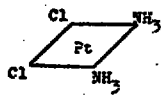
SPECIFICATION

Pharmaceutical Formulations Containing Cis-Platinum (II) Diamminedichloride

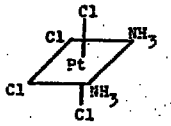
The present invention relates to stabilized aqueous solutions of cis-platinum (II) diamminedichloride (cisplatin), which is used by injection in the chemotherapy of cancer.

The platinum compounds are a unique group of compounds in the antineoplastic group of agents. They were first noted to have an antibiotic effect by Rosenberg and his colleagues in 1965 and have since found to be potent antitumour agents in animals.[1,2]

Structurally they represent a complex formed by a central atom of platinum and surrounded by various arrangements of chlorine atoms or ammonia groups in either a cis of trans planar relationship. Two of the more commonly studied platinum compounds are diagrammed below:



Cis-Platinum (II)
Diamminedichloride



Cis-Platinum (IV)
Diamminetetrachloride

As can be seen, the platinum compound, cis-platinum (II) diamminedichloride, selected for clinical trials by the National Cancer Institute has the chloride and amino groups only in the horizontal plane. The cis form of the diamminechloride complex has been synthesized according to the following reaction:[3]

$$K_2[PtCl_4 + 2NH_3 \xrightarrow{NH_4Cl} cis\text{-}[Pt(NH_3)_2Cl_2] + 2KCl$$

1. Rosenberg, B., VanCamp, L. and Krigas, T., Inhibition of cell division in *Escherichia coli* by electrolysis products from a platinum electrode. *Nature* (London) *205*: 698—699, 1965.

2. Rosenberg, B., VanCamp, L Trosko, J. E. and Mansour, V. H., Platinum compounds: A new class of potent antitumour agents. *Nature* (London) *222*: 385—386, 1969.

3. Kauffman, G. B. in J. Kleinberg (ED.), Inorganic Synthesis, McGraw-Hill Book Co., Inc., New York, 1963.

The National Cancer Institute has been conducting clinical trails in cancer chemotherapy of the chemical for which the United States Adopted Name (USAN) is now cisplatin. Certain information regarding its chemistry and its pharmaceutical formulation are given in the publication titled Clinical Brochure, Cis-platinum (II) Diamminedichloride (NSC-119875), H. Handelman et al., Investigational Drug Branch, Cancer Therapy Evaluation Program, Division of Cancer Treatment, National Cancer Institute (Revised, August 1974), on pages 1—5 and 31—32. The last two pages of Handelman et al. concern the for formulation of cisplatin supplied gratis by the N.C.I. to clinicians for their clinical evaluation in the chemotherapy of cancer and read as follows:

Pharmaceutical Data Sheet

NSC-119875 Cis-Diamminedichloroplatinum (II)

Dosage Formulation

10 mg./vial: The contents of each 20 ml. flint vial appears as an off-white lyophilized cake. Each vial contains 10 mg. of NSC-119875; 90 mg. of Sodium Chloride; 100 mg. of Mannitol and Hydrochloric acid for pH adjustment.

Solution Preparation

10 mg./vial: When reconstituted with 10 ml of Sterile Water for Injection, USP, each ml. of the resulting solution will contain 1 mg. of NSC-119875, 10 mg. of Mannitol, and 9 mg. of Sodium Chloride having a pH range of 3.5—4.5.

Storage: The dry, *unopened* vials should be stored at refrigeration temperatures (4—8°C).

Stability: Intact vials have a provisional stability of one year when stored at refrigeration temperature (4—8°C). Stability recommendations may be adjusted pending completion of a two-year shelf-life study. Reconstitution as recommended results in a pale, yellow solution which is stable for not more than one hour at room temperature (22°C), when exposed to normal room illumination and not more than eight hours at room temperature (22°C.) when protected from light. Reconstituted solutions may form a precipitate after one hour at refrigeration temperature (4—8°C).

Caution: The lyophilized dosage formulations contain no preservatives and therefore it is advised to discard solutions eight hours after reconstitution.

August, 1974
Clinical Drug Distribution Section
Drug Development Branch

Mention of this formulation and additional information on its clinical use is given, for example, in Cancer Chemotheraphy Reports, Part 1, Vol. 57, No. 4, pages 465—471 (1973):

Cancer *30*: 1451—1456 (1972) in reference to cisplatin states that

"The drug material used in this study was manufactured by Ben Venue Laboratories Inc., Bedford Ohio. It was supplied by the Cancer Therapy Evaluation Branch of the National Cancer Institute in vials containing 10 mg. of cis-diamminedichloroplatinum, 10 mg. (sic) of mannitol and 9 mg. (sic) of NaCl. The resulting yellowish white powder dissolved readily in 8—10 ml. of sterile water and was injected immediately after preparation".

Annals of Internal Med. *86*: 803—812 (1977) refers to cisplatin as "DDP" and states that

"The drug DDP is presently available as an investigational drug only to qualified specialists through the Investigational Drug Branch of the Cancer Therapy Evaluation Program, National Cancer Institute. The product is supplied as a white lyophilized powder in vials containing 10 mg. of DDP, 90 mg. of sodium chloride, 100 mg. of mannitol (U.S.P.), and hydrochloric acid for pH adjustment. When reconstituted with 10 ml. of sterile water for injection (U.S.P.), each ml. of the resulting solution will contain 1 mg. of DDP, 10 mg. of mannitol, and 9 mg. of NACl. The pH of the resulting solution will be 3.4 to 4.5. At 22°C., the reconstituted solution is stable for at least 8 h".

Thus the formulations described above are stated to require refrigeration (4—8°C.) while in vials in the solid state (i.e., before reconstitution), they are difficult to reconstitute and they have a useful life of only about twenty hours at room temperature (22°C). following reconstitution. The very act of reconstitution can cause problems if improperly performed and is better avoided. In addition, because the aqueous solubility of cisplatin is only about 1 mgm./ml., the cost of preparing dosage forms containing more than 25 mgm./vial by lyophilization becomes prohibitive.

We have now developed a stable, therapeutically acceptable, intravenously injectable dosage form of cisplatin which does not require lyophilization and reconstitution, which does not require refrigeration during shipment and storage, and which can be supplied in dosages of 50 mg. or larger.

According to the present invention there is provided a stable, sterile aqueous solution of cisplatin in a sealed container such as an ampule or vial in unit dosage form suitable for intravenous administration to man, which solution has a concentration of cisplatin in the range of from 0.1 to 1.0 mgm./ml. and preferably about 1.0 mgm./ml. and a pH in the range of from 2.0 to 3.0, preferably in the range of from 2.3 to 2.7 and most preferably a pH of about 2.5, the pH being caused by the presence of an appropriate amount of a nontoxic, pharmaceutically and therapeutically acceptable acid. The acid is preferably a strong mineral acid and most preferably is hydrochloric acid; the solution optionally containing in addition a nontoxic, pharmaceutically acceptable, inorganic source of chloride ions at a concentration equivalent to that produced by the presence of sodium chloride at a concentration in the range of from 1 to 20 mgm/ml. and most preferably about 9 mgm./ml.; the solution optionally also being either free of any other added chemicals or also containing a customary, harmless, physiologically acceptable excipient, which is preferably mannitol, at a concentration in the range of from 2 to 150 mgm./ml. and preferably a concentration of about 10 mgm/ml., the solution exhibiting less than 10% (and usually less than 4%) loss of potency as measured by high performance liquid chromatography (HPLC) upon the storage for one month at 56°C. Preservatives can be added if desired.

The present invention will be further described with reference to the following Examples.

Example 1
Cisplatin Injection 1 Mg./Ml.
[1 Mg. Cis-diamminedichloroplatinum (II) per 1 Ml.]

Formula	*Per Ml.*	*Per Liter*
Cis-diamminedichloro-Platinum (II)	0.0010 g.[A]	1.000 g.[A]
Sodium Chloride, U.S.P.	0.0090 g.	9.000 g.
Mannitol, U.S.P.	0.0100 g.	10.000 g.
Hydrochloric Acid Conc. U.S.P.	q.s. to pH 2.0—3.0[B]	q.s. to pH 2.0—3.0[B]
Water for Injection U.S.P.	q.s. 1.0 Ml	q.s. 1000.0 Ml

Notes:

A. 100% basis, adjust weight based on reported purity to provide 1.0 g. 100% cis-diamminedichloroplatinum (II) per liter.

B. Approximately 0.035—0.050 ml. of 37% hydrochloric acid required per gram of sodium chloride to obtain a pH of approximately 2.5.

Precautions:

Cis-diamminedichloroplatinum (II) is a toxic substances and is listed on page 742 in the 1976 edition of the "Registry of Toxic Effects of Chemical Substances". The OSHA Standard of Time

Weighted Average (TWA) is 2 meg./m³. Consult the above, listed references, pertinent local publications and regulations and such publications as the National Cancer Institute Safety Standards for Research Involving Chemical Carcinogens and the National Institute of Health Specifications for a Class II type 1 Safety Cabinet. Any cis-diamminedichloroplatinum (II) weighing, the working surface of the batching vessel, the filling, stoppering, and sealing must be provided with such protection.

All personnel involved with compounding of this product must be protected with full nylon head/face cover, coveralls, rubber gloves and a respirator equivalent to the MSA Ultra Filter Respirator rated for environments contaminated with dusts, fumes and mists having a TWA rating of less than 50 mcg/m³. During the sterile liquid filling the sterile head/face cover, surgeon's gauze mask and goggles can replace the respirator. Any uniforms grossly contaminated due to spills, etc. should be stored in a closed metal container until burned.

The Importance of Protecting Personnel During the Handling, Manufacturing and Assaying of this Produce in Accordance with the Above Cannot be Overemphasized

The prime bulk cis-diamminedichloroplatinum (II) must be protected from light. The processing and filling of vials described herein was conducted under diffused natural/fluorescent light.

Equipment

Batching Vessel

Glass-lined, agitated, pressure vessel. A 316 SS agitator is permissible. Working volume must be consistent with batch size. A dipstick and calibration curve of tank volume is required for determining volume.

Millipore Membrane Filter Holders

316 SS. Filter area with necessary pre-filters and 0.22 micron final sterilizing filter.

Transfer Hoses

Teflon (a Registered Trade Mark), or Tygon

All stainless steel contacts should meet 316 SS requirements. All other equipment should be appropriate to produce a sterile, non-pyrogenic, particulate-free product.

Manufacturing Instructions

A. These instructions are written for an eight-hour batching to filling operation. Storage of this product before filling has not been investigated at this writing.

B. Maintain 27°C±2°C. temperature conditions throughout entire batching and filtering operations.

1. Place 80% of the batch volume of Water for Injection, U.S.P. in a suitable vessel.
2. With agitation add the sodium chloride. Agitate ten minutes or until dissolved.
3. With good agitation carefully adjust the pH of the sodium chloride solution to 2.0—3.0 (preferably 2.5) with concentrated hydrochloric acid. See estimated amount under note "B" on the formula sheet. Agitate for ten minutes after last addition. Recheck pH.
4. With good agitation add the mannitol and agitate ten minutes or until dissolved.
5. With good agitation and taking special precautions against dusting and exposure, add the cis-diamminedichloro-platinum (II). Rinse its container sufficiently with an appropriate amount of water for injection and add to the batch.
6. Agitate until completely dissolved. Approximately 60 to 90 minutes will be required for complete dissolution. Monitor pH and add additional concentrated hydrochloric acid if required to maintain at 2.0—3.0 (optimum 2.5).
7. Carefully adjust volume to theroetical batch volume with water for injection. Make final pH check.
8. Pass the solution through a clean, sterile 0.22 micron Millipore Filter into the sterile filling line.
9. Fill as directed below for the following products:

10 Mg/Vial

Sterile, Type I amber, 15 ml. vial, with a 10-ml. fill. Stopper with red, 20 mm Teflon-faced stoppers and seal with aluminium seals. Numbered as K93, 100 and 107 with nitrogen overlay and K94, 101 and 108 without nitrogen overlay.

25 Mg./Vial

Sterile, Type I amber, 50 ml. vial with a 25-ml. fill. Stopper with red, 20 mm Teflon-faced stoppers and seal, with aluminium seals. Numbered as K95, 102 and 109 with nitrogen overlay and K96, 103 and 110 without nitrogen overlay.

50 Mg./Vial

Sterile, Type I amber, 50 ml. vial with a 50-ml. fill. Stopper with red, 20 mm Teflon-faced stoppers and seal with aluminium seals. Numbered as K97, 104 and 111 with nitrogen overlay and K98, 105 and 112 without nitrogen overlay.

These formulations were prepared in five groups (with the final pH given in parentheses) as follows:

K93 —96	(pH 2.4)
K97 —98	(pH 2.5)
K100—103	(pH 2.3)
K104—105	(pH 2.4)
K107—110	(pH 2.3)
K111—112	(pH 2.4)

Original potencies by HPLC assay were in the range of 099 to 1.00 mgm./ml.

The percentage loss in potency after storage for one or two months at the indicated temperature was found by HPLC assay to be as follows:

	56°C		*45°C*
	One Month	*Two Months*	*One Month*
K93	4.0		
K94	2.0	4.0	
K95	0.0		—1.0*
K96	1.0	4.0	0.0
K97	3.0		
K98	4.0	2.0	
K100	3.0		
K101	3.0	5.0	
K102	3.0		
K103	5.0	4.0	
K104	0.0		—1.0*
K105	0.0	5.0	0.0
K107	1.0		0.0
K108	2.0	5.0	1.0
K109	3.0		
K110	3.0		
K111	7.0		
K112	7.0		

*Negative sign means assay showed 1.0% increase in potency.

The above-described solutions, with and without nitrogen cover, thus have shown 7% or less loss in potency after storage at 56°C and 45°C with the majority showing a loss of potency of 3% or less. The pH of the solutions remained between 2.4 and 2.7.

Physically, no change is apparent at 56°C. or 45°C. after one month. Solutions remain clear and colorless. Initial Klett readings averaged 8—12; one-month 56°C. and 45°C. readings averaged 6—15. No changes or differences are noted between samples with or without N_2↑.

One sample at each temperature station for all products was tested inverted exposing the solution to the Teflon-coated plug stopper. Samples from inverted products were assayed from 56°C. at one month with and without N_2↑ exposure. Stability was not affected at one month 56°C. as samples showed only 1—2% loss of potency.

At two weeks 4°C. samples were observed for crystallization of cis-diamminedichloroplatinum (II). No crystals were observed until one month and it was only noted randomly, not in every sample. Only one lot of the 10 mg/.vial and 25 mg./vial products show some crystals forming randomly at 4°C. Crystallization is noted throughout *all* lots of 50 mg/vial products but again not in all samples. One sample from 4°C. with crystals could not be redissolved by warming the solution to 37°C. with agitation. Only partial success was obtained. It appears these products *cannot* be stored under refrigerated conditions as even redissolving of crystallized products was difficult.

Cis-platinum (II) diamminedichloride (NSC 119875) is an inorganic compound first noted to prevent replication of *E. coli* and subsequently found to possess antitumour activity. The drug exerts its effect of interfering with DNA synthesis by causing cross-linking of complementary strands of DNA. It has activity in a variety of tumour systems including L1210, Sarcoma 180, Walker 256 carcinosarcoma, DMBA induced mammary tumours and ascitic B16 melanosarcoma. The compound is especially interesting in that it exhibits synergism with a large number of currently used chemotherapeutic agents. Large animal toxicology studies showed renal tubular necrosis, enterocolitis, bone marrow hypoplasia and lymphoid atropy. Phase I studies have demonstrated the following toxicities: myelosuppression, renal insufficiency, high frequency ototoxicity and GI

intolerance. Currently used dosages with mild to moderately acceptable toxicity are in the range of 60—100 mg/m² IV as a single dose or divided over 3—5 days, to be repeated at four-week intervals. Early clinical trials show some responses to the drug in germinal cell tumours, lymphomas, sarcomas, breast and head and neck carcinomas.

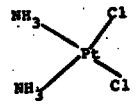
A dosage of 60 mgm/m² is roughly equal to 1.5 mgm/kg which in turn is roughly equal to 105 mgm/patient weighing 70 kg.

The solutions of the present invention are used in the same manner and for the same purposes as stated above and in the other publications and in the voluminous medical literature on this subject. As stated therein, frequent use is made of concurrent therapy with other chemotherapeutic agents for best results. When desired, the solutions of the present invention may be added immediately before use to a sterile, pharmaceutically acceptable aqueous diluent such as glucose or saline. Administration is either by direct intraveneous injection or by intravenous infusion.

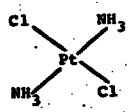
High Performance Liquid Chromatography (HPLC) Assay for Cis-Diamminedichloroplatinum.

Method

Cis-diamminedichloroplatinum is chromatographed on a Water's μ-Bondpak-NH_2 column using a loop injection technique. Detection is achieved by monitoring the U.V. absorbance at 313 nm and quantitation is accomplished by peak height measurement with external calibration. This method is applicable to bulk powders and solid dose formulations containing NaCl and mannitol. Specificity has been demonstrated by separation of the cis and trans isomers and apparent degradations (moisture, acid, base, heat and accelerated light).



Cis-$(NH_3)_2Cl_2$ Pt II



Trans-$(NH_3)_2Cl_2$ Pt II

HPLC Conditions

Column-Water's Micro-Bondpak-NH_2 (300 mm×4.0 mm ID) 027386 or equivalent.
Mobile Phase-Ethyl acetate/methanol/dimethylformamide/distilled water (25/16/5/5). Use Burdick and Jackson distilled in glass spectroquality reagents. Degas the water prior to use and the solution after mixing.
Detector—Water's Model 440 Absorbence Detector.
Wavelength—313 nm (U.V.)
Sensitivity—0.1 AUFS.
Injector—A 20 microliter loop injector.
The Loop Injector—A Valco 7000 psi stainless steel valve (CV-6-UHPa-C20).
Injection Volume—20 microliter.
Solvent Delivery System—Water's Model 6000A pump.
Flow—2.0 ml./minute.
Retention—2.8 minutes (approx).
Recorder—Heath Model SR-255B.
Chart Speed—0.5 inch/min.
Range—10 millivolt.

HPLC Analysis

Using the conditions above, obtain chromatograms of the standard and sample preparations in duplicate.

Reference Standard of Cis-Diamminedichloro-Platinum (DDP):

Lot No.=78F7 (Matthey Bishop Lot No. AM7702)
Assigned Purity=99.8%
Solvents—Burdick and Jackson (distilled in glass) spectroquality.
Standard—Weight accurately 25 mg. of cis-diamminedichloro-platinum (DDP) into a 25 ml. volumetric flask. Dissolve in and dilute to volume with dimethylformamide.
Lyophilized Injection—Reconstitute vial contents with 10.0 ml. of dimethylformamide and mechanically shake for 5 minutes (alternately a sonic bath may be used for 2 minutes). Filter 5.0 ml. of the sample solution (Millipore Filter Kit or equivalent) discarding the first ml.
Content Uniformity-Prepare 10 vials as described above and assay.

Calculations

$$\text{Standard Factor (SF)} = \frac{\text{Mg. Standard/ml}}{\text{Average Peak Height Standard}}$$

$$\text{Mg. DDP/Gram} = \frac{\text{SF} \times \text{Average Peak Height Sample} \times 25}{\text{Wt. Sample (Gm)}}$$

$$\text{Mg. DDP/Vial} = \text{SF} \times \text{Average Peak Height Sample} \times 10$$

For assay, average results obtained for 10 vials from content uniformity test.

Method

The method of assay for cisplatin described above is applied to aqueous solutions (dose formulations) containing NaCl and mannitol after making the changes indicated below.

HPLC Conditions

Mobile Phase—Acetonitrile/distilled water (75/25, v/v). Use Burdick and Jackson distilled in glass spectroquality reagents. Degas the water prior to use and the solution after mixing.

Injector—A100 microliter loop injector.

Injection Volume—100 microliter.

Retention—2.0 minutes (approx).

HPLC Analysis

Standard—Weight accurately 25 mg of cis-diamminedichloro-platinum (DDP), 225 mg. sodium chloride and 250 mg. mannitol into a 25-ml. volumetric flask. Dissolve in and dilute to volume with distilled water. Pipet 5.0 ml. of the resulting solution into a 25-ml. volumetric flask, add 2.0 ml. of distilled water and take to volume with acetonitrile.

Sample (1 mg/ml)—Pipet 5.0 ml. of the sample into a 25-ml. volumetric flask add 2.0 ml. of distilled water and take to volume with aceonitrile.

Calculations

$$\text{Standard Factor (SF)} = \frac{\text{Mg. Standard/ml.}}{\text{Average Peak Height Standard}}$$

$$\text{Mg. DDP/ml.} = \text{SF} \times \text{Average Peak Height Sample} \times 25$$

This invention is capable of industrial application.

Claims

1. A stable, sterile aqueous solution of cisplatin in unit dosage form suitable for administration to man, which solution has a concentration of cisplatin in the range of from 0.1 to 1.0 mgm./ml. and a pH in the range of from 2.0 to 3.0.

2. A stable, sterile aqueous solution of cisplatin in a sealed container in unit dosage form suitable for intravenous administration to man, which solution has a concentration of cisplatin in the range of from 0.1 to 1.0 mg./ml. and a pH in the range of from 2.0 to 3.0.

3. A solution as claimed in claim 2 which has a pH in the range of 2.3 to 2.7.

4. A solution as claimed in claim 2 or claim 3 which has a pH of about 2.5.

5. A solution as claimed in any one of claims 2 to 4 which has a concentration of cisplatin of about 1.0 mgm./ml.

6. A solution as claimed in any one of claims 2 to 5 wherein the pH is caused by the presence of an appropriate amount of a nontoxic pharmaceutically acceptable acid.

7. A solution as claimed in claim 6 wherein the pharmaceutically acceptable acid is hydrochloric acid.

8. A solution as claimed in any one of claims 2 to 7 which additionally contains a nontoxic pharmaceutically acceptable inorganic source of chloride ions at a concentration equivalent to that produced by the presence of sodium chloride at a concentration in the range of from 1 to 20 mgm/ml.

9. A solution as claimed in claim 8 which is free from any other added chemical.

10. A solution as claimed in any one of claims 1 to 8 which additionally contains a pharmacologically accepable excipient at a concentration in the range of from 2 to 15 mgm/ml.

11. A solution as claimed in claim 10 wherein the excipient is mannitol.

12. A stable, sterile aqueous solution of cisplatin in a sealed container in unit dosage form suitable for intravenous administration to man, which solution has a concentration of cisplatin of about 1.0 mgm/ml. and pH in the range of from 2.3 to 2.7, the pH being caused by the presence of an appropriate amount of hydrochloric acid; the solution containing in addition sodium chloride at a concentration of about 9 mgm/ml and mannitol at a concentration of about 10 mgm./ml. the solution exhibiting less than 10% loss of potency when measured by high pressure liquid chromatography upon storage for one month at 56°C.

$$\text{Mg. DDP/Gram} = \frac{\text{SF} \times \text{Average Peak Height Sample} \times 25}{\text{Wt. Sample (Gm)}}$$

$$\text{Mg. DDP/Vial} = \text{SF} \times \text{Average Peak Height Sample} \times 10$$

For assay, average results obtained for 10 vials from content uniformity test.

Method

The method of assay for cisplatin described above is applied to aqueous solutions (dose formulations) containing NaCl and mannitol after making the changes indicated below.

HPLC Conditions

Mobile Phase—Acetonitrile/distilled water (75/25, v/v). Use Burdick and Jackson distilled in glass spectroquality reagents. Degas the water prior to use and the solution after mixing.
Injector—A100 microliter loop injector.
Injection Volume—100 microliter.
Retention—2.0 minutes (approx).

HPLC Analysis

Standard—Weight accurately 25 mg of cis-diamminedichloro-platinum (DDP), 225 mg. sodium chloride and 250 mg. mannitol into a 25-ml. volumetric flask. Dissolve in and dilute to volume with distilled water. Pipet 5.0 ml. of the resulting solution into a 25-ml. volumetric flask, add 2.0 ml. of distilled water and take to volume with acetonitrile.
Sample (1 mg/ml)—Pipet 5.0 ml. of the sample into a 25-ml. volumetric flask add 2.0 ml. of distilled water and take to volume with aceonitrile.

Calculations

$$\text{Standard Factor (SF)} = \frac{\text{Mg. Standard/ml.}}{\text{Average Peak Height Standard}}$$

$$\text{Mg. DDP/ml.} = \text{SF} \times \text{Average Peak Height Sample} \times 25$$

This invention is capable of industrial application.

Claims

1. A stable, sterile aqueous solution of cisplatin in unit dosage form suitable for administration to man, which solution has a concentration of cisplatin in the range of from 0.1 to 1.0 mgm./ml. and a pH in the range of from 2.0 to 3.0.

2. A stable, sterile aqueous solution of cisplatin in a sealed container in unit dosage form suitable for intravenous administration to man, which solution has a concentration of cisplatin in the range of from 0.1 to 1.0 mg./ml. and a pH in the range of from 2.0 to 3.0.

3. A solution as claimed in claim 2 which has a pH in the range of 2.3 to 2.7.

4. A solution as claimed in claim 2 or claim 3 which has a pH of about 2.5.

5. A solution as claimed in any one of claims 2 to 4 which has a concentration of cisplatin of about 1.0 mgm./ml.

6. A solution as claimed in any one of claims 2 to 5 wherein the pH is caused by the presence of an appropriate amount of a nontoxic pharmaceutically acceptable acid.

7. A solution as claimed in claim 6 wherein the pharmaceutically acceptable acid is hydrochloric acid.

8. A solution as claimed in any one of claims 2 to 7 which additionally contains a nontoxic pharmaceutically acceptable inorganic source of chloride ions at a concentration equivalent to that produced by the presence of sodium chloride at a concentration in the range of from 1 to 20 mgm/ml.

9. A solution as claimed in claim 8 which is free from any other added chemical.

10. A solution as claimed in any one of claims 1 to 8 which additionally contains a pharmacologically accepable excipient at a concentration in the range of from 2 to 15 mgm/ml.

11. A solution as claimed in claim 10 wherein the excipient is mannitol.

12. A stable, sterile aqueous solution of cisplatin in a sealed container in unit dosage form suitable for intravenous administration to man, which solution has a concentration of cisplatin of about 1.0 mgm/ml. and pH in the range of from 2.3 to 2.7, the pH being caused by the presence of an appropriate amount of hydrochloric acid; the solution containing in addition sodium chloride at a concentration of about 9 mgm/ml and mannitol at a concentration of about 10 mgm./ml. the solution exhibiting less than 10% loss of potency when measured by high pressure liquid chromatography upon storage for one month at 56°C.

* C L M S *

13. A solution as claimed in claim 1 or claim 2 substantially as hereinbefore described.

14. A solution as claimed in claim 2 substantially as hereinbefore described with reference to the Example.

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