

Status: Currently Official on 15-Feb-2025
 Official Date: Official as of 01-Jan-2020
 Document Type: USP Monographs
 DocId: GUID-5244A22A-9798-433E-B0F4-72A83E2ADA57_6_en-US
 DOI: https://doi.org/10.31003/USPNF_M3890_06_01
 DOI Ref: 93p7k

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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- μ m pore size.

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45- μ m pore size.

Chromatographic system

(See [Chromatography \(621\)](#), [System Suitability](#).)

Mode: LC

Detector: UV 205 nm

Column: 4.6-mm $\times$ 25-cm; 5- μ m packing [L7](#)

Temperatures

Column: 30°

Autosampler: 10°

Flow rate: 1.5 mL/min

Injection volume: 5 μ L

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):

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

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

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

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

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- μ m pore size.

Chromatographic system

(See [Chromatography \(621\)](#), [System Suitability](#).)

Mode: LC

Detector: UV 235 nm

Columns

Guard: 4.6-mm $\times$ 1-cm, 4.6-mm $\times$ 2-cm, or 4.0-mm $\times$ 2-cm; 5- μ m packing [L1](#)

Analytical: 4.6-mm $\times$ 5-cm; 5- μ m packing [L1](#)

Flow rate: 0.8 mL/min

Injection volume: 10 μ L

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_p , 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_p , 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)