Zolpidem Tartrate Extended-Release Tablets

DEFINITION
Zolpidem Tartrate Extended-Release Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of zolpidem tartrate (C_{42}H_{48}N_{6}O_{8}).

IDENTIFICATION
• A. ULTRAVIOLET ABSORPTION (197U)
  Sample: 25 µg/mL of zolpidem tartrate in 0.01 M hydrochloric acid from a suitable quantity of powder obtained by grinding 1 Tablet
  Acceptance criteria: Meet the requirements
• B. The retention time of the major peak of the Sample solution corresponds to that of the Standard solution, as obtained in the Assay.

ASSAY

Change to read:

• PROCEDURE
  Buffer: 3.3 mL of phosphoric acid in 1 L of water. Adjust with triethylamine to a pH of 5.5.
  Mobile phase: Acetonitrile, methanol, and Buffer (4:5:1)
  Standard stock solution: 0.5 mg/mL of USP Zolpidem Tartrate RS in a mixture of alcohol and 0.01 M hydrochloric acid (4:1)
  Standard solution: 0.1 mg/mL of USP Zolpidem Tartrate RS from the Standard stock solution in Mobile phase
  Sample stock solution: Finely powder NLT 8 Tablets. Transfer the powder quantitatively to a suitable volumetric flask to obtain nominally 0.5 mg/mL of zolpidem tartrate. Add 70% of the flask volume of a mixture of alcohol and 0.01 M hydrochloric acid (3:2), and stir on a magnetic stirrer for 1 h. Dilute with alcohol to volume. Allow solid particles to settle, and pass the supernatant through a suitable filter (Whatman 40 or equivalent).
  Alternatively, the Sample stock solution can be prepared as follows. Transfer NLT 20 Tablets to a suitable volumetric flask to obtain a nominal concentration of 0.5 mg/mL of zolpidem tartrate. Add 10% of the flask volume of alcohol and stir for 30 min or until the Tablets have completely disintegrated. Add another 10% of the flask volume of alcohol and stir for another 90 min. Add 10% of the flask volume of 0.01 M hydrochloric acid followed by 40% of the flask volume of a mixture of alcohol and 0.01 M hydrochloric acid (3:2). Continue to stir for another 30 min. Remove the stirrer bar and rinse with alcohol. Dilute with alcohol to volume.
  Sample solution: Nominally 0.1 mg/mL of zolpidem tartrate from filtered Sample stock solution in Mobile phase. If the Sample stock solution is prepared using the alternative procedure, dilute the required volume of the Sample stock solution with Mobile phase and centrifuge instead of filtering before use.
  Chromatographic system (See Chromatography (621), System Suitability.)

Mode: LC
Detector: UV 240 nm
Column: 4.6-mm × 15-cm; 5-µm packing L1
Column temperature: 40°C
Flow rate: 1 mL/min
Injection volume: 15 µL

System suitability
Sample: Standard solution
Suitability requirements
Tailing factor: NMT 3.0 for zolpidem
Relative standard deviation: NMT 2.0% for zolpidem

Analysis
Samples: Standard solution and Sample solution
Calculate the percentage of the labeled amount of zolpidem tartrate (C_{42}H_{48}N_{6}O_{8}) in the portion of Tablets taken:

\[
\text{Result} = (r_0/r_s) \times (C_s/C_U) \times 100
\]

\( r_0 \) = peak response from the Sample solution
\( r_s \) = peak response from the Standard solution
\( C_s \) = concentration of USP Zolpidem Tartrate RS in the Standard solution (mg/mL)
\( C_U \) = nominal concentration of the Sample solution (mg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

• DISSOLUTION (711)
  Test 1
  Medium: 0.01 N hydrochloric acid; 500 mL
  Apparatus 1: 100 rpm
  Times: 30, 90, and 240 min
  Standard solution: Solution of USP Zolpidem Tartrate RS in Medium containing (L/500) mg/mL, where L is the label claim in mg/Tablet
  Sample solution: Pass a portion of the solution under test through a suitable filter.
  Detector: UV 295 nm
  Blank: Medium
  Analysis
  Samples: Standard solution and Sample solution
  Calculate the percentage of the labeled amount of zolpidem tartrate (C_{42}H_{48}N_{6}O_{8}) dissolved at the times specified:

\[
\text{Result} = (A_U/A_s) \times (C_s/L) \times V \times 100
\]

\( A_U \) = absorbance of the Sample solution
\( A_s \) = absorbance of the Standard solution
\( C_s \) = concentration of the Standard solution (mg/mL)
\( L \) = label claim (mg/Tablet)
\( V \) = volume of Medium, 500 mL

Tolerances: See Table 1.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Amount Dissolved</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>50%–70%</td>
</tr>
<tr>
<td>90</td>
<td>70%–85%</td>
</tr>
<tr>
<td>240</td>
<td>NLT 90%</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of zolpidem tartrate (C_{42}H_{48}N_{6}O_{8}) dissolved at the times specified conform to Acceptance Table 2 in Dissolution (711).
Test 2: If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 2.

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

Standard solution: Solution of USP Zolpidem Tartrate RS in Medium containing (L/500) mg/mL, where L is the label claim in mg/Tablet.

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

Instrumental conditions
Mode: UV
Analytical wavelength: 295 nm
Blank: Medium

Analysis
Samples: Standard solution and Sample solution
Calculate the percentage of the labeled amount of zolpidem tartrate (C$_{42}$H$_{48}$N$_{6}$O$_{8}$) dissolved:

$$\text{Result} = (A_U/A_S) \times (C_S/L) \times V \times 100$$

$A_U =$ absorbance of the Sample solution
$A_S =$ absorbance of the Standard solution
$C_S =$ concentration of the Standard solution (mg/mL)
$L =$ label claim (mg/Tablet)
$V =$ volume of Medium, 500 mL

Tolerances: See Table 2.

The percentages of the labeled amount of zolpidem tartrate (C$_{42}$H$_{48}$N$_{6}$O$_{8}$) dissolved at the times specified conform to Acceptance Table 2 in Dissolution (711).

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

Medium: 0.01 N hydrochloric acid; 500 mL
Apparatus 1: 100 rpm
Times: 30, 90, and 120 min

Standard solution: Solution of USP Zolpidem Tartrate RS in Medium containing (L/500) mg/mL, where L is the label claim in mg/Tablet.

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

Instrumental conditions
Mode: UV
Analytical wavelength: 237 nm
Blank: Medium

Analysis
Samples: Standard solution and Sample solution
Calculate the percentage of the labeled amount of zolpidem tartrate (C$_{42}$H$_{48}$N$_{6}$O$_{8}$) dissolved at each timepoint $i$ (Q):

$$Q_{10} = (A_U/A_S) \times C_S \times V \times (1/L) \times 100$$

$$Q_{90} = [(A_U/A_S) \times C_S \times V \times (1/L) \times 100] + [Q_{10} \times (V_S/V)]$$

$$Q_{120} = [(A_U/A_S) \times C_S \times V \times (1/L) \times 100] + [(Q_{10} + Q_{90}) \times (V_S/V)]$$

$A_U =$ absorbance of the Sample solution
$A_S =$ absorbance of the Standard solution
$C_S =$ concentration of USP Zolpidem Tartrate RS in the Standard solution (mg/mL)
$V =$ volume of Medium, 500 mL
$L =$ label claim (mg/Tablet)
$V_S =$ volume of the sample withdrawn (mL)

Tolerances: See Table 3.

Table 3

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Amount Dissolved</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>25%-45%</td>
</tr>
<tr>
<td>90</td>
<td>65%-85%</td>
</tr>
<tr>
<td>120</td>
<td>NLT 80%</td>
</tr>
</tbody>
</table>


The percentages of the labeled amount of zolpidem tartrate (C$_{42}$H$_{48}$N$_{6}$O$_{8}$) dissolved at the times specified conform to Acceptance Table 2 in Dissolution (711).

Test 4: If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 4.

Medium: 0.01 N hydrochloric acid; 500 mL
Apparatus 1: 100 rpm
Times: 30, 60, and 120 min

Standard solution: Solution of USP Zolpidem Tartrate RS in Medium containing (L/500) mg/mL, where L is the label claim in mg/Tablet.

Sample solution: Pass a portion of the solution under test through a suitable filter. Replace the volume withdrawn with an equal volume of Medium previously heated at 37.0 ± 0.5°.

Instrumental conditions
Mode: UV
Analytical wavelength: 294 nm
Blank: Medium

Analysis
Samples: Standard solution and Sample solution
Calculate the percentage of the labeled amount of zolpidem tartrate (C$_{42}$H$_{48}$N$_{6}$O$_{8}$) dissolved at each timepoint $i$ (Q):

$$Q_{30} = (A_U/A_S) \times C_S \times V \times (1/L) \times 100$$

$$Q_{60} = [(A_U/A_S) \times C_S \times V \times (1/L) \times 100] + [Q_{30} \times (V_S/V)]$$

$$Q_{120} = [(A_U/A_S) \times C_S \times V \times (1/L) \times 100] + [(Q_{30} + Q_{60}) \times (V_S/V)]$$

$A_U =$ absorbance of the Sample solution
$A_S =$ absorbance of the Standard solution
$C_S =$ concentration of USP Zolpidem Tartrate RS in the Standard solution (mg/mL)
$V =$ volume of Medium, 500 mL
$L =$ label claim (mg/Tablet)
$V_S =$ volume of the sample withdrawn (mL)

Tolerances: See Table 4.

Table 4

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Amount Dissolved</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>30%-55%</td>
</tr>
<tr>
<td>60</td>
<td>55%-80%</td>
</tr>
<tr>
<td>120</td>
<td>NLT 85%</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of zolpidem tartrate (C$_{42}$H$_{48}$N$_{6}$O$_{8}$) dissolved at the times specified conform to Acceptance Table 2 in Dissolution (711).

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 (Dissolve 6.8 g of monobasic potassium phosphate and 0.8 g of sodium hydroxide in 1 L of water. Adjust with phosphoric acid or 1 N sodium hydroxide to a pH of 6.8.), 900 mL
Apparatus 1: 50 rpm
Times: 1, 3, and 6 h
Buffer: Dissolve 5.6 g of phosphoric acid in 1 L of water. Adjust with triethylamine to a pH of 5.5.
Mobile phase: Methanol, acetonitrile, and Buffer (28:22:50)

Standard stock solution: 0.5 mg/mL of USP Zolpidem Tartrate RS in methanol

Standard solution: ([L/900]) mg/mL of USP Zolpidem Tartrate RS from Standard stock solution in Medium, where L is the label claim in mg/Tablet

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

Chromatographic system

(See Chromatography (621), System Suitability.)

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 7.5-cm; 3.5-µm packing L1

Column temperature: 40 °C

Flow rate: 1 mL/min

Injection volume: 25 µL

Run time: NLT 2.5 times the retention time of zolpidem

System suitability

Sample: Standard solution

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: Standard solution and Sample solution

Calculate the percentage of the labeled amount of zolpidem tartrate ([C42H48N6O8]) in the sample withdrawn at each time point (i):

\[ C_i = \left( \frac{A_i}{A_0} \right) \times C_0 \]

where

- \( A_i \) = absorbance of the Sample solution
- \( A_0 \) = absorbance of the Standard solution
- \( C_i \) = concentration of the Standard solution (mg/mL)

Tolerances: See Table 5.

The percentages of the labeled amount of zolpidem tartrate ([C42H48N6O8]) dissolved at the times specified conform to Acceptance Table 2 in Dissolution (711). The percentages of the labeled amount of zolpidem tartrate ([C42H48N6O8]) dissolved at the times specified conform to Acceptance Table 2 in Dissolution (711).

**Table 5**

<table>
<thead>
<tr>
<th>Time</th>
<th>Amount Dissolved</th>
</tr>
</thead>
<tbody>
<tr>
<td>(h)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>55%-75%</td>
</tr>
<tr>
<td>3</td>
<td>NLT 75%</td>
</tr>
<tr>
<td>6</td>
<td>NLT 85%</td>
</tr>
</tbody>
</table>

**Table 6**

<table>
<thead>
<tr>
<th>Time point (i)</th>
<th>Time (min)</th>
<th>Amount Dissolved</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15</td>
<td>45%-65%</td>
</tr>
<tr>
<td>2</td>
<td>60</td>
<td>63%-83%</td>
</tr>
<tr>
<td>3</td>
<td>120</td>
<td>NLT 80%</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of zolpidem tartrate ([C42H48N6O8]) dissolved at the times specified conform to Acceptance Table 2 in Dissolution (711).

**Uniformity of dosage units (905):** Meet the requirements

**Impurities**

**Organic impurities**

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

**System suitability solution:** Dissolve a suitable amount of USP Zolpidem Related Compound A RS in the Standard stock solution to obtain a solution containing 1 µg/mL of zolpidem related compound A. Dilute 1 mL of the resulting solution with Mobile phase to 5 mL.

**System suitability**

Sample: System suitability solution

Suitability requirements

Resolution: NLT 1.5 between zolpidem related compound A and zolpidem

Tailing factor: NMT 3.0 for the zolpidem peak

Relative standard deviation: NMT 2.0% for the zolpidem peak
Analysis

Sample: Sample solution

Calculate the percentage of each impurity in the portion of Tablets taken:

\[
\text{Result} = \left( \frac{r_i}{r_T} \right) \times \left( \frac{1}{F} \right) \times 100
\]

- \( r_i \) = peak response for each impurity from the Sample solution
- \( r_T \) = sum of the peak responses for all the peaks from the Sample solution
- \( F \) = relative response factor of the corresponding impurity (see Table 7)

Acceptance criteria: See Table 7.

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Relative Response Factor</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zolpidem acid(^a)</td>
<td>0.3</td>
<td>1.2</td>
<td>0.20</td>
</tr>
<tr>
<td>Zolpidem related compound (^a)</td>
<td>0.9</td>
<td>1.0</td>
<td>0.20</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>1.0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Any unspecified degradation product</td>
<td>—</td>
<td>1.0</td>
<td>0.20</td>
</tr>
<tr>
<td>Total impurities</td>
<td>—</td>
<td>—</td>
<td>0.5</td>
</tr>
</tbody>
</table>

\(^a\) 2-(6-Methyl-2-p-tolylimidazo[1,2-a]pyridin-3-yl)acetic acid.

\(^b\) N,N-Dimethyl-2-(7-methyl-2-p-tolylimidazo[1,2-a]pyridin-3-yl)acetamide.

ADDITIONAL REQUIREMENTS

- **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 Zolpidem Related Compound A RS
  - N,N-Dimethyl-2-(7-methyl-2-p-tolylimidazo[1,2-a]pyridin-3-yl)acetamide.
  - C\(_{10}\)H\(_{12}\)N\(_4\)O 307.39
  - USP Zolpidem Tartrate RS

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