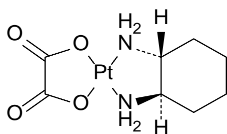
Oxaliplatin

オキサリプラチン



$C_8H_{14}N_2O_4Pt$: 397.29

(*SP*-4-2)-[(1*R*,2*R*)-Cyclohexane-1,2-diamine-κ*N*,κ*N*′][ethanedioato(2-)-κ*O*[1],κ*O*[2]]platinum

[*61825-94-3*]

Oxaliplatin contains not less than 98.0% and not more than 102.0% of oxaliplatin ($C_8H_{14}N_2O_4Pt$), calculated on the dried basis.

Description Oxaliplatin occurs as a white crystalline powder.

It is slightly soluble in water, very slightly soluble in methanol, and practically insoluble in ethanol (99.5).

Optical rotation $[\alpha]_D^{20}$: ＋74.5 – ＋78.0° (0.25 g calculated on the dried basis, water, 50 mL, 100 mm).

Identification **(1)** To 2 mL of a solution of oxaliplatin (1 in 500) add 2 to 3 drops of diluted tin (II) chloride TS (1 in 15), and allow to stand for 30 minutes: a yellow to orange-yellow precipitate is formed.

(2) Determine the absorption spectrum of a solution of Oxaliplatin (1 in 10,000) as directed under Ultraviolet-visible Spectrophotometry *<2.24>*, and compare the spectrum with the Reference Spectrum or the spectrum of a solution of Oxaliplatin RS prepared in the same manner as the sample solution: both spectra exhibit similar intensities of absorption at the same wavelengths.

(3) Determine the infrared absorption spectrum of Oxaliplatin 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 Oxaliplatin RS: both spectra exhibit similar intensities of absorption at the same wave numbers.

Purity **(1)** Acidity or Alkalinity—Dissolve 0.20 g of Oxaliplatin in freshly boiled and cooled water to make 100 mL. To 50 mL of this solution add 0.5 mL of phenolphthalein TS: no color develops. To this solution add 0.6 mL of 0.01 mol/L sodium hydroxide TS: a pale red color develops.

(2) Oxalic acid—Conduct this procedure within 20 minutes after preparation of the sample solution. Dissolve exactly 0.100 g of Oxaliplatin in water to make exactly 50 mL, and use this solution as the sample solution. Separately, dissolve exactly 14 mg of oxalic acid dihydrate in water to make exactly 250 mL. Pipet 5 mL of this solution, add water 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 the peak areas of oxalic acid in each solution by the automatic integration method: the peak area of oxalic acid obtained from the sample solution is not larger than the peak area of oxalic acid from the standard solution.

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 octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40°C.

Mobile phase: Dissolve 2.6 mL of 40% tetrabutylammonium hydroxide TS and 1.36 g of potassium dihydrogen phosphate in water to make 1000 mL, and adjust to pH 6.0 with phosphoric acid. To 800 mL of this solution add 200 mL of acetonitrile for liquid chromatography.

Flow rate: 2.0 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 oxalic acid is not less than 5000 and not more than 2.0, 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 oxalic acid is not more than 3.0%.

(3) Related substance A—Conduct this procedure within 20 minutes after preparation of the sample solution. Weigh accurately about 0.1 g of Oxaliplatin, dissolve in water to make exactly 50 mL, and use this solution as the sample solution. Separately, weigh accurately about 12.5 mg of Oxaliplatin Related Substance A Dinitrate for Purity RS, dissolve in about 63 mL of methanol, and add water to make exactly 250 mL. Pipet 5 mL of this solution add water 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 the peak areas, A_{T1} and A_S, of the related substance A in the sample solution and standard solution by the automatic integration method, and calculate the amount of the related substance A by the following equation: the amount of the related substances A is not more than 0.1%.

$$\text{Amount (\%) of the related substance A} = M_S / M_T \times A_{T1} / A_S \times 0.797$$

97 M_S: Amount (mg) of Oxaliplatin Related Substance A Dinitrate for Purity RS taken
99 M_T: Amount (mg) of Oxaliplatin taken
100 0.797: Conversion factor for the related substance A dinitrate to related substance A

102 *Operating conditions—*
103 Detector: An ultraviolet absorption photometer (wavelength: 215 nm).
105 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).
108 Column temperature: A constant temperature of about 40°C.
110 Mobile phase: Dissolve 1.36 g of potassium dihydrogen phosphate and 1 g of sodium 1-heptane sulfonate in 1000 mL of water, and adjust to pH 3.0 with phosphoric acid. To 800 mL of this solution add 200 mL of acetonitrile for liquid chromatography.
115 Flow rate: 2.0 mL per minute.
116 Time span of measurement: About 2.5 times as long as the retention time of the related substance A, beginning after the solvent peak.
119 *System suitability—*
120 Test for required detectability: Pipet 1 mL of the standard solution, add water to make exactly 10 mL. Confirm that the peak area of the related substance A obtained with 20 μL of this solution is equivalent to 7 to 13% of that with 20 μL of the standard solution.
125 System performance: Heat a solution of oxaliplatin in diluted dilute sodium hydroxide TS (1 in 20) (1 in 500) at 60°C for about 2 hours, and allow to cool. To 1 mL of this solution add water to make exactly 10 mL. When the procedure is run with 20 μL of this solution under the above operating conditions, the resolution between the related substance A and the peak having the relative retention time of about 1.4 to the related substance A is not less than 4, and the symmetry factor of the peak of the related substance A is not more than 2.0.
134 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 the related substance A is not more than 3.0%.
138 **(4)** Other related substances—Conduct this procedure within 20 minutes after preparation of the sample solution. Dissolve 0.10 g of Oxaliplatin in water to make 50 mL, and use this solution as the sample solution. Pipet 1 mL of the sample solution, and add water to make exactly 100 mL. Then, pipet 5 mL of this solution, and add water to make exactly 50 mL, and use this solution as the standard solution. 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 each peak area by the automatic integration method: the peak area of the related substance B, having the relative retention time of about 0.6 to oxaliplatin, obtained from the sample solution is not larger than 4.4 times the peak area of oxaliplatin from the standard solution. Furthermore, the total area of the peaks other than oxaliplatin and the peak mentioned above from the sample solution is not larger than the peak area of oxaliplatin from the standard solution.
156 *Operating conditions—*
157 Detector, column, column temperature, mobile phase, and flow rate: Proceed as directed in the Assay.
159 Time span of measurement: About 3 times as long as the retention time of oxaliplatin, beginning after the solvent peak.
161 *System suitability—*
162 Test for required detectability: Pipet 1 mL of the standard solution, and add water to make exactly 10 mL. Confirm that the peak area of oxaliplatin obtained with 20 μL of this solution is equivalent to 7 to 13% of that with 20 μL of the standard solution.
167 System performance: To 1 mL of a solution of oxaliplatin (1 in 500) and 1 mL of 1 mol/L sodium chloride TS add water to make 10 mL. Separately, to 1 mL of a solution of oxaliplatin (1 in 500) and 1 mL of diluted hydrogen peroxide (30) (1 in 3000) add water to make 10 mL. Heat these solutions at 60°C for about 2 hours, and allow to cool. Mix 1 mL each of these solutions, and add water to make 10 mL. When the procedure is run with 10 μL of this solution under the above operating conditions, the resolution between the peak having the relative retention time of about 0.9 to oxaliplatin and oxaliplatin is not less than 2.0, and the symmetry factor of oxaliplatin is not less than 2.0.
179 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 oxaliplatin is not more than 3.0%.
183 **(5)** Optical isomer—Dissolve 30 mg of Oxaliplatin in methanol to make 50 mL, and use this solution as the sample solution. Pipet 5 mL of the sample solution, and add methanol to make exactly 100 mL. Pipet 2 mL of this solution, add methanol 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 height in each solution by the automatic peak height method: the height of the peak having the relative retention time of about 1.2 to oxaliplatin obtained from the sample solution is not higher than the peak height of oxaliplatin from the standard solution.
196 *Operating conditions—*
197 Detector: An ultraviolet absorption photometer (wavelength: 254 nm).
199 Column: A stainless steel column 4.6 mm in inside diameter and 25 cm in length, packed with silica gel coated with

phenylcarbamoyl cellulose for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40°C.

Mobile phase: A mixture of methanol and ethanol (99.5) (7:3).

Flow rate: 0.3 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 oxaliplatin are not less than 5000 and not more than 2.0, 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 oxaliplatin is not more than 3.0%.

Loss on drying *<2.41>* Not more than 0.5% (1 g, 105°C, 2 hours).

Assay Weigh accurately about 20 mg each of Oxaliplatin and Oxaliplatin RS (separately determine the loss on drying *<2.41>* under the same conditions as Oxaliplatin), dissolve each in water to make exactly 200 mL, and use these solutions as the sample solution and the standard solution, respectively. 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 oxaliplatin in each solution.

$$\text{Amount (mg) of oxaliplatin } (C_8H_{14}N_2O_4Pt) = M_S \times A_T / A_S$$

M_S: Amount (mg) of Oxaliplatin RS taken, calculated on the dried 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 40°C.

Mobile phase: Adjust the pH of 1000 mL of water to 3.0 with phosphoric acid. To 990 mL of this solution add 10 mL of acetonitrile for liquid chromatography.

Flow rate: 1.2 mL per minute.

System suitability—

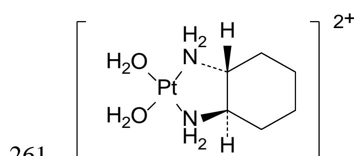
System performance: When the procedure is run with 20 μL of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of oxaliplatin are not less than 3000 and not more than 2.0, respectively.

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 oxaliplatin is not more than 1.0%.

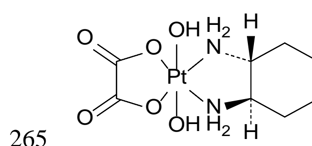
Containers and storage Containers—Tight containers.

Others

Related substance A:
(*SP*-4-2)-Diaqua[(1*R*,2R)-cyclohexane-1,2-diamine-κ*N*,κ*N*']
platinum



Related substance B:
(*OC*-6-33)-[(1*R*,2*R*)-Cyclohexane-1,2-diamine-κ*N*,κ*N*']
[ethanedioato(2-)-κO^1,κO^2] dihydroxyplatinum



Add the following to 9.01 Reference Standards (1):

Oxaliplatin RS

Oxaliplatin Related Substance A Dinitrate for Purity RS

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

Silica gel coated with phenylcarbamylated cellulose for liquid chromatography Prepared for liquid chromatography.