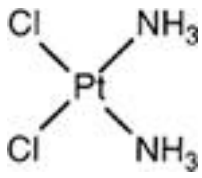
Cisplatin (Cisplatinum)



$Cl_2H_6N_2Pt$

Relative molecular mass. 300.0

Chemical name. *cis*-Diamminedichloroplatinum; (*SP*-4-2)-diamminedichloroplatinum; CAS Reg. No. 15663-27-1.

Description. White to yellowish crystals or a yellow powder.

Solubility. Slightly soluble in water; sparingly soluble in dimethylformamide R; practically insoluble in methanol R.

Category. Cytotoxic drug.

Storage. Cisplatin should be kept in a tightly closed container, protected from light, and stored at a temperature between 2 and 8 °C.

Additional information. *CAUTION:* Cisplatin must be handled with care, avoiding contact with the skin and inhalation of airborne particles.

When heated, it blackens at about 270 °C with decomposition.

Requirements

Cisplatin contains not less than **96.0%** and not more than the equivalent of **102.0%** of $Cl_2H_6N_2Pt$, calculated with reference to the anhydrous substance.

Identity tests

• Either tests A and B or tests B and C may be applied.

A. Carry out the examination as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum is concordant with the spectrum obtained from cisplatin RS or with the *reference spectrum* of cisplatin.

B. See the test described below under "Related substances". The principal spot obtained with solution A corresponds in position, appearance, and intensity with that obtained with solution B.

C. Place 0.05 g in a glass dish, add 2 mL of sodium hydroxide (~80 g/l) TS, and evaporate to dryness on a water-bath. Dissolve the residue in a mixture of 0.5 mL of nitric acid (~1000 g/l) TS and 1.5 mL of hydrochloric acid (~420 g/l) TS, and again evaporate to dryness; the residue is orange. Again dissolve the residue in 0.5 mL of water and add 0.5 mL of ammonium chloride (100 g/l) TS; a yellow, crystalline precipitate is produced.

Clarity and colour of solution. Dissolve 25 mg in 25 mL of a solution of 0.22 g of sodium chloride R dissolved in 25 mL of carbon-dioxide-free water R; the solution is clear and not more intensely coloured than standard colour Gn3 when compared as described under 1.11.1 Colour of liquids. (Keep the solution for the "pH value")

Water. Determine as described under 2.8 Determination of water by the Karl Fischer method, Method A, using 0.5 g of Cisplatin; the water content is not more than 10 mg/g.

pH value. Measure without delay the pH of the solution prepared for the "Clarity and colour of solution"; 4.5-6.0.

Related substances. Carry out the test as described under *1.14.1 Chromatography*, Thin-layer chromatography, using cellulose R2 previously activated by heating at 150 °C as the coating substance and a mixture of 1 volume of water and 9 volumes of acetone R as the mobile phase. Apply separately to the plate 2.5 µl of each of two solutions in a mixture of equal volumes of dimethylformamide R and water containing (A) 2 mg of Cisplatin per mL and (B) 2 mg of cisplatin RS per mL. Also apply 5 µl of each of two solutions in dimethylformamide R containing (C) 20 mg of Cisplatin per mL and (D) 0.4 mg of Cisplatin per mL. After removing the plate from the chromatographic chamber, allow it to dry in a current of warm air, spray it with stannous chloride/ hydrochloric acid TS, and allow to dry again. Examine the chromatogram in daylight.

With solution C no spot occurs in front of the principal spot. Any other spot obtained with solution C, other than the principal spot, is not more intense than that obtained with solution D.

Ultraviolet absorbance ratio. Prior to use, clean all glassware with a mixture of 3 volumes of hydrochloric acid (~420 g/l) TS and 1

volume of nitric acid (~1000 g/l) TS, rinse thoroughly with water, and dry. Do not use any dichromate solution for cleaning, or acetone or pressurized air for drying. Protect the test solutions from light, and use them within 1 hour of preparation.

Transfer about 98.5 mg, accurately weighed, to a 100-mL volumetric flask and dissolve in sufficient hydrochloric acid (0.1 mol/l) VS to produce 100 mL. Stir with a magnetic bar at a high speed for 5 minutes or place in an ultrasonic bath for 10 seconds or until completely dissolved.

The ratio of the absorbance measured in a 1-cm layer against hydrochloric acid (0.1 mol/l) VS at the maximum wavelength of about 301 nm to that at the minimum wavelength of about 246 nm is not less than 4.5.

Silver. Determine by atomic absorption spectrophotometry "1.8 Atomic spectrometry: emission and absorption" at a wavelength of 328 nm using a silver hollow cathode lamp, an air-acetylene flame, and a slit width of 0.5 nm. Dissolve 0.1 g in 15 mL of nitric acid (~1000 g/l) TS while heating at 80 °C and dilute with water to 25 mL. As a reference solution use silver standard (5 µg Ag/mL) TS; not more than 250 µg of Ag per g.

Assay. Dissolve about 25 mg, accurately weighed, in sufficient hydrochloric acid (~70 g/l) TS to produce 25 mL. Dilute 1.0 mL of this solution with the same acid to 25 mL. Transfer 5 mL to a glass-stoppered 25-mL volumetric flask and add 10 mL of hydrochloric acid (~70 g/l) TS. Place 15 mL of hydrochloric acid (~70 g/l) TS in a second flask to serve as a blank. Add 2.5 mL of stannous chloride/hydrochloric acid TS1 and dilute to volume with hydrochloric acid (~70 g/l) TS. Mix and allow to stand for 30 minutes.

Measure the absorbance of a 1-cm layer at the maximum at about 402 nm against a solvent cell containing the blank. Calculate the amount of $Cl_2H_6N_2Pt$ in Cisplatin being examined by comparison with cisplatin RS, similarly and concurrently examined.