P/00/001 28/5/91
Section 29

AUSTRALIA
Patents Act 1990

632036

PATENT REQUEST : STANDARD PATENT

We, FARMITALIA CARLO ERBA S.r.l. (A.R.B.N. 005 501 155) being the persons identified below as the Applicant, request the grant of a patent to the person identified below as the Nominated Person, for an invention described in the accompanying standard complete specification.

Full application details follow:

Applicant and Nominated Person:	FARMITALIA CARLO ERBA S.r.l.
Address:	VIA CARLO IMBONATI 24 20159 MILAN ITALY
Invention Title:	INJECTABLE READY-TO-USE SOLUTIONS CONTAINING AN ANTITUMOR ANTHRACYCLINE GLYCOSIDE
Names of actual inventors:	GAETANO GATTI; DIEGO OLDANI; GIUSEPPE BOTTONI; CARLO CONFALONIERI; LUCIANO GAMBINI AND ROBERTO DE PONTI
Address for service in Australia:	GRIFFITH HACK & CO 601 St. Kilda Road Melbourne, Vic 3004
Attorney Code:	HA

BASIC CONVENTION APPLICATION DETAILS

Application Number	Country	Country Code	Date of Application
8629193	U.K.	UK	5 December 1986
07/064653	U.S.A.	US	22 June 1987

PARENT INVENTION DETAILS (Patent of Addition requests only)

Application number: 58858/86 Patent Number: 598197

We request that the term of the patent of addition be the same as that for the main invention or so much of the term of the main invention.

GRIFFITH HACK & CO.

M 040110 091092

Patent Attorneys for and on behalf of the applicants

- 9 OCT 1992
Date

AUSTRALIA PATENT OFFICE

P/00/008 28/5/91
Section 29(1)
Regulation 3.1 (2)

AUSTRALIA

Patents Act 1990

NOTICE OF ENTITLEMENT

(To be filed before acceptance)

We, FARMITALIA CARLO ERBA S.r.l. (A.R.B.N. 005 501 155) of Via Carlo Imbonati 24, 20159 Milan, ITALY, being the applicant in respect of Application No. 82059/87, state the following:-

Part 1 - *Must be completed for all applications*

The person nominated for the grant of the patent has entitlement from the actual inventors by virtue of an assignment.

Part 2 - *not applicable*

Part 3 - *Must be completed for all convention applications*

The person nominated for the grant of the patent is the applicant of the first basic application listed on the patent request form.

The person nominated for the grant of the patent has entitlement from the applicants of the second basic application listed on the patent request form by virtue of an assignment.

The basic applications listed on the request form are the first applications made in a Convention country in respect of the invention.

Part 4 - *not applicable*

Part 5 - *not applicable*

Part 6 - *not applicable*

Part 7 - *not applicable*

GRIFFITH HACK & CO.

Patent Attorneys for and
on behalf of the applicants

29 OCT 1992

Date

(12) PATENT ABRIDGMENT (11) Document No. AU-B-82059/87
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 632036

(54) Title
INJECTABLE READY-TO-USE SOLUTIONS CONTAINING AN ANTITUMOR ANTHRACYCLINE GLYCOSIDE

(51)[4] International Patent Classification(s)
A61K 031/71

(21) Application No. : **82059/87** (22) Application Date : **03.12.87**

(30) Priority Data

(31) Number	(32) Date	(33) Country
8629153	05.12.86	GB UNITED KINGDOM
064653	22.06.87	US UNITED STATES OF AMERICA

(43) Publication Date : **09.06.88**

(44) Publication Date of Accepted Application : **17.12.92**

(61) Related to Addition(s) : **58858/86**

(71) Applicant(s)
FARMITALIA CARLO ERBA S.R.L.

(72) Inventor(s)
GAETANO GATTI; DIEGO OLDANI; GUISEPPE BOTTONI; CARLO CONFALONIERI; LUCIANO GAMBINI; ROBERTO DE PONTI

(74) Attorney or Agent
GRIFFITH HACK & CO , GPO Box 1285K, MELBOURNE VIC 3001

(56) Prior Art Documents
AU 58858/86 A61K

(57) Claim

1. A sterile, pyrogen-free anthracycline glycoside solution which comprises a physiologically acceptable salt of an anthracycline glycoside dissolved in a physiologically acceptable aqueous solvent therefor at an anthracycline glycoside concentration of from 0.1 to 50 mg/ml, which has not been reconstituted from a lyophilizate and the pH of which has been adjusted to from 2.5 to 3.5 by means of a glycine buffer.

AUSTRALIA

PATENTS ACT 1952

Form 10

COMPLETE SPECIFICATION

(ORIGINAL)

FOR OFFICE USE

Short Title:

Int. Cl:

632036

Application Number:
Lodged:

Complete Specification-Lodged:
Accepted:
Lapsed:
Published:

Priority:

Related Art:

TO BE COMPLETED BY APPLICANT

Name of Applicant: Farmitalia Carlo Erba S.R.L.
~~FARMITALIA CARLO ERBA S.P.A.~~

Address of Applicant: VIA CARLO IMBONATI 24
20159 MILAN
ITALY

Actual Inventor:

Address for Service: CLEMENT HACK & CO.,
601 St. Kilda Road,
Melbourne, Victoria 3004,
Australia.

Complete Specification for the invention entitled:
INJECTABLE READY-TO-USE SOLUTIONS CONTAINING AN ANTITUMOR ANTHRACYCLINE GLYCOSIDE

The following statement is a full description of this invention including the best method of performing it known to me:-

INJECTABLE READY-TO-USE SOLUTIONS CONTAINING AN ANTITUMOR ANTHRACYCLINE GLYCOSIDE

The present invention relates to a storage stable, injectable ready-to-use solution of an antitumor anthracycline glycoside, e.g. doxorubicin, and to a process for preparing such a solution.

The anthracycline glycoside compounds are a well known class of compounds in the antineoplastic group of agents, of which doxorubicin is a typical, and the most widely used, representative: Doxorubicin. Anticancer Antibiotics, Federico Arcamone, 1981, Publ: Academic Press, New York, N.Y.; Adriamycin Review, EROTC International Symposium, Brussels, May, 1974, edited by M. Staquet, Publ. Eur. Press Medikon, Ghent, Belg.; and Results of Adriamycin Therapy, Adriamycin Symposium at Frankfurt/Main 1974 edited by M.Ghione, J.Fetzer and H.Maier, publ.: Springer, New York, N.Y.

At present, anthracycline glycoside antitumor drugs, in particular, e.g. doxorubicin, are solely available in the form of lyophilized preparations, which need to be reconstituted before administration. Both the manufacture and the reconstitution of such preparations expose the involved personnel (workers, pharmacists, medical personnel, nurses) to risks of contamination which are particularly serious due to the toxicity of the antitumor substances.

The Martindale Extra Pharmacopoeia 28th edition, page 175 left column, reports on adverse effects of antineoplastic drugs and recommends that "They must be handled with great care and contact with skin and eyes avoided; they should not be inhaled. Care must be taken to avoid extravasation since pain and tissue damage may ensue.". Similarly, Scand. J. Work Environ Health vol.10 (2), pages 71-74 (1984), as well as articles in Chemistry Industry, Issue July 4, 1983, page 488, and Drug-Topics-Medical-Economics-Co, Issue February 7, 1983, page 99

report about severe adverse effects observed in medical personnel exposed to use of cytostatic agents, including doxorubicin.

To administer a lyophilized preparation, double handling of the drug is required. The lyophilized cake first has to be reconstituted and then administered. Moreover, in some cases, the complete dissolution of the powder may require prolonged shaking because of solubilization problems. Reconstitution of a lyophilized cake or powder can result in formation of aerosol droplets which can be inhaled or can come into contact with skin or mucous membranes of those handling the solution.

As the risks connected with the manufacture and the reconstitution of a lyophilized preparate would be highly reduced if a ready-to-use solution of the drug were available, we have developed a stable, therapeutically acceptable intravenously injectable solution of an anthracycline glycoside drug, e.g. doxorubicin, whose preparation and administration does not require either lyophilization or reconstitution.

Patent No. 598197 describes and claims a sterile, pyrogen-free, anthracycline glycoside solution which comprises a physiologically acceptable salt of an anthracycline glycoside such as doxorubicin dissolved in a physiologically acceptable aqueous solvent therefor at an anthracycline glycoside concentration of from 0.1 to 50 mg/ml, which has not been reconstituted from a lyophilizate and the pH of which has been adjusted to from 2.5 to 5.0 solely with a physiologically acceptable acid. An especially preferred pH is about 3. The Examples illustrate solutions with pH's ranging from 2.62 to 3.14.

According to the present invention, there is provided a sterile, pyrogen-free, anthracycline glycoside solution which comprises a physiologically acceptable salt of an anthracycline glycoside dissolved in a physiologically acceptable aqueous solvent therefor at an anthracycline glycoside concentration of from 0.1 to 50 mg/ml, which has not been reconstituted from a lyophilizate and the pH of which has been adjusted to from 2.5 to 3.5 by means of a glycine buffer.

It is thus possible to provide solutions which are

storage stable and have a commercially meaningful shelf-life.

Preferably the solution of the invention is provided in a sealed container, especially one made of glass. The solution can be provided in this way either in a unit dosage form or in a multiple dosage form.

Preferably the anthracycline glycoside is chosen from doxorubicin, 4'-epi-doxorubicin (i.e. epirubicin), 4'-desoxy-4'-iodo-doxorubicin, daunorubicin and 4-demethoxy-daunorubicin (i.e. idarubicin). Particularly preferred anthracycline glycosides are doxorubicin and 4'-epi-doxorubicin, especially doxorubicin.

Any physiologically acceptable salt of the anthracycline glycoside may be used for preparing the solution of the invention. Examples of suitable salts may be, for instance, the salts with mineral inorganic acids such as hydrochloric, hydrobromic, sulfuric or phosphoric acid and the salts with certain acids such as succinic, tartaric, ascorbic, citric, methanesulfonic or ethanesulfonic acid. The salt with hydrochloric acid is a particularly preferred salt, especially when the anthracycline glycoside is doxorubicin.

Any aqueous solvent which is physiologically acceptable and which is able to dissolve the anthracycline glycoside salt may be used. The solution of the invention may also contain one or more formulation adjuvants such as a co-solubilizing agent (which may be the same as a solvent),

a tonicity adjustment agent, a preservative and a pharmaceutically acceptable chelating agent.

Suitable solvents and co-solubilizing agents may be, for instance, water e.g. Water for Injections; a 0.9% sodium chloride solution, i.e. physiological saline; and aqueous 5% dextrose solution; and mixtures of water and one or more of:

- an aliphatic amide, e.g. N,N-dimethylacetamide or N-hydroxy-2-ethyl-lactamide;
- an alcohol, e.g. ethanol or benzyl alcohol;
- a glycol or polyalcohol, e.g. propyleneglycol or glycerin;
- an ester of a polyalcohol, e.g. diacetine or triacetine;
- a polyglycol or polyether, e.g. polyethyleneglycol 400 or a propyleneglycol methylether;
- a dioxolane, e.g. isopropylidenglycerin;
- dimethylisosorbide; and
- a pyrrolidone derivative, e.g. 2-pyrrolidone, N-methyl-2-pyrrolidone or polyvinylpyrrolidone.

Examples of preferred solvents are water, physiological saline, an aqueous 5% dextrose solution, and mixtures of water and one or more of ethanol, polyethyleneglycol and dimethylacetamide. Water, physiological saline and a 5% dextrose solution are particularly preferred.

Suitable tonicity adjustment agents may be, for instance, physiologically acceptable inorganic chlorides, e.g. sodium chloride; dextrose, lactose, mannitol, sorbitol

and the like.

Preservatives suitable for physiological administration may be, for instance, esters of para-hydroxybenzoic acid (e.g., methyl, ethyl, propyl and butyl esters, or mixtures of them), chlorocresol and the like.

A suitable pharmaceutically acceptable chelating agent may be ethylenediaminotetraacetic acid (EDTA). The chelating agent is included in a minor amount, typically from 0.001 to 0.05% by weight.

The above mentioned solvents, tonicity adjustment agents, preservatives and chelating agents can be used alone or as a mixture of two or more of them.

To adjust the pH within the range of from 2.5 to 3.5 a glycine buffer is added as desired. The range of pH for the ready-to-use solutions of the invention is from 2.5, e.g. from about 2.6, to about about 3.5. A more preferred pH range is from 3 to 3.5. A pH of about 3 is particularly preferred, especially where the solution of the invention contains sorbitol, dextrose, lactose or mannitol. Other preferred pH ranges are from greater than 3.14, e.g. from about 3.2, to 3.5. A useful solution with a pH of from 2.62 to 3.14 further comprises a pharmaceutically acceptable chelating agent.

In the solutions of the invention the concentration of the anthracycline glycoside may vary within broad ranges, preferably from 1 mg/ml to 20 mg/ml. The preferred ranges

of concentration may be slightly different for different anthracycline glycosides. Thus, for example, preferred concentrations for doxorubicin are from about 2 mg/ml to about 50 mg/ml, preferably from 2 mg/ml to 20 mg/ml, particularly appropriate values being 2 mg/ml and 5 mg/ml. Similar concentrations are preferred also for 4'-epi-doxorubicin and 4'-desoxy-4'-iodo-doxorubicin. Preferred ranges of concentration for daunorubicin and 4-demethoxy-daunorubicin are from 1 mg/ml to 20 mg/ml, concentrations of 1 mg/ml and 5 mg/ml being particularly appropriate.

Suitable packaging for the anthracycline glycoside solutions may be all approved containers intended for parenteral use, such as plastic and glass containers, ready-to-use syringes and the like. Preferably the container is a sealed glass container, e.g. a vial or an ampoule. A hermetically sealed glass vial is particularly preferred.

The invention also provides a process for producing a sterile, pyrogen-free anthracycline glycoside solution which process comprises dissolving a physiologically acceptable salt of an anthracycline glycoside, which salt is not in the form of a lyophilizate, in a physiologically acceptable aqueous solvent therefor at an anthracycline glycoside concentration of from 0.1 to 50 mg/ml and adding a glycine buffer to adjust the pH of the solution to from 2.5 to 3.5 as desired, the process being effected in such a manner that the resultant solution is sterile and pyrogen-free.

A suitable process comprises

(i) dissolving the physiologically acceptable salt in the physiologically acceptable solvent;

(ii) adding the one or more formulation adjuvants selected from co-solubilizing agents, tonicity adjustment agents, preservatives and pharmaceutically acceptable chelating agents; and

(iii) adding the glycine buffer.

Any suitable procedure may be adopted to ensure that the resultant solution is sterile and pyrogen-free. Preferably, the solution is passed through a sterilising filter after addition of the buffer although of course one or more of the materials used may be sterile and pyrogen-free anyway. Where all materials employed are sterile and pyrogen-free, there may then be no need for passing the resultant solution through a sterilising filter.

With the solutions of the invention it is possible to obtain compositions having a very high concentration of the anthracycline glycoside active substance even at 50 mg/ml. This constitutes a great advantage over the presently available lyophilized preparates wherein high concentrations of anthracycline

glycoside can only be obtained with difficulty because of solubilization problems encountered in reconstitution, mainly with saline. The presence of the excipient, e.g. lactose, in the lyophilized cake, and its generally high proportion in respect of the active substance, even up to 5 parts of excipient per part of active substance, has a negative effect on solubilization so that difficulties may arise in obtaining dissolution of the lyophilized cake, especially for concentrations of anthracycline glycoside higher than 2 mg/ml.

The solutions of the invention are characterized by a good stability. Solutions in various solvents and with different pH's and concentrations have been found to be stable for long periods at temperatures accepted for the storage of pharmaceutical preparations. This is illustrated in the Examples which follow.

Owing to the well known anti-tumor activity of the anthracycline glycoside active drug substance, the pharmaceutical compositions of the invention are useful for treating tumors in both human and animal hosts. Examples of tumors that can be treated are, for instance, sarcomas, including osteogenic and soft tissue sarcomas, carcinomas, e.g., breast-, lung-, bladder-, thyroid-, prostate- and ovarian carcinoma, lymphomas, including Hodgkin and non-Hodgkin lymphomas, neuroblastoma, melanoma, myeloma, Wilms tumor, and leukemias, including acute lymphoblastic leukemia and acute myeloblastic leukemia.

Examples of specific tumours that can be treated are Moloney Sarcoma Virus, Sarcoma 180 Ascites, solid Sarcoma 180, gross transplantable leukemia, L 1210 leukemia and lymphocytic P 388 leukemia.

Inhibition of the growth of a tumour, in particular one of those indicated above, can be achieved by administering to a host suffering from a said tumour an injectable solution according to the invention containing the active drug substance in an amount sufficient to inhibit the growth of said tumour.

The injectable solutions of the invention are administered by rapid e.g. intravenous injection or infusion according to a variety of possible dose schedules.

A Suitable dose schedule for doxorubicin may be, for example, of 60 to 75 mg of active drug substance per m^2 of body surface given as a single rapid infusion and repeated at 21 days. An alternative schedule may be of 30 mg/m^2 day be intravenous route for 3 days, every 28 days. Suitable dosages for 4'-epi-doxorubicin may be, for instance, of 75 to 90 mg/m^2 given in a single infusion to be repeated at 21 days, and similar dosages may be useful also for 4'-desoxy-4'-iodo-doxorubicin.

Idarubicin, i.e. 4-demethoxy-daunorubicin, may be, e.g. administered intravenously at a single dose of 13-15 mg/m^2 every 21 days in the treatment of solid tumours, while in the treatment of leukemias a preferred

dose schedule is, e.g., of 10-12 mg/m^2 day by intravenous route for 3 days, to be repeated every 15-21 days. Similar dosages may be, e.g., followed for daunorubicin.

The following Examples illustrate the invention.

Example 1: Doxorubicin.HCl solutions in sterile water, 5% dextrose or 0.9% saline

Doxorubicin.HCl was dissolved at a concentration of 2 mg/ml in I=0.05, pH 2.5 and 3.0 glycine buffers.

Each solution was filtered through a 0.22 μm microporous membrane under nitrogen pressure. 5.0 ml of each solution were stored at 55°C in glass vials of glass type I, 8ml top capacity vial, Teflon (Trade Mark)-faced chlorobutyl rubber bung, aluminium seal. Each solution was analysed at predetermined times (up to 120 hours) for doxorubicin.HCl assay and pH. The results are shown in Tables 1, 2 and 3 which give the doxorubicin.HCl residual concentration and percent stability at 55°C, at different pHs and times of storage for sterile water, 5% dextrose and 0.9% saline solutions, respectively.

The doxorubicin.HCl assays are the mean of three independent determinations performed in accordance with the US Pharmacopoeia (USP high performance liquid chromatography (HPLC) method (USP XXI)). At each pH value, the pseudo-first order rate constants (K_{obs}) for the degradation were calculated by linear regression analysis of the natural logarithm of the residual concentration of doxorubicin.HCl ($[Dx]_t$) versus time as depicted by the following equation:

$$\ln [Dx]_t = \ln [Dx]_o - K_{obs} \cdot t$$

Tables 4, 5 and 6 give the observed rate constants (K_{obs}) for the degradation kinetics of doxorubicin.HCl at 55°C and at different pHs for sterile water, 5% dextrose and 0.9% saline solutions, respectively.

Table 1 - Accelerated (55°C) stability data of 2 mg/ml doxorubicin.HCl solutions in sterile water at various pHs

Buffers	Tests	Time (hours) 0	8	16	24	48	72	120
	Doxorubicin.HCl assay							
pH 2.5	. mg/ml	1.992	1.926	1.835	1.718	1.557	1.00	
glycine.HCl	. % stability	100.0	96.7	92.1	86.2	78.2	50.2	
	pH	2.51	2.50	2.50	2.52	2.51	2.52	
	Doxorubicin.HCl assay							
pH 3.0	. mg/ml	2.003	1.958	1.881	1.831	1.696	1.525	1.258
glycine.HCl	. % stability	100.0	97.8	93.9	91.4	84.7	76.1	62.8
	pH	3.00	3.03	3.02	3.02	3.01	3.02	3.00

Table 2 - Accelerated (55°C) stability data of 2 mg/ml doxorubicin.HCl solutions in 5% dextrose at various pHs.

Buffers	Tests	Time (hours) 0	8	16	24	34	48	72	96	120
	Doxorubicin.HCl assay									
pH 2.5	. mg/ml	1.967	1.897	1.822	1.760	1.682	1.499	1.305		
glycine.HCl	. % stability	100.0	96.4	92.6	89.5	85.5	76.2	66.3		
	pH	2.56	2.56	2.56	2.58	2.60	2.56	2.61		
	Doxorubicin.HCl assay									
pH 3.0	. mg/ml	1.975		1.908	1.832		1.645	1.508	1.344	1.206
glycine.HCl	. % stability	100.0		96.6	92.7		83.3	76.4	68.0	61.1
	pH	3.04		3.05	3.05		3.06	3.00	3.13	3.10

Table 3 - Accelerated (55°C) stability data of 2 mg/ml doxorubicin.HCl solutions in 0.9% saline at various pHs.

Buffers	Tests	Time (hours) 0	4	8	16	24	34	48	72	96	120
	Doxorubicin.HCl assay										
pH 2.5	. mg/ml	1.946		1.875	1.670	1.602	1.368	1.132			
glycine.HCl	. % stability	100.0		96.3	85.5	82.3	70.3	58.1			
	pH	2.59		2.59	2.59	2.58	2.62	2.62			
	Doxorubicin.HCl assay										
pH 3.0	. mg/ml	1.994			1.818	1.771		1.571	1.375	1.205	1.003
glycine.HCl	. % stability	100.0			91.2	88.8		78.8	69.0	60.4	50.3
	pH	3.06			3.07	3.07		3.08	3.13	3.14	3.12

Table 4 - K_{obs} values (1/days) for the degradation of doxorubicin.HCl 2 mg/ml solutions in sterile water at various pHs at 55°C

Buffer	pH	$K_{obs} \times 10^3$	95% confidence limits
. Glycine-HCl (I = 0.05)	2.5	138.3	± 0.6
. Glycine-HCl (I = 0.05)	3.0	93.1	± 4.6

Table 5 - K_{obs} values (1/days) for the degradation of doxorubicin.HCl 2 mg/ml solutions in 5% dextrose at various pHs at 55°C

Buffer	pH	$K_{obs} \times 10^3$	95% confidence limits
. Glycine-HCl (I = 0.05)	2.5	138.7	± 9.9
. Glycine-HCl (I = 0.05)	3.0	100.5	± 5.9

Table 6 - K_{obs} values (1/days) for the degradation of doxorubicin.HCl 2 mg/ml solutions in 0.9% saline at various pHs at 55°C

Buffer	pH	$K_{obs} \times 10^3$	95% confidence limis
. Glycine-HCl (I = 0.05)	2.5	276.5	± 30.2
. Glycine-HCl (I = 0.05)	3.0	133.2	± 8.0

Example 2: 4'-epi-doxorubicin (i.e. epirubicin) solutions

Solutions of epirubicin were prepared in the same fashion as the corresponding doxorubicin solutions of Example 1. They were then tested for stability in the same way. The results are presented in Tables 7 to 12.

Table 7 - Accelerated (55°C) stability data of 2 mg/ml epirubicin.HCl solutions in sterile water at various pHs.

Buffers	Tests	Time (hours) 0	16	24	48	72	96	120
	Epirubicin.HCl assay							
pH 2.5	. mg/ml	2.023	1.972	1.923	1.823	1.777	1.622	1.572
glycine.HCl	. % initial	100.0	99.9	94.6	89.7	87.4	79.8	77.3
	pH	2.5	2.4	2.5	2.5	2.4	2.4	2.4
	Epirubicin.HCl assay							
pH 3.0	. mg/ml	2.055	2.008	1.917	1.764	1.709	1.571	1.494
glycine.HCl	. % initial	100.0	97.7	93.3	85.8	83.2	76.4	72.7
	pH	2.9	2.9	2.9	2.8	2.9	2.9	2.9

Table 8 - Accelerated (55°C) stability data of 2 mg/ml epirubicin.HCl solutions in 0.9% Sodium Chloride Injection at various pHs.

Buffers	Tests	Time (hours) 0	4	8	16	24	34	48	72	96	120	144
	Epirubicin.HCl assay											
pH 2.5	. mg/ml	2.077		2.066	1.987			1.781	1.665	1.449	1.285	1.175
glycine.HCl	. % initial	100.0	n.d.	99.5	95.7	n.d.	n.d.	85.7	80.2	69.8	61.9	56.6
	pH	2.4		2.4	2.4			2.4	2.4	2.4	2.4	2.4
	Epirubicin.HCl assay											
pH 3.0	. mg/ml	2.058			1.951	1.934	1.869	1.784	1.668	1.483	1.349	1.253
glycine.HCl	. % initial	100.0	n.d.	n.d.	94.8	94.0	90.8	86.7	81.0	72.1	65.5	60.9
	pH	3.0			2.9	2.9	2.9	2.9	2.9	2.9	2.9	2.9

n.d. = not determined

Table 9 - Accelerated (55°C) stability data of 2 mg/ml epirubicin.HCl solutions in 5% Dextrose at various pHs.

Buffers	Tests	Time (hours) 0	4	8	16	24	34	48	72	96	120	144
	Epirubicin.HCl assay											
pH 2.5	. mg/ml	2.105			1.921	1.909	1.815	1.819	1.624	1.521		1.264
glycine.HCl	. % initial	100.0	n.d.	n.d.	91.3	90.7	86.2	86.4	77.1	72.3	n.d.	60.0
	pH	2.4			2.3	2.3	2.3	2.3	2.3	2.3		2.3
	Epirubicin.HCl assay											
pH 3.0	. mg/ml	2.029		1.990	1.914	1.949	1.866	1.743		1.562	1.442	1.318
glycine.HCl	. % initial	100.0	n.d.	98.1	94.3	96.1	92.0	85.9	n.d.	77.0	71.1	65.0
	pH	2.9		2.8	2.9	2.8	2.8	2.8		2.8	2.8	2.8

n.d. = not determined

Table 10 - K_{obs} values (1/days) for the degradation of epirubicin.HCl solutions in water for Injection at various pHs at 55°C.

Buffer	pH	$K_{obs} \times 10^3$	95% confidence limits
Glycine.HCl (I = 0.05)	2.5	55.1	± 4.0
Glycine-HCl (I = 0.05)	3.0	66.8	± 5.4

Table 11 - K_{obs} values (1/days) for the degradation of epirubicin.HCl 2 mg/ml solutions in 0.9% Sodium Chloride Injection at various pHs at 55°C.

Buffer	pH	$K_{obs} \times 10^3$	95% confidence limits
Glycine.HCl (I = 0.05)	2.5	97.3	± 6.4
Glycine-HCl (I = 0.05)	3.0	84.8	± 6.5

Table 12 - K_{obs} values (1/days) for the degradation of epirubicin.HCl 2 mg/ml solutions in 5% Dextrose solution at various pHs at 55°C.

Buffer	pH	$K_{obs} \times 10^3$	95% confidence limits
Glycine.HCl (I = 0.05)	2.5	81.1	± 6.6
Glycine-HCl (I = 0.05)	3.0	70.9	± 4.8

The claims defining the invention are as follows:

1. A sterile, injectable, pyrogen-free anthracycline glycoside solution which comprises a physiologically acceptable salt of an anthracycline glycoside dissolved in a physiologically acceptable aqueous solvent therefor at an anthracycline glycoside concentration of from 0.1 to 50 mg/ml, which has not been reconstituted from a lyophilizate and the pH of which has been adjusted to from 2.5 to 3.5 by means of a glycine buffer.

2. A solution according to claim 1 in a sealed container.

3. A solution according to claim 1 or 2 wherein the anthracycline glycoside is doxorubicin or 4'-epi-doxorubicin.

4. A solution according to any one of the preceding claims having a pH of from 3 to 3.5.

5. A solution according to any one of claims 1 to 3 having a pH of about 3.

6. A solution according to any one of the preceding claims, wherein the said salt is the salt with hydrochloric acid.

7. A solution according to any one of the preceding claims which further contains one or more formulation adjuvants selected from a co-solubilising agent, a tonicity adjustment agent, a preservative and a pharmaceutically acceptable chelating agent.

8. A solution according to claim 7, containing dextrose, lactose, sorbitol or mannitol as a tonicity adjustment agent.

9. A solution according to any one of the preceding claims, wherein the physiologically acceptable solvent is water

or physiological saline or an aqueous 5% dextrose solution.

10. A process for producing a sterile, injectable, pyrogen-free anthracycline glycoside solution which process comprises dissolving a physiologically acceptable salt of an anthracycline glycoside, which salt is not in the form of a lyophilizate, in a physiologically acceptable aqueous solvent therefor at an anthracycline glycoside concentration of from 0.1 to 50 mg/ml and adding a glycine buffer to adjust the pH of the solution to from 2.5 to 3.5 as desired, the process being effected in such a manner that the resultant solution is sterile and pyrogen-free.

11. A process according to claim 10 wherein the solution is passed through a sterilising filter after addition of the glycine buffer.

12. A process according to claim 10 or 11, wherein the resultant solution is introduced into a container which is then sealed.

13. A process according to any one of claims 10 to 12, wherein the anthracycline glycoside is doxorubicin or 4'-epi-doxorubicin.

14. A process according to any one of claims 10 to 13, wherein the pH is adjusted to from 3 to 3.5.

15. A process according to any one of claims 10 to 13, wherein the pH is adjusted to about 3.

16. A process according to any one of claims 10 to 15, wherein the said salt is the salt with hydrochloric acid.

17. A process according to any one of claims 10 to 16, which process comprises:

(i) dissolving the physiologically acceptable salt in the

physiologically acceptable aqueous solvent;

(ii) adding one or more formulation adjuvants selected from co-solubilizing agents, tonicity adjustment agents, preservatives and pharmaceutically acceptable chelating agents; and

(iii) adding the glycine buffer.

18. A process according to claim 17, wherein dextrose, lactose, sorbitol or mannitol is added as a tonicity adjustment agent.

19. A process according to any one of claims 10 to 18, wherein the physiologically acceptable aqueous solvent is water or physiological saline or an aqueous 5% dextrose solution.

20. A process for producing a sterile, injectable, pyrogen-free anthracycline glycoside solution, said process being substantially as hereinbefore described in Example 1 or 2.

21. A solution prepared by a process as claimed in any one of claims 10 to 20.

22. A sterile, injectable, pyrogen-free anthracycline glycoside solution substantially as hereinbefore described in Example 1 or 2.

DATED this 9th day of October 1992

FARMITALIA CARLO ERBA S.r.l.
By Their Patent Attorneys:

GRIFFITH HACK & CO.
Fellows Institute of Patent
Attorneys of Australia

Fig. 1

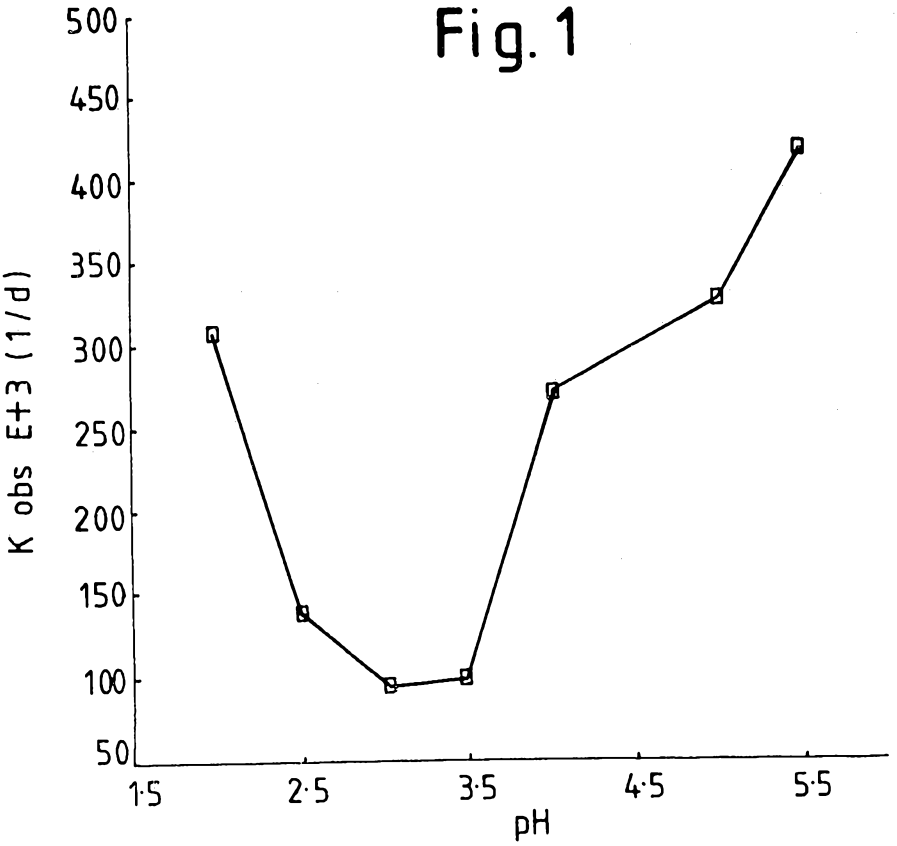

500
450
400
350
300
250
200
150
100
50
K obs E+3 (1/d)
1·5
2·5
3·5
4·5
5·5
pH

Fig. 2

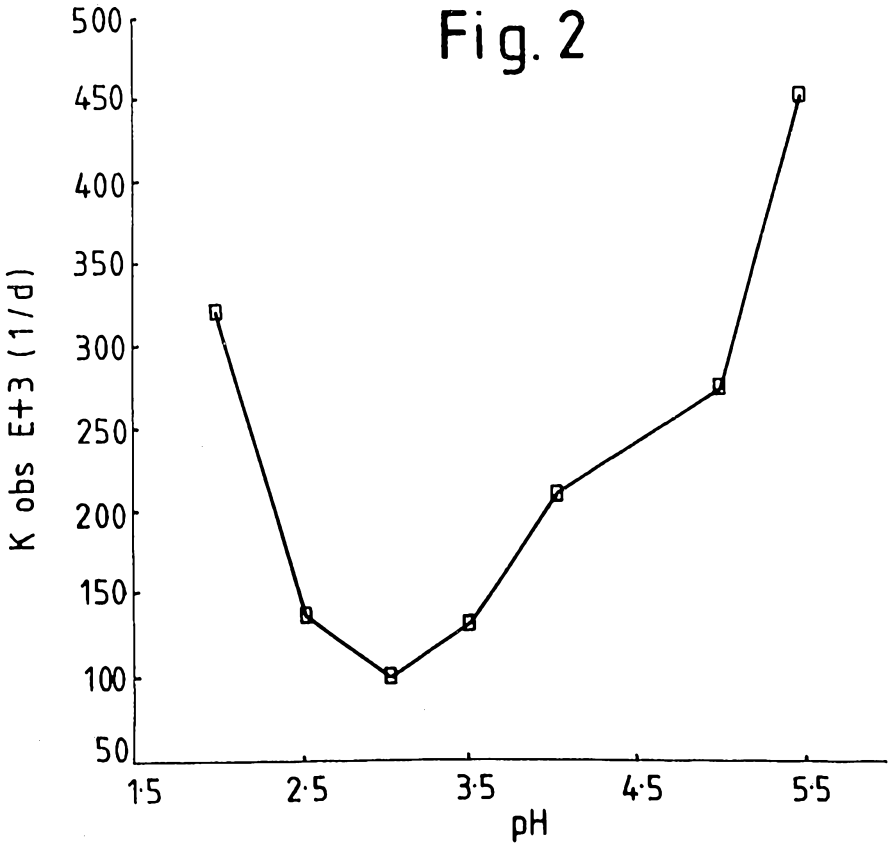

500
450
400
350
300
250
200
150
100
50
K obs E+3 (1/d)
1·5
2·5
3·5
4·5
5·5
pH

Fig. 3

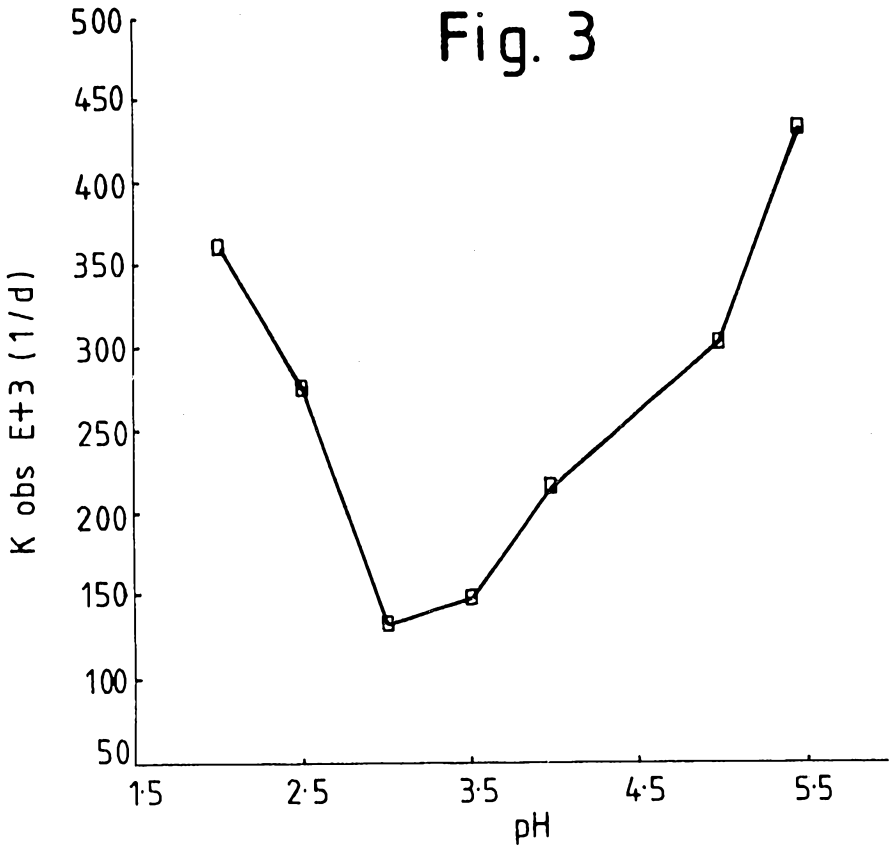

500
450
400
350
300
250
200
150
100
50
K obs E+3 (1/d)
1·5
2·5
3·5
4·5
5·5
pH

Fig. 4

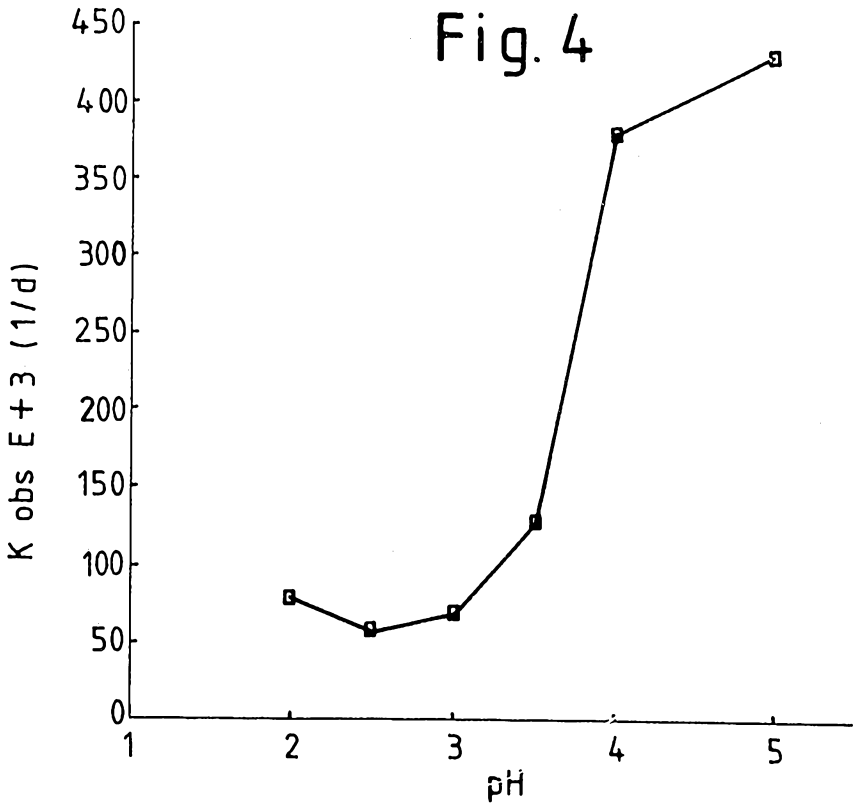

450
400
350
300
250
200
150
100
50
0
K obs E+3 (1/d)
1
2
3
4
5
pH

Fig. 5

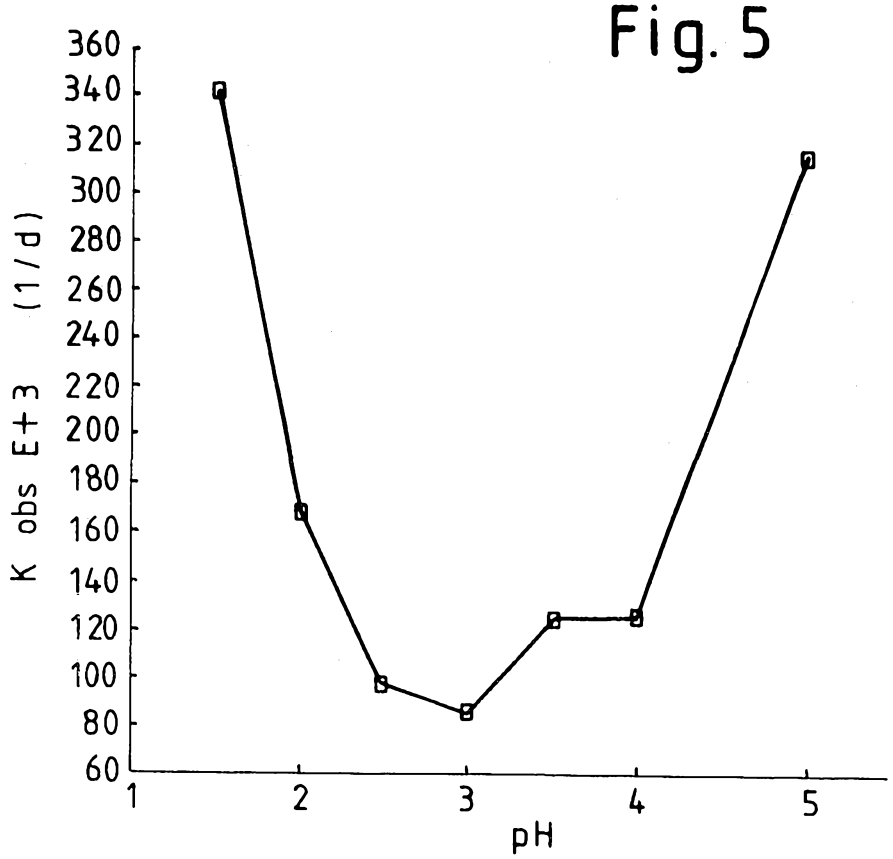
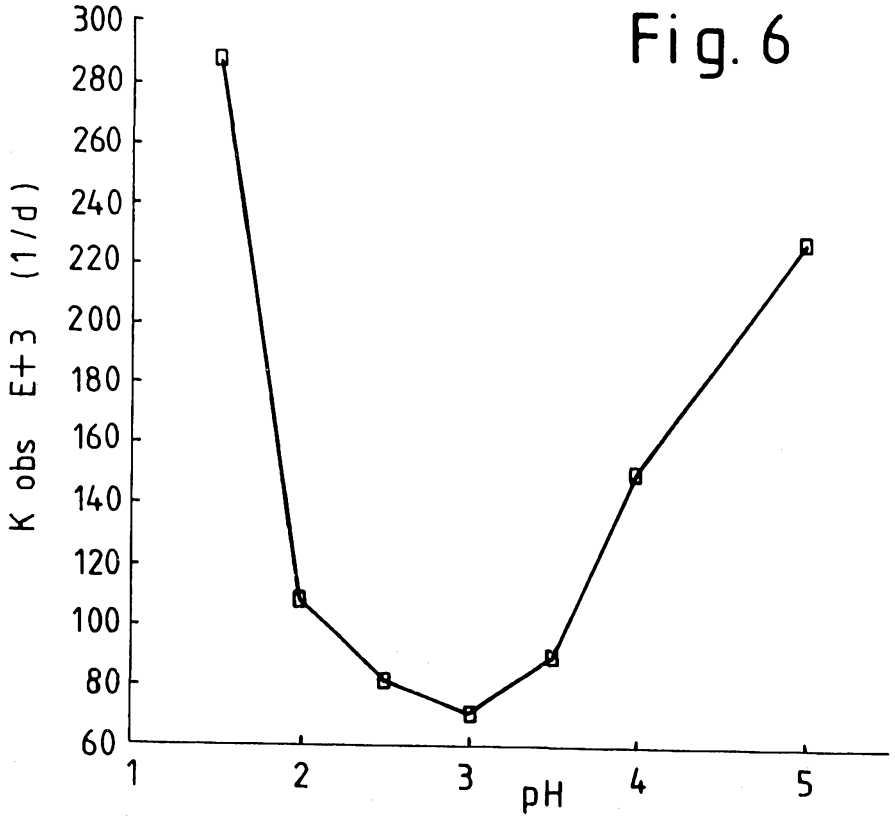

K obs E+3 (1/d)
360
340
320
300
280
260
240
220
200
180
160
140
120
100
80
60
1
2
3
4
5
pH

Fig. 6


K obs E+3 (1/d)
300
280
260
240
220
200
180
160
140
120
100
80
60
1
2
3
4
5
pH