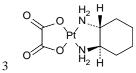
Oxaliplatin 1

オキサリプラチン 2



- 4 C₈H₁₄N₂O₄Pt: 397.29
- 5 (SP-4-2)-[(1R,2R)-Cyclohexane-1,2-diamine-κN,κN'][ethanedioato
- 6 (2-)- κO^1 , κO^2]platinum
- 7 [61825-94-3]
- 8

9 Oxaliplatin contains not less than 98.0% and not more than 102.0% of oxaliplatin (C₈H₁₄N₂O₄Pt), calcu-10

11 lated on the dried basis.

12 **Description** Oxaliplatin occurs as a white crystalline pow-13 der.

14 It is slightly soluble in water, very slightly soluble in methanol, and practically insoluble in ethanol (99.5). 15

Optical rotation $[\alpha]_{D}^{20}$: +74.5 - +78.0° (0.25 g calcu-16 17 lated on the dried basis, water, 50 mL, 100 mm).

18 **Identification** (1) To 2 mL of a solution of oxaliplatin (1

19 in 500) add 2 to 3 drops of diluted tin (II) chloride TS (1 in

20 15), and allow to stand for 30 minutes: a yellow to orange-21 yellow precipitate is formed.

22 (2) Determine the absorption spectrum of a solution of Oxaliplatin (1 in 10,000) as directed under Ultraviolet-visible 23 Spectrophotometry <2.24>, and compare the spectrum with 24 25 the Reference Spectrum or the spectrum of a solution of Oxaliplatin RS prepared in the same manner as the sample solu-26 27 tion: both spectra exhibit similar intensities of absorption at 28 the same wavelengths. 29 (3) Determine the infrared absorption spectrum of Oxal-

30 iplatin as directed in the potassium bromide disk method un-31 der Infrared Spectrophotometry <2.25>, and compare the 32 spectrum with the Reference Spectrum or the spectrum of Oxaliplatin RS: both spectra exhibit similar intensities of ab-33 34 sorption at the same wave numbers.

35 Purity (1) Acidity or Alkalinity—Dissolve 0.20 g of Oxaliplatin in freshly boiled and cooled water to make 100 mL. 36 37 To 50 mL of this solution add 0.5 mL of phenolphthalein TS: 38 no color develops. To this solution add 0.6 mL of 0.01 mol/L 39 sodium hydroxide TS: a pale red color develops.

40 (2)Oxalic acid-Conduct this procedure within 20 41 minutes after preparation of the sample solution. Dissolve exactly 0.100 g of Oxaliplatin in water to make exactly 50 mL, 42 43 and use this solution as the sample solution. Separately, dis-

44 solve exactly 14 mg of oxalic acid dihydrate in water to make 45 exactly 250 mL. Pipet 5 mL of this solution, add water to

make exactly 100 mL, and use this solution as the standard 46

47 solution. Perform the test with exactly 20 μ L each of the sam-

48 ple solution and standard solution as directed under Liquid 49

Chromatography <2.01> according to the following condi-

tions. Determine the peak areas of oxalic acid in each solution 50 51

- by the automatic integration method: the peak area of oxalic 52 acid obtained from the sample solution is not larger than the
- 53 peak area of oxalic acid from the standard solution.

54 Operating conditions—

55 Detector: An ultraviolet absorption photometer (wave-56 length: 205 nm).

57 Column: A stainless steel column 4.6 mm in inside diam-58 eter and 25 cm in length, packed with octadecylsilanized sil-59 ica gel for liquid chromatography (5 μ m in particle diameter). Column temperature: A constant temperature of about 60 61 40°C.

62 Mobile phase: Dissolve 2.6 mL of 40% tetrabutylammo-63 nium hydroxide TS and 1.36 g of potassium dihydrogen 64 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 65 66 of acetonitrile for liquid chromatography.

Flow rate: 2.0 mL per minute.

68 System suitability—

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69 System performance: When the procedure is run with 20 70 μ L of the standard solution under the above operating condi-71 tions, the number of theoretical plates and the symmetry fac-72 tor of the peak of oxalic acid is not less than 5000 and not more than 2.0, respectively. 73

74 System repeatability: When the test is repeated 6 times 75 with 20 μ L of the standard solution under the above operating 76 conditions, the relative standard deviation of the peak area of 77 oxalic acid is not more than 3.0%.

78 (3) Related substance A—Conduct this procedure within 79 20 minutes after preparation of the sample solution. Weigh 80 accurately about 0.1 g of Oxaliplatin, dissolve in water to 81 make exactly 50 mL, and use this solution as the sample so-82 lution. Separately, weigh accurately about 12.5 mg of Oxali-83 platin Related Substance A Dinitrate for Purity RS, dissolve 84 in about 63 mL of methanol, and add water to make exactly 85 250 mL. Pipet 5 mL of this solution add water to make ex-86 actly 100 mL, and use this solution as the standard solution. 87 Perform the test with exactly 20 μ L each of the sample solu-88 tion and standard solution as directed under Liquid Chroma-89 tography <2.01> according to the following conditions. De-90 termine the peak areas, A_{T1} and A_S, of the related substance A 91 in the sample solution and standard solution by the automatic 92 integration method, and calculate the amount of the related 93 substance A by the following equation: the amount of the re-94 lated substances A is not more than 0.1%.

> Amount (%) of the related substance A $=M_{\rm S}/M_{\rm T} \times A_{\rm T1}/A_{\rm S} \times 0.797$

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97	$M_{\rm S}$: Amount (mg) of Oxaliplatin Related Substance A	
98	Dinitrate for Purity RS taken	

- 99 $M_{T:}$ Amount (mg) of Oxaliplatin taken
- 100 0.797: Conversion factor for the related substance A dini-101 trate to related substance A
- 102 Operating conditions—

103 Detector: An ultraviolet absorption photometer (wave-104 length: 215 nm).

105 Column: A stainless steel column 4.6 mm in inside diam-106 eter and 25 cm in length, packed with octadecylsilanized sil-107 ica gel for liquid chromatography (5 μ m in particle diameter). 108 Column temperature: A constant temperature of about

109 40°C.

110 Mobile phase: Dissolve 1.36 g of potassium dihydrogen phosphate and 1 g of sodium 1-heptane sulfonate in 1000 mL 111 112 of water, and adjust to pH 3.0 with phosphoric acid. To 800 113 mL of this solution add 200 mL of acetonitrile for liquid chro-114 matography.

- 115 Flow rate: 2.0 mL per minute.
- 116 Time span of measurement: About 2.5 times as long as the
- 117 retention time of the related substance A, beginning after the solvent peak. 118
- 119 System suitability—
- 120 Test for required detectability: Pipet 1 mL of the standard
- 121 solution, add water to make exactly 10 mL. Confirm that the 174
- 122 peak area of the related substance A obtained with 20 μ L of
- 123 this solution is equivalent to 7 to 13% of that with 20 μ L of
- 124 the standard solution.

125 System performance: Heat a solution of oxaliplatin in di-126 luted dilute sodium hydroxide TS (1 in 20) (1 in 500) at 60°C 127 for about 2 hours, and allow to cool. To 1 mL of this solution 128 add water to make exactly 10 mL. When the procedure is run 129 with 20 μ L of this solution under the above operating condi-130 tions, the resolution between the related substance A and the 131 peak having the relative retention time of about 1.4 to the re-132 lated substance A is not less than 4, and the symmetry factor 133 of the peak of the related substance A is not more than 2.0. 134 System repeatability: When the test is repeated 6 times 135 with 20 μ L of the standard solution under the above operating 136 conditions, the relative standard deviation of the peak area of

137 the related substance A is not more than 3.0%.

138 (4) Other related substances—Conduct this procedure 139 within 20 minutes after preparation of the sample solution. 140 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 141 142 sample solution, and add water to make exactly 100 mL. 143 Then, pipet 5 mL of this solution, and add water to make ex-144 actly 50 mL, and use this solution as the standard solution. 145 Perform the test with exactly 10 μ L each of the sample solu-146 tion and standard solution as directed under Liquid Chroma-147 tography <2.01> according to the following conditions, and 148 determine each peak area by the automatic integration

149 method: the peak area of the related substance B, having the relative retention time of about 0.6 to oxaliplatin, obtained 150 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 154 the peak area of oxaliplatin from the standard solution.

Operating conditions—

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Detector, column, column temperature, mobile phase, and 158 flow rate: Proceed as directed in the Assay.

Time span of measurement: About 3 times as long as the retention time of oxaliplatin, beginning after the solvent peak. System suitability-

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 μ L of this solution is equivalent to 7 to 13% of that with 20 μ L of the standard solution.

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 μ L 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.

System repeatability: When the test is repeated 6 times with 10 μ L 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%.

(5) Optical isomer—Dissolve 30 mg of Oxaliplatin in methanol to make 50 mL, and use this solution as the sample 184 solution. Pipet 5 mL of the sample solution, and add methanol to make exactly 100 mL. Pipet 2 mL of this solution, add 186 methanol to make exactly 100 mL, and use this solution as 188 the standard solution. Perform the test with exactly 20 μ L each of the sample solution and standard solution as directed 190 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 oxali-194 platin obtained from the sample solution is not higher than the peak height of oxaliplatin from the standard solution. **Operating** conditions—

197 Detector: An ultraviolet absorption photometer (wave-198 length: 254 nm).

199 Column: A stainless steel column 4.6 mm in inside diam-200 eter and 25 cm in length, packed with silica gel coated with

- 201phenylcarbamoyl cellulose for liquid chromatography (5 μ m250202in particle diameter).251
- 203Column temperature: A constant temperature of about20440°C.
- 205Mobile phase: A mixture of methanol and ethanol (99.5)206(7:3).
- 207 Flow rate: 0.3 mL per minute.
- 208 System suitability—
- 209 System performance: When the procedure is run with 20
- 210 μ L of the standard solution under the above operating condi-
- tions, the number of theoretical plates and the symmetry fac-tor of the peak of oxaliplatin are not less than 5000 and not
- 213 more than 2.0, respectively.
- 214 System repeatability: When the test is repeated 6 times 215 with 20 μ L of the standard solution under the above operating
- 215 with 20 μ L of the standard solution under the above operating 216 conditions, the relative standard deviation of the peak area of
- 217 conditions, the relative standard deviation of the pear
- 217 oxaliplatin is not more than 3.0%.
- 218 Loss on drying <2.41> Not more than 0.5% (1 g, 105°C, 2
 219 hours).
- Assay Weigh accurately about 20 mg each of Oxaliplatin 220 221 and Oxaliplatin RS (separately determine the loss on drying 222 <2.41> under the same conditions as Oxaliplatin), dissolve 223 each in water to make exactly 200 mL, and use these solu-224 tions as the sample solution and the standard solution, respec-225 tively. Perform the test with exactly 20 μ L each of the sample 226 solution and standard solution as directed under Liquid Chro-227 matography <2.01> according to the following conditions, and determine the peak areas, $A_{\rm T}$ and $A_{\rm S}$, of oxaliplatin in 228 229 each solution.
- 230 Amount (mg) of oxaliplatin ($C_8H_{14}N_2O_4Pt$) 231 $=M_S \times A_T / A_S$
- 232 $M_{\rm S}$: Amount (mg) of Oxaliplatin RS taken, calculated on 233 the dried basis
- 234 Operating conditions—
- 235 Detector: An ultraviolet absorption photometer (wave-236 length: 210 nm).
- 237 Column: A stainless steel column 4.6 mm in inside diam-238 eter and 25 cm in length, packed with octadecylsilanized sil-239 ica gel for liquid chromatography (5 μ m in particle diameter).
- 240 Column temperature: A constant temperature of about
- 241 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.
- 246 System suitability—
- 247 System performance: When the procedure is run with 20 248 μ L of the standard solution under the above operating condi-
- 249 tions, the number of theoretical plates and the symmetry

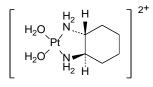
- factor of the peak of oxaliplatin are not less than 3000 andnot more than 2.0, respectively.
- 252 System repeatability: When the test is repeated 6 times 253 with 20 μ L of the standard solution under the above operating 254 conditions, the relative standard deviation of the peak area of 255 oxaliplatin is not more than 1.0%.
- 256 Containers and storage Containers Tight containers.

257 Others

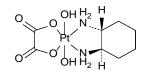
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- 258 Related substance A:
- 259 (*SP*-4-2)-Diaqua[(1*R*,2R)-cyclohexane-1,2-diamine- $\kappa N,\kappa N'$] 260 platinum



- 262 Related substance B:
- 263 (OC-6-33)-[(1R,2R)-Cyclohexane-1,2-diamine- $\kappa N,\kappa N'$]
- 264 [ethanedioato(2-)- κO^1 , κO^2] dihydroxyplatinum



266 Add the following to 9.01 Reference 267 Standards (1):

268 Oxaliplatin RS

269 Oxaliplatin Related Substance A Dinitrate for Purity RS

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270 Add the following to 9.42 Solid Sup-
271 ports/Column Packings for Chromatog-
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271 ports/Column Packings for Chromatog-272 raphy:

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