \)

Result_2 = \( (C_2 + C_1) \times V \times D \times \left(1/L\right) \times 100 \)

Result_i = \( (C_i + C_{i-1} + C_{i-2} + C_{i-3} + C_{i-x}) \times V \times D \times \left(1/L\right) \times 100 \)

\( C_i \) = 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:

\[ \text{Result} = \frac{(Y - X)}{3} \]

\( Y \) = cumulative drug released from 0–6 h

\( X \) = cumulative drug released from 0–3 h

**Tolerances:** See Table 7.

### Table 7

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12–32</td>
</tr>
<tr>
<td>4</td>
<td>50–75</td>
</tr>
<tr>
<td>10</td>
<td>NLT 80</td>
</tr>
<tr>
<td>3–6 (avg)</td>
<td>8–13 (%/h)</td>
</tr>
</tbody>
</table>

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 \( i \):

\[
\text{Result}_i = \left( \frac{r_U}{r_S} \right) \times C_S
\]

\( r_U \) = 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 \( i \):

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

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

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

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

\( C_i \) = 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 8.

Table 8

<table>
<thead>
<tr>
<th>Time Point ((i))</th>
<th>Time ((h))</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.5</td>
<td>10–30</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>28–48</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>70–90</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>NLT 85</td>
</tr>
</tbody>
</table>

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 \( \left(C_{14}H_{19}NO_2\cdot HCl\right)\) in the sample withdrawn from the vessel at each time point \( i \) shown in Table 9:

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

\( r_{U(m)} \) = 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:

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

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

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

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

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

\( C_i \) = 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

<table>
<thead>
<tr>
<th>Time Point (( i ))</th>
<th>Time (( h ))</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.5</td>
<td>NLT 20</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>NMT 37</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>38–58</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>59–79</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

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)

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

Standards 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 x 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_14H_19NO_2·HCl) in the sample withdrawn from the vessel at each time point (i) shown in Table 10:

\[ \text{Result}_i = \left\{ \left[ \frac{r_{U(m)}}{r_{S(m)}} \right] C_{S1} \right\} + \left\{ \left[ \frac{r_{U(e)}}{r_{S(a)}} \right] C_{S2} \times \left( \frac{M_r}{M_2} \right) \right\} \]

- 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 methylenidate 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:

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

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

\[
\text{Result}_3 = \text{Result}_2 + C_2 \times V \times (1/L) \times 100
\]

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

\( C_i \) = 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>
<thead>
<tr>
<th>Time Point ((i))</th>
<th>Time ((h))</th>
<th>Amount Dissolved ((%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.5</td>
<td>17–32</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>20–40</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>40–65</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>NLT 85</td>
</tr>
</tbody>
</table>

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

**Uniformity of Dosage Units (905):** Meet the requirements

**Impurities**

**Change to read:**

- **Organic Impurities**
  - **Mobile phase:** Dissolve 2 g of sodium 1-octanesulfonate in 730 mL of water. Adjust with phosphoric acid to a pH of 2.7. Mix with 270 mL of acetonitrile.
  - **Solution A:** Acidified water; adjusted with phosphoric acid to a pH of 3
  - **Diluent A:** Acetonitrile and Solution A (25:75)
  - **Diluent B:** Acetonitrile and methanol (50:50)
  - **System Suitability Solution:** 80 µg/mL of USP Methylphenidate Hydrochloride RS, 1 µg/mL of methylphenidate hydrochloride erythro isomer from USP Methylphenidate Hydrochloride Erythro Isomer
Solution RS, and 2 µg/mL of USP Methylphenidate Related Compound A RS in Diluent A

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

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

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

**Chromatographic system**
(See Chromatography (621), System Suitability.)

**Mode:** LC

**Detector:** UV 210 nm

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

**Column temperature:** 30°

**Flow rate:** 1 mL/min

**Injection volume:** 25 µL

**Run time:** 2 times the retention time of methylphenidate

**System suitability**

**Sample:** System suitability solution

**Suitability requirements**

- **Resolution:** NLT 6.0 between the methylphenidate and erythro isomer peaks
- **Tailing factor:** NMT 2.0 for the methylphenidate peak
- **Relative standard deviation:** NMT 2.0% for the methylphenidate peak; NMT 4.0% each for the methylphenidate related compound A and erythro isomer peaks

**Analysis**

**Samples:** Standard solution and Sample solution

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

$$ \text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_S}{C_U} \right) \times 100 $$

- $r_U$ = 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:

$$ \text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_S}{C_U} \right) \times 100 $$

- $r_U$ = peak response of each unspecified degradation product from the Sample solution
- $r_S$ = peak response of USP Methylphenidate Hydrochloride RS from the Standard solution
- $C_S$ = concentration of USP Methylphenidate Hydrochloride RS in the Standard solution (mg/mL)
- $C_U$ = nominal concentration of methylphenidate hydrochloride in the Sample solution (mg/mL)
Acceptance criteria: See Table 11.

Table 11 (RB 1-Oct-2020)

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylphenidate related compound A</td>
<td>0.47</td>
<td>1.5</td>
</tr>
<tr>
<td>Erythro isomer(^a)</td>
<td>0.65</td>
<td>0.5</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>1.0</td>
<td>—</td>
</tr>
<tr>
<td>Any unspecified degradation product</td>
<td>—</td>
<td>0.2</td>
</tr>
<tr>
<td>Total degradation products</td>
<td>—</td>
<td>2.5</td>
</tr>
</tbody>
</table>

\(^a\) 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
  - \(\alpha\)-Phenyl-2-piperidineacetic acid hydrochloride.
    \[\text{C}_{13}\text{H}_{17}\text{NO}_2 \cdot \text{HCl}\] 255.74

Page Information:

Not Applicable

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