CONVENTION

AUSTRALIA

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APPLICATION FOR A STANDARD PATENT 612916

Bristol-Myers Squibb Company
345 Park Avenue, New York, New York, 10154, UNITED STATES OF AMERICA

hereby applies for the grant of a standard patent for an invention entitled:

DOXORUBICIN AQUEOUS SOLUTIONS

which is described in the accompanying complete specification.

Details of basic application(s):-
279,627 UNITED STATES OF AMERICA 5 December 1988

Address for Service:

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DATED this FIFTH day of DECEMBER 1989

PHILLIPS ORMONDE & FITZPATRICK
Attorneys for:
Bristol-Myers Squibb Company

By: David P Fitzpatrick

Our Ref : 151772
POF Code: 1490/1490

6010

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DECLARATION FOR A PATENT APPLICATION

▼ INSTRUCTIONS
(a) Insert "Convention" if applicable
(b) Insert FULL name(s) of applicant(s)

In support of the (a) convention application made by
(b) BRISTOL-MYERS SQUIBB COMPANY

(c) Insert "of addition" if applicable
(d) Insert TITLE of invention

(hereinafter called "applicant(s)" for a patent (c) for an invention entitled (d)

DOXORUBICIN AQUEOUS SOLUTIONS

(e) Insert FULL name(s) AND address(es) of declarant(s) (See headnote*)

I/We (e) Isaac Jarkovsky, Vice President and Assistant General Counsel-Patents of Bristol-Myers Squibb Company: 345 Park Avenue, New York, New York 10154, United States of America

do solemnly and sincerely declare as follows:

1. I am/We are the applicant(s).
(or, in the case of an application by a body corporate)
1. I am/We are authorized to make this declaration on behalf of the applicant(s).
2. I am/We are the actual inventor(s) of the invention.
(or, where the applicant(s) is/are not the actual inventor(s))
2. (f) Murray Kaplan: 1026 Glen Cove Road, Syracuse, New York 13206, United States of America; Robert Perrone: 7353 Tomwood Drive, Liverpool, New York 13090, United States of America; Joseph Bogardus: 8239 Penstock Way, Manlius, New York 13104, United States of America

(f) Insert FULL name(s) AND address(es) of actual inventor(s)

is/~~are~~ the actual inventor(s) of the invention and the facts upon which the applicant(s) is/~~are~~ entitled to make the application are as follows:

(g) Recite how applicant(s) derive(s) title from actual inventor(s) (See headnote**)

(g) The applicant is the assignee of the invention from the said actual inventors.

(Note: Paragraphs 3 and 4 apply only to Convention applications)

(h) Insert country, filing date, and basic applicant(s) for the/or EACH basic application

3. The basic application(s) for patent or similar protection on which the application is based is/~~are~~ identified by **country, filing date, and basic applicant(s)** as follows:

(h) United States of America
5 December, 1988
Murray Kaplan; Robert Perrone; Joseph Bogardus

4. The basic application(s) referred to in paragraph 3 hereof was/~~were~~ the first application(s) made in a Convention country in respect of the invention the subject of the application.

(k) Insert PLACE of signing
(l) Insert DATE of signing
(m) Signature(s) of declarant(s)

Declared at (k) New York, N.Y. U.S.A.
Dated (l) December 22, 1989
(m) _____
Isaac Jarkovsky, Vice President
and Assistant General Counsel-Patents

Note: No legalization or other witness required

To: The Commissioner of Patents

P18/7/78

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(12) PATENT ABRIDGMENT (11) Document No. AU-B-45915/89
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DOXORUBICIN AQUEOUS SOLUTIONS

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(57) Claim

1. A pharmaceutical formulation of a stable, sterile, ready-to-use aqueous solution in a sealed container suitable for parenteral administration containing about 0.1 to 20 mg/ml of a physiologically acceptable salt of doxorubicin, a stabilizing amount of sodium acetone bisulfite of about 0.1 to 10 mg/ml, water, and, if required, an amount of a physiologically acceptable acid or base necessary to adjust the solution pH to within the range of about 2.5 to 6.0.

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COMPLETE SPECIFICATION
(ORIGINAL)

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Complete Specification Lodged:
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Related Art:

Applicant(s):

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Complete Specification for the invention entitled:

DOXORUBICIN AQUEOUS SOLUTIONS

Our Ref : 151772
POF Code: 1490/1490

The following statement is a full description of this invention, including the best method of performing it known to applicant(s):

6006

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to stable, ready-to-use aqueous solutions of doxorubicin suitable for parenteral administration.

2. Description of the Prior Art

Doxorubicin is an antineoplastic antibiotic which is isolated from the fermentation of Streptomyces peucetius var. caesius. It can also be synthesized chemically from daunorubicin.

The commercial lyophilized dosage form of doxorubicin (marketed by Adria Laboratories as Adriamycin® is supplied as the hydrochloride salt in 10, 20 and 50 mg vials in combination with lactose at 50, 100 and 250 mg, respectively. Vials are reconstituted with Sodium Chloride Injection, USP (0.9%) or Sterile Water for Injection, USP, to give a final concentration of 2 mg/ml of doxorubicin HCl and a pH range of about 4-6. The reconstituted lyophilized solution is reported by the manufacturer to be stable (≤ 10% potency loss) for only 24 hours at room temperature and 48 hours under refrigeration.

It would be desirable to have a solution dosage form of doxorubicin which would not require reconstitution prior to use. Improper reconstitution of a lyophilized product sometimes results in the formation of air-borne droplets

("blow-back") which, in the case of a potent antitumor agent such as doxorubicin, may be a health hazard to the personnel making up the solution for injection. Also, production of the present lyophilized doxorubicin HCl dosage form is quite costly, and a solution dosage form would be expected to have a lower cost of goods.

Doxorubicin HCl has recently been made commercially available as a preservative-free aqueous solution. Despite the convenience of a ready-to-use solution, the present aqueous solution is still not as stable as one would desire. The manufacturer indicates that the ready-to-use solution is stable for 18 months at 4°C. At the end of this time period, the solution may contain up to 10% of undesirable and potentially toxic degradation products.

A study carried out by Hoffman, et al. and reported in Am. J. Hosp. Pharm. 36: 1536-1538, 1979 indicates that reconstituted solutions of doxorubicin HCl are stable (≤ 10% potency loss for up to six months when refrigerated at 4°C. Ketcyhum, et al. in Am. J. Intrav. Ther. Clin. Nutri. 8: 15-18, 1981, state that a reconstituted solution of doxorubicin HCl in 0.9% NaCl solution remains stable at room temperature or 5°C for seven days. Despite such indications that reconstituted doxorubicin HCl may be sufficiently stable for up to six months at 4°C, this is still insufficient for a commercial solution dosage form.

Janssen, et al. in Int. J. Pharmaceutics 23: 1-11, 1985, report that doxorubicin HCl appears to have its maximum stability at pH 4 (Tris or phosphate buffers using

HCl to adjust pH). Poochikian, et al. in Am. J. Hosp. Pharm. 38: 483-486, 1981, note that the stability of doxorubicin HCl is pH dependent and that the optimum stability is achieved when the reconstitution solvent is 5% Dextrose Injection, USP, having a pH of approximately 4.5.

U.K. Patent Application 2,178,311 A discloses solutions of doxorubicin HCl in aqueous and non-aqueous solvent systems. There is no disclosure, however, of the use of the antioxidant, sodium acetone bisulfite, to stabilize such solutions.

European Published Application 273,60_ A2 discloses solutions of doxorubicin HCl in aqueous and non-aqueous solvent systems and appears to be substantially equivalent to U.K. 2,178,311 A, except for limiting the pH range to 2.5 to 4.0 instead of the broader pH range of 2.5 to 6.5 disclosed in UK 2,178,311.

U.S. Patent 4,675,311 discloses aqueous solutions of doxorubicin HCl containing a co-solubilizing agent selected from the group comprising a hydroxy-, mercapto-, or amino-substituted benzoic acid, an alkali metal salt thereof, a C_1-C_4 alkyl ester thereof, a ring-halogenated methyl-substituted phenol, an amino acid, and mixtures thereof.

Applicants have previously filed co-pending U.S. application serial Number 074,190 on July 16, 1987 which discloses and claims stable, ready-to-use aqueous solutions of doxorubicin HCl containing an antioxidant selected from

α-tocopherol, sodium formaldehyde bisulfite and tert-butyl hydroquinone.

The antioxidant, sodium acetone bisulfite, used in the present invention has been previously utilized as a stabilizing agent for other pharmaceutical products. For example, Canadian Patent 981,182 discloses use of sodium acetone bisulfite in combination with thioglycerol and ascorbic acid to stabilize ℓ-epinephrine aqueous solutions. Sodium acetone bisulfite is also used as a preservative in other pharmaceutical solutions, e.g. pentazocine lactate and procaine hydrochloride.

It is an object of the present invention to provide a ready-to-use aqueous solution of a physiologically acceptable salt of doxorubicin which is stable (≤ 10% potency loss) for more than three years at 4°C.

SUMMARY OF THE INVENTION

The present invention provides a stable, sterile, ready-to-use solution in a sealed container suitable for parenteral administration containing water, a physiologically acceptable salt of doxorubicin, a stabilizing amount of sodium acetone bisulfite of about 0.1 to 10 mg/ml, and, optionally, an amount of a physiologically acceptable acid or base necessary to adjust the solution pH to within the range of about 2.5 to 6.0.

DETAILED DESCRIPTION

This invention relates to stable, aqueous, ready-to-use solutions of a physiologically acceptable salt of

doxorubicin suitable for parenteral administration. Although concentrations of from about 0.1 to 20 mg/ml of the doxorubicin salt may be employed in the solutions, it is preferred to use from about 0.2 to 20 mg/ml, more preferably about 2 to 5 mg/ml and, most preferably, about 2 mg/ml.

Although the present invention is generally described below in terms of doxorubicin hydrochloride, any physiologically acceptable salt of doxorubicin may be used for preparing the aqueous solutions. Examples of suitable salts include, for example, the salts with mineral inorganic acids such as hydrochloric, hydrobromic, sulfuric, phosphoric, nitric, and the like, and the salts with organic acids such as acetic, succinic, tartaric, ascorbic, citric, glutamic, benzoic, methanesulfonic, 2-hydroxyethanesulfonic, and the like. The preferred physiologically acceptable salt is doxorubicin hydrochloride.

The pH of the solutions should be in the range of about 2.5 to 6.0. If pH adjustment is necessary to achieve this range, common physiologically acceptable acids and bases can be added. For example, the solution pH can be lowered by addition of suitable organic or inorganic acids such as hydrochloric, hydrobromic, sulfuric, phosphoric, nitric, acetic, succinic, tartaric, ascorbic, citric, glutamic, benzoic, methanesulfonic, 2-hydroxyethanesulfonic, and the like. Solution pH may be raised by addition of physiologically acceptable bases such as sodium carbonate, sodium bicarbonate, sodium hydroxide, etc. A particularly preferred acid is citric acid since this reagent acts as a

chelation agent as well as providing pH control. Without pH adjustment the solutions will generally be in the pH range of about 4.5 to 6.0. One preferred embodiment comprises solutions having a pH of from about 3.0 to 3.5. Another preferred embodiment comprises solutions having a pH in the range of about 4.5 to 6.0. This latter pH provides a solution which may have less irritation potential than the more acidic ready-to-use aqueous doxorubicin HCl solution commercially available.

It is also necessary for optimum stability of doxorubicin aqueous solutions, especially in the pH range of about 4 to 6 and at elevated temperatures which may be encountered at some time during the life of the product, e.g. during shipping, to utilize an antioxidant. We have tested a number of antioxidants including α-tocopherol, tert-butylhydroquinone (TBHQ), sodium formaldehyde bisulfite, butylated hydroxy anisole (BHA), butylated hydroxy toluene (BHT), sodium bisulfite and propyl gallate. Of the antioxidants tested, only α-tocopherol, tert-butylhydroquinone and sodium formaldehyde bisulfite resulted in the desired stability at elevated temperatures as well as at 4 °C. This finding was disclosed and claimed in our co-pending applications Serial No. 074,190 filed July 16, 1987, and incorporated by reference herein in its entirety. Later work unexpectedly found that another antioxidant, sodium acetone bisulfite, gave even superior stabilizing properties to doxorubicin solutions, especially at pH 4.5 to 6.0 at which the other antioxidants are not effective, and it is this discovery which is the subject of the present invention. Generally, an amount of sodium

acetone bisulfite is employed in the range of about 0.1 to 10 mg/ml. The preferred concentration of antioxidant is about 0.1 to 2 mg/ml with about 1 mg/ml being most preferred for solutions containing 2 mg/ml doxorubicin salt.

As noted above sodium acetone bisulfite is unique among the antioxidants in that it stabilizes doxorubicin solutions over a wide pH range, i.e. about 2.5 to 6.0, whereas the antioxidants disclosed and claimed in our co-pending application work only in the pH range of about 3 to 4. Elevated temperature data indicates that at 40°C essentially no potency loss is seen after four weeks with pH 5.1 solutions of the present invention, the approximate pH of the commercial doxorubicin HCl reconstituted lyophile.

In our studies the use of buffers at pH 4.0 such as acetate and citrate buffers had a deleterious effect on stability of the solutions and the presence of surfactants such as Tween-80 did not improve stability.

European Patent Application 273,603 A2 discloses the use of sugars and sugar alcohols as tonicity adjustment agents. While such agents have not been found to increase the stability of doxorubicin solutions, they may be used, if desired, in the solutions of the present invention. Suitable tonicity adjustment agents may be, for example, physiologically acceptable inorganic chlorides, e.g. sodium chloride (preferably 0.9% by weight sodium chloride),

dextrose, lactose, mannitol, sorbitol, and the like. When a sugar or sugar alcohol such as dextrose, lactose, mannitol or sorbitol is used as a tonicity adjustment agent, preferably from 2.5 to 7.5% by weight is used, more preferably from 4 to 6% by weight and most preferably about 5% by weight. The tonicity adjustment agent is preferably employed in an amount which will provide a solution with osmolarity of about 200 to 400 mOsm/liter of solution.

Despite reports of potency losses of doxorubicin HCl solutions via photolytic degradation and absorption to container walls, we have not noted any significant loss of potency due to container absorption or sensitivity to normal room light with our solutions. Glass vials may be used as the container or, alternatively, the solution may be filled into hypodermic syringes of pre-determined volume to provide a ready-to-use solution which is also ready to inject or mix with intravenous fluids.

We have also found that deaeration of the solvent water and inert gas purging, for example with nitrogen, argon or helium, of the filled vials before they are sealed contributes to optimum stability and is most preferred. In contrast to the antioxidants previously tested, however, including α-tocopherol, tert-butylhydroquinone and sodium formaldehyde bisulfite, inert gas purging was found to be less critical when sodium acetone bisulfite is employed. This is another indication of the unusual effectiveness of this particular antioxidant for stabilization of doxorubicin solutions. Because of this property, manufacturing control will be simplified since air need not be totally eliminated.

As an example of a stable, ready-to-use aqueous solution of doxorubicin HCl, 2.0 mg/ml doxorubicin HCl, 0.2 mg/ml citric acid (anhydrous), 1.0 mg/ml of sodium acetone bisulfite and sterile water are added to a Type I flint vial, the vial is purged with nitrogen and then sealed with a suitable Teflon coated stopper. Vials containing larger concentrations of doxorubicin HCl are prepared in a similar manner.

Elevated temperature studies using high performance liquid chromatographic (HPLC) assay indicate that our ready-to-use aqueous solutions have a shelf-life (≤ 10% potency loss) of greater than three years at 4 °C. Based on our elevated temperature studies, the commercially available preservative-free doxorubicin HCl aqueous solution would have a maximum shelf-life of about 1.5 to 2.5 years at 4°C. Thus, the solutions provided by the present invention have a greater shelf-life than the heretofore available ready-to-use doxorubicin solutions. They also show far less doxorubicin degradation products (glycone and aglycone) than prior art products when aged over a wide temperature range.

The ready-to-use solutions of the present invention are employed for the treatment of cancer in the same manner as the commercially available doxorubicin HCl aqueous solution or reconstituted lyophilized products.

The following example illustrates but does not limit in any way the present invention.

Example 1

Formula

Ingredient	mg/ml
Doxorubicin HCl	2.0
Anhydrous citric acid	0.2
Acetone sodium bisulfite	1.0
Deaerated water for injection, U.S.P. (or equivalent)	q.s. to 1 ml

Nitrogen (aqueous and headspace saturated with nitrogen)

Procedure:

1. Using a suitable glass container, deaerate U.S.P. Water for Injection, or its equivalent, by boiling or sonication under vacuum.

2. Saturate the cooled water (20°-25°C) and container head-space with nitrogen. Store protected from air.

3. Place approximately 70-80% of the required volume of the nitrogen-saturated water in a suitable volume-tared glass container. For this and the following, maintain a heavy nitrogen purge, deep within the liquid and with slow vortex-free stirring.

4. Slowly add and dissolve the required amount of acetone sodium bisulfite.

5. Cautiously and slowly add and dissolve the required amount of the doxorubicin HCl.

6. Prepare a 10 mg/ml solution of anhydrous citric acid in deaerated, nitrogen-saturated water.

Slowly add the citric acid solution until a pH of 3-3.5 is obtained. Note the amount of solution used. Assure that the pH is stabilized at 3-3.5.

7. Stop and remove the stirrer. Stop the nitrogen flow.

8. Add deaerated, nitrogen-saturated water, q.s. to the final required volume.

9. Restart nitrogen addition with slow vortex-free stirring. Stir for 20 minutes. Assure that the pH is 3-3.5.

10. Stop and remove the stirrer. Stop the nitrogen flow. Store the solution in the dark, under a nitrogen head protected from air.

11. Using aseptic and lint-free conditions for all the following and under a push of nitrogen, pass the solution through a 0.2 micron HT-Tuffryn polysulfone membrane filter (Gelman Sciences). Collect the filtrate in a suitable glass container and store in the dark under a nitrogen head.

12. Under nitrogen purge add the required amount of solution into suitable glass vials. Stopper the vials with teflon-coated stoppers and seal with aluminum seals.

Solutions prepared as above maintained full potency with virtually no increase in doxorubicinone degradation product (aglycone) when stored at 40°C for at least 1 month. This translates into a predicted shelf-life of >3 years at 4°C.

In a similar manner solutions having 0.5 mg/ml and 2 mg/ml sodium acetone bisulfite were prepared. These solutions also had a predicted shelf-life of >3 years at 4°C.

The claims defining the invention are as follows:

1. A pharmaceutical formulation of a stable, sterile, ready-to-use aqueous solution in a sealed container suitable for parenteral administration containing about 0.1 to 20 mg/ml of a physiologically acceptable salt of doxorubicin, a stabilizing amount of sodium acetone bisulfite of about 0.1 to 10 mg/ml, water, and, if required, an amount of a physiologically acceptable acid or base necessary to adjust the solution pH to within the range of about 2.5 to 6.0.

2. A formulation according to Claim 1 wherein the solution pH is in the range of about 3.0 to 3.5.

3. A formulation according to Claim 1 wherein the solution pH is in the range of about 4.5 to 6.0.

4. A formulation according to Claim 1 wherein there is also present a tonicity adjustment agent.

5. A formulation according to Claim 1 containing per ml of solution, 2 mg doxorubicin hydrochloride, 1 mg sodium acetone bisulfite, and water q.s.

6. A formulation according to Claim 1 containing per ml of solution, 2 mg doxorubicin hydrochloride, 1 mg sodium acetone bisulfite, about 0.2 mg of citric acid resulting in a pH of between about 3.0 and 3.5, and water q.s.

7. A formulation according to Claim 1 containing per ml of solution, 2 mg doxorubicin hydrochloride, 1 mg sodium acetone bisulfite, an amount of hydrochloric acid sufficient to adjust the pH to between about 3.0 and 3.5, and water q.s.

8. A formulation according to any of Claims 1, 2, 3, 4, 5, 6 or 7 wherein the air in the headspace of the container has been substantially replaced with an inert gas.

9. A formulation substantially as hereinbefore described with reference to the example.

DATED: 30 November 1989
PHILLIPS ORMONDE & FITZPATRICK
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BRISTOL-MYERS SQUIBB COMPANY