Methylphenidate Hydrochloride Extended-Release Tablets

Type of Posting: Revision Bulletin
Posting Date: 22–Nov–2019
Official Date: 01–Dec–2019
Expert Committee: Chemical Medicines Monographs 4
Reason for Revision: Compliance

In accordance with the Rules and Procedures of the 2015–2020 Council of Experts, the Chemical Medicines Monographs 4 Expert Committee has revised the Methylphenidate Hydrochloride Extended-Release Tablets monograph. The purpose for the revision is to add *Dissolution Test 10* to accommodate FDA-approved drug products with different tolerances than the existing dissolution tests.

- *Dissolution Test 10* was validated using a Waters Symmetry C8 brand of L7 column. The typical retention time for methylphenidate is about 3.5 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 (C_{19}H_{19}NO_{2}·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 10A (88:1-Dec-2019) 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_{19}H_{19}NO_{2}·HCl) in the portion of Tablets taken:

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

\[
\begin{align*}
  r_U &= \text{peak response from the Sample solution} \\
  r_S &= \text{peak response from the Standard solution} \\
  C_i &= \text{concentration of USP Methylphenidate Hydrochloride RS in the Standard solution (mg/mL)} \\
  C_U &= \text{nominal concentration of methylphenidate hydrochloride in the Sample solution (mg/mL)}
\end{align*}
\]

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.]
Methylphenidate

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 (C₈H₁₄NO₂ · 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 (C₈H₁₄NO₂ · 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 (C₈H₁₄NO₂ · 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

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 (C₈H₁₄NO₂ · 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>3–6 (avg)</td>
<td>9–15 (/h)</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of methylphenidate hydrochloride (C₈H₁₄NO₂ · 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 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

<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>
</tbody>
</table>
**Methylphenidate 3**

**Revised 11/2019**

**Table 3 (continued)**

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Flow Rate (mL/min)</th>
</tr>
</thead>
<tbody>
<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 \( (C_{14H_{19}NO_2} \cdot HCl) \) in the sample withdrawn from the vessel at each time point \( (i) \) shown in Table 4:

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

\( r_u = \text{sum of the peak responses of methylphenidate and methylphenidate related compound A from the Sample solution} \)

\( r_s = \text{peak response of methylphenidate from the Standard solution} \)

\( C_i = \text{concentration of USP Methylphenidate Hydrochloride RS in the Standard solution (mg/mL)} \)

Calculate the percentage of the labeled amount of methylphenidate hydrochloride \( (C_{14H_{19}NO_2} \cdot HCl) \) dissolved at each time point \( (i) \) shown in Table 4:

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

\( \text{Result}_3 = \left( \frac{C_i \times (V - V_3)}{L} \right) \times 100 \)

\( \text{Result}_S = \left( \frac{(C_i \times (V - (2 \times V_3))) + (C_i + C_i) \times V_3}{L} \right) \times 100 \times 100 \)

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

\( V = \text{volume of Medium, 900 mL} \)

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

\( V_3 = \text{volume of the Sample solution withdrawn from the Medium (mL)} \)

**Tolerances**: See Table 4.

<table>
<thead>
<tr>
<th>Time Point (h)</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 \( (C_{14H_{19}NO_2} \cdot HCl) \) 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**: 0.01 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 x 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) of methylphenidate hydrochloride \( (C_{14H_{19}NO_2} \cdot HCl) \) in the sample withdrawn from the vessel at each time point \( (i) \) shown in Table 5:

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

\( r_u = \text{peak response of methylphenidate from the Sample solution} \)

\( r_s = \text{peak response of methylphenidate from the Standard solution} \)

\( C_i = \text{concentration of USP Methylphenidate Hydrochloride RS in the Standard solution (mg/mL)} \)

Calculate the percentage of the labeled amount of methylphenidate hydrochloride \( (C_{14H_{19}NO_2} \cdot HCl) \) dissolved at each time point \( (i) \) shown in Table 5:

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

\( \text{Result}_3 = \left( \frac{C_i \times (V - V_3)}{L} \right) \times 100 \)

\( \text{Result}_S = \left( \frac{(C_i \times (V - (2 \times V_3))) + (C_i + C_i) \times V_3}{L} \right) \times 100 \times 100 \)

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

\( V = \text{volume of Medium, 500 mL} \)

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

\( V_3 = \text{volume of the Sample solution withdrawn from the Medium (mL)} \)

**Tolerances**: See Table 5.
**Table 5**

<table>
<thead>
<tr>
<th>Time Point (h)</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$_2$·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 x 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 ($C_1$) 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 6:

$$\text{Result}_i = (r_i/r_s) \times C_1$$

$r_1$ = peak response of methylphenidate from the Sample solution

$r_s$ = peak response of methylphenidate from the Standard solution

$C_1$ = 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$_2$·HCl) dissolved at each time point ($i$) shown in Table 6:

$$\text{Amount Dissolved} = \left( \frac{\text{Result}_i}{\text{Result}_T} \right) \times 100$$

where $\text{Result}_T$ is the total amount dissolved at the end of the dissolution test.

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

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

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

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

$C_1$ = 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 (h)</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 ($C_{14}$H$_{19}$NO$_2$·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 ($C_{14}$H$_{19}$NO$_2$·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.

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**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 2.0% 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) 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 7:

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

- \(r_i\) = 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 · HCl) dissolved at each time point (i) shown in Table 7:

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

- \(C_i\) = 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:

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

- \(Y\) = cumulative drug released from 0–6 h  
- \(X\) = cumulative drug released from 0–3 h

**Tolerances:** See Table 7.

<table>
<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>

**Methylphenidate 5**

The percentages of the labeled amount of methylphenidate hydrochloride (C_{14}H_{19}NO_2 · 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, 1, 2, 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) of methylphenidate hydrochloride (C_{14}H_{19}NO_2 · HCl) in the sample withdrawn from the vessel at each time point (i):

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

- \(r_i\) = 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 · HCl) dissolved at each time point (i):

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

- \(C_i\) = 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:

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

- \(Y\) = cumulative drug released from 0–6 h  
- \(X\) = cumulative drug released from 0–3 h

**Tolerances:** See Table 8.
6 Methylphenidate

Table 8

<table>
<thead>
<tr>
<th>Time Point (t)</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 \((C_{16}H_{23}NO_2 \cdot HCl)\) dissolved at the times specified are as shown in Table 8. Table 8.

*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 potassium 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°C
- **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 3.7, Standard solution

**Analysis**

**Samples:** Standard solution and Sample solution

Calculate the concentration \((C)\) of methylphenidate hydrochloride \((C_{16}H_{23}NO_2 \cdot HCl)\) in the sample withdrawn from the vessel at each time point \((t)\) shown in Table 9:

\[
\text{Result} = \left[ \frac{\text{Result}_i \times (1/F)}{V_i} \times 100 \right] + \left[ \frac{\text{Result}_i \times 100}{V_i} \right]
\]

\[
\text{Result}_i = \left( \frac{r_{500}}{r_{1000}} \right) \cdot \text{C}
\]

Calculate the percentage of the labeled amount of methylphenidate hydrochloride \((C_{16}H_{23}NO_2 \cdot HCl)\) dissolved at each time point \((t)\) shown in Table 9:

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

**Table 9**

<table>
<thead>
<tr>
<th>Time Point (t)</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 \((C_{16}H_{23}NO_2 \cdot HCl)\) dissolved at each time point are as shown in Table 9.
dissolved at the times specified conform to Dissolution (711), Acceptance Table 2, (RB 1-Dec-2019)

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

**IMPURITIES**

*Organic Impurities*

**Mobile phase**: Dissolve 2 g of sodium 1-octanesulfonate in 730 mL of water. Adjust with phosphoric acid to a pH of 2.7. Mix with 270 mL of acetonitrile.

**Solution A**: Acidified water; adjusted with phosphoric acid to a pH of 3

**Diluent A**: Acetonitrile and Solution A (25:75)

**Diluent B**: Acetonitrile and methanol (50:50)

**System suitability solution**: 80 µg/mL of USP Methylphenidate Hydrochloride RS, 1 µg/mL of methylphenidate hydrochloride erythro isomer from USP Methylphenidate Hydrochloride Erythro Isomer Solution RS, and 2 µg/mL of USP Methylphenidate Related Compound A RS in Diluent A

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

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

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

**Chromatographic system**

(See Chromatography (621), System Suitability.)

**Mode**: LC

**Detector**: UV 210 nm

**Column**: 3.9-mm 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**

**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:

Result = \( \frac{(r_f - r_s)}{r_o} \times \frac{C_f}{C_o} \times 100 \)

**ADDITIONAL REQUIREMENTS**

**Packaging and Storage**: Preserve in tight containers.

**Labelling**: 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

\( C_{11}H_{17}N_2O_2 \cdot HCl \) 255.74

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