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(71) Applicant *(for all designated States except US)*: SANOFI [FR/FR]; 174, avenue de France, F–75013 Paris (FR).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: ANDERSON, Nicholas, Hugh [GB/GB]; 7 The Dell, Morpeth, Northumberland NE61 3JY (GB). BLUNDELL, Ross [GB/GB]; 85 Roseberry Crescent, Jesmond, Newcastle upon Tyne NE2 1EX (GB). BROWN, Stephen [GB/GB]; 32 Victoria Avenue, Saffron Walden, Essex CB11 3AE (GB). ENGLAND, David, Alan [GB/GB]; 16 Emily Davison Avenue, Morpeth, Northumberland NE61 2PL (GB). GRAY, Martin, Robert [GB/GB]; 29 Allerburn Lea, Alnwick, Northumberland NE66 2NJ (GB).

(74) Agent: WHITE, Martin, P.; Kilburn & Strode, 20 Red Lion Street, London WC1R 4PJ (GB).

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(54) Title: FORMULATIONS

(57) Abstract

The invention relates to pharmaceutically stable oxaliplatin solution formulations, to the method of use thereof in the treatment of cancer tumors, to processes for the preparation of such formulations, and to a method for stabilizing solutions of oxaliplatin.

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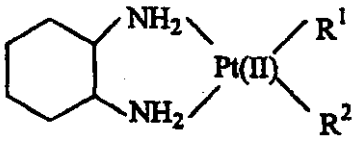
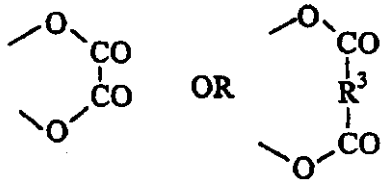
FORMULATIONS

The invention relates to pharmaceutically stable oxaliplatin solution formulations, to the method of use thereof in the treatment of cancer tumors, to processes for the preparation of such formulations and to a method for stabilizing solutions of oxaliplatin.

Kidani et al,. U.S. Patent No. 4,169,846, issued October 2, 1979, disclose cis-platinum(II) complexes of isomers (cis-, trans-d, and trans-l isomers) of 1,2-diaminocyclohexane represented by the general formula



wherein the stereoisomerism of 1,2-diaminocyclohexane is cis, trans-d, or trans-l; and R^1 and R^2 represent halogen atoms, or R^1 and R^2 may, when taken together, form a group represented by the formula:



where R^3 represents a $>CH_2$ group, a $>CHCH_3$ or $>CHCH_2CH_3$ group. Cis-oxalato(trans-l-1,2-diaminocyclohexane)platinum (II) is specifically disclosed as example 4(i). The compounds are stated to possess anti-tumor activity.

Okamoto et al., U.S. Patent No. 5,290,961, issued March 1, 1994, disclose a process for preparing various platinum compounds including cis-oxalato(trans-l-1,2-cyclohexane-diamine)platinum (II). A similar disclosure is found in EP 617043, published September 28, 1994.

Tozawa et al., U.S. Patent No. 5,298,642, issued March 29, 1994, disclose a process for optically resolving optically active platinum compounds by the use of chiral high

perfomance liquid chromatography. The resolution of cis-oxalato(trans-d and trans-l-1,2-cyclohexane-diamine)platinum (II) is specifically disclosed. Nakanishi et al., U.S. Patent No. 5,338,874, issued August 16, 1994, disclose optically pure cis-oxalato(trans-l-1,2-cyclohexanediamine)platinum (II) and methods of preparing the same. A similar disclosure is found in EP 567438, published October 27, 1993.

Okamoto et al., U.S. Patent No. 5,420,319, issued May 30, 1995, disclose cis-oxalato(trans-l-1,2-cyclohexanediamine)platinum(II) having high optical purity and a process for preparing the same. A similar disclosure is found in EP 625523, published November 23, 1994.

Masao et al., EP . 715854, published June 12, 1996, disclose a process of compatibly administering cis-oxalato(1R,2R-diaminocyclohexane)platinum(II), abbreviated as ("l-OHP"), with one or more existing carcinostatic substances and a carcinostatic substance comprising one or more compatible agents and l-OHP.

Kaplan et al., Canadian patent application No. 2,128,641, published February 12, 1995, disclose stable solutions of malonato platinum (II) antitumor agents, such as carboplatin, containing a stabilizing amount of 1,1-cyclobutanedicarboxylic acid or a salt thereof and a pharmaceutically acceptable carrier, said solution having a pH about 4 to about 8.

Ibrahim et al., WO94/12193, published June 9, 1994, disclose a composition for jointly administering cisplatin and oxaliplatin, said composition being a freeze-dried composition containing cisplatin and oxaliplatin in a weight ratio of about 2:1 to 1:2 and a pharmaceutically acceptable chloride ion-free acidic buffer with a neutral substance being used as a ballast.

Tsurutani et al., EP 486998, published May 27, 1992, disclose a slow-releasing composition comprising a platinum-containing anticancer agent bound to deacetylated chitin. A similar disclosure is found in U.S. Patent No. 5,204,107, issued April 20, 1993.

Ibrahim et al., Australian patent application No. 29896/95, published March 7, 1996 (a patent family member of WO 96/04904, published February 22, 1996), disclose a pharmaceutically stable preparation of oxaliplatin for parenteral administration consisting of a solution of oxaliplatin in water at a concentration in the range of 1 to 5 mg/mL and having a pH in the range of 4.5 to 6. A similar disclosure is found in U.S. Patent No. 5,716,988, issued February 10, 1998.

Johnson, U.S. Patent No. 5,633,016, issued May 27, 1997, discloses pharmaceutical compositions comprising a compound of the camptothecin analog class and a platinum coordination compound and a pharmaceutically acceptable carrier or diluent. A similar disclosure is found in WO93/09782, published May 27, 1993.

Bach et al., EP 393575, published October 24, 1990, disclose a combination therapy of therapeutically-effective amounts of a cytoprotective copolymer and one or more directly acting antineoplastic agents for the treatment of neoplastic disease.

Nakanishi et al., EP 801070, published October 15, 1997, disclose a process for preparing various platinum complexes including cis-oxalato(trans-l-1,2-cyclohexane-diamine)Pt(II).

Oxaliplatin is currently available for both preclinical and clinical trials as a lyophilized powder which is reconstituted just before administration to a patient with water for injection or a 5% glucose solution, followed by dilution with a 5% glucose solution. Such a lyophilized product can, however, have several disadvantages. First of all, the lyophilization process can be relatively complicated and expensive to perform. In addition, the use of a lyophilized product requires that the product be reconstituted at the time of use,

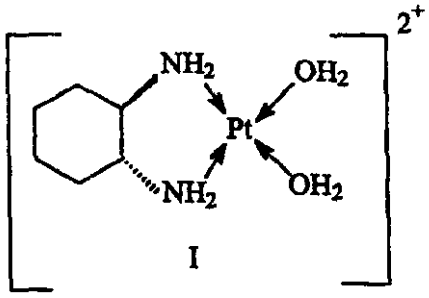
which provides an opportunity for there to be an error in choosing the appropriate solution for the reconstitution. For instance, the mistaken use of a 0.9% NaCl solution, which is a very common solution for the reconstitution of lyophilized products or for the dilution of liquid preparations, in the reconstitution of a lyophilized oxaliplatin product would be detrimental to the active ingredient in that a rapid reaction would occur, resulting not only in the loss of oxaliplatin, but in the precipitation of the species produced. Other disadvantages of a lyophilized product are:

(a) reconstitution of a lyophilized product increases the risk of microbial contamination over a sterile product which does not require reconstitution;

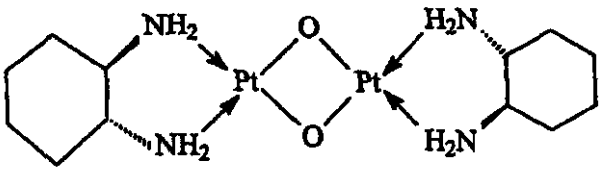
(b) there is a greater risk of sterility failure with a lyophilized product as compared to a solution product sterilized by filtration or by heat (terminal) sterilization; and

(c) a lyophilized product has a potential for incomplete dissolution upon reconstitution resulting in particles which are undersirable for an injectable product.

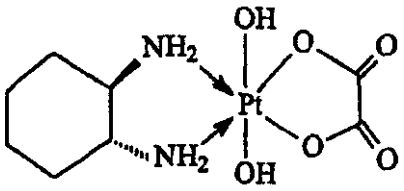
It has been shown that in aqueous solutions oxaliplatin can, over time, degrade to produce as impurities varying amounts of diaquo DACH platin (formula I), diaquo



I



II



III

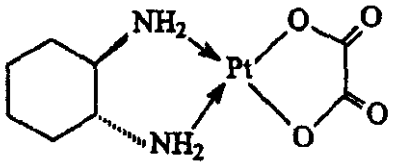
DACH platin dimer (formula II) and a platinum (IV) species (formula III). As the level of impurities present in any pharmaceutical formulation can, and in many cases does, affect the toxicological profile of the formulation, it would be desirable to develop a more stable solution formulation of oxaliplatin which either does not produce the above-described impurities at all or which produces such impurities in significantly smaller quantities than has heretofore been known.

Accordingly, a need exists for solution formulations of oxaliplatin in a ready-to-use (RTU) form, which overcome the above-described disadvantages and which are pharmaceutically stable over prolonged periods of storage, i.e., 2 years or more. It is accordingly an object of the present invention to overcome these disadvantages by providing a pharmaceutically stable oxaliplatin solution formulation in ready-to-use form.

More specifically, the present invention relates to a stable oxaliplatin solution formulation comprising oxaliplatin, an effective stabilizing amount of a buffering agent and a pharmaceutically acceptable carrier.

Oxaliplatin, which is known chemically as cis-oxalato(trans-l-1,2-cyclohexane-diamine)platinum (II) (can also be named as [SP-4-2]- (1R,2R)-(cyclohexane-1,2-diamine-k^2N,N' (oxalato(2-)-k^2O^1,O^2]platinum (II), (1,2-cyclohexanediamine-N,N')[ethanedioato(2-)-O,O']-[SP-4-2-(1R-trans)]-platinum, cis-[oxalato(1R,2R-cyclohexanediamine)platinum (II)], [(1R,2R)-1,2-cyclohexanediamine-N,N'][oxalato(2-)-O,O']platinum, [SP-4-2-(1R-trans)]-(1,2-cyclohexane-diamine-N,N')[ethanedioato(2-)-O,O']platinum, l-OHP, and cis-

oxalato(trans-l-1,2-diaminocyclo-hexane(platinum (II)), and has the chemical structure shown below,



is a cytostatic antineoplastic agent which is useful in the therapeutic treatment of various types of susceptible cancers and tumors, such as , for example, colon cancer, ovarian cancer, epidermoid cancer, cancers of germinal cells (e.g., testicular, mediastina, pineal gland), non-small cell lung cancers, non-Hodgkins' lymphoma, breast cancer, cancers of the upper respiratory and digestive tracts, malignant melanoma, hepatocarcinoma, urothelial cancers, prostate cancers, small cell lung cancer, pancreatic cancer, gall bladder cancer, anal cancer, rectal cancer, bladder cancer, small intestine cancer, stomach cancer, leukemia and various other types of solid tumors.

The preparation, physical properties and beneficial pharmacological properties of oxaliplatin are described in, for example, U.S. Patents Nos. 4,169,846, 5,290,961, 5,298,642, 5,338,874, 5,420,319 and 5,716,988, European patent application No. 715854 and Australian patent application No. 29896/95, the entire contents of which are herein incorporated by reference.

Oxaliplatin is conveniently present in the formulations of the present invention in the amount of from about 1 to about 7 mg/mL, preferably in the amount of from about 1 to about 5 mg/mL, more preferably in the amount of from about 2 to about 5 mg/mL, and in particular in the amount of about 5 mg/mL.

The term buffering agent as used herein means any acidic or basic agent which is capable of stabilizing oxaliplatin solutions and thereby preventing or retarding the formation of unwanted impurities such as diaquo DACH platin and diaquo DACH platin dimer. The

term thus includes such agents as oxalic acid or alkali metal salts (e.,g., lithium, sodium, potassium and the like) of oxalic acid, and the like or mixtures thereof. The buffering agent is preferably oxalic acid or sodium oxalate and most preferably is oxalic acid.

The buffering agent is present in the formulations of the present invention in an effective stabilizing amount. The buffering agent is conveniently present in a molar concentration in the range of from about 5×10^{-5} M to about 1×10^{-2} M, preferably in a molar concentration in the range of about 5×10^{-5} M to about 5×10^{-3} M, more preferably in a molar concentration in the range of from about 5×10^{-5} M to about 2×10^{-3} M, most preferably in a molar concentration in the range of from about 1×10^{-4} M to about 2×10^{-3} M, especially in a molar concentration in the range of from about 1×10^{-4} M to about 5×10^{-4} M, and in particular in a molar concentration of about 2×10^{-4} M or about 4×10^{-4} M.

The term pharmaceutically acceptable carrier as used herein refers to the various solvents which can be employed in the preparation of the oxaliplatin solution formulations of the present invention. In general, the carrier will be water, one or more other suitable solvents, or a mixture of water and one or more other suitable solvents. Preferably, the carrier will be either water or a mixture of water and one or more other suitable solvents, and more preferably, the carrier is water. The water that is used is preferably pure water, i.e., sterile water for injection. Representative examples of the other suitable carriers (solvents) which can be utilized according to the present invention include polyalkylene glycols, such as polyethylene glycol, polypropylene glycol, polybutylene glycol and the like and mixtures thereof; ethanol, 1-vinyl-2-pyrrolidone polymer (povidone) and sugar solutions of pharmaceutically acceptable lactose, dextrose (glucose), sucrose, mannose, mannitol, cyclodextrins and the like or mixtures thereof.

The pH of the oxaliplatin solution formulations of the present invention is generally in the range of about 2 to about 6, preferably in the range of about 2 to about 5, and more preferably in the range of about 3 to about 4.5.

The oxaliplatin solution formulations of particular interest include those described in the accompanying examples and so formulations substantially as defined in the accompanying examples are provided as a further feature of the present invention.

As mentioned above, oxaliplatin is a cytostatic antineoplastic agent which is useful in the therapeutic treatment of various types of susceptible cancers and tumors. Thus, the present invention also provides a method for treating cancer or a solid tumor in a mammal which comprises administering to said mammal an effective amount of an oxaliplatin solution formulation of the present invention.

The present invention further relates to the use of an oxaliplatin solution formulation of the present invention for the preparation of a medicament for treating cancer or a solid tumor in a mammal.

The present invention further relates to a method for stabilizing a solution of oxaliplatin which comprises adding an effective stabilizing amount of a buffering agent to said solution. In a preferred aspect of this method, the solution is an aqueous (water) solution and the buffering agent is oxalic acid or an alkali metal salt thereof.

The present invention further relates to a process for preparing the oxaliplatin solution formulations of the present invention which comprises mixing a pharmaceutically acceptable carrier, a buffering agent and oxaliplatin.

A preferred process for preparing the oxaliplatin solution formulations of the present invention comprises the steps of:

(a) mixing a pharmaceutically acceptable carrier and a buffering agent, preferably at about 40 °C;

(b) dissolving oxaliplatin into said mixture, preferably at about 40 °C;

(c) cooling the mixture resulting from step (b), preferably to about room temperature, and making up to final volume with a pharmaceutically acceptable carrier;

(d) filtering the solution from step (c); and

(e) optionally sterilizing the product resulting from step (d).

It should be noted that while the above process can conveniently be carried out either in the presence or absence of an inert atmosphere, it is preferably carried out under an inert atmosphere, such as nitrogen.

In a particularly preferred process for preparing the oxaliplatin solution formulations of the present invention the product resulting from step (d) above is sterilized by filtration or exposure to heat (terminal sterilization), preferably by exposure to heat.

The present invention further relates to a packaged pharmaceutical product comprising an oxaliplatin solution formulation of the present invention in a sealable container. The sealable container is preferably an ampoule, vial, infusion bag (pouch), or syringe. If the sealable container is a syringe, the syringe is preferably a graduated syringe which allows for the measured (metered) administration of the oxaliplatin solution formulations of the present invention, and in particular allows for the measured (metered) administration of such solution formulations directly into an infusion bag.

It should also be noted that the above-described oxaliplatin solution formulations of the present invention have, as is described more fully hereinbelow, been found to possess certain advantages over the presently known formulations of oxaliplatin.

Unlike the lyophilized powder form of oxaliplatin, the ready-to-use formulations of the instant invention are made by a less expensive and less complicated manufacturing process.

In addition, the formulations of the instant invention require no additional preparation or handling, e.g., reconstitution, before administration. Thus, there is no chance that an error will occur in choosing the appropriate solvent for the reconstitution as there is with a lyophilized product.

The formulations of the instant invention have also been found to be more stable during the manufacturing process than the previously known aqueous formulations of oxaliplatin which means that less impurities, e.g., diaquo DACH platin and diaquo DACH platin dimer, are produced in the instant formulations than in the previously known aqueous formulations of oxaliplatin.

The formulations of the instant invention can also be sterilized by filtration or exposure to heat (terminal sterilization) without adversely affecting the quality of the formulations.

These and other advantages of the formulations of the instant invention will become more evident upon further consideration of the instant specification and claims.

The formulations of the present invention are generally administered to patients, which include, but are not limited to, mammals, such as, for example, man, by conventional routes well known in the art. For example, the formulations can be administered to patients parenterally (e.g., intravenously, intraperitoneally and the like). The formulations are preferably administered parenterally and in particular are administered intravenously. When infused intravenously, the formulation is generally administered over a period of up to 5 days, preferably over a period of up to 24 hours and more preferably over a period of 2 to 24 hours.

It will also be apparent to those skilled in the art that the oxaliplatin solution formulations of the present invention can be administered with other therapeutic and/or prophylactic agents and/or medicaments that are not medically incompatible therewith.

The percentage of active component, i.e., oxaliplatin, in the formulations of the present invention may be varied so that a suitable dosage is obtained. The dosage administered to a particular patient is variable depending upon the clinician's judgment using as criteria: the route of administration, the duration of treatment, the size, age and physical condition of the patient, the severity of the condition, the potency of the active component and the patient's response thereto. An effective dosage amount of the active component can thus readily be determined by the clinician after a consideration of all criteria and using his best judgment on the patient's behalf. In general, the active component of the formulations of the present invention can be administered to patients in doses ranging from about 10 mg/m^2 to about 250 mg/m^2, more preferably from 20 mg/m^2 to about 200 mg/m^2 and most preferably from about 30 mg/m^2 to about 180 mg/m^2. The preferred dosing regimen for oxaliplatin includes administration of repeated dosages of oxaliplatin in cycles of 1 to 5 days at intervals of 1 to 5 weeks.

The following examples will further illustrate the invention without, however, limiting it thereto. All temperatures are expressed in degrees Celsius (°C).

The formulations of Examples 1-14 set forth in Tables 1A and 1B were prepared by the following general procedure:

Dispense hot water (40 °C) for injection (W.F.I.) and bubble through with filtered nitrogen for approximately 30 minutes.

Transfer an appropriate amount of the W.F.I. required to a suitable mixing vessel while maintaining under nitrogen. Set aside the remaining W.F.I. to make up to the final volume.

Weigh appropriate buffering agent (either in the form of a solid or preferably in the form of an aqueous buffer solution of the appropriate molarity) into a suitable container and transfer to the mixing vessel (rinse container with part of the remaining W.F.I.). Mix, e.g., on

a magnetic stirrer/hotplate, for approximately 10 minutes or, if necessary, until all of the solids have dissolved, while keeping the temperature of the solution at 40 °C.

Weigh oxaliplatin into a suitable container and transfer to the mixing vessel (rinse container with part of the remaining hot (40 °C) W.F.I.). Mix, e.g., on a magnetic stirrer/hotplate, until all of the solids have dissolved, while keeping the temperature of the solution at 40 °C.

Allow the solution to cool to room temperature, then make up to the final volume with the remaining W.F.I.

Filter the solution under vacuum through a 0.22 μm filter (e.g., a millipore type GV, 47 mm diameter filter).

Fill the solution under nitrogen into suitable sterilized and sealable containers (e.g., vials or ampoules) using a filler unit, e.g, a sterile 0.2 μm disposable hydrophilic filler unit (Minisart - NML, Sartorius), with the sealable containers being purged with nitrogen before filling and the headspace being purged with nitrogen before sealing.

Autoclave, i.e., terminally sterilize, the solution for 15 minutes at 121 °C using, for example, an SAL (PD270) autoclave.

It should be noted that while the above process has preferably been carried out under an inert atmosphere, such as nitrogen, the formulations of the instant invention can also be conveniently prepared in the absence of such an inert atmosphere.

TABLE 1A

Ingredient	Example 1 0.00001 M sodium oxalate	Example 2 0.00005 M sodium oxalate	Example 3 0.0001 M sodium oxalate	Example 4 0.0003 M sodium oxalate	Example 5 0.0005 M sodium oxalate	Example 6 0.001 M sodium oxalate	Example 7 0.002 M sodium oxalate
Oxaliplatin	5.000 g	5.000 g	5.000 g	5.000 g	5.000 g	5.000 g	5.000 g
Water for injection	1000 mL	1000 mL	1000 mL	1000 mL	1000 mL	1000 mL	1000 mL
Amount sodium oxalate	1.340 mg	6.700 mg	13.40 mg	40.20 mg	67.00 mg	134.00 mg	268.00 mg

Note: The sealable containers which were utilized for the formulations of Examples 1-7 were 20 mL clear glass ampoules.

TABLE 1B

Ingredient	Example 8 0.00001 M oxalic acid	Example 9 0.00005 M oxalic acid	Example 10 0.0001 M oxalic acid	Example 11 0.0003 M oxalic acid	Example 12 0.0005 M oxalic acid	Example 13 0.001 M oxalic acid	Example 14 0.002 M oxalic acid
Oxaliplatin	5.000 g	5.000 g	5.000 g	5.000 g	5.000 g	5.000 g	5.000 g
Water for injection	1000 mL	1000 mL	1000 mL	1000 mL	1000 mL	1000 mL	1000 mL
Amount Oxalic Acid*	1.260 mg	6.300 mg	12.60 mg	37.80 mg	63.00 mg	126.10 mg	252.10 mg

Note: The sealable containers which were utilized for the formulations of Examples 8-14 were 20 mL clear glass ampoules.

* Oxalic acid is added as the dihydrate; the weights shown here are of oxalic acid dihydrate added.

The formulations of Examples 15 and 16 set forth in Table 1C were prepared in a manner similar to that described above for the preparation of the formulations of Examples 1-14.

TABLE 1C

Ingredient	Example 15 0.0002 M oxalic acid	Example 16 0.0004 M oxalic acid
Oxaliplatin	7.500 g	7.500 g
Water for injection	1500 mL	1500 mL
Amount Oxalic Acid*	37.82 mg	75.64 mg

Note: The sealable containers which were utilized for the formulations of Examples 15-16 were 20 mL clear glass ampoules.

* Oxalic acid is added as the dihydrate; the weights shown here are of oxalic acid dihydrate added.

The formulation of Example 17 set forth in Table 1D was prepared in a manner similar to that described above for the preparation of the formulations of Examples 1-14, except that: (a) the solution was filled into the sealable containers in the absence of nitrogen (i.e., in the presence of oxygen); (b) the sealable containers were not purged with nitrogen before filling; (c) the headspace was not purged with nitrogen before sealing the containers; and (d) the sealable containers were vials rather than ampoules.

TABLE 1D

Ingredient	Example 17 0.0002 M oxalic acid
Oxaliplatin	10.000 g
Water for injection	2000 mL
Amount Oxalic Acid*	50.43 mg

Note: 1000 mL of the solution formulation of Example 17 was filled into 5 mL clear glass vials (4 mL of solution per vial) which were sealed with a West Flurotec stopper [hereinafter referred to as Example 17(a)] and the remaining 1000 mL of the solution formulation of Example 17 was filled into 5 mL clear glass vials (4 mL of solution per vial) which were sealed with a Helvoet Omniflex stopper [hereinafter referred to as Example 17(b)].

* Oxalic acid is added as the dihydrate; the weights shown here are of oxalic acid dihydrate added.

Preparation of 0.0005 M Sodium Oxalate Buffer

Dispense greater than 2000 mL of water for injection (W.F.I.) and bubble filtered nitrogen through the water for approximately 30 minutes.

Transfer 1800 ml of the W.F.I. into a 2000 mL Schott bottle and maintain under an N_2 cloud. Set aside the remainder (200 mL) to make up the final volume.

Weigh sodium oxalate (134.00 mg) into a weighing boat and transfer into the Schott bottle (rinsing with approximately 50 mL of W.F.I.).

Stir the mixture on a magnetic stirrer/hotplate until all of the solids have dissolved.

Transfer the solution to a 2000 mL volumetric flask and make up to 2000 mL with W.F.I. and then purge the headspace of the flask with nitrogen before stoppering.

The various other sodium oxalate and oxalic acid buffer solutions set forth in Tables 1A, 1B, 1C and 1D were prepared following a procedure similar to that described above for the preparation of the 0.0005 M sodium oxalate buffer solution.

Example 18

For comparative purposes, an aqueous oxaliplatin formulation, such as those disclosed in Australian patent application No. 29896/95, published March 7, 1996, was prepared as follows:

Dispense greater than 1000 mL of water for injection (W.F.I.) and bubble filtered nitrogen through the solution for approximately 30 minutes. Stir on a magnetic stirrer/ hotplate and heat the W.F.I. to 40 °C.

Transfer 800 mL of W.F.I. into a 1000 mL Schott bottle and maintain under an N_2 cloud. Set aside the remainder of W.F.I. (200 mL) to make up the final volume.

Weigh oxaliplatin (5.000 g) into a small glass beaker (25 mL) and transfer into a Schott bottle, rinsing the beaker with approximately 50 mL of hot W.F.I.

Stir the mixture on a magnetic stirrer/hotplate until all of the solids have dissolved, while keeping the temperature at 40 °C.

Allow the solution to cool to room temperature, then transfer it to a 1000 mL volumetric flask and make up the flask to 1000 mL with cool (approximately 20 °C) W.F.I.

The solution was filtered into a 1000 mL flask through a Millipore type GV, 47 mm diameter, 0.22 μm filter using a vacuum line.

The solution was then filled into washed and sterilized 20 mL glass ampoules using a sterile 1.2 μm disposable hydrophilic filter unit (Minisart - NML, Sartorius). The ampoules were purged with nitrogen before filling and the headspace was purged with nitrogen before sealing.

Twenty-three of the ampoules were kept unautoclaved [hereinafter referred to as Example 18(a)], i.e., they were not terminally sterilized, and the remaining 27 ampoules [hereinafter referred to as Example 18(b)] were autoclaved for 15 minutes at 121 °C using a SAL (PD 270) autoclave.

Stability Studies

In the stability studies described hereinbelow, the following chromatographic methods were utilized to evaluate the stability of the various oxaliplatin solution formulations.

The percentage of the platinum (IV) species, the unspecified impurities and oxaliplatin was determined by high performance liquid chromatography (HPLC) using a Hypersil™ C18 column and a mobile phase containing dilute orthophosphoric acid and acetonitrile. Under these conditions, the platinum (IV) species and oxaliplatin had retention times of approximately 4.6 and 8.3 minutes, respectively.

The percentage of the diaquo DACH platin and the diaquo DACH platin dimer, as well as the unspecified impurities referred to in Tables 4-8, was determined by HPLC using a Hypersil™ BDS C18 column and a mobile phase containing phosphate buffer and acetonitrile. Under these conditions, the diaquo DACH platin and diaquo DACH platin dimer had retention times of approximately 4.3 and 6.4 minutes respectively, whereas oxaliplatin eluted with the solvent front.

Oxaliplatin in various aqueous buffers

A 2 mg/mL oxaliplatin solution in a 0.0005 M sodium oxalate buffer solution (0.0670 mg/mL of sodium oxalate) was prepared in a manner similar to that described above for the preparation of Examples 1-14 and the stability of this solution , as well as various other oxaliplatin solutions (2 mg/mL) in a range of commonly used aqueous buffer solutions, was analyzed. The results obtained when each solution was stressed for approximately one month at 40 °C are given in Table 2.

TABLE 2

Buffer	Initial Assay (% of theoretical)	Assay after ~1 month at 40 °C (% of theoretical)
0.0005M sodium oxalate	102.1	98.8
0.1M citrate, pH 3	100.4	63.6
0.1M citrate, pH 5	95.8	24.7
0.1M acetate, pH 5	100.3	76.5
0.1M tris, pH 7	80.1	1.0
0.1M tris, pH 9	22.1	0.0
0.1M glycine, pH3	96.8	0.1
0.1M glycine, pH 9	49.7	0.0
0.1M phosphate, pH 7	98.4	19.0

These results demonstrate that oxaliplatin was not stable in various commonly used aqueous buffer solutions, such as citrate, acetate, tris, glycine and phosphate buffers when the solution was stressed. However, it was discovered that stable aqueous solutions of oxaliplatin can be obtained when a buffering agent, such as oxalic acid or an alkali metal salt thereof, e.g., sodium oxalate, is utilized.

Autoclaved oxaliplatin solutions in oxalate buffer

A 2 mg/mL oxaliplatin solution in a 0.01 M sodium oxalate buffer (1.340 mg/mL of sodium oxalate), with a sample solution pH of approximately 4, was prepared in a manner similar to that described above for the preparation of Examples 1-14. The stability results for this solution after 0, 1, 2 and 3 autoclave cycles (with each cycle lasting 15 minutes at 121° C) are summarized in Table 3.

TABLE 3

Number of Autoclave Cycles	Assay (mg/mL)	Diaquo DACH Platin (% w/w)	Diaquo DACH Platin Dimer (% w/w)	Platinum (IV) Species (% w/w)	Total Impurities (% w/w)
0	2.03	ND <0.01	ND <0.01	0.02	0.02
1 (15 min/121°C)	1.96	ND <0.01	ND <0.01	0.06	0.05
2 (30 min/121°C)	2.01	ND <0.01	ND <0.01	0.09	0.10
3 (45 min/121°C)	1.97	ND <0.01	ND <0.01	0.12	0.15

ND = None Detected

A 5 mg/mL oxaliplatin solution in a 0.0002 M oxalic acid buffer and a 5 mg/mL oxaliplatin solution in a 0.0004 M oxalic acid buffer were prepared, both in the presence and the absence of oxygen, in a manner similar to that described above for the preparation of Examples 1-16. The stability results for these solutions after 0, 1, 2 and 3 autoclave cycles (with each cycle lasting for 15 minutes at 121°C) and three autoclave cycles of 15 minutes at 121°C and a fourth autoclave cycle lasting for 75 minutes at 121°C (total 120 minutes) are summarized in Table 3A.

TABLE 3A

5 mg/mL Oxaliplatin in:	Time at 121°C (min)	Diaquo DACH Platin (% w/w)	Diaquo DACH Platin Dimer (% w/w)	Pt(IV) Species (% w/w)	Total Unspecified Impurities (% w/w)	Total Chromatographic Impurites (% w/w)
0.0002M oxalic acid manufactured under nitrogen	0	0.10	ND <0.01	ND <0.003	ND < 0.03	0.10
	15 (1 cycle)	0.13	ND <0.01	ND <0.003	T < 0.03	0.13
	30 (2 cycles)	0.10	ND <0.01	T < 0.01	T < 0.03	0.10
	45 (3 cycles)	0.10	ND <0.01	T <0.01	T < 0.03	0.10
	120 (4 cycles)	0.09	ND <0.01	T <0.01	T < 0.03	0.09
0.0002M oxalic acid manufactured under oxygen	0	0.14	ND <0.01	0.02	T <0.05	0.16
	15 (1 cycle)	0.13	ND <0.01	0.01	T <0.05	0.14
	30 (2 cycles)	0.11	ND <0.01	T <0.01	T <0.05	0.14
	45 (3 cycles)	0.12	ND <0.01	T <0.01	T <0.05	0.15
	120 (4 cycles)	0.12	ND <0.01	T <0.01	T <0.05	0.16
0.0004M oxalic acid manufactured under nitrogen	0	0.14	ND <0.01	T <0.01	T <0.05	0.14
	15 (1 cycle)	0.14	ND <0.01	T <0.01	T <0.05	0.14
	30 (2 cycles)	0.12	ND <0.01	T <0.01	T <0.05	0.12
	45 (3 cycles)	0.11	ND <0.01	T <0.01	T <0.05	0.11
	120 (4 cycles)	0.12	ND <0.01	T <0.01	T <0.05	0.12
0.0004M oxalic acid manufactured under oxygen	0	0.13	ND <0.01	0.02	ND <0.05	0.15
	15 (1 cycle)	0.13	ND <0.01	0.01	T <0.05	0.14
	30 (2 cycles)	0.13	ND <0.01	0.01	T <0.05	0.14
	45 (3 cycles)	0.11	ND <0.01	0.01	T <0.05	0.12
	120 (4 cycles)	0.11	ND <0.01	T <0.01	T <0.05	0.11

ND = Not detected
T = Trace

The above results demonstrate that the oxaliplatin solution formulations of the present invention can be terminally sterilized without adversely affecting the quality of the formulation.

Stability studies for formulations of Examples 1-17

The oxaliplatin solution formulations of Examples 1-14 were stored for up to 6 months at 40° C and the stability results of this study are summarized in Tables 4 and 5.

TABLE 4

Example No.	Sodium Oxalate Molarity	Time at 40°C	Measured pH	Diaquo DACH Platin (% $^{w}/_{w}$)	Diaquo DACH Platin Dimer (% $^{w}/_{w}$)	Unspecified Impurities (% $^{w}/_{w}$)
1	0.00001	initial	5.26	0.20	0.15	0.03
	0.00001	1 month	5.25	0.21	0.15	0.13
2	0.00005	initial	5.75	0.18	0.12	0.04
	0.00005	1 month	5.32	0.16	0.11	0.12
3	0.0001	initial	5.64	0.14	0.11	0.05
	0.0001	1 month	5.33	0.14	0.08	0.11
4	0.0003	initial	5.77	0.09	0.07	0.06
	0.0003	1 month	5.74	0.10	0.07	0.10
5	0.0005	initial	5.71	0.06	0.06	0.06
	0.0005	1 month	5.68	0.08	0.05	0.08
6	0.001	initial	5.48	0.04	0.04	0.06
	0.001	1 month	5.85	0.05	0.03	0.07
7	0.002	initial	5.90	0.06	0.03	0.06
	0.002	1 month	6.02	0.03	trace <0.03	0.05

TABLE 5

Example No.	Oxalic Acid Molarity	Time at 40°C	Measured pH	Diaquo DACH Platin (% $^{w}/_{w}$)	Diaquo DACH Platin Dimer (% $^{w}/_{w}$)	Unspecified Impurities (% $^{w}/_{w}$)
8	0.00001	initial	5.92	0.22	0.17	0
	0.00001	1 month	5.23	0.27	0.19	0.04
9	0.00005	initial	4.40	0.15	0.05	0
	0.00005	1 month	4.71	0.16	0.03	0.02
10	0.0001	initial	3.70	0.13	trace <0.03	0
	0.0001	1 month	4.10	0.12	ND <0.01	0.02
	0.0001	3 month	3.94	0.13	ND <0.01	trace <0.03
	0.0001	6 month	4.17	0.13	ND <0.01	trace <0.03
11	0.0003	initial	3.47	0.13	ND <0.01	0
	0.0003	1 month	3.52	0.11	ND <0.01	0.01

TABLE 5 (con't.)

Example No.	Oxalic Acid Molarity	Time at 40°C	Measured pH	Diaquo DACH Platin (% w/w)	Diaquo DACH Platin Dimer (% w/w)	Unspecified Impurities (% w/w)
	0.0003	3 month	3.56	0.12	ND <0.01	trace <0.03
	0.0003	6 month	3.48	0.10	ND <0.01	trace <0.03
12	0.0005	initial	3.28	0.13	ND <0.01	0
	0.0005	1 month	3.35	0.10	ND <0.01	0.01
	0.0005	3 month	3.30	0.13	ND <0.01	trace <0.03
	0.0005	6 month	3.34	0.11	ND <0.01	trace <0.03
13	0.001	initial	3.05	0.13	ND <0.01	0
	0.001	1 month	3.02	0.11	ND <0.01	0.01
14	0.002	initial	2.85	0.14	ND <0.01	0
	0.002	1 month	2.70	0.13	ND <0.01	0.01

ND = None Detected.

The oxaliplatin solution formulations of Examples 15 and 16 were stored for up to 9 months at 25°C/60% relative humidity (RH) and 40°C/75% relative humidity (RH) and the stability results of this study are summarized in Table 6.

TABLE 6

Example No.	Oxalic Acid Molarity	Time	Measured pH	Diaquo DACH Platin (% w/w)	Diaquo DACH Platin Dimer (% w/w)	Platinum (IV) Species (% w/w)	Total Chromato-graphic Impurities (% w/w)
15	0.0002	Initial	3.83	0.10	ND <0.01	ND <0.003	0.10
	0.0002	1 Month (25°C/60%RH)	3.75	0.12	ND <0.01	Trace <0.01	0.12
	0.0002	1 Month (40°C/75%RH)	3.78	0.13	ND <0.01	Trace <0.01	0.13
	0.0002	3 Months (25°C/60%RH)	4.13	0.10	ND <0.01	Trace <0.01	0.10
	0.0002	3 Months (40°C/75%RH)	4.16	0.12	ND <0.01	Trace <0.01	0.12
	0.0002	6 Months (25°C/60%RH)	3.45	0.12	ND <0.01	Trace <0.01	0.12
	0.0002	6 Months (40°C/75%RH)	3.52	0.11	ND <0.01	Trace <0.01	0.11

TABLE 6 (con't.)

Example No.	Oxalic Acid Molarity	Time	Measured pH	Diaquo DACH Platin (% w/w)	Diaquo DACH Platin Dimer (% w/w)	Platinum (IV) Species (% w/w)	Total Chromato-graphic Impurities (% w/w)
	0.0002	9 Months (25°C/60%RH)	3.62	0.14	ND <0.01	Trace < 0.01	0.14
	0.0002	9 Months (40°C/75%RH)	3.64	0.11	ND <0.01	Trace < 0.01	0.11
16	0.0004	Initial	3.45	0.10	ND <0.01	Trace < 0.01	0.10
	0.0004	1 Month (25°C/60%RH)	3.40	0.13	ND <0.01	Trace < 0.01	0.13
	0.0004	1 Month (40°C/75%RH)	3.44	0.12	ND <0.01	Trace < 0.01	0.12
	0.0004	3 Months (25°C/60%RH)	3.59	0.11	ND <0.01	Trace < 0.01	0.11
	0.0004	3 Months (40°C/75%RH)	3.71	0.12	ND <0.01	Trace < 0.01	0.12
	0.0004	6 Months (25°C/60%RH)	3.24	0.11	ND <0.01	Trace < 0.01	0.11
	0.0004	6 Months (40°C/75%RH)	3.26	0.11	ND <0.01	Trace < 0.01	0.11
	0.0004	9 Months (25°C/60%RH)	3.26	0.12	ND <0.01	Trace < 0.01	0.12
	0.0004	9 Months (40°C/75%RH)	3.31	0.12	ND <0.01	Trace < 0.01	0.12

ND = None Detected.

The oxaliplatin solution formulations of Examples 17(a) and 17(b) were stored for up to 1 month at 25°C/60% relative humidity (RH) and 40°C/75% relative humidity (RH) and the stability results of this study are summarized in Table 7.

TABLE 7

Example No.	Oxalic Acid Molarity	Time	Measured pH	Diaquo DACH Platin (% w/w)	Diaquo DACH Platin Dimer (% w/w)	Platinum (IV) Species (% w/w)	Unspecified Impurities (% w/w)
17(a)	0.0002	Initial	3.81	0.13	ND <0.01	0.02	Trace <0.05
	0.0002	1 Month (25°C/60%RH)	3.82	0.12	ND <0.01	0.03	Trace <0.05
	0.0002	1 Month (40°C/75%RH)	3.79	0.13	ND <0.01	0.05	0.13
17(b)	0.0002	Initial	3.53	0.14	ND <0.01	0.03	0.05
	0.0002	1 Month (25°C/60%RH)	3.72	0.12	ND <0.01	0.07	0.16
	0.0002	1 Month (40°C/75%RH)	3.73	0.12	ND <0.01	0.09	0.07

ND = None Detected.

The results of these stability studies demonstrate that buffering agents, such as sodium oxalate and oxalic acid are extremely effective in controlling the levels of impurities, such as diaquo DACH platin and diaquo DACH platin dimer, in the solution formulations of the present invention.

Stability of Comparative Example 18

The unbuffered oxaliplatin solution formulation of Example 18(b) was stored for one month at 40°C and the results of this stability study are summarized in Table 8.

TABLE 8

Time at 40 °C	Measured pH	Diaquo DACH Platin (% w/w)	Diaquo DACH Platin Dimer (% w/w)	Unspecified Impurities (% w/w)
Initial	5.47	0.27	0.16	0.04
1 Month	5.27	0.23	0.16	0.14

In addition three separate batches of an aseptically prepared (i.e., prepared under aseptic conditions but not autoclaved) solution product (2 mg/mL of oxaliplatin in pure water) were prepared in a manner similar to that described in Example 18(a) and the batches were stored at ambient temperature for approximately 15 months. The results of this stability study are summarized in Table 9.

TABLE 9

Batch No.	Temperature	Diaquo DACH Platin (% w/w)	Diaquo DACH Platin Dimer (% w/w)
A	Ambient	0.34	0.29
B	Ambient	0.36	0.28
C	Ambient	0.38	0.29

What Is Claimed Is:

1. A stable oxaliplatin solution formulation comprising oxaliplatin, an effective stabilizing amount of a buffering agent and a pharmaceutically acceptable carrier.

2. A formulation according to claim 1 wherein the pharmaceutically acceptable carrier is water and the buffering agent is oxalic acid or an alkali metal salt thereof.

3. A formulation according to claim 2 wherein the buffering agent is oxalic acid or sodium oxalate.

4. A formulation according to claim 3 wherein the buffering agent is oxalic acid.

5. The formulation according to any one of claims 1-4 wherein the amount of buffering agent is a molar concentration in the range of from

(a) about 5×10^{-5} M to about 1×10^{-2} M,

(b) about 5×10^{-5} M to about 5×10^{-3} M,

(c) about 5×10^{-5} M to about 2×10^{-3} M,

(d) about 1×10^{-4} M to about 2×10^{-3} M, or

(e) about 1×10^{-4} M to about 5×10^{-4} M.

6. A formulation according to claim 5 wherein the amount of buffering agent is a molar concentration in the range of from about 1×10^{-4} M to about 5×10^{-4}M.

7. A formulation acording to claim 6 wherein the amount of buffering agent is a molar concentration of about 2×10^{-4} M.

8. A formulation according to claim 6 wherein the amount of buffering agent is a molar concentration of about 4×10^{-4} M.

9. A formulation according to any one of claims 1-8 wherein the amount of oxaliplatin is from about 1 to about 7 mg/mL.

10. A formulation according to any one of claims 1-8 wherein the amount of oxaliplatin is from about 1 to about 5 mg/mL.

11. A formulation according to any one of claims 1-8 wherein the amount of oxaliplatin is from about 2 to about 5 mg/mL.

12. A formulation according to any one of claims 1-8 wherein the amount of oxaliplatin is about 5 mg/mL.

13. A formulation according to claim 4 wherein the amount of oxaliplatin is about 5 mg/mL and the amount of buffering agent is a molar concentration of about 2×10^{-4} M.

14. A formulation according to claim 4 wherein the amount of oxaliplatin is about 5 mg/mL and the amount of buffering agent is a molar concentration of about 4×10^{-4} M.

15. A formulation according to any of claims 1-14 for use in medicine.

16. The use of oxaliplatin in preparing a formulation according to any one of claims 1-14 for treating cancer.

17. The use of oxaliplatin in preparing a formulation according to any one of claims 1-14 for treating a solid tumor.

18. A method for treating cancer in a mammal which comprises administering to said mammal an effective amount of a formulation according to any one of claims 1-14.

19. A method for treating a solid tumor in a mammal which comprises administering to said mammal an effective amount of a formulation according to any one of claims 1-14.

20. A method for stabilizing a solution of oxaliplatin which comprises adding an effective stabilizing amount of a buffering agent to said solution.

21. A method according to claim 20 wherein said solution is an aqueous solution and the buffering agent is oxalic acid or an alkali metal salt thereof.

22. A process for preparing a formulation according to any one of claims 1-14 which comprises mixing a pharmaceutically acceptable carrier, a buffering agent and oxaliplatin.

23. A process for preparing a formulation according to any one of claims 1-14 which comprises the steps of:

(a) mixing a pharmaceutically acceptable carrier and a buffering agent;

(b) dissolving oxaliplatin into said mixture;

(c) cooling the mixture resulting from step (b) and making up to final volume with the pharmaceutically acceptable carrier;

(d) filtering the solution resulting from step (c); and

(e) optionally sterilizing the product resulting from step (d).

24. A process according to claim 23 wherein said process is carried out under an inert atmosphere.

25. A process according to claim 23 wherein the product resulting from step (d) is sterilized by exposure to heat.

26. A packaged pharmaceutical product comprising a formulation according to any one of claims 1-14 in a sealable container.

27. A packaged pharmaceutical product according to claim 26 wherein the container is an ampoule, vial, infusion bag or syringe.

28. A packaged pharmaceutical product according to claim 27 wherein the container is a graduated syringe.

29. A method for the measured administration of a formulation according to any one of claims 1-14, which comprises adminstering said formulation from a graduated syringe.

30. The invention as substantially hereinbefore described.

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[71]申请人 圣诺菲－合成实验室公司
地址 法国巴黎
[72]发明人 N·H·安德森 R·布伦德尔
S·布朗 D·A·恩格兰德
M·R·格雷
[74]专利代理机构 中国专利代理(香港)有限公司
代理人 吴大建 谭明胜

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[54]发明名称 制剂

[57]摘要

本发明涉及药学上稳定的奥沙利铂溶液制剂，应用该制剂治疗肿瘤的方法，制 备该制剂的方法，以及稳定奥沙利铂溶液的方法。

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权　利　要　求　书

1. 稳定的奥沙利铂溶液制剂，含有奥沙利铂、有效稳定量的缓冲剂和可药用载体.

2. 权利要求 1 所述的制剂，其中可药用载体是水，缓冲剂是草酸或其碱金属盐.

3. 权利要求 2 所述的制剂，其中缓冲剂是草酸或草酸钠.

4. 权利要求 3 所述的制剂，其中缓冲剂是草酸.

5. 权利要求 1-4 中任一项所述的制剂，其中以摩尔浓度表示的缓冲剂的含量范围为

(a) 约 5×10^{-5} M~约 1×10^{-2} M,

(b) 约 5×10^{-5} M~约 5×10^{-3} M,

(c) 约 5×10^{-6} M~约 2×10^{-3} M,

(d) 约 1×10^{-4} M~约 2×10^{-3} M, 或

(e) 约 1×10^{-4} M~约 5×10^{-4} M.

6. 权利要求 5 所述的制剂，其中以摩尔浓度表示的缓冲剂的含量范围为约 1×10^{-4} M~约 5×10^{-4} M.

7. 权利要求 6 所述的制剂，其中以摩尔浓度表示的缓冲剂的量为约 2×10^{-4} M.

8. 权利要求 6 所述的制剂，其中以摩尔浓度表示的缓冲剂的量为约 4×10^{-4} M.

9. 权利要求 1-8 中任一项所述的制剂，其中奥沙利铂的量为约 1~约 7 mg/mL.

10. 权利要求 1-8 中任一项所述的制剂，其中奥沙利铂的量为约 1~约 5 mg/mL.

11. 权利要求 1-8 中任一项所述的制剂，其中奥沙利铂的量为约 2~约 5 mg/mL.

12. 权利要求 1-8 中任一项所述的制剂，其中奥沙利铂的量为 5 mg/mL.

13. 权利要求 4 所述的制剂，其中奥沙利铂的量为约 5 mg/mL，用摩尔浓度表示的缓冲剂的量为约 2×10^{-4} M.

14. 权利要求 4 所述的制剂，其中奥沙利铂的量为约 5 mg/mL，用摩尔浓度表示的缓冲剂的量为约 4×10^{-4} M.

15. 用于药物中的权利要求 1-14 任一项所述的制剂.

16. 奥沙利铂在制备用于治疗肿瘤的权利要求 1-14 任一项所述的制剂中的用途.

17. 奥沙利铂在制备用于治疗实体瘤的权利要求 1-14 任一项所述的制剂中的用途.

18. 治疗哺乳动物癌症的方法，其包括将有效量的权利要求 1-14 中任一项所述的制剂施用于所述哺乳动物.

19. 治疗哺乳动物实体瘤的方法，其包括将有效量的权利要求 1-14 中任一项所述的制剂施用于所述哺乳动物.

20. 稳定奥沙利铂溶液的方法，其包括向所述溶液中加入有效稳定量的缓冲剂.

21. 权利要求 20 所述的方法，其中所述溶液是含水溶液，缓冲剂是草酸或其碱金属盐.

22. 制备权利要求 1-14 中任一项所述制剂的方法，其包括将可药用载体、缓冲剂和奥沙利铂进行混合.

23. 制备权利要求 1-14 中任一项所述制剂的方法，其包括下列步骤:

(a) 混合可药用载体和缓冲剂;

(b) 将奥沙利铂溶解于所述混合物中;

(c) 将步骤(b)得到的混合物冷却至室温，并用可药用载体补足至终体积;

(d) 过滤步骤(c)得到的溶液; 以及

(e) 任选地将步骤(d)得到的产品灭菌.

24. 权利要求 23 所述的方法，其中该方法是在惰性气氛下进行的.

25. 权利要求 23 所述的方法，其中步骤(d)得到的产品通过加热灭菌.

26. 一种包装的药物产品，其在可密封容器中含有权利要求 1-14 中任一项所述的制剂.

27. 权利要求 26 所述包装的药物产品，其中容器是安瓿、小瓶、输液袋或注射器.

28. 权利要求 27 所述包装的药物产品，其中容器是带刻度的注

射器.

29. 权利要求 1-14 中任一项所述制剂的定量给药的方法，其包括将所述制剂由带刻度的注射器给药.

30. 基本上如前所描述的发明.

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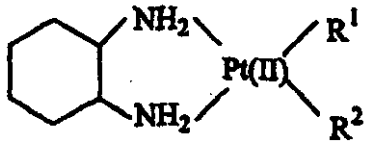
说　明　书

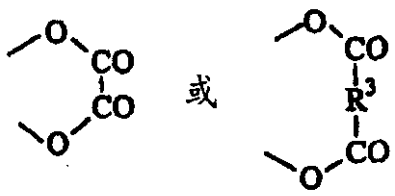
制剂

本发明涉及药学上稳定的奥沙利铂溶液制剂，应用该制剂治疗肿瘤的方法，制备该制剂的方法，以及稳定奥沙利铂溶液的方法。

Kidani 等，在 1979 年 10 月 2 日颁布的美国专利 4,169,846 中，公开了由下面通式代表的 1,2-二氨基环己烷的异构体（顺-、反-d 和反-l 异构体）的顺铂(II)配合物



其中，1,2-二氨基环己烷的立体异构体是顺-、反-d 或反-l；R^1 和 R^2 是卤素原子，或者 R^1 与 R^2 一起形成用下式所表示的基团：



其中 R^3 是>CH2 基团，>CHCH3 或>CHCH2CH3 的基团．实施例 4(i)具体公开了顺-草酸根合(反-l-1,2-二氨基环己烷)铂(II)．指出该化合物具有抗肿瘤活性．

Okamoto 等，在 1994 年 3 月 1 日颁布的美国专利 5,290,961 中，公开了制备包括顺-草酸根合(反-1-1,2-环己烷二胺)铂 (II)在内的各种铂化合物的方法．在 1994 年 9 月 28 日公开的 EP 617043 中也有相似的公开．

Tozawa 等，在 1994 年 3 月 29 日颁布的美国专利 5,298,624 中公开了使用手性高效液相色谱法光学拆分旋光活性铂化合物的方法．具体公开了顺-草酸根合(反-d 和反-l-1,2-环己烷二胺)铂(II)

的拆分. Nakanishi 等，在 1994 年 8 月 16 日颁布的美国专利 5,338,874 中，公开了光学纯的顺-草酸根合(反-1-1,2-环己烷二胺)铂(II)及其制备方法. 1993 年 10 月 27 日公开的 EP 567438 中也有类似的公开.

Okamoto 等，在 1995 年 5 月 30 日颁布的美国专利 5,420,319 中公开了具有高光学纯的顺-草酸根合(反-1-1,2-环己烷二胺)铂(II)及其制备方法. 1994 年 11 月 23 日公开的 EP 625523 中也有类似的公开.

Masao 等，在 1996 年 6 月 12 日公开的 EP 715854 中公开了顺-草酸根合(1R,2R-二氨基环己烷)铂(II)，缩写为（“1-OHP”），与一种或多种现有的制癌物质以及含有一种或多种相容试剂和 1-OHP 的制癌物质的配伍给药方法.

Kaplan 等，在 1995 年 2 月 12 日公开的加拿大专利申请 2,128,641 中公开了丙二酸根合铂(II)抗肿瘤剂如卡铂的含有稳定量的 1,1-环丁烷二羧酸或其盐和可药用载体的稳定溶液，所述溶液的 pH 值为约 4～约 8.

Ibrahim 等，在 1994 年 6 月 9 日公开的 WO94/12193 中公开了顺铂与奥沙利铂联合给药的组合物，所述组合物是冷冻干燥组合物，其含有重量比为约 2:1 ～ 1:2 的顺铂和奥沙利铂以及带有起稳定作用的中性物质的可药用的不含氯离子的酸性缓冲液.

Tsurutani 等，在 1992 年 5 月 27 日公开的 EP 486998 中公开了含有与去乙酰基甲壳质键合的含铂抗肿瘤剂的缓释组合物. 在 1993 年 4 月 20 日颁布的美国专利 5，204，107 中也可见到类似的公开.

Ibrahim 等，在 1996 年 3 月 7 日公开的澳大利亚专利申请 29896/95（同族专利为 WO96/04904，1996 年 2 月 22 日公开）中，公开了用于非肠道给药的药学稳定的奥沙利铂制剂，所述制剂由浓度范围为 1～5 mg/mL 的奥沙利铂水溶液组成，其 pH 为 4.5 ～ 6. 在 1998 年 2 月 10 日颁布的美国专利 5，716，988 中可以见到类似的公开.

Johnson，在 1997 年 5 月 27 日颁布的美国专利 5,633,016 中公开了含有喜树碱类似物和铂配位化合物以及可药用载体或稀释剂的药物组合物. 在 1993 年 5 月 27 日公开的 WO93/09782 中可以见到类似的公开.

Bach 等，在 1990 年 10 月 24 日公开的 EP 393575 中公开了治疗有效量的细胞保护性共聚物和一种或多种直接作用的抗肿瘤剂在治疗肿瘤性疾病中的联合疗法.

Nakanishi 等，在 1997 年 10 月 15 日公开的 EP 801070 中公开了制备包括顺-草酸根合(反-l-1,2-环己烷二胺)铂(II)在内的各种铂配合物的方法.

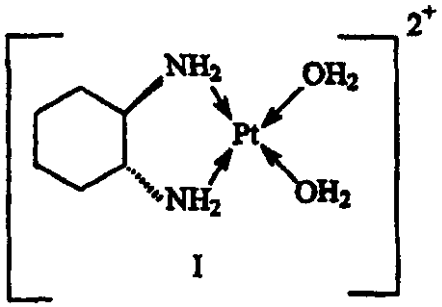
目前，奥沙利铂以冻干粉末形式用于临床前试验和临床试验，其只是在对给病人给药前才使用注射水或 5% 葡萄糖溶液来重新组配，然后用 5% 葡萄糖溶液进行稀释. 但是，这样的冻干产品具有一些缺点. 首先，冻干法过程相对复杂且操作昂贵. 此外，冻干产品的使用需要在使用时将产品重配，这为在选择合适的组配溶液时提供了发生差错的机会. 例如，如果在奥沙利铂冻干产品的重配时误用了 0.9% NaCl 溶液，后者是重配冻干产品或稀释液体制剂时极为常用的溶液，则将对活性成分有害，这在于将会发生快速反应，不仅造成奥沙利铂的损失，还会导致样品沉淀产生. 冻干产品的其它缺点有:

(a) 相对于不需要重配的无菌产品而言，冻干产品的重配增加了微生物污染的风险;

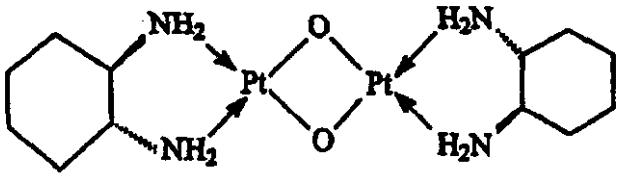
(b) 与经过滤灭菌或加热（最后的）灭菌的溶液产品比较，冻干产品具有更大的灭菌失败的风险; 以及

(c) 冻干产品在重配时具有不完全溶解的潜在性，导致不合乎注射产品需求的颗粒.

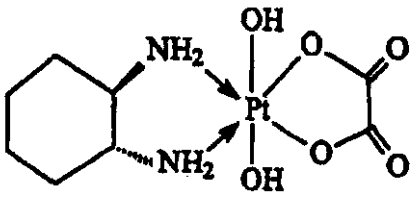
业已证实，奥沙利铂的含水溶液随着时间推移可以降解产生不同量的二水 DACH 铂(式 I)、二水 DACH 铂二聚物(式 II)和铂(IV)类(式 III)杂质.



I



II



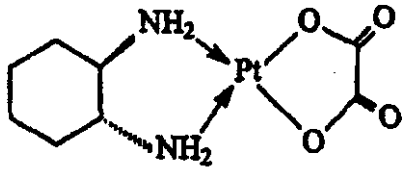
III

由于任何药物制剂中存在的杂质量可以，且在许多情况下，影响制剂的毒理学特性，所以，期望开发更为稳定的奥沙利铂溶液制剂，其或者一点也不会产生上述杂质，或者产生的杂质量明显低于前述已知的杂质量.

因此，存在对即用(RTU)形式的奥沙利铂溶液制剂的需要，所述溶液制剂克服上述缺点并且在长期贮存期间（即 2 年或更长时间）是药学上稳定的. 因此，本发明的一个目的就是通过提供药学上稳定的即用形式的奥沙利铂溶液制剂来克服这些缺点.

更具体而言，本发明涉及稳定的含有奥沙利铂、有效稳定量缓冲剂和可药用载体的奥沙利铂溶液制剂.

奥沙利铂，已知其化学名称为顺-草酸根合(反-1-1,2-环己烷二胺)铂(II)(也称作[SP-4-2]-(1R,2R)-(环己烷-1,2-二胺-k^2N,N')(草酸根合(2-)-k^2O^1,O^2]铂(II)，(1,2-环己烷二胺-N,N')[乙二酸根合(2-)-O,O']-[SP-4-2-(1R-反)]-铂，顺-[草酸根合(1R,2R-环己烷二胺)铂(II)]，[(1R,2R)-1,2-环己烷二胺-N,N'][草酸根合(2-)-O,O']铂，[SP-4-2-(1R-反)]-(1,2-环己烷-二胺-N,N')[乙二酸根合(2-)-O,O']铂，1-OHP，和顺-草酸根合(反-1-1,2-二氨基环己烷)铂(II))，并具有下面所示的化学结构，



它是细胞抑制性抗肿瘤剂，在治疗各种类型的易感癌和肿瘤如结肠癌、卵巢癌、表皮样癌、生发细胞（如，睾丸、纵隔、松果腺）癌、非-小细胞肺癌、非-何杰金氏淋巴瘤、乳腺癌、上呼吸道癌和消化道癌、恶性黑素瘤、肝癌、尿道癌、前列腺癌、小细胞肺癌、胰腺癌、胆囊癌、肛管癌、直肠癌、膀胱癌、小肠癌、胃癌、白血病和各种其它实体瘤中非常有用。

奥沙利铂的制备方法、物理特性和有益的药理特性在例如美国专利4,169,846、5,290,961、5,298,642、5,338,874、5,420,319和5,716,988，欧洲专利申请715854和澳大利亚专利申请29896/95中作了描述，其全文在此引作参考。

奥沙利铂适宜地以约1～约7 mg/mL的量存在于本发明的制剂中，优选的量为约1～约5 mg/mL，更优选约2～约5 mg/mL，特别为约5 mg/mL。

本文使用的术语缓冲剂是指能够稳定奥沙利铂溶液并由此防止或延缓不期望的杂质如二水DACH铂和二水DACH铂二聚物形成的任何酸性或碱性试剂。因此，该术语包括这样一些试剂如草酸或草酸的碱金属（如，锂、钠、钾等）盐等或其混合物。缓冲剂优选草酸或草酸钠，最优选草酸。

本发明制剂中的缓冲剂以有效稳定量存在．缓冲剂的适宜存在的摩尔浓度为约 5×10^{-5} M～约 1×10^{-2} M，优选约 5×10^{-5} M～约 5×10^{-3} M，更优选约 5×10^{-5} M～约 2×10^{-3} M，最优选约 1×10^{-4} M～约 2×10^{-3} M，尤其是约 1×10^{-4} M～约 5×10^{-4} M，特别是约 2×10^{-4} M～约 4×10^{-4} M.

本文使用的术语可药用载体是指可用于配制本发明奥沙利铂溶液制剂的各种溶剂．通常，载体是水、一种或多种其它适宜溶剂，或者水与一种或多种其它适宜溶剂的混合物．优选地，载体是水或者水与一种或多种适宜溶剂的混合物，更优选地，载体是水．所用的水优选是纯水，即无菌注射用水．可用于本发明的其它适宜载体（溶剂）的代表性实例包括聚亚烷基二醇，如聚乙二醇、聚丙二醇、聚丁二醇等及其混合物；乙醇，1-乙烯基-2-吡咯烷酮聚合物（聚乙烯吡咯酮）和可药用乳糖、右旋糖（葡萄糖）、蔗糖、甘露糖、甘露醇、环糊精等或其混合物的糖溶液．

本发明奥沙利铂溶液制剂的 pH 通常在约 2～约 6 的范围内，优选为约 2～约 5，更优选约 3～约 4.5.

特别令人感兴趣的奥沙利铂溶液制剂包括所附实施例中描述的那些制剂，因此，基本上在所附实施例中定义的制剂作为本发明的进一步特征而提供．

如上所述，奥沙利铂是细胞抑制性抗肿瘤剂，其适于治疗各种类型的易感癌症和肿瘤．因此，本发明也提供治疗哺乳动物癌或实体瘤的方法，该方法包括向所述哺乳动物施用有效量的本发明奥沙利铂溶液制剂．

本发明进一步涉及本发明奥沙利铂溶液制剂在制备治疗哺乳动物癌或实体瘤的药物中的用途．

本发明还涉及稳定奥沙利铂溶液的方法，该方法包括向所述溶液中加入有效稳定量的缓冲剂．在该方法一个优选方面中，溶液是含水（水）溶液，而缓冲剂是草酸或其碱金属盐．

本发明还涉及制备本发明奥沙利铂溶液制剂的方法，该方法包括将可药用载体、缓冲剂和奥沙利铂混合．

制备本发明奥沙利铂溶液制剂的一个优选的方法包括下列步骤：

(a) 混合可药用载体与缓冲剂，优选在约 40℃进行;

(b) 将奥沙利铂溶解在所述混合物中，优选在约 40℃进行;

(c) 冷却步骤(b)得到的混合物，优选冷却至约室温，且用可药用载体补足至终体积;

(d) 过滤步骤(c)得到的溶液；以及

(e) 任选地，灭菌处理步骤(d)得到的产品.

应当注意，尽管上述方法可以很方便地于存在或不存在惰性气氛的条件下进行，但是，优选在惰性气氛如氮气下进行.

在制备本发明奥沙利铂溶液制剂的一个特别优选的方法中，上面步骤(d)得到的产品经过过滤或者加热（终灭菌）进行灭菌，优选加热.

本发明进一步涉及包装的药物产品，其在一可密封容器中包含本发明奥沙利铂溶液制剂. 该密封容器优选是安瓿、小瓶、输液袋（小袋）或注射器. 如果可密封容器是注射器，那么该注射器优选是有刻度的注射器，使得能够测量（计量）本发明奥沙利铂溶液制剂的给药，特别是能够测量（计量）直接注入输液袋的该溶液制剂的给药.

还应当注意，正如下面将要更全面地阐述的那样，上述本发明奥沙利铂溶液制剂具有超出目前已知奥沙利铂制剂的一些优点.

与冻干粉末形式的奥沙利铂不同，本发明的即用制剂的制造成本低廉且生产过程简单.

此外，本发明制剂在给药前不需要额外的配制或处理，如重配. 因此，就没有机会发生如冻干产品重配时选择适宜溶剂时可能发生的差错.

也已发现，本发明制剂在制备过程中较以前已知的奥沙利铂含水制剂更为稳定，这意味着本发明制剂产生的杂质（如二水 DACH 铂和二水 DACH 铂二聚物）较以前已知的奥沙利铂含水制剂产生较少的杂质.

本发明制剂也可以通过过滤或加热（终灭菌）进行灭菌，而不会负面影响制剂的质量.

通过进一步考虑本发明说明书和权利要求书，本发明制剂的这些和其它优点将变得更为明显.

通常，本发明制剂通过本领域众所周知的常规给药途径施用于患

者，患者包括但不限于哺乳动物，如人．例如，制剂可以经非肠道途径（例如，静脉内、腹膜内等）施用于患者．优选将制剂以非肠道途径给药，特别优选静脉内给药．当静脉内输注时，该制剂一般经长达5天的期间给药，优选经长达24小时的期间给药，更优选经2～24小时期间给药．

对于本领域技术人员而言，显而易见本发明奥沙利铂溶液制剂可以与其它没有药物间配伍禁忌的治疗剂和/或预防剂和/或药物一起给药．

本发明制剂中活性化合物即奥沙利铂的百分比可以改变的，由此而获得适宜的剂量．对于特定患者的给药剂量根据临床医师的判断而变化，其采用下列判据：给药途径，治疗持续时间，患者的体型、年龄和生理状况，病情严重程度，活性化合物的效力以及患者对活性化合物的反应．因此，活性化合物的有效剂量可由临床医师在考虑所有判据并采用医师为病人作出的最佳判断之后来决定．通常，本发明制剂的活性化合物施用于患者的剂量范围为约10 mg/m^2 ～约250 mg/m^2，更优选20 mg/m^2 ～约200 mg/m^2，最优选约30 mg/m^2 ～约180 mg/m^2．奥沙利铂优选的剂量方案包括以1～5周间隔以1～5天的周期重复给药．

下面的实施例进一步阐明本发明，但是不限制本发明．所有温度用摄氏度（℃）表示．

列于表1A和1B中的实施例1-14的制剂按照下述一般步骤制备：

分散热（40℃）的注射水（W.F.I.），并通入过滤的氮气鼓泡约30分钟．

在保持氮气的条件下，将所需适宜量的W.F.I.转移至适宜混合容器中．将剩余的W.F.I.放置一边用于补足终体积．

在适宜容器中称量适宜缓冲剂（固体形式或优选为适宜体积摩尔浓度的含水缓冲液形式），并转移至混合容器（用部分剩余W.F.I.清洗容器）．在保持溶液温度为40℃的同时，混合（例如，磁力搅拌器/电炉）约10分钟，或者，如果需要，直至所有固体溶解．

称量奥沙利铂至适宜容器中，并转移至混合容器中（用部分剩余热(40℃)W.F.I. 清洗容器）．在保持溶液温度为40℃的同时，混合（例如，磁力搅拌器/电炉）直至所有固体溶解．

冷却溶液至室温，然后用剩余 W.F.I.补足至终体积.

在真空下用 0.22 μm 滤片过滤溶液（例如，millipore GV 型，直径 47 mm 的滤片）.

在氮气下使用充填器，如无菌 0.2 μm 可自由使用的亲水充填器（Minisart-NML, Sartorius）将溶液装入适宜的无菌和可密封的容器中（例如，小瓶或安瓿），可密封容器在盛装前以氮气吹扫，并在密封前用氮气吹扫顶部空间.

使用例如 SAL (PD270)高压灭菌器，于 121℃将溶液高压灭菌 15 分钟，即终灭菌.

应当注意，当上述方法优选在惰性气氛如氮气下进行时，本发明制剂也可以在没有这样一种惰性气氛时方便地完成.

表 1A

组分	实施例 1 0.00001 M 草酸钠	实施例 2 0.00005 M 草酸钠	实施例 3 0.0001M 草酸钠	实施例4 0.0003M 草酸钠	实施例 5 0.0005M 草酸钠	实施例 6 0.001 M 草酸钠	实施例7 0.002 M 草酸钠
奥沙利铂	5.000 g	5.000 g	5.000 g	5.000 g	5.000 g	5.000 g	5.000 g
注射水	1000 mL	1000 mL	1000 mL	1000 mL	1000 mL	1000 mL	1000 mL
草酸钠的量	1.340 mg	6.700 mg	13.40 mg	40.20 mg	67.00 mg	134.00 mg	268.00 mg

注意：实施例 1-7 的制剂所用的可密封容器是 20 mL 洁净玻璃安瓿.

表 1B

组分	实施例8 0.00001 M 草酸	实施例9 0.00005 M 草酸	实施例 10 0.0001 M 草酸	实施例11 0.0003 M 草酸	实施例12 0.0005 M 草酸	实施例 13 0.001 M 草酸	实施例 14 0.002 M 草酸
奥沙利铂	5.000 g	5.000 g	5.000 g	5.000 g	5.000 g	5.000 g	5.000 g
注射水	1000 mL	1000 mL	1000 mL	1000 mL	1000 mL	1000 mL	1000 mL
草酸的量	1.260 mg	6.300 mg	12.60 mg	37.80 mg	63.00 mg	126.10 mg	252.10 mg

注意：实施例 8-14 的制剂所用的可密封容器是 20 mL 洁净玻璃安瓿.

*草酸以二水合物形式加入；表中所示的重量是所加草酸二水合物的重量。

表 1C 中列出的实施例 15 和 16 的制剂是按照与上述制备实施例 1-14 的制剂相似的方式制备的。

表 1C

组分	实施例 15 0.0002 M 草酸	实施例 16 0.0004 M 草酸
奥沙利铂	7.500 g	7.500 g
注射水	1500 mL	1500 mL
草酸的量	37.82 mg	75.64 mg

注意：实施例 15-16 制剂所用的可密封容器是 20 mL 洁净玻璃安瓿。

*草酸以二水合物形式加入；表中所示的重量是所加草酸二水合物的重量。

表 1D 中列出的实施例 17 的制剂是按照与上述制备实施例 1-14 的制剂相似的方式制备的，除了：(a) 溶液在不存在氮气（即，氧气存在下）的条件下盛入可密封的容器中；(b)可密封容器在盛装溶液前不以氮气吹扫；(c) 在密封容器前，顶部空间不以氮气吹扫；以及(d)可密封容器是小瓶而不是安瓿。

表 1D

组分	实施例 17 0.0002 M 草酸
奥沙利铂	10.000 g
注射水	2000 mL
草酸的量	50.43 mg

注意：1000 mL 实施例 17 的溶液制剂充入 5 mL 洁净玻璃小瓶中（每个小瓶 4 mL 溶液），用 West Flurotec 塞子密封[此后称为实施例 17(a)]，剩余的 1000mL 实施例 17 溶液制剂充入 5 mL 洁净玻璃小瓶中(每个小瓶装 4 mL)并用 Helvoet Omniflex 塞子密封[此后称为实施例 17(b)]。

*草酸以二水合物形式加入；表中所示的重量是所加草酸二水合物的重量.

配制 0.0005 M 草酸钠缓冲液

分散超过 2000 mL 的注射水（W.F.I.），将过滤氮气通入水中鼓泡约 30 分钟.

在 N_2 下，将 1800 mL W.F.I. 转移至 2000 mL Schott 瓶中并保存. 用剩余的(200 mL)W.F.I. 补足至终体积.

称量草酸钠(134.00 mg)至称量瓶中，并转移至 Schott 瓶中（用约 50 mL 的 W.F.I. 清洗）.

在磁力搅拌器/电炉上搅拌混合物直至所有固体溶解.

将溶液转移至 2000 mL 容量瓶中，用 W.F.I. 补足至 2000 mL，然后在加塞之前用氮气吹扫顶部空间.

表 1A、1B、1C 和 1D 所列的各种其它草酸钠和草酸缓冲液按照类似于上述制备 0.0005 M 草酸钠缓冲液的方法进行制备.

实施例 18

为了比较，含水奥沙利铂制剂，如 1996 年 3 月 7 日公开的澳大利亚专利申请 29896/95 中所公开的，如下制备:

分解多于 1000 mL 的注射水（W.F.I.），将过滤氮气通入溶液鼓泡约 30 分钟. 在磁力搅拌器/电炉上搅拌并加热 W.F.I 至 40℃.

在保持 N_2 下，将 800 mL W.F.I. 转移至 1000 mL Schott 瓶中. 用剩余的(200 mL)W.F.I. 补足至终体积.

称量奥沙利铂(5.000 g)至玻璃烧杯(25 mL)中，并转移至 Schott 瓶，用约 50 mL 的热 W.F.I. 清洗烧杯.

保持温度为 40℃，在磁力搅拌器/电炉上搅拌混合物直至所有固体溶解.

溶液冷却至室温，然后转移至 1000 mL 容量瓶中，并用冷(约 20℃) W.F.I. 补足 1000 mL.

使用真空管使溶液通过 Millipore GV 型直径 47 mm 的滤片过滤至 1000 mL 容量瓶中.

然后，使用无菌的 1.2 μm 可随意使用的亲水滤片(Minisart-NML, Sartorius）将溶液盛入洗净并灭菌的 20 mL 玻璃安瓿中. 安瓿在盛装溶液前用氮气吹扫，且顶部空间在密封前用氮气吹扫.

23 个安瓿不进行高压灭菌[此后称为实施例 18(a)]，即它们不进行终灭菌，剩余 27 个安瓿[此后称为实施例 18(b)]使用 SAL (PD 270) 高压灭菌器在 121℃下高压灭菌 15 分钟.

稳定性研究

在下述稳定性研究中，下述色谱分析方法用于评价各种奥沙利铂溶液制剂的稳定性.

用高效液相色谱(HPLC)测定铂(IV)类、未具体指明的杂质和奥沙利铂的百分含量，HPLC 使用 Hypersil™ C18 柱，流动相含有稀释的正磷酸和乙腈. 在此条件下，铂(IV)类和奥沙利铂的保留时间分别为约 4.6 和 8.3 分钟.

用 HPLC 测定二水 DACH 铂和二水 DACH 铂二聚物以及表 4-8 中未具体指明的杂质的百分含量，HPLC 使用 Hypersil™ BDS C18 柱，流动相含有磷酸缓冲液和乙腈. 在此条件下，二水 DACH 铂和二水 DACH 铂二聚物的保留时间分别为约 4.3 和 6.4 分钟，而奥沙利铂以溶剂前沿洗脱.

各种含水缓冲液中的奥沙利铂

0.0005 M 草酸钠缓冲液(0.0670 mg/mL 草酸钠)中的 2 mg/mL 奥沙利铂溶液用类似于上述实施例 1-14 的制备方法进行配制，分析该溶液以及在常用含水缓冲液中的各种其它奥沙利铂溶液(2 mg/mL) 的稳定性. 将每种溶液于 40℃存放(stressed)约 1 个月后得到的结果列于表 2.

表 2

缓冲液	最初分析 (理论值的%)	40℃下放置~1月后进行的分析 (理论值的%)
0.0005M 草酸钠	102.1	98.8
0.1M 柠檬酸盐，pH 3	100.4	63.6
0.1M 柠檬酸盐，pH 5	95.8	24.7
0.1M 醋酸盐，pH 5	100.3	76.5
0.1M tris, pH 7	80.1	1.0
0.1M tris, pH 9	22.1	0.0
0.1M 甘氨酸，pH3	96.8	0.1
0.1M 甘氨酸，pH 9	49.7	0.0
0.1M 磷酸盐，pH 7	98.4	19.0

这些结果证明，当溶液被存放时，奥沙利铂在各种常用的含水缓冲液如柠檬酸盐、醋酸盐、tris、甘氨酸和磷酸盐缓冲液中不稳定.

但是发现，当使用缓冲剂如草酸或其碱金属盐如草酸钠时，可以得到稳定的奥沙利铂水溶液。

草酸缓冲液中的高压灭菌的奥沙利铂溶液

按照类似于上述实施例 1-14 的制备方法配制在 0.01 M 草酸钠缓冲液（1.340 mg/mL 草酸钠）中的 2 mg/mL 奥沙利铂溶液，溶液 pH 约为 4. 该溶液在 0、1、2 和 3 高压灭菌循环（每一循环在 121℃下持续 15 分钟）后的稳定性结果总结于表 3.

表 3

高压灭菌循环编号	分析 (mg/mL)	二水 DACH 铂 (% w/w)	二水 DACH 铂二聚物 (% w/w)	铂(IV) 类 (% w/w)	总杂质 (% w/w)
0	2.03	ND <0.01	ND <0.01	0.02	0.02
1 (15 分 /121℃)	1.96	ND <0.01	ND <0.01	0.06	0.05
2 (30 分 /121℃)	2.01	ND <0.01	ND <0.01	0.09	0.10
3 (45 分 /121℃)	1.97	ND <0.01	ND <0.01	0.12	0.15

ND = 未检测到

用类似于上述实施例 1-16 中的制备方法，在有氧和无氧条件下配制奥沙利铂在 0.0002M 草酸缓冲液中的 5mg/ml 溶液和奥沙利铂在 0.0004 M 草酸缓冲液中的 5 mg/mL 溶液. 这些溶液在 0、1、2 和 3 高压灭菌循环（每一循环于 121℃持续 15 分钟）之后以及在 121℃下 3 个 15 分钟高压灭菌循环和 121℃下持续 75 分钟的第 4 高压灭菌循环（总共 120 分钟）之后的稳定性结果总结于表 3A.

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表 3A

5 mg/mL 奥沙利铂在：	于121℃的时间 (min)	二水DACH铂 (% w/w)	二水DACH的二聚物 (% w/w)	Pt(IV)类 (% w/w)	未具体指明的杂质总量 (% w/w)	色谱分析杂质总量 (% w/w)
0.0002M 草酸，在 N_2 下操作	0	0.10	ND <0.01	ND <0.003	ND < 0.03	0.10
	15 (1循环)	0.13	ND <0.01	ND <0.003	T < 0.03	0.13
	30 (2 循环)	0.10	ND <0.01	T < 0.01	T < 0.03	0.10
	45 (3 循环)	0.10	ND <0.01	T <0.01	T < 0.03	0.10
	120 (4 循环)	0.09	ND <0.01	T <0.01	T < 0.03	0.09
0.0002M 草酸，在 O_2 下操作	0	0.14	ND <0.01	0.02	T <0.05	0.16
	15 (1循环)	0.13	ND <0.01	0.01	T <0.05	0.14
	30 (2 循环)	0.11	ND <0.01	T <0.01	T <0.05	0.14
	45 (3 循环)	0.12	ND <0.01	T <0.01	T <0.05	0.15
	120 (4 循环)	0.12	ND <0.01	T <0.01	T <0.05	0.16
0.0004M 草酸，在 N_2 下操作	0	0.14	ND <0.01	T <0.01	T <0.05	0.14
	15 (1循环)	0.14	ND <0.01	T <0.01	T <0.05	0.14
	30 (2 循环)	0.12	ND <0.01	T <0.01	T <0.05	0.12
	45 (3 循环)	0.11	ND <0.01	T <0.01	T <0.05	0.11
	120 (4 循环)	0.12	ND <0.01	T <0.01	T <0.05	0.12
0.0004M 草酸，在 O_2 下操作	0	0.13	ND <0.01	0.02	ND <0.05	0.15
	15 (1 循环)	0.13	ND <0.01	0.01	T <0.05	0.14
	30 (2 循环)	0.13	ND <0.01	0.01	T <0.05	0.14
	45 (3 循环)	0.11	ND <0.01	0.01	T <0.05	0.12
	120 (4 循环)	0.11	ND <0.01	T <0.01	T <0.05	0.11

ND = 未检测

T = 痕量

上述结果证明本发明奥沙利铂溶液制剂可在对制剂质量无负面影响时终灭菌.

实施例 1-17 制剂的稳定性研究

实施例 1-14 的奥沙利铂溶液制剂于 40℃下贮存达 6 个月，其稳定性研究结果总结于表 4 和 5 中.

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表 4

实施例编号	草酸钠摩尔浓度	于40℃的时间	测得的pH	二水DACH铂 (%w/w)	二水DACH铂二聚物 (%w/w)	未具体说明的杂质 (%w/w)
1	0.00001	最初	5.26	0.20	0.15	0.03
	0.00001	1月	5.25	0.21	0.15	0.13
2	0.00005	最初	5.75	0.18	0.12	0.04
	0.00005	1月	5.32	0.16	0.11	0.12
3	0.0001	最初	5.64	0.14	0.11	0.05
	0.0001	1月	5.33	0.14	0.08	0.11
4	0.0003	最初	5.77	0.09	0.07	0.06
	0.0003	1月	5.74	0.10	0.07	0.10
5	0.0005	最初	5.71	0.06	0.06	0.06
	0.0005	1月	5.68	0.08	0.05	0.08
6	0.001	最初	5.48	0.04	0.04	0.06
	0.001	1月	5.85	0.05	0.03	0.07
7	0.002	最初	5.90	0.06	0.03	0.06
	0.002	1月	6.02	0.03	痕量 <0.03	0.05

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表 5

实施例编号	草酸钠摩尔浓度	于40℃的时间	测得的 pH	二水DACH铂 (% w/w)	二水DACH铂二聚物 (% w/w)	未具体说明的杂质 (% w/w)
8	0.00001	最初	5.92	0.22	0.17	0
	0.00001	1 月	5.23	0.27	0.19	0.04
9	0.00005	最初	4.40	0.15	0.05	0
	0.00005	1 月	4.71	0.16	0.03	0.02
10	0.0001	最初	3.70	0.13	痕量 <0.03	0
	0.0001	1 月	4.10	0.12	ND <0.01	0.02
	0.0001	3 月	3.94	0.13	ND <0.01	痕量 <0.03
	0.0001	6 月	4.17	0.13	ND <0.01	痕量 <0.03
11	0.0003	最初	3.47	0.13	ND <0.01	0
	0.0003	1 月	3.52	0.11	ND <0.01	0.01

表 5(续)

实施例编号	草酸钠摩尔浓度	于40℃的时间	测得的 pH	二水DACH铂 (% w/w)	二水DACH铂二聚物 (% w/w)	未具体说明的杂质 (% w/w)
	0.0003	3 月	3.56	0.12	ND <0.01	痕量 <0.03
	0.0003	6 月	3.48	0.10	ND <0.01	痕量 <0.03
12	0.0005	最初	3.28	0.13	ND <0.01	0
	0.0005	1 月	3.35	0.10	ND <0.01	0.01
	0.0005	3 月	3.30	0.13	ND <0.01	痕量 <0.03
	0.0005	6 月	3.34	0.11	ND <0.01	痕量 <0.03
13	0.001	最初	3.05	0.13	ND <0.01	0
	0.001	1 月	3.02	0.11	ND <0.01	0.01
14	0.002	最初	2.85	0.14	ND <0.01	0
	0.002	1 月	2.70	0.13	ND <0.01	0.01

ND = 未检测到

实施例15和16的奥沙利铂溶液制剂，于25℃/60%相对湿度(RH)和40℃/75%相对湿度(RH)贮存达9个月，其稳定性研究结果总结于表6.

表6

实施例编号	草酸摩尔浓度	时间	测得的pH	二水DACH铂 (%w/w)	二水DACH铂二聚物 (%w/w)	铂（IV）类 (%w/w)	色谱分析杂质总量 (%w/w)
15	0.0002	最初	3.83	0.10	ND <0.01	ND <0.003	0.10
	0.0002	1月 (25°C/60%RH)	3.75	0.12	ND <0.01	痕量 <0.01	0.12
	0.0002	1月 (40°C/75%RH)	3.78	0.13	ND <0.01	痕量 <0.01	0.13
	0.0002	3月 (25°C/60%RH)	4.13	0.10	ND <0.01	痕量 <0.01	0.10
	0.0002	3月 (40°C/75%RH)	4.16	0.12	ND <0.01	痕量 <0.01	0.12
	0.0002	6月 (25°C/60%RH)	3.45	0.12	ND <0.01	痕量 <0.01	0.12
	0.0002	6月 (40°C/75%RH)	3.52	0.11	ND <0.01	痕量 <0.01	0.11

表6(续)

实施例编号	草酸钠摩尔浓度	时间	测得的pH	二水DACH铂 (%w/w)	二水DACH铂二聚物 (%w/w)	铂（IV）类 (%w/w)	色谱分析杂质总量 (%w/w)
	0.0002	9月 (25°C/60%RH)	3.62	0.14	ND <0.01	痕量 <0.01	0.14
	0.0002	9月 (40°C/75%RH)	3.64	0.11	ND <0.01	痕量 <0.01	0.11
16	0.0004	最初	3.45	0.10	ND <0.01	痕量 <0.01	0.10
	0.0004	1月 (25°C/60%RH)	3.40	0.13	ND <0.01	痕量 <0.01	0.13
	0.0004	1月 (40°C/75%RH)	3.44	0.12	ND <0.01	痕量 <0.01	0.12
	0.0004	3月 (25°C/60%RH)	3.59	0.11	ND <0.01	痕量 <0.01	0.11
	0.0004	3月 (40°C/75%RH)	3.71	0.12	ND <0.01	痕量 <0.01	0.12
	0.0004	6月 (25°C/60%RH)	3.24	0.11	ND <0.01	痕量 <0.01	0.11
	0.0004	6月 (40°C/75%RH)	3.26	0.11	ND <0.01	痕量 <0.01	0.11
	0.0004	9月 (25°C/60%RH)	3.26	0.12	ND <0.01	痕量 <0.01	0.12
	0.0004	9月 (40°C/75%RH)	3.31	0.12	ND <0.01	痕量 <0.01	0.12

ND = 未检测到

实施例 17(a)和 17(b)的奥沙利铂溶液制剂，于 25℃/60％相对湿度(RH)和 40℃/75％相对湿度(RH)贮存达 1 个月，其稳定性研究结果总结于表 7.

表 7

实施例编号	草酸摩尔浓度	时间	测得的 pH	二水DACH铂 (%w/w)	二水DACH铂二聚物 (%w/w)	铂（IV）类 (%w/w)	未具体说明的杂质 (%w/w)
17(a)	0.0002	最初	3.81	0.13	ND <0.01	0.02	痕量 <0.05
	0.0002	1 月 (25°C/60%RH)	3.82	0.12	ND <0.01	0.03	痕量 <0.05
	0.0002	1 月 (40°C/75%RH)	3.79	0.13	ND <0.01	0.05	0.13
17(b)	0.0002	最初	3.53	0.14	ND <0.01	0.03	0.05
	0.0002	1 月 (25°C/60%RH)	3.72	0.12	ND <0.01	0.07	0.16
	0.0002	1 月 (40°C/75%RH)	3.73	0.12	ND <0.01	0.09	0.07

ND = 未检测到

这些稳定性研究结果证明，本发明溶液制剂中的缓冲剂如草酸钠和草酸对于控制杂质如二水 DACH 铂和二水 DACH 铂二聚物的量是极为有效的.

对比实施例 18 的稳定性

实施例 18(b)未缓冲的奥沙利铂溶液制剂于 40℃贮存 1 个月，其稳定性研究结果总结于表 8.

表 8

在40℃的时间	测得的pH	二水DACH铂 (%w/w)	二水DACH铂二聚物 (%w/w)	未具体说明的杂质 (%w/w)
最初	5.47	0.27	0.16	0.04
1 月	5.27	0.23	0.16	0.14

另外，按照类似于实施例 18(a)中描述的方法制备三批分离的无菌制备的(即，在无菌条件下制备，而不是高压灭菌)溶液产品(2 mg/mL 奥沙利铂纯水溶液)，这几批产品于室温贮存约 15 个月. 稳定性研

究结果总结于表 9.

表 9

批号	温度	二水DACH铂 (%w/w)	二水DACH铂 二聚物 (%w/w)
A	室温	0.34	0.29
B	室温	0.36	0.28
C	室温	0.38	0.29

FORMULATIONS

The invention relates to pharmaceutically stable oxaliplatin solution formulations, to the method of use thereof in the treatment of cancer tumors, to processes for the preparation of such formulations, and to a method for stabilizing solutions of oxaliplatin.