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_{4}H_{11}N_{5}·HCl).

**IDENTIFICATION**
- 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 heptanesulfonate and 0.5 g/L of sodium chloride in water. Prior to 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 of 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 accurately add 500 mL of 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°
- **Flow rate**: 1 mL/min
- **Injection size**: 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 peaks due to metformin related compound B and metformin
- **Tailing factor**: NLT 0.8 and NMT 2.0 for the metformin peak.

**PERFORMANCE TESTS**

**Change to read:**

- **Dissolution (711)**

  **Table 1**

  | Medium: pH 6.8 phosphate buffer (6.8 g of monobasic potassium phosphate in 1000 mL of water; adjust with 0.2 N sodium hydroxide to a pH of 6.8±0.1); 1000 mL | Apparatus 1: 100 rpm for Tablets labeled to contain 500 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 the Standard solution. |
  | Analysis: Calculate the percentage of C_{4}H_{11}N_{5}·HCl released at each time point: |
  | Result = [(A_{60}/A_{0}) + (C_{180} × V_{6}) + (C_{60} × V_{6}) + (C_{60} × V_{6}) × 100]/L |
  | A_{0} = absorbance of the Sample solution |
  | A_{60} = absorbance of the Standard solution |
  | C_{60} = concentration of the Standard solution (mg/mL) |
  | V_{6} = volume withdrawn from the vessel for previous samplings (mL) |
  | C_{180} = concentration of metformin hydrochloride in Medium determined at 1 h (mg/mL) |
  | L = label claim (mg/Tablet) |
  | Tolerances: The percentages of the labeled amount of C_{4}H_{11}N_{5}·HCl dissolved at the times specified conform to 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>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>
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, to a concentration that is similar to the Standard solution.

Analysis: Calculate, in mg/mL, the content of C4H11N5·HCl, C4, in Medium at each time point, t:

\[
\text{Result} = \frac{(A_0 \times C_4 \times D_0)}{A_0}
\]

\(A_0\) = absorbance of the Sample solution
\(C_4\) = concentration of metformin hydrochloride in the Standard solution (mg/mL)
\(D_0\) = dilution factor of the solution under test
\(A_0\) = absorbance of the Standard solution

Calculate the percentage of C4H11N5·HCl dissolved at each time point by the following formulas. Percentage dissolved at the first time point (1 h):

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

\(C_1\) = 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):

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

\(C_2\) = content of metformin hydrochloride in Medium at the second time interval (mg/mL)
\(V_S\) = 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:

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

\(C_n\) = content of metformin hydrochloride in Medium at the nth time interval (mg/mL)
\(V\) = volume of Medium, 1000 mL
\(n\) = time interval of interest
\(V_S\) = volume of sample withdrawn at each time interval (mL)
\(C\) = as C1, C2, C3, \ldots, Cn-1, the content of metformin hydrochloride in Medium at each time interval (mg/mL)
\(L\) = label claim (mg/Tablet)

Tolerances: The percentages of the labeled amount of C4H11N5·HCl dissolved at the times specified conform to Acceptance 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>

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

Medium, Apparatus 1, Apparatus 2, and Analysis: Proceed as directed in Test 1.
Times: 1, 2, 3, and 10 h for Tablets labeled to contain 500 mg; 2, 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 polyethylene filter of 0.45-µm pore size. Dilute, if necessary, with Medium to a concentration similar to the Standard solution.

Analysis: Calculate the percentage of C4H11N5·HCl released at each time point:

\[
\text{Result} = \left[\left((A_0/A) \times C_1 \times (V - V_S)\right) + (C_2 \times V_S) + (C_3 \times V_S) + \ldots\right] \times 100)/L
\]

\(A_0\) = absorbance of the Sample solution
\(A\) = absorbance of the Standard solution
\(C_1\) = concentration of the Standard solution (mg/mL)
\(V_S\) = initial volume of Medium in the vessel (mL)
\(V\) = volume withdrawn from the vessel for previous samplings (mL)
\(C_2\) = concentration of metformin hydrochloride in Medium determined at 1 h (mg/mL)
\(C_3\) = concentration of metformin hydrochloride in Medium determined at 2 h (mg/mL)
\(C_6\) = concentration of metformin hydrochloride in Medium determined at 3 h (mg/mL)
\(C_10\) = concentration of metformin hydrochloride in Medium determined at 5 h (mg/mL)
\(C_12_0\) = concentration of metformin hydrochloride in Medium determined at 10 h (mg/mL)
\(L\) = label claim (mg/Tablet)

Tolerances: The percentages of the labeled amount of C4H11N5·HCl dissolved at the times specified conform to Acceptance Table 2.

For Tablets Contained 50 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>6</td>
<td>65%–85%</td>
</tr>
<tr>
<td>10</td>
<td>NLT 85%</td>
</tr>
</tbody>
</table>

For Tablets Contained 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>

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 similar to the Standard solution.
Analysis: Calculate, in mg/mL, the content of C₆H₁₃N₅·HCl, C₀, in Medium at each time point, t, by the formulas specified in Test 2.

Tolerances: The percentages of the labeled amount of C₆H₁₃N₅·HCl dissolved at the times specified conform to Acceptance Table 2.

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved</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>
<td></td>
</tr>
<tr>
<td>8</td>
<td>60%-85%</td>
<td>65%-90%</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>NLT 90%</td>
<td>NLT 90%</td>
<td></td>
</tr>
</tbody>
</table>

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 (6.8 g of monobasic potassium phosphate in 1000 mL of water; adjust with 0.2 N sodium hydroxide to a pH of 6.8 ± 0.1); 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 hydrophilic polyethylene filter of 0.45-µm pore size. Dilute, if necessary, with Medium to a concentration similar to 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 C₆H₁₃N₅·HCl in Medium at each time point, t, by the formulas specified in Test 2.

Tolerances: The percentages of the labeled amount of C₆H₁₃N₅·HCl dissolved at the times specified conform to Acceptance Table 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 (6.8 g of monobasic potassium phosphate in 1000 mL of water; adjust with 0.2 N sodium hydroxide to a pH of 6.8 ± 0.05); 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 filter of 0.45-µm pore size. Dilute, if necessary, with Medium to a concentration similar to the Standard solution.

Analysis: Calculate the percentage of C₆H₁₃N₅·HCl dissolved at each time point, t, by the formulas specified in Test 2.

Result = \[\left(\frac{Ct}{C0}\right) \times 100\]

A₀ = absorbance of the Standard solution

Aₜ = absorbance of the Sample solution

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: 50 rpm, with USP sinker, 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 filter of 0.45-µm pore size. Dilute, if necessary, with Medium to a concentration similar to the Standard solution.

Analysis: Calculate the percentage of C₆H₁₃N₅·HCl released at each time point:

Result = \[\left(\frac{V \times (Ct - V)}{L} + \frac{Ct \times V}{100}\right) \times 100\]

A₀ = absorbance of the Sample solution

Aₜ = absorbance of the Standard solution

C₀ = concentration of the Standard solution (mg/mL)

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

Cₜ = concentration of the Standard solution (mg/mL)

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

Cₜ = concentration of metformin hydrochloride in Medium determined at 1 h (mg/mL)

Cₜ = concentration of metformin hydrochloride in Medium determined at 3 h (mg/mL)

Cₜ = concentration of metformin hydrochloride in Medium determined at 10 h (mg/mL)

L = label claim (mg/Tablet)

Tolerances: The percentages of the labeled amount of C₆H₁₃N₅·HCl dissolved at the times specified conform to Acceptance Table 2.
**Metformin**

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 0.5 mg/mL of USP Metformin Hydrochloride RS in Medium.

**Detector**: UV 232 nm

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

**Apparatus 2**: 100 rpm, with sinker, for Tablets labeled to contain 750 mg

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

**Sample solution**: Add 6.8 g of potassium dihydrogen 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, pH 6.8; 1000 mL

**Apparatus 1**: 100 rpm for Tablets labeled to contain 500 mg

**Apparatus 2**: 100 rpm for Tablets labeled to contain 750 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 Tablet label claim in mg. 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 Tablet label claim in mg.

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**Analysis**:

**Result** = \[
\left( \frac{A_0}{A_S} \times C_5 \times (V - V_5) + (C_{600} \times V_5) + (C_{120} \times V_5) + (C_{360} \times V_5) + (C_{600} \times V_5) \right] \times 100/L
\]

**Time Amount Dissolved, Amount Dissolved, Amount Dissolved, Time**

**For Tablets Labeled to Contain 500 mg**

<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>

**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>
<tr>
<td>10</td>
<td>70%–95%</td>
</tr>
<tr>
<td>24</td>
<td>NLT 85%</td>
</tr>
</tbody>
</table>

**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 potassium dihydrogen 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), pH 6.8; 1000 mL

**Apparatus 1**: 100 rpm for Tablets labeled to contain 500 mg

**Apparatus 2**: 100 rpm for Tablets labeled to contain 750 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 Tablet label claim in mg. 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 Tablet label claim in mg.
Detector: UV 233 nm  
Path length: 1 cm  
Blank: Medium  

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

\[ C_i = \left( \frac{A_i}{A_0} \right) \times C_s \]

\[ A_0 = \text{absorbance of the Sample solution} \]
\[ A_s = \text{absorbance of the Standard solution} \]

Calculate the cumulative percentage of metformin hydrochloride dissolved (Qi) at each time point (i):

At i = 1:

\[ Q_i = C_i \times V/L \times 100 \]

At i = 3:

\[ Q_i = C_i (V - V_s) + (C_1 \times V_s) \times 100/L \]

At i = 10:

\[ Q_{10} = C_{10} (V - 2V_s) + (C_1 + C_3) V_s \times 100/L \]

\[ V = \text{initial volume of Medium, 1000 mL} \]
\[ V_s = \text{sampling volume, 10 mL} \]
\[ L = \text{label claim (mg/Tablet)} \]

Tolerances: The percentages of the labeled amount of \( \text{C}_4\text{H}_11\text{N}_5 \cdot \text{HCl} \) dissolved at the times specified conform to Acceptance Table 2.

<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 85%</td>
</tr>
</tbody>
</table>

At 1 h:  

Result = Q1

At 3 h:  

Result = Q3 + \( (Q1 \times 10)/V \)

At 10 h:  

Result = Q10 + \( (Q1 \times 10)/V \) + \( (Q3 \times 10)/V \)

\[ A_i = \text{absorbance of the Sample solution} \]
\[ A_s = \text{absorbance of the Standard solution} \]
\[ C_i = \text{concentration of the Standard solution (mg/mL)} \]
\[ L = \text{label claim (mg/Tablet)} \]
\[ V = \text{volume of Medium, 1000 mL} \]
\[ D = \text{dilution factor of the Sample solution} \]

Tolerances: The percentages of the labeled amount of \( \text{C}_4\text{H}_11\text{N}_5 \cdot \text{HCl} \) dissolved at the times specified conform to Acceptance Table 2.

**IMPURITIES**

**Organic Impurities**

**PROCEDURE**

Mobile phase, Sample solution, and Chromatographic system: Prepare 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:

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

\[ r_U = \text{peak response for each impurity} \]
\[ r_T = \text{sum of all the peak responses} \]

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
- USP Metformin Related Compound C RS

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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
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 2