Oxaliplatin

C₈H₁₄N₂O₄Pt

M 397.3

[61825-94-3]

DEFINITION

(SP4-2)-[(1R,2R)-cyclohexane-1,2-diamine-κN,κN']
[ethanediato(2-)]-κO¹,κO²[Pt]platinum.

Content: 98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance: white or almost white, crystalline powder.

Solubility: slightly soluble in water, very slightly soluble in methanol, practically insoluble in ethanol.

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison: oxaliplatin CRS.

B. It complies with the test for specific optical rotation (see Tests).
TESTS

**Appearance of solution.** The solution is clear (2.2.1) and colourless (2.2.2, Method II).

Dissolve 0.10 g in water R and dilute to 50 ml with the same solvent.

**Acidity.** Dissolve 0.10 g in carbon dioxide-free water R, dilute to 50 ml with the same solvent and add 0.5 ml of phenolphthalein solution R1. The solution is colourless. Not more than 0.60 ml of 0.01 M sodium hydroxide is required to change the colour of the indicator to pink.

**Specific optical rotation** (2.2.7): +74.5 to +78.0 (dried substance).

Dissolve 0.250 g in water R and dilute to 50.0 ml with the same solvent.

**Related substances**

A. Impurity A. Liquid chromatography (2.2.29). Use vigorous shaking and very brief sonication to dissolve the substance to be examined. Inject the test solution within 20 min of preparation.

**Test solution.** Dissolve 0.100 g of the substance to be examined in water R and dilute to 50.0 ml with the same solvent.

**Reference solution (a).** Dissolve 14.0 mg of oxalic acid R (impurity A) in water R and dilute to 250.0 ml with the same solvent.

**Reference solution (b).** Dilute 5.0 ml of reference solution (a) to 200.0 ml with water R.

**Reference solution (c).** Dissolve 12.5 mg of sodium nitrate R in water R and dilute to 250.0 ml with the same solvent. Dilute a mixture of 2.0 ml of this solution and 25.0 ml of reference solution (a) to 100.0 ml with water R.

**Column:**
- size: l = 25 cm, Ø = 4.6 mm,
- stationary phase: base-deactivated octadecylsilyl silica gel for chromatography R (5 µm).

**Temperature:** 40 °C.

**Mobile phase:** mix 20 volumes of acetonitrile R with 80 volumes of a solution prepared as follows: to 10 ml of a 320 g/l solution of tetrabutylammonium hydroxide R add 1.36 g of potassium dihydrogen phosphate R and dilute to 1000 ml with water R; adjust this solution to pH 6.0 with phosphoric acid R.

**Flow rate:** 2 ml/min.

**Detection:** spectrophotometer at 215 nm.

**Injection:** 20 µl.

**Run time:** 2.5 times the retention time of impurity B.

**Retention times:** impurity B = about 4.3 min; impurity A = about 4.7 min.

**System suitability:**
- resolution: minimum 9 between the peaks due to nitrate and impurity A in the chromatogram obtained with reference solution (c),
- signal-to-noise ratio: minimum of 10 for the peak due to impurity A in the chromatogram obtained with reference solution (b).

**Limits:**
- impurity A: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent).

B. Impurity B. Liquid chromatography (2.2.29). Use vigorous shaking and very brief sonication to dissolve the substance to be examined. Inject the test solution within 20 min of preparation. Use suitable polypropylene containers for the preparation and injection of all solutions. Glass pipettes may be used for diluting solutions.

**Test solution.** Dissolve 0.100 g of the substance to be examined in water R and dilute to 50.0 ml with the same solvent.

**Reference solution (a).** Dissolve 12.5 mg of oxaliplatin impurity B CRS in 63 ml of methanol R and dilute to 250.0 ml with water R. Dilute 3.0 ml to 200.0 ml with water R.

**Reference solution (b).** In order to prepare in situ the degradation compound (impurity E) dissolve 12.5 mg of oxaliplatin impurity B CRS in 63 ml of methanol R and dilute to 250.0 ml with water R. Adjust to pH 6.0 with a 0.2 g/l solution of sodium hydroxide R. Heat for 4 h at 70 °C and allow to cool.

**Column:**
- size: l = 25 cm, Ø = 4.6 mm,
- stationary phase: base-deactivated octadecylsilyl silica gel for chromatography R (5 µm).

**Temperature:** 40 °C.

**Mobile phase:** mix 20 volumes of acetonitrile R with 80 volumes of a solution prepared as follows: dissolve 1.36 g of potassium dihydrogen phosphate R and 1 g of sodium heptanesulphonate R in 1000 ml of water R; adjust this solution to pH 3.0 ± 0.05 with phosphoric acid R.

**Flow rate:** 2.0 ml/min.

**Detection:** spectrophotometer at 215 nm.

**Injection:** 20 µl.

**Run time:** 2.5 times the retention time of impurity B.

**Retention times:** impurity B = about 4.3 min; impurity E = about 6.4 min.

**System suitability:**
- resolution: minimum 7 between the peaks due to impurity B and impurity E in the chromatogram obtained with reference solution (b),
- signal-to-noise ratio: minimum of 10 for the peak due to impurity B in the chromatogram obtained with reference solution (a).

**Limits:**
- impurity B: not more than 3.3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent).

C. Impurity C and other related substances. Liquid chromatography (2.2.29). Use vigorous shaking and very brief sonication to dissolve the substance to be examined. Inject the test solution within 20 min of preparation.

**Test solution (a).** Dissolve 0.100 g of the substance to be examined in water R and dilute to 50.0 ml with the same solvent.

**Test solution (b).** Dissolve 50.0 mg of oxaliplatin impurity C CRS and 10 mg of oxaliplatin CRS in water R and dilute to 100.0 ml with the same solvent.

**Reference solution (a).** Dissolve 10 mg of oxaliplatin impurity C CRS and 10 mg of oxaliplatin CRS in water R and dilute to 100.0 ml with the same solvent.

**Reference solution (b).** Dilute 1.0 ml of reference solution (a) to 100.0 ml with water R.
Reference solution (c). Dissolve 5 mg of dichlorodiaminocyclohexaneplatinum CRS in methanol R and dilute to 50.0 ml with the same solvent. To 10.0 ml of this solution add 10.0 ml of reference solution (a) and dilute to 100.0 ml with water R.

Reference solution (d). Dissolve 50.0 mg of oxaliplatin CRS in water R and dilute to 500.0 ml with the same solvent.

Reference solution (e). Dissolve 5.0 mg of dichlorodiaminocyclohexaneplatinum CRS in reference solution (d) and dilute to 50.0 ml with the same solvent.

Reference solution (f). To 0.100 g of the substance to be examined add 1.0 ml of reference solution (a) and dilute to 50.0 ml with water R.

Column:
- size: l = 25 cm, Ø = 4.6 mm,
- stationary phase: octadecylsilyl silica gel for chromatography R (5 µm).

Temperature: 40 °C.

- solution A: dilute 0.6 ml of dilute phosphoric acid R in 1000 ml of water R and adjust to pH 3.0 with either sodium hydroxide solution R or phosphoric acid R;
- solution B: acetonitrile R.

Flow rate: 1.2 ml/min.

Detection: spectrophotometer at 254 nm.

Injection: 10 µl; inject test solution (a) and reference solutions (b), (c) and (f).

Run time: 3 times the retention time of oxaliplatin.

Retention times: impurity C = about 4.4 min; dichlorodiaminocyclohexaneplatinum = about 6.9 min; oxaliplatin = about 8.0 min.

System suitability:
- resolution: minimum 2.0 between the peaks due to dichlorodiaminocyclohexaneplatinum and oxaliplatin in the chromatogram obtained with reference solution (c).
- signal-to-noise ratio: minimum 50 for the peak due to impurity C and minimum 10 for the peak due to oxaliplatin in the chromatogram obtained with reference solution (b).

Limits:
- impurity C: not more than half the area of the peak due to impurity C in the chromatogram obtained with reference solution (f) (0.1 per cent).
- any other impurity: not more than twice the area of the peak due to oxaliplatin in the chromatogram obtained with reference solution (b) (0.1 per cent).
- total of other impurities: not more than twice the area of the peak due to oxaliplatin in the chromatogram obtained with reference solution (b) (0.1 per cent).
- disregard limit: the area of the peak due to oxaliplatin in the chromatogram obtained with reference solution (b) (0.05 per cent); disregard any peak with a retention time less than 2 min.

D. Total of impurities: the sum of impurities A, B, C and other related impurities is not greater than 0.30 per cent.

Impurity D. Liquid chromatography (2.2.29).

Test solution. Dissolve 30 mg of the substance to be examined in methanol R and dilute to 50.0 ml with the same solvent.

Reference solution (a). Dissolve 5 mg of oxaliplatin impurity D CRS in methanol R and dilute to 100.0 ml with the same solvent.

Reference solution (b). Dilute 15.0 ml of reference solution (a) to 50.0 ml with methanol R.

Reference solution (c). Dissolve 150.0 mg of oxaliplatin CRS in methanol R and dilute to 200.0 ml with the same solvent.

Reference solution (d). Dilute 5.0 ml of reference solution (c) to 100.0 ml with methanol R.

Reference solution (e). To 40 ml of reference solution (c) add 1.0 ml of reference solution (b) and dilute to 50.0 ml with methanol R.

Reference solution (f). Mix 4.0 ml of reference solution (a) and 5.0 ml of reference solution (d) and dilute to 50.0 ml with methanol R.

Column:
- size: l = 25 cm, Ø = 4.6 mm,
- stationary phase: silica gel OC for chiral separations R.

Temperature: 40 °C.


Flow rate: 0.3 ml/min.

Detection: spectrophotometer at 254 nm.

Injection: 20 µl; inject the test solution and reference solutions (e) and (f).

Run time: twice the retention time of oxaliplatin.

Retention times: oxaliplatin = about 14 min; impurity D = about 16 min.

System suitability:
- resolution: minimum 1.5 between the peaks due to oxaliplatin and impurity D in the chromatogram obtained with reference solution (f),
- signal-to-noise ratio: minimum 10 for the peak due to impurity D in the chromatogram obtained with reference solution (e).

Limits:
- impurity D: not more than twice the peak height of the corresponding peak in the chromatogram obtained with reference solution (e) (0.1 per cent).

Silver: maximum 5.0 ppm.

Atomic absorption spectrometry (2.2.23, Method II).

Test solution. Dissolve 0.1000 g of the substance to be examined in water R and dilute to 50.0 ml with the same solvent. Dilute 20 µl of this solution to 40 µl with 0.5 M nitric acid.

Reference solution (a). Dilute a solution of silver nitrate R containing 1000 ppm of silver in 0.5 M nitric acid with 0.5 M nitric acid to obtain a solution which contains 10 ppb of silver.

Reference solution (b). Mix 20 µl of the test solution and 8 µl of reference solution (a) and dilute to 40 µl with 0.5 M nitric acid.

Reference solution (c). Mix 20 µl of the test solution and 16 µl of reference solution (a) and dilute to 40 µl with 0.5 M nitric acid.

Source: silver hollow-cathode lamp.

Wavelength: 328.1 nm.

Atomisation device: furnace.

Measure the absorbance of the test solution and reference solutions (b) and (c).

Loss on drying (2.2.32): maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 2 h.

Bacterial endotoxins (2.6.14): less than 1.0 IU/mg, if intended for use in the manufacture of parenteral dosage forms without a further appropriate procedure for the removal of bacterial endotoxins.
ASSAY
Liquid chromatography (2.2.29) as described in the test for impurity C and other related substances with the following modifications.
Injection: 20 µl; inject test solution (b) and reference solutions (d) and (e).
System suitability:
- resolution: minimum 2.0 between the peaks due to dichlorodiaminocyclohexaneplatinum and oxaliplatin in the chromatogram obtained with reference solution (e).
- repeatability: reference solution (d).
Calculate the percentage content of oxaliplatin using the chromatogram obtained with reference solution (d).

IMPURITIES
Specified impurities: A, B, C, D.
Other detectable impurities: E.

A. ethanedioic acid (oxalic acid),

B. (SP-4-2)-diaqua[(1R,2R)-cyclohexane-1,2-diamine-κN,κN′]platinum (diaquodiaminocyclohexaneplatinum),

C. (OC-6-33)-[(1R,2R)-cyclohexane-1,2-diamine-κN,κN′][ethanedioato(2-)κO1,κO2]dihydroxyplatinum,

D. (SP-4-2)-[1S,2S]-cyclohexane-1,2-diamine-κN,κN′][ethanedioato(2-)κO1,κO2]platinum (S,S-enantiomer of oxaliplatin),

E. (SP-4-2)-dip-oxobis[(1R,2R)-cyclohexane-1,2-diamine-κN,κN′]platinum (diaquodiaminocyclohexaneplatinum dimer).

OXAZEPAM
Oxazepamum

C₁₅H₁₁ClN₂O₂
Mr 286.7
[604-75-1]

DEFINITION
(3RS)-7-Chloro-3-hydroxy-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one.
Content: 99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS
Appearance: white or almost white, crystalline powder.
Solubility: practically insoluble in water, slightly soluble in ethanol (96 per cent).

IDENTIFICATION
Infrared absorption spectrophotometry (2.2.24).
Comparison: oxazepam CRS.

TESTS
Related substances. Liquid chromatography (2.2.29).
Prepare the solutions immediately before use.
Test solution. Dissolve 40.0 mg of the substance to be examined in 25 ml of a mixture of equal volumes of acetonitrile R and water R and dilute to 50.0 ml with the same mixture of solvents.
Reference solution (a). Dilute 1.0 ml of the test solution to 100.0 ml with a mixture of equal volumes of acetonitrile R and water R. Dilute 2.0 ml of this solution to 10.0 ml with a mixture of equal volumes of acetonitrile R and water R.
Reference solution (b). Dissolve the contents of a vial of oxazepam for peak identification CRS (containing impurities A, B, C, D and E) in 1.0 ml of the test solution.
Column:
- size: l = 0.25 m, Ø = 4.6 mm;
- stationary phase: end-capped octadecylsilyl silica gel for chromatography R (5 µm) resistant to bases up to pH 11.
Mobile phase:
- mobile phase A: dissolve 3.48 g of dipotassium hydrogen phosphate R in 900 ml of water R, adjust to pH 10.5 with a 40 g/1 solution of sodium hydroxide R and dilute to 1000 ml with water R;
- mobile phase B: acetonitrile R;

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Mobile phase A (per cent V/V)</th>
<th>Mobile phase B (per cent V/V)</th>
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<tbody>
<tr>
<td>0 - 4</td>
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<td>25</td>
</tr>
<tr>
<td>4 - 34</td>
<td>75 → 25</td>
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<td>34 - 45</td>
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<td>45 - 50</td>
<td>25 → 75</td>
<td>75 → 25</td>
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<tr>
<td>50 - 60</td>
<td>75</td>
<td>25</td>
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In the following monographs, after the heading ‘Other detectable impurities’ in the Impurities section, read:
‘(the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph
Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use)’

<table>
<thead>
<tr>
<th>Substance</th>
<th>Substance</th>
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<tbody>
<tr>
<td>Articaine hydrochloride (1688)</td>
<td>Norethisterone acetate (0850)</td>
</tr>
<tr>
<td>Biperiden hydrochloride (1074)</td>
<td>Oxaliplatin (2017)</td>
</tr>
<tr>
<td>Caffeine (0267)</td>
<td>Potassium clavulanate (1140)</td>
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<tr>
<td>Caffeine monohydrate (0268)</td>
<td>Potassium clavulanate, diluted (1653)</td>
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<td>Ibuprofen (0721)</td>
<td>Testosterone propionate (0297)</td>
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<td>Ifosfamide (1529)</td>
<td>Thiamine hydrochloride (0303)</td>
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<td>Metformin hydrochloride (0931)</td>
<td>Thiamine nitrate (0531)</td>
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<tr>
<td>Naphazoline hydrochloride (0730)</td>
<td>Tranexamic acid (0875)</td>
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