Levetiracetam Extended-Release Tablets

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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 tolerance limits for additional strengths to the existing *Dissolution Test 7* based on FDA approval. The revision also necessitates a change in the table numbering in the *Performance Tests* and *Organic Impurities* sections.

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

Should you have any questions, please contact Ren-Hwa Yeh, 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 ($C_8H_{14}N_2O_2$).

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 ($C_8H_{14}N_2O_2$) in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = 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

Change to read:

• **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*

Calculate the concentration, C_i, of levetiracetam ($C_8H_{14}N_2O_2$) in *Medium* (mg/mL) after time point *i*:

$$\text{Result}_i = (r_U/r_S) \times C_S$$

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 ($C_8H_{14}N_2O_2$) dissolved at each time point (*i*):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$
$$\text{Result}_2 = [(C_2 \times V) + (C_1 \times V_S)] \times (1/L) \times 100$$
$$\text{Result}_3 = \{(C_3 \times V) + [(C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$
$$\text{Result}_4 = \{(C_4 \times V) + [(C_3 + C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

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 1

Time Point (*i*)	Time (h)	Amount Dissolved	
		500 mg/Tablet (%)	750 mg/Tablet (%)
1	1	25–45	33–53
2	2	45–65	45–65
3	4	60–80	65–85
4	8	NLT 80	NLT 80

The percentages of the labeled amount of levetiracetam ($C_8H_{14}N_2O_2$), 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: (*L*/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; 5-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 ($C_8H_{14}N_2O_2$) in *Medium* (mg/mL) after time point *i*:

$$\text{Result}_i = (r_U/r_S) \times C_S$$

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 ($C_8H_{14}N_2O_2$) dissolved at each time point (*i*):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$
$$\text{Result}_2 = \{[C_2 \times (V - V_S)] + (C_1 \times V_S)\} \times (1/L) \times 100$$
$$\text{Result}_3 = (\{C_3 \times [V - (2 \times V_S)]\} + [(C_2 + C_1) \times V_S]) \times (1/L) \times 100$$
$$\text{Result}_4 = (\{C_4 \times [V - (3 \times V_S)]\} + [(C_3 + C_2 + C_1) \times V_S]) \times (1/L) \times 100$$

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 2

Time Point (*i*)	Time (h)	Amount Dissolved	
		500 mg/Tablet (%)	750 mg/Tablet (%)
1	1	22–42	16–36
2	2	39–59	30–50
3	4	62–82	50–70
4	8	NLT 80	NLT 80

The percentages of the labeled amount of levetiracetam ($C_8H_{14}N_2O_2$), 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 ($C_8H_{14}N_2O_2$) in *Medium* (mg/mL) after time point *i*:

$$\text{Result}_i = (r_U/r_S) \times C_S$$

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)

Calculate the percentage of the labeled amount of levetiracetam ($C_8H_{14}N_2O_2$) dissolved at each time point (*i*):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$
$$\text{Result}_2 = \{[C_2 \times (V - V_S)] + (C_1 \times V_S)\} \times (1/L) \times 100$$
$$\text{Result}_3 = (\{C_3 \times [V - (2 \times V_S)]\} + [(C_2 + C_1) \times V_S]) \times (1/L) \times 100$$
$$\text{Result}_4 = (\{C_4 \times [V - (3 \times V_S)]\} + [(C_3 + C_2 + C_1) \times V_S]) \times (1/L) \times 100$$

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 3*.

Table 3

Time Point (*i*)	Time (h)	Amount Dissolved		
		500 mg/Tablet (%)	750 mg/Tablet (%)	1000 mg/Tablet (%)
1	1	42–62	35–55	35–55
2	2	59–79	50–70	50–70
3	4	78–98	70–90	70–90
4	8	NLT 80	NLT 80	NLT 80

The percentages of the labeled amount of levetiracetam ($C_8H_{14}N_2O_2$), 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 sodium hydroxide 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 ($C_8H_{14}N_2O_2$) in *Medium* (mg/mL) after time point *i*:

$$\text{Result}_i = (A_U/A_S) \times C_S$$

A_U = absorbance of the *Sample solution*
A_S = absorbance of the *Standard solution*
C_S = concentration of the *Standard solution* (mg/mL)

Calculate the percentage of the labeled amount of levetiracetam ($C_8H_{14}N_2O_2$) dissolved at each time point (*i*):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$
$$\text{Result}_2 = [(C_2 \times V) + (C_1 \times V_S)] \times (1/L) \times 100$$
$$\text{Result}_3 = \{(C_3 \times V) + [(C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$
$$\text{Result}_4 = \{(C_4 \times V) + [(C_3 + C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

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 4*.

Table 4

Time Point (*i*)	Time (h)	Amount Dissolved	
		500 mg/Tablet (%)	750 mg/Tablet (%)
1	1	22–42	16–36
2	2	39–59	30–50
3	4	62–82	50–70
4	8	NLT 80	NLT 80

The percentages of the labeled amount of levetiracetam ($C_8H_{14}N_2O_2$), 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 ($C_8H_{14}N_2O_2$) dissolved in *Medium* (mg/mL) after time point *i*:

$$\text{Result}_i = (r_U/r_S) \times C_S \times V \times (1/L) \times 100$$

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
L = label claim (mg/Tablet)

Tolerances: See *Table 5*.

Table 5

Time Point (*i*)	Time for 500 and 750 mg/Tablet (h)	Time for 1000 mg/Tablet (h)	Amount Dissolved	
			500 and 750 mg/Tablet (%)	1000 mg/Tablet (%)
1	1	1	NMT 40	20–40
2	4	2	55–80	35–55
3	8	4	NLT 75	55–75
4	12	8	NLT 85	NLT 80

The percentages of the labeled amount of levetiracetam ($C_8H_{14}N_2O_2$), 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
Column temperature: 30°
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 2.0
Relative standard deviation: NMT 2.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the concentration, C_i, of levetiracetam ($C_8H_{14}N_2O_2$) in *Medium* (mg/mL) after time point *i*:

$$\text{Result}_i = (r_U/r_S) \times C_S$$

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 ($C_8H_{14}N_2O_2$) dissolved at each time point (*i*):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$
$$\text{Result}_2 = \{[C_2 \times (V - V_S)] + (C_1 \times V_S)\} \times (1/L) \times 100$$
$$\text{Result}_3 = (\{C_3 \times [V - (2 \times V_S)]\} + [(C_2 + C_1) \times V_S]) \times (1/L) \times 100$$
$$\text{Result}_4 = (\{C_4 \times [V - (3 \times V_S)]\} + [(C_3 + C_2 + C_1) \times V_S]) \times (1/L) \times 100$$

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 solution under test (mL)

Tolerances: See *Table 6*.

Table 6

Time Point (*i*)	Time (h)	Amount Dissolved (%)
1	1	25–45
2	2	45–65
3	4	60–80
4	8	NLT 80

The percentages of the labeled amount of levetiracetam ($C_8H_{14}N_2O_2$), 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
▲**For 1000- and 1500-mg Tablets:** 1, 4, and 12 h▲ (RB 1-Jan-2020)
Buffer: 13.6 g/L of monobasic potassium phosphate in water. Adjust with 5 N sodium hydroxide 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, C_i, of levetiracetam ($C_8H_{14}N_2O_2$) in *Medium* (mg/mL) after time point *i*:

$$\text{Result}_i = (r_U/r_S) \times D \times C_S$$

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
D = dilution factor, as needed
C_S = concentration of the *Standard solution* (mg/mL)

Calculate the percentage of the labeled amount of levetiracetam ($C_8H_{14}N_2O_2$) dissolved at each time point (*i*):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$
$$\text{Result}_2 = C_2 \times V \times (1/L) \times 100 + \text{Result}_1$$
$$\text{Result}_3 = C_3 \times V \times (1/L) \times 100 + \text{Result}_2$$
$$\text{Result}_4 = C_4 \times V \times (1/L) \times 100 + \text{Result}_3$$

C_i = concentration of levetiracetam in the portion of sample withdrawn at the specified time point (mg/mL)
V = volume of *Medium*, 230 mL
L = label claim (mg/Tablet)

Tolerances: See *Table 7* ▲and *Table 8*.▲ (RB 1-Jan-2020)

Table 7

Time Point (*i*)	Time (h)	Amount Dissolved	
		500 mg/Tablet (%)	750 mg/Tablet (%)
1	1	15–35	10–30
2	2	30–50	25–45
3	4	50–75	45–70
	8	NLT 80	—
4	10	—	NLT 80

Table 8

Time Point (*i*)	Time (h)	Amount Dissolved	
		1000 mg/Tablet (%)	1500 mg/Tablet (%)
1	1	15–35	15–35
2	4	45–65	40–60
3	12	NLT 80	NLT 80▲ (RB 1-Jan-2020)

The percentages of the labeled amount of levetiracetam ($C_8H_{14}N_2O_2$), 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.
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 ($C_8H_{14}N_2O_2$) in *Medium* (mg/mL) after time point *i*:

$$\text{Result}_i = (r_U/r_S) \times C_S$$

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 ($C_8H_{14}N_2O_2$) dissolved at each time point (*i*):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$
$$\text{Result}_2 = \{[C_2 \times (V - V_S)] + (C_1 \times V_S)\} \times (1/L) \times 100$$
$$\text{Result}_3 = (\{C_3 \times [V - (2 \times V_S)]\} + [(C_2 + C_1) \times V_S]) \times (1/L) \times 100$$
$$\text{Result}_4 = (\{C_4 \times [V - (3 \times V_S)]\} + [(C_3 + C_2 + C_1) \times V_S]) \times (1/L) \times 100$$

C_i = concentration of levetiracetam 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 9*.

Table 9▲ (RB 1-Jan-2020)

Time Point (*i*)	Time (h)	Amount Dissolved (%)
1	1	25–45
2	2	40–60
3	4	55–75
4	12	NLT 80

The percentages of the labeled amount of levetiracetam ($C_8H_{14}N_2O_2$), dissolved at the times specified, conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

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 ($C_8H_{14}N_2O_2$) in *Medium* (mg/mL) after time point *i*:

$$\text{Result}_i = (r_U/r_S) \times C_S$$

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 ($C_8H_{14}N_2O_2$) dissolved at each time point (*i*):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$
$$\text{Result}_2 = \{[C_2 \times (V - V_S)] + (C_1 \times V_S)\} \times (1/L) \times 100$$
$$\text{Result}_3 = (\{C_3 \times [V - (2 \times V_S)]\} + [(C_2 + C_1) \times V_S]) \times (1/L) \times 100$$
$$\text{Result}_4 = (\{C_4 \times [V - (3 \times V_S)]\} + [(C_3 + C_2 + C_1) \times V_S]) \times (1/L) \times 100$$

C_i = concentration of levetiracetam 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 10*.

Table 10▲ (RB 1-Jan-2020)

Time Point (*i*)	Time (h)	Amount Dissolved (%)
1	1	10–30
2	2	25–45
3	4	45–70
4	12	NLT 80

The percentages of the labeled amount of levetiracetam ($C_8H_{14}N_2O_2$), dissolved at the times specified, conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

• **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 suitable volumetric flask. Add NLT 30 mL of acetonitrile. Sonicate for 10 min, and shake using a mechanical shaker for 10 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 NMT 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:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of each impurity from the *Sample solution*

r_S = peak response of USP Levetiracetam RS 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: See ▲*Table 11*.

Table 11▲ (RB 1-Jan-2020)

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Levetiracetam related compound B[a, b]	0.40	—
Levetiracetam	1.0	—
Levetiracetam acid[c]	1.3	0.30
Levetiracetam related compound A[b, d]	1.9	—
Any individual unspecified degradation product	—	0.10
Total impurities	—	1.0

[a] (*S*)-2-Aminobutanamide.

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

[c] (*S*)-2-(2-Oxopyrrolidin-1-yl)butanoic acid.

[d] (*S*)-*N*-(1-Amino-1-oxobutan-2-yl)-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