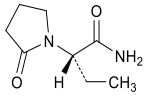
Levetiracetam

レベチラセタム



$C_8H_{14}N_2O_2$: 170.21

(2*S*)-2-(2-Oxopyrrolidin-1-yl)butanamide

[*102767-28-2*]

Levetiracetam contains not less than 98.0% and not more than 102.0% of $C_8H_{14}N_2O_2$, calculated on the dried basis.

Description Levetiracetam occurs as a white to light grayish white crystalline powder.

It is very soluble in water, freely soluble in ethanol (99.5), and soluble in 2-propanol.

Optical rotation <*2.49*> $[\alpha]_D^{20}$: −76 – −82° (0.2 g, water, 10 mL, 100 mm).

Identification Determine the infrared absorption spectrum of Levetiracetam as directed in the potassium bromide disk method under Infrared Spectrophotometry <*2.25*>, and compare the spectrum with the Reference Spectrum or the spectrum of Levetiracetam RS: both spectra exhibit similar intensities of absorption at the same wave numbers. Alternatively, perform the test by the ATR method, and compare the spectrum with the spectrum of Levetiracetam RS: both spectra exhibit similar intensities of absorption at the same wave numbers.

Purity **(1)** Related substances—Use the sample solution obtained in the Assay as the sample solution. Weigh accurately about 5 mg of Levetiracetam Related Substance A for Purity RS, and dissolve in a mixture of acetonitrile for liquid chromatography and water (24:1) to make exactly 500 mL. Pipet 1 mL of this solution, add a mixture of acetonitrile for liquid chromatography and water (24:1) to make exactly 100 mL, and use this solution as the standard solution (1). Pipet 1 mL of the standard solution obtained in the Assay, and add a mixture of acetonitrile for liquid chromatography and water (24:1) to make exactly 20 mL. Pipet 1 mL of this solution, add a mixture of acetonitrile for liquid chromatography and water (24:1) to make exactly 100 mL, and use this solution as the standard solution (2). Perform the test with exactly 10 μL each of the sample solution and standard solutions (1) and (2) as directed under Liquid Chromatography <*2.01*> according to the following conditions. Determine the peak areas, A_{T1} and A_{S1}, of the related substance A in the sample solution and standard solution (1), the area, A_{Tn}, of each other peak in the sample solution, and the peak area, A_S, of levetiracetam in the standard solution (2) by the automatic integration method. Calculate the amount of each related substance by the following equations: the amount of the related substance A is not more than 0.3%, the amount of other related substances is not more than 0.05%, the total amount of other related substances is not more than 0.1%, and the total amount of the related substances is not more than 0.4%.

$$\text{Amount (\%) of the related substance A} = M_{S1}/M_T \times A_{T1}/A_{S1} \times 1/2$$

$$\text{Amount (\%) of each of other related substances} = M_S/M_T \times A_{Tn}/A_S \times 1/20$$

M_{S1}: Amount (mg) of Levetiracetam Related Substance A for Purity RS taken

M_S: Amount (mg) of Levetiracetam RS taken, calculated on the anhydrous basis

M_T: Amount (mg) of Levetiracetam

Operating conditions—

Detector, column, column temperature, mobile phase, and flow rate: Proceed as directed in the operating conditions in the Assay.

Time span of measurement: About 3 times as long as the retention time of levetiracetam, beginning after the solvent peak.

System suitability—

System performance: Proceed as directed in the system suitability in the Assay.

Test for required detectability: When the procedure is run with 10 μL of the standard solution (2) under the above operating conditions, the SN ratio of the peak of levetiracetam is not less than 10.

System repeatability: When the test is repeated 6 times with 10 μL of the standard solution (1) under the above operating conditions, the relative standard deviation of the peak area of the related substance A is not more than 10%.

(2) Enantiomer—Dissolve 0.20 g of Levetiracetam in 2-propanol for liquid chromatography to make 10 mL. To 1 mL of this solution add the mobile phase to make 20 mL, and use this solution as the sample solution. Perform the test with 20 μL of the sample solution as directed under Liquid Chromatography <*2.01*> according to the following conditions. Determine the peak area, A_2, of levetiracetam and the peak area, A_1 of the related substance B (enantiomer) having the relative retention time of about 0.8 to levetiracetam by the automatic integration method: $A_1/(A_1+A_2)$ is not more than 0.007.

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 205 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 25 cm in length, packed with cellulose tris-(3,5-

dimethylphenylcarbamate)-coated silica gel for liquid chromatography (10 μm particle diameter).

Column temperature: A constant temperature of about 20°C.

Mobile phase: A mixture of hexane for liquid chromatography and 2-propanol for liquid chromatography (41:9).

Flow rate: 0.8 mL per minute.

System suitability—

Test for required detectability: Dissolve 25 mg each of Levetiracetam RS and Levetiracetam Related Substance B for System Suitability RS in the mobile phase to make 25 mL, and use this solution as the solution for system suitability test. Pipet 1 mL of the solution for system suitability test, and add the mobile phase to make exactly 10 mL. Pipet 1 mL of this solution, and add the mobile phase to make exactly 25 mL. When the procedure is run with 20 μL of this solution under the above operating conditions, the SN ratio of the peak of the related substance B (enantiomer) is not less than 10.

System performance: When the procedure is run with 20 μL of the solution for system suitability test under the above operating conditions, the resolution between the peaks of levetiracetam and the related substance B (enantiomer) is not less than 1.5, and the symmetry factor of the peak of levetiracetam is not more than 2.3.

System repeatability: When the test is repeated 5 times with 20 μL of the solution for system suitability test under the above operating conditions, the relative standard deviation of the peak area of levetiracetam is not more than 1.0%.

Water <*2.48*> Not more than 0.5% (0.3 g, coulometric titration).

Residue on ignition <*2.44*> Not more than 0.1% (1 g).

Assay Weigh accurately about 50 mg each of Levetiracetam and Levetiracetam RS (separately determine the water <*2.48*> in the same manner as Levetiracetam), dissolve each in a mixture of acetonitrile for liquid chromatography and water (24:1) to make exactly 250 mL, and use these solutions as the sample solution and the standard solution, respectively. Perform the test with exactly 10 μL each of the sample solution and standard solution as directed under Liquid Chromatography <*2.01*> according to the following conditions, and determine the peak areas, A_T and A_S, of levetiracetam in each solution.

Amount (mg) of levetiracetam ($C_8H_{14}N_2O_2$)
$= M_S \times A_T / A_S$

M_S: Amount (mg) of Levetiracetam RS taken, calculated on the anhydrous basis

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 205 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 25 cm in length, packed with silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 20°C.

Mobile phase: A mixture of acetonitrile for liquid chromatography and diluted sulfuric acid (11 in 10,000) (24:1).

Flow rate: 1.0 mL per minute.

System suitability—

System performance: Dissolve 5 mg each of Levetiracetam RS and 2-pyrrolidone in 25 mL of a mixture of acetonitrile for liquid chromatography and water (24:1). When the procedure is run with 10 μL of this solution under the above operating conditions, levetiracetam and 2-pyrrolidone are eluted in this order with the resolution between these peaks being not less than 1.5, and the symmetry factor of the peak of levetiracetam is not more than 1.4.

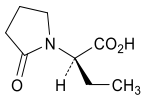
System repeatability: When the test is repeated 6 times with 10 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of levetiracetam is not more than 1.0%.

Containers and storage Containers — Well-closed containers

Others

Related Substance A:

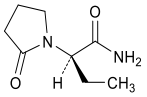
(2*RS*)-2-(2-Oxopyrrolidin-1-yl)butanoic acid



and enantiomer

Related Substance B:

(2*R*)-2-(2-Oxopyrrolidin-1-yl)butanamide



Add the following to 9.01 Reference Standards (1):

Levetiracetam Reference Standard
Levetiracetam related substance A for Purity RS
Levetiracetam Related Substance B for System Suitability RS

Add the following to 9.42 Solid Supports/Column Packings for Chromatography:

Cellulose tris-(3,5-dimethylphenylcarbamate)-coated silica gel for liquid chromatography Prepared for liquid chromatography.