Metformin Hydrochloride Extended-Release Tablets

Type of Posting: Notice of Intent to Revise
Posting Date: 31-Jan-2020
Targeted Official Date: To Be Determined, Revision Bulletin
Expert Committee: Chemical Medicines Monographs 3

In accordance with section 7.04 (c) of the 2015–2020 Rules and Procedures of the Council of Experts and the Pending Monograph Guideline, this is to provide notice that the Chemical Medicines Monographs 3 Expert Committee intends to revise the Metformin Hydrochloride Extended-Release Tablets monograph.

Based on the supporting data received from a manufacturer awaiting FDA approval, the Expert Committee proposes to revise the Metformin Hydrochloride Extended-Release Tablets monograph to add Dissolution Test 20.

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

See below for additional information about the proposed text.¹

Should you have any questions, please contact Andrea F. Carney, Scientific Liaison to the Chemical Medicines Monographs 3 Expert Committee (301-816-8155 orafc@usp.org).

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

USP provides this text to indicate changes that we anticipate will be made official once the product subject to this proposed revision under the Pending Monograph Program receives FDA approval. Once FDA approval is granted for the associated revision request, a Revision Bulletin will be posted that will include the changes indicated herein, as well as any changes indicated in the product’s final approval, combined with the text of the monograph as effective on the date of approval. Any revisions made to a monograph under the Pending Monograph Program that are posted without prior publication for comment in the Pharmacopeial Forum must also meet the requirements outlined in the USP Guideline on Use of Accelerated Processes for Revisions to the USP–NF.
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 (\(\text{C}_4\text{H}_2\text{N}_{11}\cdot\text{HCl}\)).

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: (L/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. Alternate, 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°
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 (\(\text{C}_4\text{H}_2\text{N}_{11}\cdot\text{HCl}\)) in the portion of Tablets taken:

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

\[
\begin{align*}
\text{r}_U &= \text{peak response from the Sample solution} \\
\text{r}_S &= \text{peak response from the Standard solution} \\
\text{C}_U &= \text{concentration of USP Metformin Hydrochloride RS in the Standard solution (mg/mL)} \\
\text{C}_S &= \text{nominal concentration of metformin hydrochloride in the Sample solution}
\end{align*}
\]

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.

Calculate the percentage of the labeled amount of metformin hydrochloride (\(\text{C}_4\text{H}_2\text{N}_{11}\cdot\text{HCl}\)) released at each time point:

\[
\text{Result} = \left[ \left( \frac{A_U}{A_S} \times C_S \times (V - V_1) + (C_{60} \times V_1) + (C_{180} \times V_2) \right) \times (100/L) \right]
\]

\[
\begin{align*}
A_U &= \text{absorbance of the Sample solution} \\
A_S &= \text{absorbance of the Standard solution} \\
C_S &= \text{concentration of the Standard solution (mg/mL)} \\
V &= \text{initial volume of Medium in the vessel (mL)} \\
V_1 &= \text{volume withdrawn from the vessel for previous samplings (mL)} \\
C_{60} &= \text{concentration of metformin hydrochloride in Medium determined at 1 h (mg/mL)} \\
C_{180} &= \text{concentration of metformin hydrochloride in Medium determined at 3 h (mg/mL)} \\
L &= \text{label claim (mg/Tablet)}
\end{align*}
\]

Tolerances: See 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>
2 Metformin

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 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 mg/mL, the content of metformin hydrochloride \((C_6H_{11}N_2 \cdot HCl)\) \((C)\) in Medium at each time point \((t)\):

\[
\text{Result} = \left( A_j \times C_j \times D_{ij} \right) / A_i
\]

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

Calculate the percentage of the labeled amount of metformin hydrochloride \((C_6H_{11}N_2 \cdot HCl)\) dissolved at each time point by the following formulas.
Percentage dissolved at the first time point (1 h):

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

\(C_1\) = 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):

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

\(C_2\) = content of metformin hydrochloride in Medium at the second time interval (mg/mL)
\(V\) = volume of Medium, 1000 mL
\(SV_j\) = volume of 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:

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

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

Tolerances: See Table 2.

<table>
<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 \((C_6H_{11}N_2 \cdot HCl)\) 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 \((C_6H_{11}N_2 \cdot HCl)\) released at each time point:

\[
\text{Result} = \left[ \left( (A_j/A_i) \times C_j \times (V - V_j) + (C_{60} \times V_j) \right) + \left( C_{120} \times V_j \right) + \left( C_{720} \times V_j \right) \right] \times \left( 100/L \right)
\]

\(A_j\) = absorbance of the Sample solution
\(A_i\) = absorbance of the Standard solution
\(C_j\) = 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)
\(C_{720}\) = 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>
<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 (C₄H₁₁N₅·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 (C₄H₁₁N₅·HCl) (C), in Medium at each time point (t), by the formulas specified in Test 2.

Tolerances: See Table 5.

Table 5 (continued)

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<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 (C₄H₁₁N₅·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 (C₄H₁₁N₅·HCl) (C), in Medium at each time point (t), by the formulas specified in Test 2.
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
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

Tolerances: See 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 (C₄H₁₁N₅·HCl) dissolved at the times specified conform to Dissolution (711), Acceptance Table 2.

Figure 2

Test 6: If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 6.
Medium: pH 6.8 phosphate buffer solution; 1000 mL, deaerated
Apparatus 2: 100 rpm, with USP sinker, if necessary
Detector: UV 233 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 (C₄H₁₁N₅·HCl) released at each time point.
6 Metformin

**Notice of Intent to Revise**
Official: To Be Determined

Result = \[\left(\frac{A_A}{A_s}\right) \times C_s \times (V - V_s) + (C_{60} \times V_s) + (C_{180} \times V_s) + (C_{600} \times V_s) \times 100\] / L

\[\begin{align*}
A_A &= \text{absorbance of the Sample solution} \\
A_s &= \text{absorbance of the Standard solution} \\
C_s &= \text{concentration of the Standard solution (mg/mL)} \\
V &= \text{initial volume of Medium in the vessel (mL)} \\
V_s &= \text{volume withdrawn from the vessel for previous samplings (mL)} \\
C_{60} &= \text{concentration of metformin hydrochloride in Medium determined at 1 h (mg/mL)} \\
C_{180} &= \text{concentration of metformin hydrochloride in Medium determined at 3 h (mg/mL)} \\
C_{600} &= \text{concentration of metformin hydrochloride in Medium determined at 10 h (mg/mL)} \\
L &= \text{label claim (mg/Tablet)}
\end{align*}\]

**Tolerances:** See Table 7.

<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>45–65</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 (C₄H₁₁N₂·HCl) dissolved at the times specified conform to Dissolution (711), Acceptance Table 2.

**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 7; 1000 mL.

**Apparatus 1:** 100 rpm for Tablets labeled to contain 500 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 (C₄H₁₁N₂·HCl) dissolved at each time point:

Result = \[\left(\frac{A_A}{A_s}\right) \times C_s \times (V - V_s) + (C_{60} \times V_s) + (C_{180} \times V_s) + (C_{600} \times V_s) \times 100\] / L

\[\begin{align*}
A_A &= \text{absorbance of the Sample solution} \\
A_s &= \text{absorbance of the Standard solution} \\
C_s &= \text{concentration of the Standard solution (mg/mL)} \\
V &= \text{initial volume of Medium in the vessel (mL)} \\
V_s &= \text{volume withdrawn from the vessel for previous samplings (mL)} \\
C_{60} &= \text{concentration of metformin hydrochloride in Medium determined at 1 h (mg/mL)} \\
C_{180} &= \text{concentration of metformin hydrochloride in Medium determined at 3 h (mg/mL)} \\
C_{600} &= \text{concentration of metformin hydrochloride in Medium determined at 10 h (mg/mL)} \\
L &= \text{label claim (mg/Tablet)}
\end{align*}\]

**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>

The percentages of the labeled amount of metformin hydrochloride (C₄H₁₁N₂·HCl) dissolved at the times specified conform to Dissolution (711), Acceptance Table 2.

**Table 7**

<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>45–65</td>
</tr>
<tr>
<td>10</td>
<td>NLT 85</td>
<td>NLT 85</td>
</tr>
</tbody>
</table>

**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>

The percentages of the labeled amount of metformin hydrochloride (C₄H₁₁N₂·HCl) dissolved at the times specified conform to Dissolution (711), Acceptance Table 2.

<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>35–55</td>
<td>35–55</td>
</tr>
<tr>
<td>6</td>
<td>75–95</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 (C₄H₁₁N₂·HCl) dissolved at the times specified conform to Dissolution (711), Acceptance Table 2.

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C247955-M871-CHM32015, rev. 00 20200131
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$_7$H$_{13}$N$_2$·HCl) released at each time point:
Result = \left( \frac{(A_0/A_1) \times C_1 \times (V - V_s) + (C_1 \times V_s)}{(C_1 \times V_s) + (C_2 \times V_s) + (C_3 \times V_s) + (C_4 \times V_s) + 100} \right) \times L

A_0 = absorbance of the Sample solution
A_1 = absorbance of the Standard solution
C_1 = concentration of the Standard solution (mg/mL)
V = initial volume of Medium in the vessel (mL)
V_s = volume withdrawn from the vessel for previous samplings (mL)
C_1 = 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>
<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>
<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>
<tr>
<td>10</td>
<td>70–95</td>
</tr>
<tr>
<td>24</td>
<td>NLT 85</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of metformin hydrochloride (C$_7$H$_{13}$N$_2$·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 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°C. 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, in mg/mL, of metformin hydrochloride (C) at each time point:
C = (A_1/A_0) \times C_1
A_0 = absorbance of the Sample solution
A_1 = absorbance of the Standard solution
C_1 = concentration of the Standard solution (mg/mL)

Calculate the cumulative percentage of the labeled amount of metformin hydrochloride (C$_7$H$_{13}$N$_2$·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_1(V - V_s) + (C_1 \times V_s)] \times 100/L
At i = 10:
Q_{10} = [C_{10}(V - 2V_s) + (C_1 + C_9) \times V_s] \times 100/L
V = initial volume of Medium, 1000 mL
V_s = sampling volume, 10 mL
L = label claim (mg/Tablet)

Tolerances: See Table 12.
Notice of Intent to Revise

Official: To Be Determined

8 Metformin

The percentages of the labeled amount of metformin hydrochloride \((\text{C}_6\text{H}_{11}\text{N}_2 \cdot \text{HCl})\) 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.

**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°C.

**Detector:** UV 232 nm

**Path length:** 1 cm

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

**Analysis:** Calculate the concentration of metformin hydrochloride in the solution at each time point:

\[ Q_i = (A_i / A_0) \times (C_0 / L) \times V \times D \times 100 \]

At 1 h:
\[ \text{Result} = Q_i \]

At 3 h:
\[ \text{Result} = Q_i + [(Q_i \times 10) / V] \]

At 10 h:
\[ \text{Result} = Q_i + [(Q_i \times 10) / V] + [(Q_i \times 10) / V] \]

\( A_i \) = absorbance of the Sample solution

\( A_0 \) = absorbance of the Blank 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.

<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>
<tr>
<td>10</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of metformin hydrochloride \((\text{C}_6\text{H}_{11}\text{N}_2 \cdot \text{HCl})\) 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, 6, and 14 h

**Standard stock solution:** 0.2 mg/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 10 mL of Medium previously equilibrated at 37.0 ± 0.5°C. 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

**Analysis:** Calculate the concentration of metformin hydrochloride \((\text{C}_6\text{H}_{11}\text{N}_2 \cdot \text{HCl})\) dissolved (Q) at each time point (i):

\[ \text{Result}_i = (A_i / A_0) \times C_i \times D \]

\( A_i \) = absorbance of the Sample solution

\( A_0 \) = absorbance of the Blank 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 \((\text{C}_6\text{H}_{11}\text{N}_2 \cdot \text{HCl})\) dissolved (Q) at each time point (i):

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

\( C_i \) = 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)

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

**Tolerances:** See Table 14.

<table>
<thead>
<tr>
<th>Time Point (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NMT 15</td>
</tr>
<tr>
<td>2</td>
<td>35–65</td>
</tr>
<tr>
<td>3</td>
<td>NLT 85</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of metformin hydrochloride \((\text{C}_6\text{H}_{11}\text{N}_2 \cdot \text{HCl})\) 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°. 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 (C₅), in mg/mL, of metformin hydrochloride (C₅H₁₁N₄·HCl) in the sample withdrawn from the vessel at each time point (t):

\[
\text{Result}_1 = \left( \frac{A_3}{A_5} \right) \times C_5 \times D
\]

\[
A_3 = \text{absorbance of the Sample solution}
\]

\[
A_5 = \text{absorbance of the Standard solution}
\]

\[
C_5 = \text{concentration of the Standard solution (mg/mL)}
\]

\[
D = \text{dilution factor of the Sample solution}
\]

Calculate the percentage of the labeled amount of metformin hydrochloride (C₅H₁₁N₄·HCl) dissolved at each time point (t):

\[
\text{Result}_1 = C_5 \times V \times (1/L) \times 100
\]

\[
\text{Result}_2 = \left( [C_5 \times V] + [(C_5 + C_5) \times V_3] \right) \times (1/L) \times 100
\]

\[
\text{Result}_3 = \left( [C_5 \times V] + [(C_5 + C_5) \times V_3] \right) \times (1/L) \times 100
\]

\[
\text{Result}_4 = \left( [C_5 \times V] + [(C_5 + C_5 + C_5) \times V_3] \right) \times (1/L) \times 100
\]

\[
C_5 = \text{concentration of metformin hydrochloride in the portion of sample withdrawn at the specified time point (mg/mL)}
\]

\[
V = \text{volume of Medium, 1000 mL}
\]

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

\[
V_3 = \text{volume of the Sample solution withdrawn at each time point and replaced with Medium (mL)}
\]

Tolerances: See Table 15.

<table>
<thead>
<tr>
<th>Time Point (h)</th>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>NMT 20</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>45–65</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>65–85</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>NLT 85</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of metformin hydrochloride (C₅H₁₁N₄·HCl) dissolved at the times specified conform to Dissolution (711), Acceptance Table 2.

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 10-μm pore size. Pass a portion of the filtered solution through a suitable filter of 0.45-μm pore size, discarding the first few milliliters. Dilute with Medium to a concentration similar to that of the Standard solution.

Instrumental conditions
Mode: UV
Analytical wavelength: 232 nm
Blank: Medium

Analysis
Samples: Standard solution, Sample solution, and Blank
Calculate the concentration (C₅), in mg/mL, of metformin hydrochloride (C₅H₁₁N₄·HCl) in the sample withdrawn from the vessel at each time point (t):

\[
\text{Result}_1 = \left( \frac{A_3}{A_5} \right) \times C_5 \times D
\]

\[
A_3 = \text{absorbance of the Sample solution}
\]

\[
A_5 = \text{absorbance of the Standard solution}
\]

\[
C_5 = \text{concentration of the Standard solution (μg/mL)}
\]

\[
D = \text{dilution factor of the Sample solution}
\]

Calculate the percentage of the labeled amount of metformin hydrochloride (C₅H₁₁N₄·HCl) dissolved at each time point (t):

\[
\text{Result}_1 = C_5 \times V \times (1/L) \times 100
\]

\[
\text{Result}_2 = \left( [C_5 \times V] + [(C_5 + C_5) \times V_3] \right) \times (1/L) \times 100
\]

\[
\text{Result}_3 = \left( [C_5 \times V] + [(C_5 + C_5 + C_5) \times V_3] \right) \times (1/L) \times 100
\]

\[
\text{Result}_4 = \left( [C_5 \times V] + [(C_5 + C_5 + C_5 + C_5) \times V_3] \right) \times (1/L) \times 100
\]

\[
C_5 = \text{concentration of metformin hydrochloride in the portion of sample withdrawn at the specified time point (mg/mL)}
\]

\[
V = \text{volume of Medium, 1000 mL}
\]

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

\[
V_3 = \text{volume of the Sample solution withdrawn at each time point and replaced with Medium (mL)}
\]

Tolerances: See Table 16.

<table>
<thead>
<tr>
<th>Time Point (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30–50</td>
</tr>
<tr>
<td>2</td>
<td>55–75</td>
</tr>
<tr>
<td>3</td>
<td>85–100</td>
</tr>
</tbody>
</table>

Table 16

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The percentages of the labeled amount of metformin hydrochloride \((C_{g}H_{12}N_{5} \cdot \text{HCl})\) dissolved at the times specified conform to Dissolution (711), Acceptance Table 2.

**Test 16:** If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 16.

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

**Apparatus 1:** 100 rpm

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

**Standard solution:** 0.015 mg/mL of USP Metformin Hydrochloride RS in Medium. Sonicate as needed.

**Sample stock solution:** At the specified times, withdraw 10 mL of the solution under test and pass it through a suitable filter.

**Sample solution**

- **For Tablets labeled to contain 500 mg:** Dilute 3 mL of the Sample stock solution with Medium to 100 mL.
- **For Tablets labeled to contain 750 mg:** Dilute 2 mL of the Sample stock solution with Medium to 100 mL.

**Instrumental conditions**

- **(See Ultraviolet-Visible Spectroscopy (857));**
- **Mode:** UV-Vis
- **Analytical wavelength:** UV 232 nm
- **Path length:** 1 cm
- **Blank:** Medium

**System suitability**

- **Sample:** Standard solution
- **Suitability requirements**
  - **Relative standard deviation:** NMT 2.0%

**Analysis**

- **Samples:** Standard solution and Sample solution
- Calculate the concentration \((C_{i})\) of metformin hydrochloride \((C_{g}H_{12}N_{5} \cdot \text{HCl})\) in the sample withdrawn from the vessel at each time point \((t)\):

\[
\text{Result} = (A_{i}/A_{j}) \times C_{s} \times D
\]

- \(A_{i}\) = absorbance of the Sample solution
- \(A_{j}\) = absorbance of the Standard solution
- \(C_{s}\) = concentration of the Standard solution (mg/mL)
- \(D\) = dilution factor for the Sample solution

- Calculate the percentage of the labeled amount of metformin hydrochloride \((C_{g}H_{12}N_{5} \cdot \text{HCl})\) dissolved at the specified time point:

\[
\text{Result}_{1} = C_{i} \times V \times (1/L) \times 100
\]

\[
\text{Result}_{2} = [(C_{i} \times (V - V_{j})) + (C_{s} \times V_{j})] \times (1/L) \times 100
\]

\[
\text{Result}_{3} = [(C_{i} \times (V - (2 \times V_{j})))] + [(C_{s} + C_{s}) \times V_{j}] \times (1/L) \times 100
\]

- \(C_{i}\) = 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)
- \(V_{j}\) = volume of the Sample solution withdrawn at each time point (mL)

**Tolerances:** See Table 18.

### Table 18

<table>
<thead>
<tr>
<th>Time Point (h)</th>
<th>Time Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25–45</td>
</tr>
<tr>
<td>2</td>
<td>50–70</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of metformin hydrochloride \((C_{g}H_{12}N_{5} \cdot \text{HCl})\) dissolved at the times specified conform to Dissolution (711), Acceptance Table 2.

**Test 20:** If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 20.

**Medium:** 0.05 M phosphate buffer, pH 6.8; 1000 mL

**Apparatus 1:** 100 rpm

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

**Standard solution:** \(L/1000 \text{ mg/mL of USP Metformin Hydrochloride RS in Medium, where } L\) is the label claim of metformin hydrochloride in mg/Tablet. Sonicate if needed.

**Sample solution:** Pass a portion of the solution under test through a suitable filter.

**Instrumental conditions**

- **(See Ultraviolet-Visible Spectroscopy (857));**
- **Mode:** UV-Vis
- **Analytical wavelength:** UV 233 nm, with background correction at 490 nm
- **Cell length:** 0.02 cm flow cell
- **Blank:** Medium

**System suitability**

- **Sample:** Standard solution
- **Suitability requirements**
  - **Relative standard deviation:** NMT 3.0%

**Analysis**

- **Samples:** Standard solution, Sample solution, and Blank
- Calculate the percentage of the labeled amount of metformin hydrochloride \((C_{g}H_{12}N_{5} \cdot \text{HCl})\) dissolved at each time point \((t)\):

\[
\text{Result} = A_{i}/A_{j} \times C_{s} \times V \times (1/L) \times 100
\]

- \(A_{i}\) = absorbance of the Sample solution
- \(A_{j}\) = absorbance of the Standard solution
- \(C_{s}\) = concentration of the Standard solution (mg/mL)
- \(V\) = volume of Medium, 1000 mL
- \(L\) = label claim (mg/Tablet)

**Tolerances:** See Table 19.

### Table 19

<table>
<thead>
<tr>
<th>Time Point (h)</th>
<th>Time Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15–35</td>
</tr>
<tr>
<td>2</td>
<td>52–72</td>
</tr>
<tr>
<td>3</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of metformin hydrochloride \((C_{g}H_{12}N_{5} \cdot \text{HCl})\) dissolved at the times specified conform to Dissolution (711), Acceptance Table 2.

**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
    1-Methylbiguanide hydrochloride.
    \( \text{C}_3\text{H}_9\text{N}_5\text{HCl} \) 151.60
  - USP Metformin Related Compound C RS
    \( N,N\)-Dimethyl-[1,3,5]triazine-2,4,6-triamine.
    \( \text{C}_5\text{H}_{10}\text{N}_6 \) 154.17