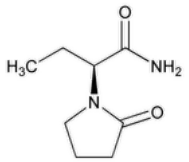
Status: Currently Official on 15-Feb-2025
Official Date: Official as of 01-May-2020
Document Type: USP Monographs
DocId: GUID-403D62FD-CB37-4A73-9AAD-9B7A6E6DCE48_4_en-US
DOI: https://doi.org/10.31003/USPNF_M2646_04_01
DOI Ref: 4h8lf

Levetiracetam



$C_8H_{14}N_2O_2$ 170.21

1-Pyrrolidineacetamide, α-ethyl-2-oxo-, (α*S*)-;

(−)-*(S)*-α-Ethyl-2-oxo-1-pyrrolidineacetamide CAS RN®: 102767-28-2; UNII: 44YRR34555.

DEFINITION

Levetiracetam contains NLT 98.0% and NMT 102.0% of levetiracetam ($C_8H_{14}N_2O_2$), calculated on the anhydrous and solvent-free basis.

IDENTIFICATION

Change to read:

• **A.** ▲Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*: **197K**▲ (CN 1-May-2020)

• **B.** The retention time of the major peak of the *Identification solution* corresponds to that of the levetiracetam *S*-enantiomer from the *System suitability solution*, as obtained in the test for *Limit of Levetiracetam R-Enantiomer*.

ASSAY

• **Procedure**

Buffer: 2.7 g/L of monobasic potassium phosphate in water. Adjust with 2% aqueous potassium hydroxide (w/v) to a pH of 5.5.

Solution A: Acetonitrile and *Buffer* (1:19)

Solution B: Acetonitrile

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	100	0
3	100	0
20	71	29

System suitability solution: 0.2 mg/mL of USP Levetiracetam RS and 0.08 mg/mL of USP Levetiracetam Related Compound A RS in *Solution A*. Prepare by first dissolving the required amount of USP Levetiracetam RS in a suitable volumetric flask. Add 10% of the flask 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. Add the required amount of USP Levetiracetam Related Compound A RS, sonicate to dissolve, dilute with *Solution A* to volume, and mix. [Note—Levetiracetam related compound A is included for peak identification purposes.]

Standard solution: 0.1 mg/mL of USP Levetiracetam RS in *Solution A*

Sample solution: 0.1 mg/mL of Levetiracetam in *Solution A*

Chromatographic system

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

Mode: LC

Detector: UV 205 nm

Column: 4.6-mm × 15-cm; packing L1

Flow rate: 0.9 mL/min

Injection volume: 10 µL

System suitability

Sample: *System suitability solution*

[NOTE—See *Table 2* for relative retention times.]

Suitability requirements

Relative standard deviation: NMT 1.0%, for the levetiracetam peak

[NOTE—If system suitability criteria cannot be met, it is recommended that the column temperature be maintained at 20° to stabilize the system.]

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of levetiracetam ($C_8H_{14}N_2O_2$) in the portion of Levetiracetam taken:

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

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 = concentration of Levetiracetam in the *Sample solution* (mg/mL)

F = percentage of levetiracetam *R*-enantiomer from the test for *Limit of Levetiracetam R-Enantiomer*

Acceptance criteria: 98.0%–102.0% on the anhydrous and solvent-free basis

IMPURITIES

- **RESIDUE ON IGNITION ⟨281⟩:** NMT 0.1%
- **LIMIT OF LEVETIRACETAM *R*-ENANTIOMER**

Mobile phase: *n*-Hexane and dehydrated alcohol (80:20)

System suitability solution: 0.1 mg/mL of USP Levetiracetam Racemic Mixture RS in *Mobile phase*

Standard solution: 0.05 mg/mL of USP Levetiracetam RS in *Mobile phase*

Sample solution: 10 mg/mL of Levetiracetam in *Mobile phase*

Identification solution: 0.05 mg/mL of Levetiracetam from *Sample solution* in *Mobile phase*

Chromatographic system

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

Mode: LC

Detector: UV 215 nm

Column: 4.6-mm × 25-cm; 10-µm packing L51

Flow rate: 1.0 mL/min

Injection volume: 20 µL

System suitability

Samples: *System suitability solution* and *Identification solution*

[NOTE—The relative retention times for levetiracetam *R*-enantiomer and levetiracetam *S*-enantiomer are 0.55 and 1.0, respectively. Use the chromatogram from the *Identification solution* for *Identification* test *B*.]

Suitability requirements

Resolution: NLT 4.0 between the *R*- and *S*-enantiomers, *System suitability solution*. [NOTE—If a loss of resolution (less than 4.0) is observed, it is recommended that the column temperature be maintained at 25° to stabilize the system.]

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of levetiracetam *R*-enantiomer in the portion of Levetiracetam taken:

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

r_U = peak response of levetiracetam *R*-enantiomer 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 = concentration of Levetiracetam in the *Sample solution* (mg/mL)

Acceptance criteria: NMT 0.8%

- **LIMIT OF LEVETIRACETAM RELATED COMPOUND B**

[NOTE—Perform this test only if levetiracetam related compound B is a known process impurity.]

Buffer: 1.22 g of sodium 1-decanesulfonate in 1 L of water containing about 1.3 mL of phosphoric acid. Adjust with 20% (w/v) potassium hydroxide to a pH of 3.0.

Mobile phase: Acetonitrile and *Buffer* (3:17)

System suitability solution: 2 mg/mL of USP Levetiracetam Related Compound B RS in *Mobile phase*

Standard solution: 0.002 mg/mL of USP Levetiracetam Related Compound B RS in *Mobile phase*

Sample solution: 2.0 mg/mL of Levetiracetam in *Mobile phase*

Chromatographic system

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

Mode: LC

Detector: UV 200 nm

Column: 4.6-mm × 25-cm; packing L1

Flow rate: 1.0 mL/min

Injection volumes

System suitability: 10 µL

Analysis: 50 µL

System suitability

Sample: *System suitability solution*

[Note—The retention time for levetiracetam related compound B is 9 min.]

Suitability requirements

Tailing factor: NMT 3.0. [Note—If a significant tailing of the levetiracetam related compound B peak is observed (greater than 3.0), it is recommended that the column temperature be maintained at 27° to stabilize the system.]

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of levetiracetam related compound B in the portion of Levetiracetam taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak response of levetiracetam related compound B from the *Sample solution*

r_S = peak response of levetiracetam related compound B from the *Standard solution*

C_S = concentration of USP Levetiracetam Related Compound B RS in the *Standard solution* (mg/mL)

C_U = concentration of Levetiracetam in the *Sample solution* (mg/mL)

M_{r1} = molecular weight of levetiracetam related compound B free base, 102.1

M_{r2} = molecular weight of levetiracetam related compound B, 138.6

Acceptance criteria: NMT 0.10%

[Note—The amount of levetiracetam related compound B measured is to be included in the total impurities in the test for *Organic Impurities*.]

• **Organic Impurities**

Buffer, Solution A, Solution B, Mobile phase, System suitability solution, Chromatographic system, and **System suitability:** Proceed as directed in the *Assay*.

Standard solution: 0.005 mg/mL of USP Levetiracetam RS in *Solution A*

Sample solution: 5 mg/mL of Levetiracetam in *Solution A*

Analysis

Samples: *Standard solution* and *Sample solution*

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

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

r_U = peak response of each impurity 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 = concentration of Levetiracetam in the *Sample solution* (mg/mL)

F = relative response factor (see *Table 2*)

[Note—Disregard any peak with a relative retention time of 0.19 or less.]

Acceptance criteria: See *Table 2*.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Pyridin-2-ol[a]	0.37	1.0	0.025
Levetiracetam acid[b]	0.62	1.2	0.3
Levetiracetam	1.00	—	—
Levetiracetam related compound A[c]	1.25	0.35	0.05
Any individual unspecified impurity	—	1.0	0.05
Total impurities	—	—	0.4

[a] Not included in the total impurities limit.

[b] *(S)*-2-(2-Oxopyrrolidin-1-yl)butanoic acid. Included in the total impurities limit.

[c] *(S)*-*N*-(1-Amino-1-oxobutan-2-yl)-4-chlorobutanamide. Included in the total impurities limit only if levetiracetam related compound B is a known process impurity.

SPECIFIC TESTS

• **Water Determination ⟨921⟩, *Method Ia*:** NMT 0.5%

ADDITIONAL REQUIREMENTS

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

• **USP Reference Standards ⟨11⟩**

USP Levetiracetam RS

USP Levetiracetam Racemic Mixture RS

A 1:1 mixture of:
Levetiracetam *S*-enantiomer-(2*S*)-2-(2-oxopyrrolidin-1-yl)butanamide;
Levetiracetam *R*-enantiomer (2*R*)-2-(2-oxopyrrolidin-1-yl)butanamide.

USP Levetiracetam Related Compound A RS

(*S*)-*N*-(1-Amino-1-oxobutan-2-yl)-4-chlorobutanamide.
$C_8H_{15}ClN_2O_2$ 206.67

USP Levetiracetam Related Compound B RS

(*S*)-2-Aminobutanamide hydrochloride.
$C_4H_{10}N_2O \cdot HCl$ 138.6

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
LEVETIRACETAM	Documentary Standards Support	SM42020 Small Molecules 4

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
Pharmacopeial Forum: Volume No. PF 41(3)

Current DocID: GUID-403D62FD-CB37-4A73-9AAD-9B7A6E6DCE48_4_en-US

DOI: https://doi.org/10.31003/USPNF_M2646_04_01

DOI ref: 4h8lf