Levetiracetam Extended-Release Tablets

Type of Posting: Revision Bulletin
Posting Date: 27–Apr–2018
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Expert Committee: Chemical Medicines Monographs 4
Reason for Revision: Compliance

In accordance with the Rules and Procedures of the 2015-2020 Council of Experts, the Chemical Medicines Monographs 4 Expert Committee has revised the Levetiracetam Extended-Release Tablets monograph. The purpose for the revision is to add Dissolution Test 9 to accommodate drug products that were approved with different dissolution conditions and acceptance criteria.

- Dissolution Test 9 was validated using a Thermo Fisher Hypersil BDS C8 brand of 4.6-mm x 15-cm, 5-µm packing L7 column. The typical retention time for levetiracetam is about 1.9 min.

The revision also necessitates a change in the table numbering in the test for Organic Impurities.

The Levetiracetam Extended-Release Tablets Revision Bulletin supersedes the currently official monograph. The Revision Bulletin will be incorporated in USP 42–NF 37.

Should you have any questions, please contact Ren-Hwa Yeh, Ph.D., Senior Scientific Liaison (301-998-6818 or rhy@usp.org).
Levetiracetam Extended-Release Tablets

**DEFINITION**
Levetiracetam Extended-Release Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of levetiracetam (C8H17N2O3).

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

**ASSAY**
- **PROCEDURE**
  - Buffer: 1.4 g/L of anhydrous dibasic sodium phosphate in water. Adjust with phosphoric acid to a pH of 3.5.
  - Mobile phase: Acetonitrile and Buffer (10:90)
  - **Standard stock solution:** 1.0 mg/mL of USP Levetiracetam RS prepared as follows. Weigh a suitable quantity of the Reference Standard into a volumetric flask. Add Mobile phase to fill 60% of flask volume and tetrahydrofuran to fill 4% of flask volume. Sonicate in cool water to dissolve. Equilibrate to room temperature. Dilute with Mobile phase to volume.
  - **Standard solution:** 0.08 mg/mL of USP Levetiracetam RS in Mobile phase from Standard stock solution. Pass a portion of the solution through a suitable filter of 0.45-µm pore size.
  - **Sample stock solution:** Nominally (L/100) mg/mL of levetiracetam from NLT 5 Tablets prepared as follows, where L is the label claim in mg/Tablet. Transfer the Tablets to a volumetric flask containing tetrahydrofuran to fill about 5% of flask volume. Stir for 30 min, and allow to stand for 5 min. Sonicate for 20 min with intermittent shaking. Add Mobile phase to fill 80% of final volume, and sonicate in cold water for 20 min with intermittent shaking. Add methanol to fill 10% of flask volume. Dilute with Mobile phase to volume. Centrifuge for 15 min, and pass a portion of the solution through a suitable filter of 0.2-µm pore size. Alternatively, the Sample stock solution, having a nominal concentration of 3 mg/mL of levetiracetam, may be prepared as follows. Finely grind NLT 10 Tablets, and transfer an amount equivalent to 750 mg of levetiracetam to a suitable volumetric flask. Add 18% of the flask volume of acetonitrile. Sonicate for 10 min followed by shaking using a mechanical shaker for 10 min. Add 18% of the flask volume of water, and shake for 15 min using a mechanical shaker. Allow the sample to equilibrate to room temperature, and dilute with a mixture of acetonitrile and water (50:50) to volume. Pass a portion of the solution through a suitable filter of 0.45-µm pore size.
  - **Sample solution:** Nominally 0.08 mg/mL of levetiracetam in Mobile phase from Sample stock solution.

**Chromatographic system**
(See Chromatography (621), System Suitability.)
- **Mode:** LC
- **Detector:** UV 205 nm
- **Column:** 4.6-mm × 25-cm; 5-µm packing L7
- **Temperatures**
  - Column: 30°
  - Autosampler: 10°
- **Flow rate:** 1.5 mL/min
- **Injection volume:** 10 µL
- **Run time:** 3 times the retention time of levetiracetam

**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 levetiracetam (C8H17N2O3) in the portion of Tablets taken:

\[
\text{Result} = \left( \frac{r_r}{r_s} \right) \times \left( \frac{C_s}{C_U} \right) \times 100
\]

- where \( r_r \) = peak response of levetiracetam from the Sample solution
- \( r_s \) = peak response of levetiracetam from the Standard solution
- \( C_s \) = concentration of USP Levetiracetam RS in the Standard solution (mg/mL)
- \( C_U \) = nominal concentration of levetiracetam in the Sample solution (mg/mL)

**Acceptance criteria:** 90.0%–110.0%

**PERFORMANCE TESTS**

**Dissolution (711)**
- **Test 1**
  - **Buffer A:** Dissolve 6.8 g of potassium dihydrogen phosphate and 0.2 g of sodium hydroxide in 1 L of water. If necessary, adjust with 1 N sodium hydroxide to a pH of 6.0.
  - **Medium:** Buffer A; 900 mL
  - **Apparatus:** 1; 100 rpm
  - **Times:** 1, 2, 4, and 8 h
  - **Buffer B:** 1.4 g/L of anhydrous dibasic sodium phosphate in water. Adjust with phosphoric acid to a pH of 3.5.
  - **Mobile phase:** Acetonitrile and Buffer B (10:90)
  - **Standard stock solution:** 1.7 mg/mL of USP Levetiracetam RS in water. Sonication may be used to aid in dissolution.
  - **Standard solution:** (L/900) mg/mL of USP Levetiracetam RS in Medium from Standard stock solution, where L is the label claim in mg/Tablet. Pass a portion through a suitable filter of 0.45-µm pore size.
  - **Sample solution:** Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size.

**Chromatographic system**
(See Chromatography (621), System Suitability.)
- **Mode:** LC
- **Detector:** UV 205 nm
- **Column:** 4.6-mm × 25-cm; 5-µm packing L7
- **Temperatures**
  - Column: 30°
  - Autosampler: 10°
- **Flow rate:** 1.5 mL/min
- **Injection volume:** 5 µL
- **Run time:** 2 times the retention time of levetiracetam

**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

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2 Levetiracetam

Calculate the concentration, \( C_i \), of levetiracetam (\( C_{6H_{14}N_{2}O_{2}} \)) in Medium (mg/mL) after time point \( i \):

\[
\text{Result}_i = (r_i / r_s) \times C_i
\]

\( r_u \) = peak response from the Sample solution
\( r_s \) = peak response from the Standard solution
\( C_s \) = concentration of the Standard solution (mg/mL)

Calculate the percentage of the labeled amount of levetiracetam (\( C_{6H_{14}N_{2}O_{2}} \)) dissolved at each time point \( i \):

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

\[
\text{Result}_2 = (\{C_i \times V\} + \{C_s \times V_s\}) \times (1/L) \times 100
\]

\[
\text{Result}_3 = (\{C_i \times V\} + \{C_s \times C_s \times V_s\}) \times (1/L) \times 100
\]

\( C_i \) = concentration of levetiracetam in the portion of sample withdrawn at the specified time point (mg/mL)
\( V \) = volume of Medium, 900 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 1.

<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/Tablet (%)</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>25–45</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>45–65</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>60–80</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of levetiracetam (\( C_{6H_{14}N_{2}O_{2}} \)), dissolved at the times specified, conform to Dissolution (711), Acceptance Table 2.

### Test 2: If the product complies with this procedure, the labeling indicates that it meets USP Dissolution Test 2. Buffer A: Dissolve 6.8 g of potassium dihydrogen phosphate and 0.2 g of sodium hydroxide in 1 L of water. If necessary, adjust with 1 N sodium hydroxide to a pH of 6.0.

Medium: Buffer A; 900 mL

Apparatus 1: 100 rpm

Times: 1, 2, 4, and 8 h

Buffer B: 2.82 g/L of potassium dihydrogen phosphate in water

Mobile phase: Acetonitrile and Buffer B (5:95). Adjust with phosphoric acid to a pH of 2.0.

Standard solution: (1L/900) mg/mL of USP Levetiracetam RS 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 of 0.45-µm pore size.

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

Mode: LC

Detector: UV 235 nm

### Columns

Guard: 4.6-mm × 1-cm, 4.6-mm × 2-cm, or 4.0-mm × 2-cm; 5-µm packing L1

Analytical: 4.6-mm × 5-cm; 3-µm packing L1

Flow rate: 0.8 mL/min

Injection volume: 10 µL

Run time: 2 times the retention time of levetiracetam

### System suitability

Sample: Standard solution

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 1.5% for five replicate injections

### Analysis

Samples: Standard solution and Sample solution

Calculate the concentration, \( C_i \), of levetiracetam (\( C_{6H_{14}N_{2}O_{2}} \)) in Medium (mg/mL) after time point \( i \):

\[
\text{Result}_i = (r_i / r_s) \times C_i
\]

\( r_u \) = peak response from the Sample solution
\( r_s \) = peak response from the Standard solution
\( C_s \) = concentration of the Standard solution (mg/mL)

Calculate the percentage of the labeled amount of levetiracetam (\( C_{6H_{14}N_{2}O_{2}} \)) dissolved at each time point \( i \):

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

\[
\text{Result}_2 = \{C_i \times V\} + \{C_s \times V_s\} \times (1/L) \times 100
\]

\[
\text{Result}_3 = \{C_i \times V\} + \{C_s \times C_s \times V_s\} \times (1/L) \times 100
\]

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

\( V \) = volume of Medium, 900 mL

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

\( V_s \) = volume of the Sample solution withdrawn from the Medium (mL)

### Tolerances: See Table 2.

<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/Tablet (%)</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>22–42</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>39–59</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>62–82</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of levetiracetam (\( C_{6H_{14}N_{2}O_{2}} \)), dissolved at the times specified, conform to Dissolution (711), Acceptance Table 2.

### Test 3: If the product complies with this procedure, the labeling indicates that it meets USP Dissolution Test 3. Buffer A: Dissolve 6.8 g of potassium dihydrogen phosphate and 0.5 g of sodium hydroxide in 1 L of water. Adjust to a pH of 6.0.

Medium: Buffer A; 900 mL

Apparatus 1: 100 rpm
Times: 1, 2, 4, and 8 h

Buffer B: 7.8 g/L of monobasic sodium phosphate dihydrate in water. Adjust with sodium hydroxide to a pH of 5.6.

Mobile phase: Acetonitrile and Buffer B (15:85)

Standard solution: (L/900) mg/mL of USP Levetiracetam RS in Medium, where L is the label claim in mg/Tablet

Sample solution: Centrifuge a portion of the solution under test.

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

Mode: LC

Detector: UV 220 nm

Column: 4.6-mm × 15-cm; 5-µm packing L1

Column temperature: 30°

Flow rate: 1.5 mL/min

Injection volume: 10 µL

Run time: 2 times the retention time of levetiracetam

System suitability
Sample: Standard solution

Suitability requirements
Column efficiency: NLT 1500 theoretical plates

Relative standard deviation: NMT 2.0% for six replicate injections

Analysis
Samples: Standard solution and Sample solution

Calculate the concentration, \( C_i \), of levetiracetam (\( C_4H_8N_2O_2 \)) in Medium (mg/mL) after time point \( t \):

\[
\text{Result}_{1} = (r_{i}/r_{S}) \times C_i
\]

\( r_{i} \) = peak response from the Sample solution

\( r_{S} \) = peak response from the Standard solution

\( C_i \) = concentration of USP Levetiracetam RS in the Standard solution (mg/mL)

Calculate the percentage of the labeled amount of levetiracetam (\( C_4H_8N_2O_2 \)) dissolved at each time point \( t \):

\[
\text{Result}_{2} = C_i \times V \times (1/L) \times 100
\]

\[
\text{Result}_{3} = [(C_i \times [V - (V_i)]) + (C_i \times V_i)] \times (1/L) \times 100
\]

\[
\text{Result}_{5} = (C_i \times [V - (3 \times V_i)]) \times (1/L) \times 100
\]

\( C_i \) = concentration of levetiracetam in Medium in the portion of sample withdrawn at time point \( t \) (mg/mL)

\( V \) = volume of Medium, 900 mL

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

\( V_i \) = volume of the Sample solution withdrawn from the Medium (mL)

Tolerances: See Table 3.

<table>
<thead>
<tr>
<th>Time Point (h)</th>
<th>Time (h)</th>
<th>Amount Dissolved</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>500 mg/Tablet (%)</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>42–62</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>59–79</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>78–98</td>
</tr>
</tbody>
</table>

Table 3 (continued)

The percentages of the labeled amount of levetiracetam (\( C_4H_8N_2O_2 \)), dissolved at the times specified, conform to Dissolution (711), Acceptance Table 2. Test 4: If the product complies with this procedure, the labeling indicates that it meets USP Dissolution Test 4.

Buffer: 6.8 g/L of monobasic potassium phosphate in water. Adjust with hydrochloric acid to a pH of 6.0.

Medium: Buffer; 900 mL

Apparatus 1: 100 rpm

Times: 1, 2, 4, and 8 h

Standard solution: (L/900) mg/mL of USP Levetiracetam RS in Medium, where L is the label claim in mg/Tablet.

Sample solution: Pass a suitable portion of the solution under test through a suitable filter of 0.45-µm pore size. Discard the first 3 mL of the filtrate. Dilute a known volume of the remaining filtrate quantitatively with Medium.

Blank: Medium

Instrumental conditions
Mode: UV

Analytical wavelength: 210 nm

Analysis
Samples: Standard solution and Sample solution

Calculate the concentration, \( C_i \), of levetiracetam (\( C_4H_8N_2O_2 \)) in Medium (mg/mL) after time point \( t \):

\[
\text{Result}_{1} = A_{u}/A_{S} \times C_i
\]

\( A_{u} \) = absorbance of the Sample solution

\( A_{S} \) = absorbance of the Standard solution

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

Calculate the percentage of the labeled amount of levetiracetam (\( C_4H_8N_2O_2 \)) dissolved at each time point \( t \):

\[
\text{Result}_{2} = C_i \times V \times (1/L) \times 100
\]

\[
\text{Result}_{3} = [(C_i \times [V - (V_i)]) + (C_i \times V_i)] \times (1/L) \times 100
\]

\[
\text{Result}_{5} = (C_i \times [V - (3 \times V_i)]) \times (1/L) \times 100
\]

\( C_i \) = concentration of levetiracetam in the portion of sample withdrawn at the specified time point (mg/mL)

\( V \) = volume of Medium, 900 mL

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

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

Tolerances: See Table 4.

<table>
<thead>
<tr>
<th>Time Point (h)</th>
<th>Time (h)</th>
<th>Amount Dissolved</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>500 mg/Tablet (%)</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>22–42</td>
</tr>
</tbody>
</table>
### Table 4 (continued)

<table>
<thead>
<tr>
<th>Time Point (t)</th>
<th>Time (h)</th>
<th>Amount Dissolved</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>500 mg/Tablet (%)</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>39–59</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>62–82</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of levetiracetam (C₂H₁₅N₂O₃), dissolved at the times specified, conform to Dissolution (711), Acceptance Table 2.

**Test 5:** If the product complies with this procedure, the labeling indicates that it meets USP Dissolution Test 5.

**Medium:** pH 6.0 phosphate buffer (6.8 g/L of monobasic potassium phosphate in water. Adjust with sodium hydroxide to a pH of 6.0); 900 mL

**Apparatus 1:** 100 rpm

**Times**

For 500- and 750-mg Tablets: 1, 4, 8, and 12 h

For 1000-mg Tablets: 1, 2, 4, and 8 h

**Buffer:** 2.7 g/L of monobasic potassium phosphate in water

**Mobile phase:** Acetonitrile and Buffer (10:90)

**Standard stock solution:** 2.8 mg/mL of USP Levetiracetam RS in Medium prepared as follows.

- Transfer a suitable quantity of USP Levetiracetam RS to a suitable volumetric flask. Dissolve in 20% of the flask volume of methanol. Dilute with Medium to volume.

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

**Sample solution:** At each time point withdraw 1 mL of the solution under test, and pass it through a suitable filter of 0.45-µm pore size.

**Chromatographic system**

(See Chromatography (621), System Suitability.)

**Mode:** LC

**Detector:** UV 220 nm

**Column:** 4.6-mm × 15-cm; 5-µm packing L11

**Flow rate:** 1 mL/min

**Injection volume**

For 500- and 750-mg Tablets: 10 µL

For 1000-mg Tablets: 5 µL

**Run time:** 2 times the retention time of levetiracetam

**System suitability**

**Sample:** Standard solution

**Suitability requirements**

- Column efficiency: NLT 4000 theoretical plates
- Tailing factor: NMT 1.5
- Relative standard deviation: NMT 2.0% for five replicate injections

**Analysis**

**Samples:** Standard solution and Sample solution

Calculate the percentage of the labeled amount of levetiracetam (C₂H₁₅N₂O₃) dissolved in Medium (mg/mL) after time point i:

\[
\text{Result}_i = \frac{r_u - r_s}{100} \times C_s \times V \times \frac{1}{L} \times 100
\]

- \(r_u\) = peak response from the Sample solution
- \(r_s\) = peak response from the Standard solution
- \(C_s\) = concentration of USP Levetiracetam RS in the Standard solution (mg/mL)
- \(V\) = volume of Medium, 900 mL

**Tolerances:** See Table 5.

### Table 5

<table>
<thead>
<tr>
<th>Time Point (t)</th>
<th>Time for 500 and 750 mg/Tablet (h)</th>
<th>Time for 1000 mg/Tablet (h)</th>
<th>Amount Dissolved</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>500 and 750 mg/Tablet (%)</td>
<td>1000 mg/Tablet (%)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>1</td>
<td>NMT 40</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>2</td>
<td>55–80</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>4</td>
<td>NLT 75</td>
</tr>
<tr>
<td>4</td>
<td>12</td>
<td>8</td>
<td>NLT 85</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of levetiracetam (C₂H₁₅N₂O₃), dissolved at the times specified, conform to Dissolution (711), Acceptance Table 2.

**Test 6:** If the product complies with this procedure, the labeling indicates that it meets USP Dissolution Test 6.

**Medium:** pH 6.0 phosphate buffer (6.9 g of monobasic potassium phosphate, and 0.23 g of sodium hydroxide in 1 L of water. Adjust with sodium hydroxide or phosphoric acid to a pH of 6.0); 900 mL

**Apparatus 1:** 100 rpm

**Times:** 1, 2, 4, and 8 h

**Mobile phase:** Acetonitrile and water (10:90)

**Standard solution:** 0.5 mg/mL of USP Levetiracetam RS in Medium prepared as follows.

- Transfer a suitable quantity of USP Levetiracetam RS to a suitable volumetric flask. Add 4% of the flask volume of methanol and 60% of the flask volume of the Medium. Sonicate for NLT 5 min. Dilute with Medium to volume.

**Sample solution:** At the end of specified time interval, withdraw a known volume of the solution from the dissolution vessel. Pass a suitable portion of the solution under test through a suitable filter of 0.45-µm pore size.

**Chromatographic system**

(See Chromatography (621), System Suitability.)

**Mode:** LC

**Detector:** UV 230 nm

**Column:** 4.6-mm × 5-cm; 5-µm packing L1

**Temperature:** 30°C

**Flow rate:** 0.9 mL/min

**Injection volume:** 10 µL

**Run time:** 2 times the retention time of levetiracetam

**System suitability**

**Sample:** Standard solution

**Suitability requirements**

- Tailing factor: NMT 1.5
- Relative standard deviation: NMT 2.0%

**Analysis**

**Samples:** Standard solution and Sample solution

Calculate the concentration, \(C_s\), of levetiracetam (C₂H₁₅N₂O₃) in Medium (mg/mL) after time point i:

\[
\text{Result}_i = \frac{r_u - r_s}{100} \times C_s
\]

- \(r_u\) = peak response from the Sample solution
- \(r_s\) = peak response from the Standard solution
- \(C_s\) = concentration of the Standard solution (mg/mL)
Calculate the percentage of the labeled amount of levetiracetam (C₆H₁₀N₂O₃) dissolved at each time point (𝑖):

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

\[
\text{Result}_1 = \left(\frac{C_1 \times (V - V_f)}{(1/L)}\right) \times 100
\]

\[
\text{Result}_2 = \left(\frac{C_2 \times (V - 2 \times V_f)}{(1/L)}\right) \times 100
\]

\[
\text{Result}_3 = \left(\frac{(C_1 + C_2 + C_3 \times V_f)}{(1/L)}\right) \times 100
\]

\[
\text{Result}_4 = \left(\frac{(C_1 + 3 \times V_f)}{(1/L)}\right) \times 100
\]

\[
C_i = \text{concentration of levetiracetam in Medium in the portion of sample withdrawn at time point } i (\text{mg/mL})
\]

\[
V = \text{volume of Medium, } 900 \text{ mL}
\]

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

\[
V_i = \text{volume of the Sample solution withdrawn from the solution under test (mL)}
\]

**Tolerances:** See Table 6.

### Table 6

<table>
<thead>
<tr>
<th>Time Point (𝑖)</th>
<th>Time (ℎ)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>25–45</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>45–65</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>60–80</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of levetiracetam (C₆H₁₀N₂O₃), dissolved at the times specified, conform to Dissolution (711), Acceptance Table 2.

**Test 7:** If the product complies with this procedure, the labeling indicates that it meets USP Dissolution Test 7.

**Medium:** Acetate buffer, pH 4.5, prepared as follows. Dissolve 3.0 g of sodium acetate in 1 L of water and add 1.4 mL of glacial acetic acid. Adjust with 5 N sodium hydroxide or glacial acetic acid to a pH of 4.5; 230 mL.

**Apparatus 3:** 15 dips per min, with suitable screens

**Times**

- For 500-mg Tablets: 1, 2, 4, and 8 h
- For 750-mg Tablets: 1, 2, 4, and 10 h

**Buffer:** 13.6 g/L of monobasic potassium phosphate in water. Adjust with 5 N sodium hydroxide or glacial acetic acid to a pH of 6.0.

**Mobile phase:** Methanol and Buffer (15:85)

**Standard solution:** 0.55 mg/mL of USP Levetiracetam RS in Medium. Sonication may be used to aid in dissolution.

**Sample solution:** Pass a suitable portion of the solution under test through a suitable filter of 0.45-μm pore size. Discard the first 5 mL. Dilute a suitable volume of the filtrate with Medium, as needed.

**Chromatographic system**

(See Chromatography (621), System Suitability.)

**Mode:** LC

**Detector:** UV 210 nm

**Column:** 4.6-mm × 10-cm; 3-μm packing L1

**Column temperature:** 30°

**Flow rate:** 1 mL/min

**Injection volume:** 10 μL

**Run time:** 2 times the retention time of levetiracetam

**System suitability**

**Sample:** Standard solution

**Suitability requirements**

- **Tailing factor:** NMT 2.0
- **Relative standard deviation:** NMT 2.0%

**Analysis**

**Samples:** Standard solution and Sample solution

Calculate the concentration, Cᵢ, of levetiracetam (C₆H₁₀N₂O₃) in Medium (mg/mL) after time point i:

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

\[
r_i = \text{peak response from the Sample solution}
\]

\[
r_s = \text{peak response from the Standard solution}
\]

\[
D = \text{dilution factor, as needed}
\]

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

Calculate the percentage of the labeled amount of levetiracetam (C₆H₁₀N₂O₃) dissolved at each time point (𝑖):

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

\[
\text{Result}_1 = \left(\frac{C_1 \times (V - V_f)}{(1/L)}\right) \times 100
\]

\[
\text{Result}_2 = \left(\frac{C_2 \times (V - 2 \times V_f)}{(1/L)}\right) \times 100
\]

\[
\text{Result}_3 = \left(\frac{(C_1 + C_2 + C_3 \times V_f)}{(1/L)}\right) \times 100
\]

\[
\text{Result}_4 = \left(\frac{(C_1 + 3 \times V_f)}{(1/L)}\right) \times 100
\]

\[
C_i = \text{concentration of levetiracetam in Medium in the portion of sample withdrawn at the specified time point (mg/mL)}
\]

\[
V = \text{volume of Medium, } 230 \text{ mL}
\]

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

**Tolerances:** See Table 7.

### Table 7

<table>
<thead>
<tr>
<th>Time Point (𝑖)</th>
<th>Time (ℎ)</th>
<th>Amount Dissolved (mg/Tablet)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>500 mg/Tablet (15–35%)</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>500 mg/Tablet (30–50%)</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>750 mg/Tablet (50–75%)</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>750 mg/Tablet (45–70%)</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of levetiracetam (C₆H₁₀N₂O₃), dissolved at the times specified, conform to Dissolution (711), Acceptance Table 2.

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

**Medium:** Phosphate buffer, pH 6.0, prepared as follows. Dissolve 6.8 g of monobasic potassium phosphate in 1 L of water. Adjust with 10 N sodium hydroxide solution to a pH of 6.0; 900 mL.

**Apparatus 1:** 100 rpm

**Times**

- 1, 2, 4, and 12 h

**Buffer:** 0.26 g/L of monobasic potassium phosphate in water. Adjust with 20 g/L aqueous potassium hydroxide to a pH of 5.5.

**Solution A:** Acetonitrile and Buffer (5:95)

**Mobile phase:** Acetonitrile and Solution A (10:90)

**Standard solution:** (L/900) mg/mL of USP Levetiracetam RS in Medium, where L is the label claim in mg/Tablet. Sonicate to dissolve as needed.

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

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

Mode: LC
Detector: UV 220 nm
Column: 4.6-mm × 15-cm; 5-µm packing L1
Column temperature: 20°
Flow rate: 1 mL/min
Injection volume: 5 µL
Run time: NLT 1.6 times the retention time of levetiracetam

System suitability
Sample: Standard solution
Suitability requirements
Tailing factor: NMT 1.5
Relative standard deviation: NMT 1.8%

Analysis
Samples: Standard solution and Sample solution
Calculate the concentration, \( C_i \), of levetiracetam (C\(_4\)H\(_8\)N\(_2\)O\(_2\)) in Medium (mg/mL) after time point \( i \):

\[
Result_i = \left( \frac{r_i}{r_s} \right) \times C_i
\]

\( r_i \) = peak response from the Sample solution
\( r_s \) = peak response from the Standard solution
\( C_i \) = concentration of the Standard solution (mg/mL)

Calculate the percentage of the labeled amount of levetiracetam (C\(_4\)H\(_8\)N\(_2\)O\(_2\)) dissolved at each time point \( i \):

\[
\text{Percentage} = \left( \frac{V \times C_i}{V_1 \times C_1} \right) \times 100
\]

\( V \) = volume of Medium, 900 mL
\( L \) = label claim (mg/Tablet)
\( V_1 \) = volume of the Sample solution withdrawn from the Medium (mL)

Tolerances: See Table 8.

<table>
<thead>
<tr>
<th>Time Point (( i ))</th>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>25–45</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>40–60</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>55–75</td>
</tr>
<tr>
<td>4</td>
<td>12</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of levetiracetam (C\(_4\)H\(_8\)N\(_2\)O\(_2\)), dissolved at the times specified, conform to Dissolution (711), Acceptance Table 2.▲ (88-1-Jun-2017)

Test 9: If the product complies with this procedure, the labeling indicates that it meets USP Dissolution Test 9.

Medium: Phosphate buffer, pH 6.0, prepared as follows. Dissolve 6.8 g of monobasic potassium phosphate in 1 L of water. Adjust with 50% (w/v) potassium hydroxide solution to a pH of 6.0; 900 mL.

Apparatus 1: 100 rpm

Times: 1, 2, 4, and 12 h
Buffer: 5.0 g/L of monobasic potassium phosphate in water
Mobile phase: Acetonitrile and Buffer (15:85)
Standard solution: 0.56 mg/mL of USP Levetiracetam RS in Medium. Sonicate to dissolve as necessary.
Sample solution: Centrifuge a portion of the solution under test and use the clear supernatant.

[NOTE—The use of a centrifuge speed of 2500 rpm for 10 min may be suitable.]

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

Mode: LC
Detector: UV 220 nm
Column: 4.6-mm × 15-cm; 5-µm packing L7
Flow rate: 1.5 mL/min
Injection volume: 5 µL
Run time: NLT 2 times the retention time of levetiracetam

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

Analysis
Samples: Standard solution and Sample solution
Calculate the concentration, \( C_i \), of levetiracetam (C\(_4\)H\(_8\)N\(_2\)O\(_2\)) in Medium (mg/mL) after time point \( i \):

\[
Result_i = \left( \frac{r_i}{r_s} \right) \times C_i
\]

\( r_i \) = peak response from the Sample solution
\( r_s \) = peak response from the Standard solution
\( C_i \) = concentration of the Standard solution (mg/mL)

Calculate the percentage of the labeled amount of levetiracetam (C\(_4\)H\(_8\)N\(_2\)O\(_2\)) dissolved at each time point \( i \):

\[
\text{Percentage} = \left( \frac{V \times C_i}{V_1 \times C_1} \right) \times 100
\]

\( V \) = volume of Medium, 900 mL
\( L \) = label claim (mg/Tablet)
\( V_1 \) = volume of the Sample solution withdrawn from the Medium (mL)

Tolerances: See Table 9.

<table>
<thead>
<tr>
<th>Time Point (( i ))</th>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>10–30</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>25–45</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>45–70</td>
</tr>
<tr>
<td>4</td>
<td>12</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of levetiracetam (C\(_4\)H\(_8\)N\(_2\)O\(_2\)), dissolved at the times...
specifically conform to *Dissolution* (711), *Acceptance
Table 2* (08-1-May-2018)

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

**Impurities**

**Change to read:**

- **Organic Impurities**

  **Solution A:** Dilute 2 mL of phosphoric acid with water
to 1 L.
  **Diluent:** Acetonitrile and **Solution A** (5:95)
  **Buffer:** 1.4 g/L of anhydrous dibasic sodium phosphate
in water. Adjust with phosphoric acid to a pH of 3.5.
  **Mobile phase:** Acetonitrile and **Buffer** (5:95). To each L
of the mixture, add 1 g of sodium 1-hexanesulfonate
monohydrate.

  **System suitability solution:** 0.3 mg/mL of USP Levetiracetam RS
in *Diluent* prepared as follows. Dissolve the required amount of USP Levetiracetam RS
in 10% of the final volume of 0.1 N potassium hydroxide. Let the mixture react at room temperature
for about 15 min, and then neutralize by adding 0.1 N hydrochloric acid at 10% of the flask volume. Dilute with
**Diluent** to volume. [Note—This solution contains
levetiracetam and levetiracetam acid.]

  **Standard solution:** 12.5 µg/mL of USP Levetiracetam RS
in water. Sonication may be used to aid in
dissolution. Pass a portion of the solution through a
suitable filter of 0.2-µm pore size.

  **Sample solution:** Nominally equivalent to 2.5 mg/mL
of levetiracetam in water, from a portion of crushed Tablets (NLT 20) prepared as follows. Transfer the
weighed amount of crushed Tablet powder to a
volumetric flask containing water to fill 80% of final
volume. Sonicate in cold water for 10 min. Equilibrate
to room temperature. Dilute with water to volume.
Pass a portion through a suitable filter of 0.2-µm pore
size.

  Alternatively, the **Sample solution** having a nominal
concentration of 2–3 mg/mL of levetiracetam may be
prepared as follows. Finely grind NLT 10 Tablets, and
transfer an amount equivalent to one Tablet to a
volumetric flask with a mechanical shaker. Add NLT 30 mL of
acetonitrile. Sonicate for 10 min, and shake using a
mechanical shaker for 15 min. Add NLT 30 mL of
water, and shake for 15 min using a mechanical
shaker. Allow the resulting mixture to equilibrate to
room temperature. Add NLT 25% of the final flask
volume of acetonitrile. Dilute with water to volume.
Centrifuge for 15 min, and pass a portion through a
suitable filter of 0.45-µm pore size.

**Chromatographic system**

(See *Chromatography* (621), *System Suitability.*)

**Mode:** LC

**Detector:** UV 205 nm

**Column:** 4.6-mm × 25-cm; 5-µm packing L1

**Temperatures**

**Column:** 30°

**Autosampler:** 10°

**Flow rate:** 2 mL/min

**Injection volume:** 20 µL

**Run time:** 5 times the retention time of levetiracetam

**System suitability**

**Samples:** System suitability solution and **Standard
solution**

**Suitability requirements**

**Resolution:** NLT 1.5 between levetiracetam and
levetiracetam acid peaks, System suitability solution

**Tailing factor:** NMT 2.0, **Standard solution**

**Relative standard deviation:** NMT 5.0%, **Standard
solution**

**Analysis**

**Samples:** **Standard solution** and **Sample solution**

Calculate the percentage of any unspecified
degradation product in the portion of Tablets taken:

\[
\text{Result} = \left( \frac{r_d}{r_b} \right) \times \left( \frac{C_b}{C_d} \right) \times 100
\]

\[
r_d = \text{peak response of each impurity from the Sample solution}
\]

\[
r_b = \text{peak response of USP Levetiracetam RS from the Standard solution}
\]

\[
C_b = \text{concentration of USP Levetiracetam RS in the Standard solution (mg/mL)}
\]

\[
C_d = \text{nominal concentration of levetiracetam in the Sample solution (mg/mL)}
\]

**Acceptance criteria:** See **Table 10.**

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levitiracetam related compound B</td>
<td>0.40</td>
<td>—</td>
</tr>
<tr>
<td>Levitiracetam</td>
<td>1.0</td>
<td>—</td>
</tr>
<tr>
<td>Levetiracetam acid</td>
<td>1.3</td>
<td>0.30</td>
</tr>
<tr>
<td>Levetiracetam related compound A</td>
<td>1.9</td>
<td>—</td>
</tr>
<tr>
<td>Any individual unspecified degradation product</td>
<td>—</td>
<td>0.10</td>
</tr>
<tr>
<td>Total impurities</td>
<td>—</td>
<td>1.0</td>
</tr>
</tbody>
</table>

* (3)-2-Aminobutanamide.

* Process impurities controlled in the drug substance. Included for
identification purposes only. Not reported for the drug product, and not
included in total impurities.

* (3)-2-(2-Oxopyrrolidin-1-yl)butanoic acid.

* (3)-N-(1-Amino-1-oxobutan-2-y1)-4-chlorobutanamide.

**Additional requirements**

- **Packaging and Storage:** Preserve in well-closed
containers. 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 Levetiracetam RS

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