Metformin Hydrochloride Extended-Release Tablets

Type of Posting               Revision Bulletin
Posting Date                 21–Sep–2018
Official Date                24–Sep–2018
Expert Committee             Chemical Medicines Monographs 3
Reason for Revision          Compliance

In accordance with the Rules and Procedures of the 2015–2020 Council of Experts, the Chemical Medicines Monographs 3 Expert Committee has revised the Metformin Hydrochloride Extended-Release Tablets monograph. The purpose of the revision is to add *Dissolution Test 14* to accommodate FDA-approved drug products with different tolerances than the existing dissolution tests.

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

Should you have any questions, please contact Andrea F. Carney, Scientific Liaison to the Chemical Medicines Monographs 3 Expert Committee (301-816-8155 or [afc@usp.org](mailto:afc@usp.org)).
Metformin Hydrochloride Extended-Release Tablets

DEFINITION
Metformin Hydrochloride Extended-Release Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of metformin hydrochloride (C$_{6}$H$_{11}$N$_{3}$·HCl).

IDENTIFICATION
• A. The retention time of the major peak from the Sample solution corresponds to that from the Standard solution, as obtained in the Assay.

ASSAY
• PROCEDURE
Buffer solution: 0.5 g/L of sodium 1-heptanesulfonate and 0.5 g/L of sodium chloride in water. Before final dilution, adjust with 0.06 M phosphoric acid to a pH of 3.85.

Mobile phase: Acetonitrile and Buffer solution (1:9). [NOTE—To improve the separation, the composition of acetonitrile and Buffer solution may be changed to 1:19, if necessary.]

Diluent: 1.25% solution of acetonitrile in water

Standard solution: (U/4000) mg/mL of USP Metformin Hydrochloride RS in Diluent, where L is the labeled quantity, in mg, of metformin hydrochloride in each Tablet

System suitability stock solution: 12.5 µg/mL each of USP Metformin Related Compound B RS and USP Metformin Related Compound C RS in Diluent

System suitability solution: Dilute 0.5 mL of the System suitability stock solution with the Standard solution to 50 mL.

Sample stock solution: Finely powder NLT 10 Tablets. Transfer powder, equivalent to the average Tablet weight, to a homogenization vessel, and add 500 mL of a 10% acetonitrile solution. Alternately, homogenize and allow to soak until the sample is fully homogenized. [NOTE—A suggested homogenization sequence is as follows. Homogenize the sample using five pulses, each of 5 s, at about 20,000 rpm, and allow to soak for 2 min. Repeat these steps two additional times.]

Sample solution: Pass a portion of the Sample stock solution through a suitable filter of 0.45-µm pore size, discarding the first 3 mL of filtrate. Transfer 25 mL of the filtrate to a 200-mL volumetric flask, and dilute with water to volume.

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

Mode: LC
Detector: UV 218 nm
Column: 3.9-mm × 30-cm; 10-µm packing L1
Column temperature: 30°C
Flow rate: 1 mL/min
Injection volume: 10 µL
Run time: Until after the elution locus of metformin related compound C

System suitability
Sample: System suitability solution
[NOTE—The relative retention times for metformin related compound B, metformin, and metformin related compound C are 0.86, 1.0, and 2.1–2.3, respectively. Metformin related compound C can have a variable retention time. The composition of the Mobile phase may be changed to 1:19, if it elutes at a relative retention time of less than 2.1.]

Suitability requirements
Resolution: NLT 1.5 between the peaks due to metformin related compound B and metformin

Tailing factor: NLT 0.8 and NMT 2.0 for the metformin peak

Relative standard deviation: NMT 1.5% for the metformin peak and NMT 10% for each of the peaks due to metformin related compound B and metformin related compound C

Analysis
Samples: Standard solution and Sample solution
Calculate the percentage of the labeled amount of metformin hydrochloride (C$_{6}$H$_{11}$N$_{3}$·HCl) in the portion of Tablets taken:

Result = \((r_u/r_s) \times (C_s/C_d) \times 100\)

\(r_u\) = peak response from the Sample solution
\(r_s\) = peak response from the Standard solution
\(C_s\) = concentration of USP Metformin Hydrochloride RS in the Standard solution (mg/mL)
\(C_d\) = nominal concentration of metformin hydrochloride in the Sample solution

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

• DISSOLUTION (711)

Test 1
Medium: pH 6.8 phosphate buffer solution; 1000 mL
Apparatus 1: 100 rpm for Tablets labeled to contain 750 mg
Apparatus 2: 100 rpm for Tablets labeled to contain 500 mg
Times: 1, 3, and 10 h
Detector: UV 232 nm

Standard solution: USP Metformin Hydrochloride RS in Medium

Sample solution: Pass a portion of the solution under test through a suitable hydrophilic polyethylene filter of 0.45-µm pore size. Dilute, if necessary, with Medium to a concentration similar to that of the Standard solution.

Analysis: Calculate the percentage of the labeled amount of metformin hydrochloride (C$_{6}$H$_{11}$N$_{3}$·HCl) released at each time point:

Result = \([(A_U/A_T) \times C_U \times (V - V_2) + (C_{60} \times V_2) + (C_{180} \times V_3)] \times 100/L\)

\(A_U\) = absorbance of the Sample solution
\(A_T\) = absorbance of the Standard solution
\(C_U\) = concentration of the Standard solution (mg/mL)
\(V\) = initial volume of Medium in the vessel (mL)
\(V_2\) = volume withdrawn from the vessel for previous samplings (mL)
\(C_{60}\) = concentration of metformin hydrochloride in Medium determined at 1 h (mg/mL)
\(C_{180}\) = concentration of metformin hydrochloride in Medium determined at 3 h (mg/mL)
\(L\) = label claim (mg/Tablet)

Tolerances: See Table 1.
2 Metformin

Table 1

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved, 500-mg Tablet (%)</th>
<th>Amount Dissolved, 750-mg Tablet (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20-40</td>
<td>22-42</td>
</tr>
<tr>
<td>3</td>
<td>45-65</td>
<td>49-69</td>
</tr>
<tr>
<td>10</td>
<td>NLT 85</td>
<td>NLT 85</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of metformin hydrochloride (C₆H₁₁N₃·HCl) dissolved at the times specified conform to Dissolution (711), Acceptance Table 2.

Test 2: If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 2.

Medium: Prepare as directed for Test 1; 1000 mL.

Apparatus 2: 100 rpm

Times: 1, 2, 6, and 10 h

Detector: UV 232 nm

Standard solution: USP Metformin Hydrochloride RS in Medium

Sample solution: Pass a portion of the solution under test through a suitable polyethylene filter of 0.45-µm pore size. Dilute, if necessary, with Medium to a concentration that is similar to that of the Standard solution.

Analysis: Calculate, in the content of metformin hydrochloride (C₆H₁₁N₃·HCl) (C₁), in Medium at each time point (t):

\[
\text{Result} = \left( \frac{A_{ij} \times C_1 \times D_{ij}}{A_i} \right)
\]

- \( A_{ij} \) = absorbance of the Sample solution
- \( C_1 \) = concentration of metformin hydrochloride in the Standard solution (mg/mL)
- \( D_{ij} \) = dilution factor of the solution under test
- \( A_i \) = absorbance of the Standard solution

Calculate the percentage of the labeled amount of metformin hydrochloride (C₆H₁₁N₃·HCl) dissolved at each time point by the following formulas.

Percentage dissolved at the first time point (1 h):

\[
\text{Result} = \left( C_1 \times V \times 100 \right) / \text{L}
\]

- \( C_1 \) = content of metformin hydrochloride in Medium at the first time interval (mg/mL)
- \( V \) = volume of Medium, 1000 mL
- \( L \) = label claim (mg/Tablet)

Percentage dissolved at the second time point (2 h):

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

- \( C_2 \) = content of metformin hydrochloride in Medium at the second time interval (mg/mL)
- \( V \) = volume of Medium, 1000 mL
- \( SV_j \) = volume of the sample withdrawn at 1 h (mL)
- \( C_1 \) = content of metformin hydrochloride in Medium at 1 h (mg/mL)
- \( L \) = label claim (mg/Tablet)

Percentage dissolved at the nth time point:

\[
\text{Result} = \left( C_n \times [V - (n - 1)V_j] + (C_1 + C_2 + \ldots + C_{n-1}) \times V_j \right) \times (100/L)
\]

- \( C_n \) = content of metformin hydrochloride in Medium at the nth time interval (mg/mL)
- \( V \) = volume of Medium, 1000 mL
- \( V_j \) = volume withdrawn at each time interval (mL)
- \( C_1 \) as \( C_1, C_2, C_3, \ldots, C_{n-1} \), the content of metformin hydrochloride in Medium at each time interval (mg/mL)
- \( L \) = label claim (mg/Tablet)

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>20-40</td>
</tr>
<tr>
<td>2</td>
<td>35-55</td>
</tr>
<tr>
<td>6</td>
<td>65-85</td>
</tr>
<tr>
<td>10</td>
<td>NLT 85</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of metformin hydrochloride (C₆H₁₁N₃·HCl) dissolved at the times specified conform to Dissolution (711), Acceptance Table 2.

Test 3: If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 3.

Medium, Apparatus 1, and Apparatus 2: Proceed as directed in Test 1.

Times: 1, 2, 5, and 12 h for Tablets labeled to contain 500 mg; and 1, 3, and 10 h for Tablets labeled to contain 750 mg

Detector: UV 232 nm

Standard solution: USP Metformin Hydrochloride RS in Medium

Sample solution: Pass a portion of the solution under test through a suitable hydrophilic polyethylene filter of 0.45-µm pore size. Dilute, if necessary, with Medium to a concentration similar to that of the Standard solution.

Analysis: Calculate the percentage of the labeled amount of metformin hydrochloride (C₆H₁₁N₃·HCl) released at each time point:

\[
\text{Result} = \left( \frac{[(A_{ij} \times A_i) \times C_2 \times (V - V_j) + (C_{60} \times V_j) + (C_{120} \times V_j) + (C_{300} \times V_j) + (C_{720} \times V_j)] \times 100}{L} \right)
\]

- \( A_{ij} \) = absorbance of the Sample solution
- \( A_i \) = absorbance of the Standard solution
- \( C_2 \) = concentration of the Standard solution (mg/mL)
- \( V \) = initial volume of Medium in the vessel (mL)
- \( V_j \) = volume withdrawn from the vessel for previous samplings (mL)
- \( C_{60} \) = concentration of metformin hydrochloride in Medium determined at 1 h (mg/mL)
- \( C_{120} \) = concentration of metformin hydrochloride in Medium determined at 2 h (mg/mL)
- \( C_{300} \) = concentration of metformin hydrochloride in Medium determined at 5 h (mg/mL)
- \( C_{720} \) = concentration of metformin hydrochloride in Medium determined at 12 h (mg/mL)
- \( L \) = label claim (mg/Tablet)

Tolerances: See Tables 3 and 4.
Table 3. For Tablets Labeled to Contain 500 mg

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20–40</td>
</tr>
<tr>
<td>2</td>
<td>35–55</td>
</tr>
<tr>
<td>5</td>
<td>60–80</td>
</tr>
<tr>
<td>12</td>
<td>NLT 85</td>
</tr>
</tbody>
</table>

Table 4. For Tablets Labeled to Contain 750 mg

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>22–42</td>
</tr>
<tr>
<td>3</td>
<td>49–69</td>
</tr>
<tr>
<td>10</td>
<td>NLT 85</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of metformin hydrochloride \((C_4H_11N_5 \cdot HCl)\) 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:** Prepare as directed for Test 1; 1000 mL.

**Apparatus 2:** 100 rpm

**Times:** 1, 3, 6, and 10 h

**Detector:** UV 250 nm (shoulder)

**Standard solution:** USP Metformin Hydrochloride RS in Medium

**Sample solution:** Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size. Dilute, if necessary, with Medium to a concentration similar to that of the Standard solution.

**Analysis:** Calculate, in mg/mL, the content of metformin hydrochloride \((C_4H_11N_5 \cdot HCl)\) \((C)\), in Medium at each time point \((t)\), by the formulas specified in Test 2.

Tolerances: See Table 5.

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20–40</td>
</tr>
<tr>
<td>3</td>
<td>45–65</td>
</tr>
<tr>
<td>6</td>
<td>65–85</td>
</tr>
<tr>
<td>10</td>
<td>NLT 85</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of metformin hydrochloride \((C_4H_11N_5 \cdot HCl)\) 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:** pH 6.8 phosphate buffer solution; 900 mL, deaerated

**Apparatus 1:** 100 rpm, with the vertical holder described in Figure 1 and Figure 2

**Times:** 2, 8, and 16 h

**Detector:** UV 250 nm

**Standard solution:** USP Metformin Hydrochloride RS in Medium

**Sample solution:** Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size. Dilute, if necessary, with Medium to a concentration similar to that of the Standard solution.

**Analysis:** Place a vertical sample holder into each basket (see Figures 1 and 2). Place 1 Tablet inside the sample holder, making sure that the Tablets are vertical at the bottom of the baskets.

Calculate, in mg/mL, the content of metformin hydrochloride \((C_4H_11N_5 \cdot HCl)\) \((C)\), in Medium at each time point \((t)\), by the formulas specified in Test 2.

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NOTES:
1. MATERIAL: 316SS OR EQUIVALENT .017 WIRE VERTICAL MEAS SQUARE WEAVE WITH .039 SQUARE OPENINGS.
2. ALL DIMENSIONS ARE IN INCHES. TOLERANCES TO BE +/- .010

Figure 1
Table 6

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved, 500-mg Tablet (%)</th>
<th>Amount Dissolved, 1000-mg Tablet (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>NMT 30</td>
<td>NMT 30</td>
</tr>
<tr>
<td>8</td>
<td>60–85</td>
<td>65–90</td>
</tr>
<tr>
<td>16</td>
<td>NLT 90</td>
<td>NLT 90</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of metformin hydrochloride (C$_4$H$_{11}$N$_5$·HCl) dissolved at the times specified conform to Dissolution (711), Acceptance Table 2.
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Test 7: If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 7.

Medium: Prepare as directed in Test 1; 1000 mL.

Apparatus 1: 100 rpm for Tablets labeled to contain 750 mg

Apparatus 2: 100 rpm, with sinker, for Tablets labeled to contain 500 mg

Times: 1, 2, 6, and 10 h

Detector: UV 232 nm

Standard solution: USP Metformin Hydrochloride RS in Medium

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-μm pore size. Dilute, if necessary, with Medium to a concentration similar to that of the Standard solution.

Analysis: Calculate the percentage of the labeled amount of metformin hydrochloride (C₆H₁₄N₇·HCl) released at each time point:

\[
\text{Result} = \left[ \frac{(A_0/A_s) \times C_s \times (V - V_1) + (C_{60} \times V_0) + (C_{180} \times V_1) + (C_{600} \times V_2) \times 100}{L} \right] \%
\]

A₀ = absorbance of the Sample solution
Aₛ = absorbance of the Standard solution
Cₛ = concentration of the Standard solution (mg/mL)
V = initial volume of Medium in the vessel (mL)
V₁ = volume withdrawn from the vessel for previous samplings (mL)
C₆₀ = concentration of metformin hydrochloride in Medium determined at 1 h (mg/mL)
C₁₈₀ = concentration of metformin hydrochloride in Medium determined at 3 h (mg/mL)
C₆₀₀ = concentration of metformin hydrochloride in Medium determined at 10 h (mg/mL)
L = label claim (mg/Tablet)

The percentages of the labeled amount of metformin hydrochloride (C₆H₁₄N₇·HCl) dissolved at the times specified conform to Dissolution (711), Acceptance Table 2.

Test 8: If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 8.

Medium: Prepare as directed in Test 1; 1000 mL.

Apparatus 1: 1000 mL.

Apparatus 2: 100 rpm for Tablets labeled to contain 750 mg

Apparatus 2: 100 rpm, with sinker, for Tablets labeled to contain 500 mg

Times: 1, 2, 6, and 10 h

Detector: UV 232 nm

Standard solution: USP Metformin Hydrochloride RS in Medium

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-μm pore size. Dilute, if necessary, with Medium to a concentration similar to that of the Standard solution.

Analysis: Calculate the percentage of the labeled amount of metformin hydrochloride (C₆H₁₄N₇·HCl) released at each time point:

\[
\text{Result} = \left[ \frac{(A_0/A_s) \times C_s \times (V - V_1) + (C_{60} \times V_0) + (C_{120} \times V_1) + (C_{180} \times V_2) + (C_{300} \times V_3) \times 100}{L} \right] \%
\]

A₀ = absorbance of the Sample solution
Aₛ = absorbance of the Standard solution
Cₛ = concentration of the Standard solution (mg/mL)
V = initial volume of Medium in the vessel (mL)
V₁ = volume withdrawn from the vessel for previous samplings (mL)
C₆₀ = concentration of metformin hydrochloride in Medium determined at 1 h (mg/mL)
C₁₂₀ = concentration of metformin hydrochloride in Medium determined at 2 h (mg/mL)
C₁₈₀ = concentration of metformin hydrochloride in Medium determined at 3 h (mg/mL)
C₃₀₀ = concentration of metformin hydrochloride in Medium determined at 10 h (mg/mL)
L = label claim (mg/Tablet)

Tolerances: See Table 8.

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved, 500-mg Tablet (%)</th>
<th>Amount Dissolved, 750-mg Tablet (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20–40</td>
<td>20–40</td>
</tr>
<tr>
<td>3</td>
<td>45–65</td>
<td>40–60</td>
</tr>
<tr>
<td>10</td>
<td>NLT 85</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

Tolerances: See Table 9.

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved, 500-mg Tablet (%)</th>
<th>Amount Dissolved, 750-mg Tablet (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20–40</td>
<td>20–40</td>
</tr>
<tr>
<td>2</td>
<td>30–50</td>
<td>35–55</td>
</tr>
<tr>
<td>6</td>
<td>65–85</td>
<td>75–95</td>
</tr>
<tr>
<td>10</td>
<td>NLT 85</td>
<td>NLT 85</td>
</tr>
</tbody>
</table>
The percentages of the labeled amount of metformin hydrochloride (\(C_6H_{11}N_2 \cdot HCl\)) 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:** 0.05 M phosphate buffer, pH 6.8; 1000 mL

**Apparatus 1:** 100 rpm, for Tablets labeled to contain 750 mg

**Apparatus 2:** 100 rpm, for Tablets labeled to contain 500 mg

**Times:** 1, 5, 12, and 20 h for Tablets labeled to contain 500 mg; and 1, 4, 10, and 24 h for Tablets labeled to contain 750 mg

**Standard solution:** 0.5 mg/mL of USP Metformin Hydrochloride RS in **Medium**

**Sample solution:** Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size.

**Detector:** UV 232 nm

**Path length:** 0.01 cm, flow cell

**Blank:** **Medium**

**Analysis:** Calculate the percentage of the labeled amount of metformin hydrochloride (\(C_6H_{11}N_2 \cdot HCl\)) released at each time point:

\[
\text{Result} = \left\{ \left( \frac{A_i - A_j}{A_i} \times V - V_j \right) + \left( C_i \times V_j \right) + \left( C_1 \times V_2 \right) + \left( C_2 \times V_3 \right) + \left( C_3 \times V_4 \right) \right\} \times 100 / L
\]

\(A_i\) = absorbance of the **Sample solution**

\(A_j\) = absorbance of the **Standard solution**

\(C_i\) = concentration of the **Standard solution** (mg/mL)

\(V\) = initial volume of **Medium** in the vessel (mL)

\(V_j\) = volume withdrawn from the vessel for previous samplings (mL)

\(C_i\) = concentration of metformin hydrochloride in **Medium** determined at the first time point (mg/mL)

\(C_2\) = concentration of metformin hydrochloride in **Medium** determined at the second time point (mg/mL)

\(C_3\) = concentration of metformin hydrochloride in **Medium** determined at the third time point (mg/mL)

\(C_4\) = concentration of metformin hydrochloride in **Medium** determined at the fourth time point (mg/mL)

\(L\) = label claim (mg/Tablet)

**Tolerances:** See Tables 10 and 11.

### Table 10. For Tablets Labeled to Contain 500 mg

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20–40</td>
</tr>
<tr>
<td>5</td>
<td>45–65</td>
</tr>
<tr>
<td>12</td>
<td>70–90</td>
</tr>
<tr>
<td>20</td>
<td>NLT 85</td>
</tr>
</tbody>
</table>

### Table 11. For Tablets Labeled to Contain 750 mg

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20–45</td>
</tr>
<tr>
<td>4</td>
<td>45–70</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of metformin hydrochloride (\(C_6H_{11}N_2 \cdot HCl\)) 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**.

**Medium:** 0.05 M phosphate buffer (prepared by dissolving 6.8 g of monobasic potassium phosphate in 250 mL of water, adding 77 mL of 0.2 N sodium hydroxide and 500 mL of water, adjusting with 2 N sodium hydroxide or 2 N hydrochloric acid to a pH 6.8, and diluting with water to 1000 mL)

**Apparatus 1:** 100 rpm for Tablets labeled to contain 750 mg

**Apparatus 2:** 100 rpm for Tablets labeled to contain 500 mg

**Times:** 1, 3, and 10 h

**Standard solution:** (\(L/100,000\)) mg/mL of USP Metformin Hydrochloride RS in **Medium**, where \(L\) is the label claim, in mg/Tablet. This solution is stable for 72 h at room temperature.

**Sample solution:** At the times specified, withdraw 10 mL of the solution under test and replace with 10 mL of **Medium** previously equilibrated at 37.0 ± 0.5°. Centrifuge at 2500 rpm for 10 min. Dilute a portion of the supernatant with **Medium** to obtain a theoretical concentration of (\(L/100,000\)) mg/mL, where \(L\) is the label claim, in mg/Tablet.

**Detector:** UV 233 nm

**Path length:** 1 cm

**Blank:** **Medium**

**Analysis:** Calculate the concentration (mg/mL) of metformin hydrochloride (\(C\)) at each time point:

\[
C_i = (A_i / A_j) \times C_j
\]

\(A_i\) = absorbance of the **Sample solution**

\(A_j\) = absorbance of the **Standard solution**

\(C_j\) = concentration of the **Standard solution** (mg/mL)

Calculate the cumulative percentage of the labeled amount of metformin hydrochloride (\(C_6H_{11}N_2 \cdot HCl\)) dissolved (\(Q\)) at each time point (\(i\)):

At \(i = 1\): \(Q_1 = (C_1 \times V/L) \times 100\)

At \(i = 3\): \(Q_3 = [C_j (V - V_j) + (C_j \times V_j)] \times 100 / L\)

At \(i = 10\): \(Q_{10} = [C_{10} (V - 2V_j) + (C_j + C_{10}) V_j] \times 100 / L\)

\(V\) = initial volume of **Medium**, 1000 mL

\(V_j\) = sampling volume, 10 mL

\(L\) = label claim (mg/Tablet)

**Tolerances:** See Table 12.
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If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 11.

**Test 11:** If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 11.

**Medium:** pH 6.8 phosphate buffer solution; 1000 mL

**Apparatus 1:** 100 rpm for Tablets labeled to contain 750 mg

**Apparatus 2:** 100 rpm for Tablets labeled to contain 500 mg

**Times:** 1, 3, and 10 h

**Standard solution:** 7.5 µg/mL of USP Metformin Hydrochloride RS in Medium

**Sample solution:** At the times specified, withdraw 10 mL of the solution under test, and pass it through a suitable filter of 0.45-µm pore size, discarding the first 3 mL of filtrate. Dilute 3.0 mL of the filtrate with Medium to 200 mL. For Tablets labeled to contain 750 mg, dilute 2.0 mL of the filtrate with Medium to 200 mL. Replace the volume of Medium taken with the same volume of Medium preheated at 37.0 ± 0.5°.

**Detector:** UV 232 nm

**Path length:** 1 cm

**Blank:** Medium

**Analysis:** Calculate the percentage of the labeled amount of metformin hydrochloride (C₆H₁₁N₃·HCl) dissolved at each time point:

\[ Q_i = \left( \frac{A_i}{A_j} \right) \times \left( \frac{C_i}{L} \right) \times V \times D \times 100 \]

At 1 h:

Result = \( Q_1 \)

At 3 h:

Result = \( Q_1 + \left[ \left( Q_1 \times 10 \right) / V \right] \)

At 10 h:

Result = \( Q_{10} + \left[ \left( Q_{10} \times 10 \right) / V \right] + \left[ \left( Q_1 \times 10 \right) / V \right] \)

\( A_i \) = absorbance of the Sample solution

\( A_j \) = absorbance of the Standard solution

\( C_i \) = concentration of the Standard solution (mg/mL)

\( L \) = label claim (mg/Tablet)

\( V \) = volume of Medium, 1000 mL

\( D \) = dilution factor of the Sample solution

**Tolerances:** See Table 13.

The percentages of the labeled amount of metformin hydrochloride (C₆H₁₁N₃·HCl) dissolved at the times specified conform to Dissolution (711), Acceptance Table 2.

**Test 12:** If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 12.

**Medium:** pH 6.8 phosphate buffer solution; 1000 mL

**Apparatus 1:** 100 rpm

**Times:** 1, 4, and 12 h

**Standard stock solution:** 0.01 mg/mL of USP Metformin Hydrochloride RS in Medium

**Standard solution:** 0.2 mg/mL of USP Metformin Hydrochloride RS in water, from the Standard stock solution

**Sample solution:** At the times specified, withdraw 10 mL of the solution under test, and replace with 10 mL of Medium previously equilibrated at 37.0 ± 0.5°. Pass it through a suitable filter, discarding the first few mL of the filtrate.

For Tablets labeled to contain 500 mg: Dilute 2.0 mL of the filtrate with water to 100 mL.

For Tablets labeled to contain 1000 mg: Dilute 1.0 mL of the filtrate with water to 100 mL.

**Detector:** UV 232 nm

**Blank:** Dilute 1 mL of Medium with water to 100 mL.

**Analysis:** Calculate the concentration (C), in mg/mL of metformin hydrochloride (C₆H₁₁N₃·HCl) in the sample withdrawn at each time point (i):

\[ \text{Result} = \left( A_i / A_j \right) \times C_i \times D \]

\( A_i \) = absorbance of the Sample solution

\( A_j \) = absorbance of the Standard solution

\( C_i \) = concentration of the Standard solution (mg/mL)

\( D \) = dilution factor of the Sample solution

Calculate the percentage of the labeled amount of metformin hydrochloride (C₆H₁₁N₃·HCl) dissolved (Q) at each time point (i):

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

\[ \text{Result}_2 = \left( \left[ C_j \times V \right] + \left[ C_j \times V_j \right] \right) \times (1/L) \times 100 \]

\[ \text{Result}_3 = \left( \left[ C_j \times V \right] + \left[ C_j + C_i \right] \times V_j \right) \times (1/L) \times 100 \]

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

\( V \) = initial volume of Medium, 1000 mL

\( L \) = label claim (mg/Tablet)

\( V_j \) = volume of the Sample solution withdrawn, 10 mL

**Tolerances:** See Table 14.

<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>3</td>
<td>50–70</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NLT 15</td>
</tr>
<tr>
<td>2</td>
<td>35–65</td>
</tr>
</tbody>
</table>

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C205170-M871-CHM32015, rev. 00 20180921
The percentages of the labeled amount of metformin hydrochloride (C₆H₁₁N₂·HCl) dissolved at the times specified conform to Dissolution (711), Acceptance Table 2.

### Test 13: If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 13.

**Medium:** pH 6.8 phosphate buffer solution; 1000 mL

**Apparatus 1:** 100 rpm

**Times:** 1, 4, 6, and 14 h

**Standard stock solution:** 0.2 mg/mL of USP Metformin Hydrochloride RS prepared as follows. Transfer a suitable amount of USP Metformin Hydrochloride RS into an appropriate volumetric flask. Dissolve by adding Medium to fill 50% of the flask volume and dilute with Medium to volume.

**Standard solution:** 0.01 mg/mL of USP Metformin Hydrochloride RS from Standard stock solution in water

**Sample stock solution:** At the times specified, withdraw 10 mL of the solution under test, and replace with the same volume of Medium preheated at 37.0 ± 0.5°C. Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size, discard the first few mL, and use the filtrate.

**Sample solution**

- For Tablets labeled to contain 500 mg: Dilute 2 mL of Sample stock solution with water to 100 mL.
- For Tablets labeled to contain 1000 mg: Dilute 1 mL of Sample stock solution with water to 100 mL.

#### Instrumental conditions

(See Ultraviolet-Visible Spectroscopy (857).)

**Mode:** UV

**Analytical wavelength:** 232 nm

**Blank**

- For Tablets labeled to contain 500 mg: Dilute 2 mL of Medium with water to 100 mL.
- For Tablets labeled to contain 1000 mg: Dilute 1 mL of Medium with water to 100 mL.

**System suitability**

**Sample:** Standard solution

**Suitability requirements**

**Relative standard deviation:** NMT 2.0%

**Analysis**

**Samples:** Standard solution, Sample solution, and Blank

Calculate the concentration (Cᵢ) in mg/mL, of metformin hydrochloride (C₆H₁₁N₂·HCl) in the sample withdrawn from the vessel at each time point (t):

\[
Resultᵢ = (Aᵢ / A₀) × Cᵢ × D
\]

\(Aᵢ\) = absorbance of the Sample solution

\(A₀\) = absorbance of the Standard solution

\(Cᵢ\) = concentration of the Standard solution (mg/mL)

\(D\) = dilution factor of the Sample solution

Calculate the percentage of the labeled amount of metformin hydrochloride (C₆H₁₁N₂·HCl) dissolved at each time point (t):

\[
Resultᵢ = Cᵢ × V × (1/L) × 100
\]

\(Cᵢ\) = concentration of metformin hydrochloride in the portion of sample withdrawn at the specified time point (mg/mL)

\(V\) = volume of Medium, 1000 mL

\(L\) = label claim (mg/Tablet)

\(Vᵢ\) = volume of the Sample solution withdrawn at each time point and replaced with Medium (mL)

**Tolerances:** See Table 15.

#### Test 14: If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 14.

**Medium:** pH 6.8 phosphate buffer solution; 1000 mL

**Apparatus 1:** 100 rpm for Tablets labeled to contain 750 mg

**Apparatus 2:** 100 rpm for Tablets labeled to contain 500 mg

**Times:** 1, 3, and 10 h

**Standard solution:** 7.5 µg/mL of USP Metformin Hydrochloride RS in Medium

**Sample solution:** At the times specified, withdraw 10 mL of the solution under test and replace with the same volume of Medium. Pass the solution under test through a suitable filter of 0.45-µm pore size. Discard the first few mL, and dilute to a concentration similar to that of the Standard solution.

**Instrumental conditions**

**Mode:** UV

**Analytical wavelength:** 232 nm

**Blank**

**Analysis**

**Samples:** Standard solution, Sample solution, and Blank

Calculate the concentration (Cᵢ) in µg/mL, of metformin hydrochloride (C₆H₁₁N₂·HCl) in the sample withdrawn from the vessel at each time point (t):

\[
Resultᵢ = (Aᵢ / A₀) × Cᵢ × D
\]

\(Aᵢ\) = absorbance of the Sample solution

\(A₀\) = absorbance of the Standard solution

\(Cᵢ\) = concentration of the Standard solution (µg/mL)

\(D\) = dilution factor of the Sample solution

Calculate the percentage of the labeled amount of metformin hydrochloride (C₆H₁₁N₂·HCl) dissolved at each time point (t):

\[
Resultᵢ = Cᵢ × V × (1/L) × 100
\]

**Tolerances:**
Result$_2$ = \[(C_2 \times V) + (C_3 \times V_S)\] \times \left(\frac{1}{L}\right) \times 100

Result$_3$ = \[(C_2 \times V) + (C_3 + C_4) \times V_S\] \times \left(\frac{1}{L}\right) \times 100

Result$_4$ = \[(C_2 \times V) + (C_3 + C_4 + C_5) \times V_S\] \times \left(\frac{1}{L}\right) \times 100

\[C_i\] = concentration of metformin hydrochloride in the portion of sample withdrawn at the specified time point (mg/mL)

\[V\] = volume of Medium, 1000 mL

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

\[V_S\] = volume of the Sample solution withdrawn at each time point and replaced with Medium (mL)

Tolerances: See Table 16.

<table>
<thead>
<tr>
<th>Time Point (i)</th>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>500 mg Tablets</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>30–50</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>55–75</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>NLT 85</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of metformin hydrochloride \((C_{9i11N_5-HCl})\) dissolved at the times specified conform to Dissolution (711), Acceptance Table 2. [on 24-Sep-2018)

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

**Impurities**

- **Organic Impurities**

  Mobile phase, Sample solution, and Chromatographic system: Proceed as directed in the Assay.

**Analysis:** From the chromatogram of the Sample solution obtained in the Assay, calculate the percentage of each impurity in the portion of Tablets taken:

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

\[r_U\] = peak response for each impurity

\[r_T\] = sum of all the peak responses

**Acceptance criteria**

- Individual impurities: NMT 0.1%
- Total impurities: NMT 0.6%
  
  [Note—Disregard any peak less than 0.05%, and disregard any peak observed in the blank.]

**Additional requirements**

- **Packaging and Storage:** Preserve in well-closed, light-resistant containers, and store at controlled room temperature.

- **Labeling:** When more than one dissolution test is given, the labeling states the Dissolution test used only if Test 1 is not used.

- **USP Reference Standards (11)**
  USP Metformin Hydrochloride RS
  USP Metformin Related Compound B RS
  N,N-Dimethyl-[1,3,5]triazine-2,4,6-triamine.

C$_5$H$_{10}$N$_6$ \[\text{154.17}\]