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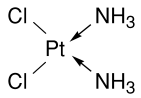
CISPLATIN

Cisplatinum



$[PtCl_2(NH_3)_2]$ M_r 300.0
[15663-27-1]

DEFINITION

Cisplatin contains not less than 97.0 per cent and not more than the equivalent of 102.0 per cent of *cis*-diamminedi-chloroplatinum (II).

CHARACTERS

A yellow powder or yellow or orange-yellow crystals, slightly soluble in water, sparingly soluble in dimethylformamide, practically insoluble in alcohol.

It decomposes with blackening at about 270 °C.

Carry out identification test B, the tests (except that for silver) and the assay protected from light.

IDENTIFICATION

First identification: A, B.

Second identification: B, C.

A. Examine by infrared absorption spectrophotometry (*2.2.24*), comparing with the spectrum obtained with *cisplatin CRS*. Examine the substances prepared as discs in *potassium bromide R*.

B. Examine the chromatograms obtained in the test for related substances. The principal spot in the chromatogram obtained with test solution (a) is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

C. Add 50 mg to 2 ml of *dilute sodium hydroxide solution R* in a glass dish. Evaporate to dryness. Dissolve the residue in a mixture of 0.5 ml of *nitric acid R* and 1.5 ml of *hydrochloric acid R*. Evaporate to dryness. The residue is orange. Dissolve the residue in 0.5 ml of *water R* and add 0.5 ml of *ammonium chloride solution R*. A yellow, crystalline precipitate is formed.

TESTS

Solution S1. Dissolve 25 mg in a 9 g/l solution of *sodium chloride R* prepared with *carbon dioxide-free water R* and dilute to 25 ml with the same solvent.

Solution S2. Dissolve 0.20 g in *dimethylformamide R* and dilute to 10 ml with the same solvent.

Appearance of solution S1. Solution S1 is clear (*2.2.1*) and not more intensely coloured than reference solution GY_5 (*2.2.2, Method II*).

Appearance of solution S2. Solution S2 is clear (*2.2.1*).

pH (*2.2.3*). The pH of solution S1, measured immediately after preparation, is 4.5 to 6.0.

Related substances. Examine by thin-layer chromatography (*2.2.27*), using *cellulose for chromatography R1* as the coating substance. Activate the plate by heating at 150 °C for 1 h.

Test solution (a). Dilute 1 ml of solution S2 to 10 ml with *dimethylformamide R*.

Test solution (b). Use solution S2.

Reference solution (a). Dissolve 10 mg of *cisplatin CRS* in 5 ml of *dimethylformamide R*.

Reference solution (b). Dilute 1 ml of solution S2 to 50 ml with *dimethylformamide R*.

Apply separately to the plate 2.5 µl of test solution (a), 2.5 µl of reference solution (a), 5 µl of test solution (b) and 5 µl of reference solution (b). Develop over a path of 15 cm using a mixture of 10 volumes of *acetone R* and 90 volumes of *dimethylformamide R*. Allow the plate to dry in air and spray with a 50 g/l solution of *stannous chloride R* in a mixture of equal volumes of *dilute hydrochloric acid R* and *water R*. After 1 h, the chromatogram obtained with test solution (b) shows no spot with an R_F value less than that of the principal spot and any spot with an R_F value greater than that of the principal spot is not more intense than the spot in the chromatogram obtained with reference solution (b).

Silver. Not more than 2.5×10^2 ppm of Ag, determined by atomic absorption spectrometry (*2.2.23, Method I*).

Test solution. Dissolve 0.100 g of the substance to be examined in 15 ml of *nitric acid R*, heating to 80 °C. Cool and dilute to 25.0 ml with *water R*.

Reference solutions. To suitable volumes (10 ml to 30 ml) of *silver standard solution (5 ppm Ag) R* add 50 ml of *nitric acid R* and dilute to 100.0 ml with *water R*.

Measure the absorbance at 328 nm using a silver hollow-cathode lamp as source of radiation, a fuel-lean air-acetylene flame and, preferably, a spectral slit width of 0.5 nm. Carry out a blank determination.

ASSAY

Examine by liquid chromatography (*2.2.29*).

Test solution. Dissolve 50.0 mg of the substance to be examined in a 9 g/l solution of *sodium chloride R* and dilute to 100.0 ml with the same solvent.

Reference solution. Dissolve 50.0 mg of *cisplatin CRS* in a 9 g/l solution of *sodium chloride R* and dilute to 100.0 ml with the same solvent.

The chromatographic procedure may be carried out using:

– a column 0.25 m long and 4.6 mm in internal diameter packed with *strong-anion-exchange silica gel for chromatography R* (10 µm),

– as mobile phase at a flow rate of 1.2 ml/min a mixture of 10 volumes of a 9 g/l solution of *sodium chloride R* and 90 volumes of *methanol R*,

– as detector a spectrophotometer set at 220 nm.

Use a sample loop. Inject separately 20 µl of the test solution and 20 µl of the reference solution.

STORAGE

Store in an airtight container, protected from light.

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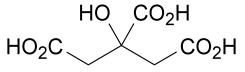
corrected 6.0

CITRIC ACID, ANHYDROUS

Acidum citricum anhydricum



$C_6H_8O_7$ M_r 192.1
[77-92-9]

DEFINITION

2-Hydroxypropane-1,2,3-tricarboxylic acid.

Content: 99.5 per cent to 100.5 per cent (anhydrous substance).

CHARACTERS

Appearance: white or almost white, crystalline powder, colourless crystals or granules.

Solubility: very soluble in water, freely soluble in ethanol (96 per cent).

mp: about 153 °C, with decomposition.

IDENTIFICATION

First identification: B, E.

Second identification: A, C, D, E.

A. Dissolve 1 g in 10 ml of *water R*. The solution is strongly acidic (*2.2.4*).

B. Infrared absorption spectrophotometry (*2.2.24*).

Preparation: dry the substance to be examined and the reference substance at 100-105 °C for 2 h.

Comparison: *anhydrous citric acid CRS*.

C. Add about 5 mg to a mixture of 1 ml of *acetic anhydride R* and 3 ml of *pyridine R*. A red colour develops.

D. Dissolve 0.5 g in 5 ml of *water R*, neutralise using *1 M sodium hydroxide* (about 7 ml), add 10 ml of *calcium chloride solution R* and heat to boiling. A white precipitate is formed.

E. Water (see Tests).

TESTS

Appearance of solution. The solution is clear (*2.2.1*) and not more intensely coloured than reference solution Y_7, BY_7 or GY_7 (*2.2.2, Method II*).

Dissolve 2.0 g in *water R* and dilute to 10 ml with the same solvent.

Readily carbonisable substances. To 1.0 g in a cleaned test tube add 10 ml of *sulphuric acid R* and immediately heat the mixture in a water-bath at 90 ± 1 °C for 60 min. Cool rapidly immediately afterwards. The solution is not more intensely coloured than a mixture of 1 ml of red primary solution and 9 ml of yellow primary solution (*2.2.2, Method I*).

Oxalic acid: maximum 360 ppm, calculated as anhydrous oxalic acid.

Dissolve 0.80 g in 4 ml of *water R*. Add 3 ml of *hydrochloric acid R* and 1 g of *zinc R* in granules. Boil for 1 min. Allow to stand for 2 min. Transfer the supernatant liquid to a test-tube containing 0.25 ml of a 10 g/l solution of *phenylhydrazine hydrochloride R* and heat to boiling. Cool rapidly, transfer to a graduated cylinder and add an equal volume of *hydrochloric acid R* and 0.25 ml of a 50 g/l solution of *potassium ferricyanide R*. Shake and allow to stand for 30 min. Any pink colour in the solution is not more intense than that in a standard prepared at the same time in the same manner using 4 ml of a 0.1 g/l solution of *oxalic acid R*.

Sulphates (*2.4.13*): maximum 150 ppm.

Dissolve 2.0 g in *distilled water R* and dilute to 30 ml with the same solvent.

Aluminium (*2.4.17*): maximum 0.2 ppm, if intended for use in the manufacture of dialysis solutions.

Prescribed solution. Dissolve 20 g in 100 ml of *water R* and add 10 ml of *acetate buffer solution pH 6.0 R*.

Reference solution. Mix 2 ml of *aluminium standard solution (2 ppm Al) R*, 10 ml of *acetate buffer solution pH 6.0 R* and 98 ml of *water R*.

Blank solution. Mix 10 ml of *acetate buffer solution pH 6.0 R* and 100 ml of *water R*.

Heavy metals (*2.4.8*): maximum 10 ppm.

Dissolve 5.0 g in several portions in 39 ml of *dilute sodium hydroxide solution R* and dilute to 50 ml with *distilled water R*. 12 ml of the solution complies with test A. Prepare the reference solution using *lead standard solution (1 ppm Pb) R*.

Water (*2.5.12*): maximum 1.0 per cent, determined on 2.000 g.

Sulphated ash (*2.4.14*): maximum 0.1 per cent, determined on 1.0 g.

Bacterial endotoxins (*2.6.14*): less than 0.5 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

Dissolve 0.550 g in 50 ml of *water R*. Titrate with *1 M sodium hydroxide*, using 0.5 ml of *phenolphthalein solution R* as indicator.

1 ml of *1 M sodium hydroxide* is equivalent to 64.03 mg of $C_6H_8O_7$.

LABELLING

The label states, where applicable, that the substance is intended for use in the manufacture of dialysis solutions.

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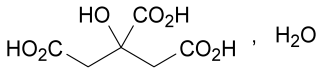
CITRIC ACID MONOHYDRATE

Acidum citricum monohydricum



$C_6H_8O_7,H_2O$ M_r 210.1

[5949-29-1]

DEFINITION

2-Hydroxypropane-1,2,3-tricarboxylic acid monohydrate.

Content: 99.5 per cent to 100.5 per cent (anhydrous substance).

CHARACTERS

Appearance: white or almost white, crystalline powder, colourless crystals or granules, efflorescent.

Solubility: very soluble in water, freely soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: B, E.

Second identification: A, C, D, E.

A. Dissolve 1 g in 10 ml of *water R*. The solution is strongly acidic (*2.2.4*).

B. Infrared absorption spectrophotometry (*2.2.24*).

Preparation: dry the substance to be examined and the reference substance at 100-105 °C for 2 h.

Comparison: *citric acid monohydrate CRS*.

C. Add about 5 mg to a mixture of 1 ml of *acetic anhydride R* and 3 ml of *pyridine R*. A red colour develops.

D. Dissolve 0.5 g in 5 ml of *water R*, neutralise using *1 M sodium hydroxide* (about 7 ml), add 10 ml of *calcium chloride solution R* and heat to boiling. A white precipitate is formed.

E. Water (see Tests).