of a 120 g/l solution of *sodium hydroxide R* and 3 ml of *cupri-tartaric solution R*. Heat. A red precipitate is formed.

TESTS

Solution S. Dissolve 0.20 g in 15 ml of *water R*, heating on a water-bath. Allow to cool and dilute to 20.0 ml with the same solvent.

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

Specific optical rotation (*2.2.7*). −30 to −33, determined on solution S and calculated with reference to the anhydrous substance.

Related substances. Examine by thin-layer chromatography (*2.2.27*),using *silica gel G R* as the coating substance.

Test solution. Dissolve a quantity of the substance to be examined corresponding to 20 mg of the anhydrous substance in 1.0 ml of a mixture of 32 volumes of *water R*, 100 volumes of *chloroform R* and 100 volumes of *methanol R*.

Reference solution (a). Dissolve a quantity of *ouabain CRS* corresponding to 20 mg of the anhydrous substance in 1.0 ml of a mixture of 32 volumes of *water R*, 100 volumes of *chloroform R* and 100 volumes of *methanol R*.

Reference solution (b). Dissolve a quantity of *ouabain CRS* corresponding to 10 mg of the anhydrous substance in a mixture of 32 volumes of *water R*, 100 volumes of *chloroform R*, 100 volumes of *methanol R* and dilute to 25 ml with the same mixture of solvents.

Reference solution (c). Dilute 2.5 ml of reference solution (b) to 10 ml with a mixture of 32 volumes of *water R*, 100 volumes of *chloroform R* and 100 volumes of *methanol R*.

Apply separately to the plate 5 µl of each solution. Develop over a path of 13 cm using a homogeneous mixture of 4 volumes of *water R*, 15 volumes of *methanol R*, 15 volumes of *dimethyl sulphoxide R* and 70 volumes of *chloroform R*. Dry the plate immediately at 140 °C for 30 min in a ventilated drying oven. Allow to cool, spray with *alcoholic sulphuric acid solution R* and heat at 140 °C for 15 min. Any spot in the chromatogram obtained with the test solution, apart from the principal spot, is not more intense than the spot in the chromatogram obtained with reference solution (b) (2.0 per cent). The test is not valid unless the principal spot in the chromatogram obtained with reference solution (a) and the principal spot in the chromatogram obtained with the test solution migrate over a distance sufficient to give unequivocal separation of the secondary spots and the spot in the chromatogram obtained with reference solution (c) is clearly visible.

Alkaloids and strophanthin-K. To 5.0 ml of solution S add 0.5 ml of a 100 g/l solution of *tannic acid R*. No precipitate is formed.

Water (*2.5.12*). 18.0 per cent to 22.0 per cent, determined on 0.100 g by the semi-micro determination of water.

Sulphated ash (*2.4.14*). Not more than 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 40.0 mg in *alcohol R* and dilute to 50.0 ml with the same solvent. Dilute 5.0 ml of the solution to 100.0 ml with *alcohol R*. Prepare a reference solution in the same manner using 40.0 mg of *ouabain CRS*. To 5.0 ml of each solution add 3.0 ml of *alkaline sodium picrate solution R*, allow to stand protected from bright light for 30 min and measure the absorbance (*2.2.25*) of each solution at the maximum at 495 nm using as the compensation liquid a mixture of 5.0 ml of *alcohol R* and 3.0 ml of *alkaline sodium picrate solution R* prepared at the same time.

Calculate the content of $C_{29}H_{44}O_{12}$ from the absorbances measured and the concentrations of the solutions.

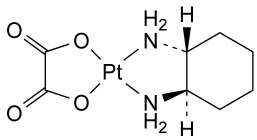
STORAGE

Store protected from light.

01/2005:2017

OXALIPLATIN

Oxaliplatinum



$C_8H_{14}N_2O_4Pt$ M_r 397.3

DEFINITION

(*SP*-4-2)-[(1*R*,2*R*)-Cyclohexane-1,2-diamine-κ*N*,κ*N*′][ethanedioato(2-)-κ*O*^{1},κ*O*^{2}]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 205 nm.

Injection: 20 µl; inject the test solution and reference solutions (b) and (c).

Run time: twice the retention time of impurity A.

Retention times: nitrate = about 2.7 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 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 the substance to be examined in *water R* and dilute to 500.0 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.

Mobile phase: mixture of solutions A and B (99:1 *V/V*).

– *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 210 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.

Mobile phase: *ethanol R, methanol R* (3:7 *V/V*).

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 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 100-105 °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).

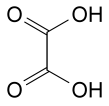
LABELLING

The label states where applicable, that the substance is free from bacterial endotoxins.

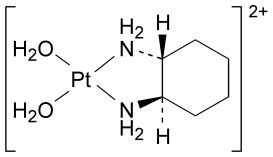
IMPURITIES

Specified impurities: A, B, C, D.

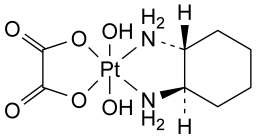
Other detectable impurities: E.



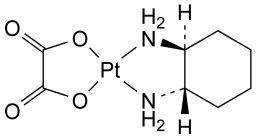
A. ethanedioic acid (oxalic acid),



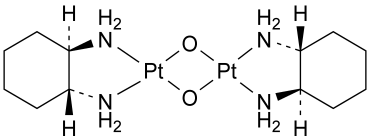
B. (*SP*-4-2)-diaqua[(1*R*,2*R*)-cyclohexane-1,2-diamine-κ*N*, κ*N*′]platinum (diaquodiaminocyclohexaneplatinum),



C. (*OC*-6-33)-[(1*R*,2*R*)-cyclohexane-1,2-diamine-κ*N*, κ*N*′][ethanedioato(2-)-κ*O*^{1},κ*O*^{2}]dihydroxyplatinum,



D. (*SP*-4-2)-[(1*S*,2*S*)-cyclohexane-1,2-diamine-κ*N*, κ*N*′][ethanedioato(2-)-κ*O*^{1},κ*O*^{2}]platinum (*S,S*-enantiomer of oxaliplatin),

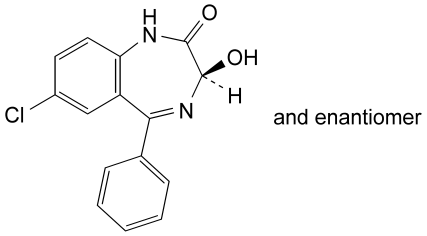


E. (*SP*-4-2)-di-μ-oxobis[(1*R*,2*R*)-cyclohexane-1,2-diamine-κ*N*, κ*N*′]diplatinum (diaquodiaminocyclohexaneplatinum dimer).

01/2005:0778

OXAZEPAM

Oxazepamum



$C_{15}H_{11}ClN_2O_2$ M_r 286.7

DEFINITION

Oxazepam contains not less than 98.5 per cent and not more than the equivalent of 101.0 per cent of (3*RS*)-7-chloro-3-hydroxy-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one, calculated with reference to the dried substance.

CHARACTERS

A white or almost white, crystalline powder, practically insoluble in water, slightly soluble in alcohol and in methylene chloride.

IDENTIFICATION

First identification: B, C.

Second identification: A, C, D.

A. *Prepare the solutions immediately before use, protected from light.* Dissolve 20.0 mg in *alcohol R* and dilute to 100.0 ml with the same solvent. Dilute 10.0 ml of the solution to 50.0 ml with *alcohol R* (solution A). Dilute 10.0 ml of solution A to 100.0 ml with *alcohol R* (solution B). Examined between 300 nm and 350 nm (*2.2.25*), solution A shows an absorption maximum at 316 nm. Examined between 220 nm and 250 nm, solution B shows an absorption maximum at 229 nm. The specific absorbance at the maximum at 229 nm is 1220 to 1300.

B. Examine by infrared absorption spectrophotometry (*2.2.24*) comparing with the spectrum obtained with *oxazepam CRS*. Examine the substances prepared as discs.

C. Examine the chromatograms obtained in the test for related substances in ultraviolet light at 254 nm. The principal spot in the chromatogram obtained with test solution (b) is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

D. Dissolve about 20 mg in a mixture of 5 ml of *hydrochloric acid R* and 10 ml of *water R*. Heat to boiling for 5 min and cool. Add 2 ml of a 1 g/l solution of *sodium nitrite R* and allow to stand for 1 min. Add 1 ml of a 5 g/l solution of *sulphamic acid R*, mix and allow to stand for 1 min. Add 1 ml of a 1 g/l solution of *naphthylethylenediamine dihydrochloride R*. A red colour develops.

TESTS

Related substances. *Carry out the test protected from light.* Examine by thin-layer chromatography (*2.2.27*), using as the coating substance a suitable silica gel with a fluorescent indicator having an optimal intensity at 254 nm. Before use, wash the plate with *methanol R* until the solvent front has migrated at least 17 cm. Allow the plate to dry in air and heat at 100 °C to 105 °C for 30 min.

Test solution (a). Dissolve 50 mg of the substance to be examined in *acetone R* and dilute to 10 ml with the same solvent.

Test solution (b). Dilute 2 ml of test solution (a) to 10 ml with *acetone R*.

Reference solution (a). Dissolve 10 mg of *oxazepam CRS* in *acetone R* and dilute to 10 ml with the same solvent.

Reference solution (b). Dissolve 10 mg of *oxazepam CRS* and 10 mg of *bromazepam CRS* in *acetone R* and dilute to 10 ml with the same solvent.

Reference solution (c). Dilute 1 ml of test solution (b) to 100 ml with *acetone R*.

Reference solution (d). Dilute 5 ml of reference solution (c) to 10 ml with *acetone R*.

Apply separately to the plate 20 μl of each solution. Develop over a path of 15 cm, in the same direction as the washing with *methanol R*, using a mixture of 10 volumes of *methanol R* and 100 volumes of *methylene chloride R*. Allow the plate to dry in air and examine in ultraviolet light at 254 nm. Any spot in the chromatogram obtained with test solution (a), apart from the principal spot, is not more intense than the spot in the chromatogram obtained with reference solution (c) (0.2 per cent) and at most one such spot is more intense than the spot in the chromatogram obtained with reference solution (d) (0.1 per cent). The test is not valid unless the chromatogram obtained with reference solution (b) shows two clearly separated spots.

Loss on drying (*2.2.32*). Not more than 0.5 per cent, determined on 1.000 g by drying in an oven at 100 °C to 105 °C at a pressure not exceeding 0.7 kPa.

Sulphated ash (*2.4.14*). Not more than 0.1 per cent, determined on 1.0 g.