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\textsubscript{14}H\textsubscript{19}NO\textsubscript{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 test for Organic Impurities.

ASSAY
• PROCEDURE
Buffer: Dissolve 1.64 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 (4:3:3)
Internal standard solution: 0.4 mg/mL of phenylephrine hydrochloride in Mobile phase
Standard stock solution: 0.2 mg/mL of USP Methylphenidate Hydrochloride RS in Mobile phase
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: Nominally 0.2 mg/mL of methylphenidate hydrochloride in Mobile phase, prepared as follows. Finely powder NLT 20 Tablets. Transfer a suitable amount of the powder to a suitable volumetric flask to obtain the nominal concentration. Add 70% of the flask volume of Mobile phase, and sonicate for 15 min. Cool to room temperature, dilute with Mobile phase to volume, and mix. Pass a portion of this solution through a suitable membrane filter, discarding the first portion of the filtrate.
NOTE—Avoid the use of glass filters. Polypropylene filters are suitable for use.
Sample solution: Transfer 10.0 mL of the clear filtrate to a glass-stoppered, 25-mL conical flask, and add 5.0 mL of the Internal standard solution.
Chromatographic system
(See Chromatography (621), System Suitability.)
Mode: LC
Detector: UV 210 nm
Column: 4.6-mm x 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\textsubscript{14}H\textsubscript{19}NO\textsubscript{2} \cdot HCl) in the portion of Tablets taken:
Result = \( \frac{R_0}{R_0 - R_1} \times \left( \frac{C_{USP}}{C_0} \right) \times 100 \)

R\textsubscript{0} = peak response ratio of methylphenidate hydrochloride to the internal standard from the Sample solution
R\textsubscript{1} = peak response ratio of methylphenidate hydrochloride to the internal standard from the Standard solution
C\textsubscript{USP} = concentration of USP Methylphenidate Hydrochloride RS in the Standard solution (mg/mL)
C\textsubscript{0} = 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
Sample 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.
Analysis: Calculate the percentage of the labeled amount of methylphenidate hydrochloride (C\textsubscript{14}H\textsubscript{19}NO\textsubscript{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>

The percentages of the labeled amount of methylphenidate hydrochloride (C\textsubscript{14}H\textsubscript{19}NO\textsubscript{2} \cdot HCl) dissolved at the times specified conform to Acceptance Table 2 in Dissolution (711).

Test 2 (for products labeled for dosing every 24 h): 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 (see Drug Release (724)): 30 cycles/min; 2–3 cm amplitude. Use Sample Preparation A using a metal coil sample holder (Figure 4d). 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 test tubes containing 50 mL of fresh Medium.

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

Calculate the percentages of the labeled amount of methylphenidate hydrochloride (C_{14}H_{19}NO_{2} · HCl) dissolved by using the following method.

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

**Mobile phase:** Acetonitrile and Solution A (3:7)

**Diluent:** Acetonitrile and Medium (1:3)

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

**Standard solutions:** Prepare at least six solutions by (PTFE) filter of 0.45-

Standard stock 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:** 3.2-mm × 5-cm; 5-μm packing L1

**Column temperature:** 30°C

**Flow rate:** 1 mL/min

**Injection volume:** 25 μL

**Suitability requirements**

- **Capacity factor:** NLT 2.0
- **Tailing factor:** NMT 2.0
- **Relative standard deviation:** NMT 2.0%

**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} · HCl) in each interval by linear regression analysis of the standard curve.

**Tolerances:** See Table 2.

### 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>Average from 3 to 6 h</td>
<td>9%–15%/h</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of methylphenidate hydrochloride (C_{14}H_{19}NO_{2} · HCl) dissolved at the times specified conform to Acceptance Table 2 in Dissolution (711).

Calculate the average percentage released from 3 to 6 h:

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

- Y = cumulative drug released from 0 to 6 h
- X = cumulative drug released from 0 to 3 h

**Test 3** (for products labeled for dosing every 24 h): 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

**Buffer:** pH 6.8 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 6.00)

**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°C

**Flow rate:** See Table 3.

### 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>

**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) of methylphenidate hydrochloride (C_{14}H_{19}NO_{2} · HCl) in the sample withdrawn from the vessel at each time point i shown in Table 4:

\[ \text{Result} = \left( \frac{R_i}{R_S} \right) \times C_i \]

- \( R_i \) = 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
- \( C_i \) = concentration of USP Methylphenidate Hydrochloride RS in the Standard solution

Calculate the percentage of the labeled amounts of methylphenidate hydrochloride (C_{14}H_{19}NO_{2} · HCl) dissolved at each time point i shown in Table 4:

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

\[ \text{Result}_2 = (C_i \times \frac{V - V_i}{V_i}) + [C_i \times V_i] \times (1/L) \times 100 \]

\[ \text{Result}_3 = (\left( C_i \times \frac{V - (2 \times V_i)}{V_i} \right) + [C_i + C_i] \times V_i] \times (1/L) \times 100 \]
Methylphenidate 3

Calculate the percentage of the labeled amounts of methylphenidate hydrochloride (C₁₄H₁₉NO₂·HCl) dissolved at each time point i shown in Table 5:

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

\[
\text{Result}_2 = \left( \frac{C_i \times [V - (V_i)] + [C_i \times V_i]}{1/(L \times 100)} \right)
\]

\[
\text{Result}_3 = \left( \frac{C_i \times [V - (2 \times V_i)] + [C_i \times 2 \times V_i]}{1/(L \times 100)} \right)
\]

\[
\text{Result}_4 = \left( \frac{C_i \times [V - (3 \times V_i)] + [C_i + C_i + C_i \times V_i]}{1/(L \times 100)} \right)
\]

\[
C_i = \text{concentration of methylphenidate hydrochloride in the portion of sample withdrawn at time point i (mg/mL)}
\]

\[
V = \text{volume of Medium (mL)}
\]

\[
L = \text{label claim (mg/Tablet)}
\]

\[
V_i = \text{volume of Sample solution withdrawn from the Medium (mL)}
\]

**Tolerances:** See Table 5.

### 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 (C₁₄H₁₉NO₂·HCl) dissolved at the times specified conform to Acceptance Table 2 in Dissolution (711).

**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

**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°C

**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) of methylphenidate hydrochloride (C₁₄H₁₉NO₂·HCl) in the sample withdrawn from the vessel at each time point i shown in Table 5:

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

\[
r_S = \text{peak response of methylphenidate from the Standard solution}
\]

\[
C_S = \text{concentration of USP Methylphenidate Hydrochloride RS in the Standard solution}
\]

### 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 (C₁₄H₁₉NO₂·HCl) dissolved at the times specified conform to Acceptance Table 2 in Dissolution (711).

**IMPURITIES**

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

**Change to read:**

**ORGANIC IMPURITIES**

Mobile phase: Dissolve 2 g of 1-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:** Acetonitrile and water (1:3)

**Diluent A:** Acetonitrile and Solution A (1:3)

**Diluent B:** Acetonitrile and methanol (1:1)

**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 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:** Dissolve 10 Tablets in a suitable volumetric flask to obtain a nominal concentration of 1 mg/mL of methylphenidate hydrochloride containing 20% of the total flask volume of Diluent B. [Note—Alternatively, a suitable number of Tablets may be dissolved at the times specified conform to Acceptance Table 2 in Dissolution (711).]
powdered and suspended in 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 x 15-cm; 5-µm packing L1  
**Column temperature:** 30°C  
**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**  
- **Tailing factor:** NMT 2.0 for the methylphenidate peak  
- **Resolution:** NLT 6.0 between the methylphenidate and erythro isomer peaks  
- **Relative standard deviation:** NMT 2.0% for the methylphenidate peak; NMT 4.0% each for the unspecified degradation product

**Analysis**  
**Samples:** Standard solution and Sample solution

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

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

$r_U$ = 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)

Calculate the percentage of any unspecified degradation product in the portion of Tablets taken:

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

**Table 6**

<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</td>
<td>0.65</td>
<td>0.5</td>
</tr>
<tr>
<td>Methylphenidate hydrochloride</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 unspecified degradation products</td>
<td>—</td>
<td>2.5</td>
</tr>
</tbody>
</table>

Additional requirements  
- **Packaging and Storage:** Preserve in tight containers.  
- **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  
  This solution contains 0.5 mg of methylphenidate hydrochloride erythro isomer per mL in methanol.  
  USP Methylphenidate Related Compound A RS  
  α-Phenyl-2-piperidineacetic acid hydrochloride. $C_{13}H_{17}NO_2 \cdot HCl \ 255.75$