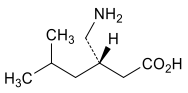
Pregabalin

プレガバリン



$C_8H_{17}NO_2$: 159.23

(3*S*)-3-(Aminomethyl)-5-methylhexanoic acid

[*148553-50-8*]

Pregabalin contains not less than 98.0% and not more than 102.0% of pregabalin ($C_8H_{17}NO_2$), calculated on the anhydrous basis.

Description Pregabalin occurs as a white crystalline powder.

It is sparingly soluble in water, and slightly soluble in ethanol (99.5).

Optical rotation $[\alpha]_D^{20}$: $+10 - +12^\circ$ (0.2 g calculated on the anhydrous basis, water, 20 mL, 100 mm).

Identification Determine the infrared absorption spectrum of Pregabalin 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 Pregabalin RS: both spectra exhibit similar intensities of absorption at the same wave numbers.

Purity (1) Related substances—(i) Polar related substances—Dissolve 0.1 g of Pregabalin in the mobile phase to make 10 mL, and use this solution as the sample solution. Pipet 1 mL of the sample solution, and add the mobile phase to make exactly 10 mL. Pipet 1 mL of this solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 20 μL each of the sample solution and standard solution as directed under Liquid Chromatography <*2.01*> according to the following conditions. Determine each peak area, A_T, of related substances other than pregabalin in the sample solution and the peak area, A_S, of pregabalin in the standard solution by the automatic integration method, and calculate the amount of each polar related substance by the following formula: each polar related substance is not more than 0.10%. For the peak area of related substance C, having the relative retention time of about 0.6 to pregabalin, multiply the correction factor 0.01.

$$\text{Amount (\%) of polar related substance} = A_T / A_S \times 1/10$$

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: Until pregabalin is eluted, beginning after the solvent peak.

System suitability—

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

Test for required detectability: Pipet 5 mL of the standard solution, and add the mobile phase to make exactly 10 mL. Confirm that the peak area of pregabalin obtained with 20 μL of this solution is equivalent to 35 to 65% of that with 20 μL of the standard solution.

(ii) Nonpolar related substances—Dissolve 0.1 g of Pregabalin in the mobile phase to make 10 mL, and use this solution as the sample solution. Pipet 1 mL of the sample solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 20 μL each of the sample solution and standard solution as directed under Liquid Chromatography <*2.01*> according to the following conditions. Determine each peak area, A_T, in the sample solution and the peak area, A_S, of pregabalin in the standard solution by the automatic integration method, and calculate the amount of each nonpolar related substance by the following formula: the amount of the related substance A having the relative retention time of about 2.4 to pregabalin is not more than 0.15%, and the amount of each nonpolar related substance other than related substance A is not more than 0.10%. For the areas of the peaks of related substances A and D, having the relative retention times of about 2.4 and about 2.8 to pregabalin, multiply their correction factors, 0.05 and 0.01, respectively.

$$\text{Amount (\%) of nonpolar related substance} = A_T / A_S$$

Operating conditions—

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

Mobile phase: Dissolve 3.40 g of potassium dihydrogen phosphate in 1000 mL of water, and adjust to pH 6.3 with ammonia solution (28). To 450 mL of this solution add 550 mL of methanol for liquid chromatography.

Time span of measurement: For 30 minutes after injection, beginning after the pregabalin peak.

System suitability—

System performance: When the procedure is run with 20 μL of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of pregabalin are not less than 4000 and not more than 1.8, respectively.

System repeatability: Pipet 5 mL of the standard solution, add the mobile phase to make exactly 100 mL. When the test

is repeated 6 times with 20 μL of this solution under the above operating conditions, the relative standard deviation of the peak area of pregabalin is not more than 10%.

(iii) Total amount of related substances—The total of the amount of related substances obtained in the Polar related substances and the Nonpolar related substances is not more than 0.5%.

(2) Enantiomer—Dissolve 20 mg of Pregabalin in water to make 10 mL. Transfer 500 μL of this solution, 500 μL of a solution of 1-fluoro-2,4-dinitrophenyl-5-L-alanine amide in acetonitrile (1 in 200) and 50 μL of a solution of sodium hydrogen carbonate (21 in 250) into a vial, stopper, shake, allow to stand at 40°C for 1 hour, then add 50 μL of 1 mol/L hydrochloric acid TS and mix. To 400 μL of this solution add 1600 μL of the mobile phase, 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 the pregabalin derivative in the sample solution and the peak area, A_1, of related substance B (enantiomer) derivative having the relative retention time of about 1.2 to the pregabalin derivative by the automatic integral method: $A_1/(A_1+A_2)$ is not more than 0.0015.

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 340 nm).

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

Column temperature: A constant temperature of about 30°C.

Mobile phase: To 620 mL of diluted triethylamine (1 in 100) adjusted to pH 3.0 with phosphoric acid add 380 mL of acetonitrile for liquid chromatography.

Flow rate: Adjust so that the retention time of the pregabalin derivative is about 10 minutes.

System suitability—

System performance: To 1 mL of the sample solution add the mobile phase to make 100 mL and use this solution as the solution for system suitability test. When the procedure is run with 20 μL of the solution for system suitability test under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of the pregabalin derivative are not less than 10,000 and not more than 1.5, respectively.

System repeatability: To 1 mL of the solution for system suitability test add the mobile phase to make 20 mL. When the test is repeated 6 times with 20 μL of this solution under the above operating conditions, the relative standard deviation of the peak area of the pregabalin derivative is not more than 10%.

Water <*2.48*>: Not more than 0.5% (0.2 g, coulometric titration).

Residue on ignition <*2.44*>: Not more than 0.1% (2 g).

Assay Weigh accurately about 0.1 g each of Pregabalin and Pregabalin RS (separately determine the water <*2.48*> in the same manner as Pregabalin), dissolve in the mobile phase to make exactly 10 mL, respectively, and use these solutions as the sample solution and the standard solution. Perform the test with exactly 20 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 pregabalin in each solution.

$$\text{Amount (mg) of pregabalin } (C_8H_{17}NO_2) = M_S \times A_T / A_S$$

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

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 210 nm).

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

Column temperature: A constant temperature of about 30°C.

Mobile phase: Dissolve 3.40 g of potassium dihydrogen phosphate in 1000 mL of water, and adjust to pH 6.3 with ammonia solution (28). To 850 mL of this solution add 150 mL of methanol for liquid chromatography.

Flow rate: 1.0 mL per minute.

System suitability—

System performance: When the procedure is run with 20 μL of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of pregabalin are not less than 6600 and not more than 1.1, respectively.

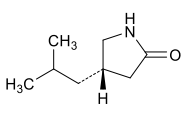
System repeatability: When the test is repeated 6 times with 20 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of pregabalin is not more than 1.0%.

Containers and storage Containers—Well-closed containers.

Others

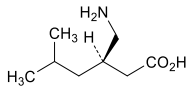
Related substance A:

(4*S*)-4-(2-Methylpropyl)pyrrolidin-2-one

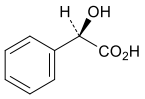


Related substance B (enantiomer):

(3*R*)-3-(Aminomethyl)-5-methylhexanoic acid

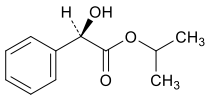


Related substance C:
(2*RS*)-2-Hydroxy-2-phenylacetic acid



and enantiomer

Related substance D:
1-Methylethyl (2*RS*)-2-hydroxy-2-phenylacetate



and enantiomer

Add the following to 9.01 Reference Standards section (1):

Pregabalin RS

Add the following to 9.41 Reagents, Test Solutions:

1-Fluoro-2,4-dinitrophenyl-5-L-alanine amide
$C_9H_9FN_4O_5$ Light yellow or orange, crystals or powder.

Melting point 226 – 229°C (beginning to melt)