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Title: Injectable ready-to-use solutions containing an antitumor anthracycline glycoside.

The present invention relates to a stable intravenously injectable ready-to-use solution of an antitumor anthracycline glycoside, e.g. doxorubicin, to a process for preparing such a solution, and provide the same in a sealed container, and to a method for treating tumors by the use of the said ready-to-use solution.

The anthracycline glycoside compounds are a well known class of compounds in the antineoplastic group of agents, wherein 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.;
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 manufacturing 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.

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The Martindale Extra Pharmacopoeia 28th edition, page 175 left column, reports, indeed, about adverse effects of antineaplastic 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 on 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 having to be first reconstituted and then administered and,moreover,in some cases, the complete dissolution of the powder may require prolonged shaking because of solubilization problems.

As the risks connected with the manufacturing 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.

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According to the present invention, there is provided an injectable, ready-to-use, sterile, pyrogen-free, anthracycline glycoside solution which consists essentially of 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 5.0 solely with a physiologically acceptable acid, the said acid being selected from hydrochloric, sulfuric, phosphoric, acetic, succinic, tartaric, ascorbic, citric, glutamic, methanesulphonic or ethanesulphonic acid.

The invention also provides an injectable, ready-to-use, sterile, pyrogen-free, anthracycline glycoside solution which consists essentially of 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 about 3 solely with a physiologically acceptable acid, the said acid being selected from hydrochloric, sulfuric, phosphoric, acetic, succinic, tartaric, ascorbic, citric, glutamic, methanesulphonic or ethanesulphonic acid.

Preferably the solution of the invention is provided in a sealed container.

Preferably the anthracycline glycoside is chosen

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from the group consisting of doxorubicin, 4'-epi-doxorubicin (i.e. epirubicin), 4'-desoxy-doxorubicin (i.e. esorubicin), 4'-desoxy-4'-iodo-doxorubicin, daunorubicin and 4-demethoxy-daunorubicin (i.e. idarubicin). A particularly preferred anthracycline glycoside is 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, phosphoric and the like, and the salts with certain organic acids such as succinic, tartaric, ascorbic, citric, methanesulfonic, ethanesulfonic and the like. 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 additional components such as a co-solubilizing agent (which may be the same as a solvent), a tonicity adjustment agent and a preservative. Examples of solvents, tonicity adjustment agents and preservatives which can be used for the preparation of the anthracycline glycoside solutions of the invention are hereunder reported.

Suitable solvents and co-solubilizing agents may be, for instance, water; physiological saline; and mixtures of water and one or more:-

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

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

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

Examples of preferred solvents are water, and mixtures of water and one or more of ethanol, polyethyleneglycol and dimethylacetamide. Water is a

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particularly preferred solvent.

To adjust the pH within the range of from 2.5 to about 5.0 a physiologically acceptable acid is added. The acid is hydrochloric, sulfuric, phosphoric, acetic, succinic, tartaric, ascorbic, citric, glutamic, methanesulphonic or ethanesulfonic acid.

The preferred range of pH for the ready-to-use solution of the invention is from 2.62 to 3.14. A pH of about 3 is a particularly preferred value.

In the solutions of the invention the concentration of the anthracycline glycoside is from 0.1 mg/ml to 50 mg/ml, 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, 4'-desoxy-doxorubicin and 4'-desoxy-4'-iodo-doxorubicin. Preferred ranges of concentration for daunorubicin and 4-demethoxy-daunorubicin are from 0.1 mg/ml to 50 mg/ml, preferably 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-

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to-use syringes and the like. Preferably the container is a sealed glass container, e.g. a vial or an ampoule.

According to a particularly preferred feature of the invention, there is provided an injectable, ready-to-use, sterile, pyrogen-free, doxorubicin solution which consists essentially of a physiologically acceptable salt of doxorubicin dissolved in a physiologically acceptable aqueous solvent therefor at a concentration of doxorubicin of from 2 mg/ml to 20 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, the said acid being selected from hydrochloric, sulfuric, phosphoric, acetic, succinic, tartaric, ascorbic, citric, glutamic, methanesulphonic or ethanesulphonic acid.

The invention also preferably provides an injectable, ready-to-use, sterile, pyrogen-free, doxorubicin solution which consists essentially of a physiologically acceptable salt of doxorubicin dissolved in a physiologically acceptable aqueous solvent therefor at a concentration of doxorubicin of from 2 mg/ml to 20 mg/ml, which has not been reconstituted from a lyophilizate and the pH of which has been adjusted to about 3 solely with a physiologically acceptable acid, the said acid being selected from hydrochloric, sulfuric, phosphoric, acetic, succinic, tartaric, ascorbic, citric, glutamic, methanesulphonic or ethanesulphonic acid.

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In the above indicated preferred feature of the invention the physiologically acceptable salt of doxorubicin may be, e.g., the salt with a mineral inorganic acid such as hydrochloric, hydrobromic, sulfuric, phosphoric and the like, or the salt with an organic acid such as succinic, tartaric, ascorbic, citric, methanesulfonic, ethanesulfonic and the like. The hydrochloride salt is a particularly preferred salt.

For the solution hereabove indicated as a preferred feature of the invention suitable solvents, co-solubilizing agents, tonicity adjustment agents and preservatives may be the same as those previously recited in this specification. Water is a particularly preferred solvent.

Also, the physiologically acceptable acid which is added to adjust the pH is one of those previously specified. Hydrochloric acid is an especially preferred acid. Preferred pH values for the above said preferred solution of the invention are from 2.62 to 3.14. The pH value of 3 is especially preferred.

The concentration of doxorubicin in the above preferred feature varies from 2 mg/ml to 20 mg/ ml. Examples of especially preferred concentrations of doxorubicin are 2 mg/ml and 5 mg/ml.

The invention also provides a process for producing a sterile, pyrogen-free anthracycline glycoside solution with a pH of from 2.5 to 5.0, which process comprises dissolving the physiologically acceptable salt of the

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anthracycline glycoside, which salt is not in the form of a lyophilizate, in the physiologically acceptable aqueous solvent therefor; adding the physiologically acceptable acid to adjust the pH within the said range as desired; passing the resulting solution through a sterilising filter; and, optionally, adding an additional component selected from a co-solubilizing agent, a tonicity adjustment agent and a preservative, for instance of the kind previously specified, to the solution prior to passing the solution through the 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 lyc ilized cake,

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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.

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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.

The growth of a tumour, in particular one of those indicated above, can therefore be inhibited by administering to a host suffering from said tumour an injectable solution according to the invention containing the anthracycline glycoside in an amount sufficient to inhibit the growth of said tumour.

The injectable solutions of the inventon are administered by rapid intravenous injection or infusion according to a variety of possible dose schedules. 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 by intravenous route for 3 days, every 25 days. Suitable dosages for 4'-epi-doxorubicin and 4'-desoxy-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.,

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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 also for daunorubicin.

The following examples illustrate but do not limit in any way the invention.

With reference to the examples, the stability controls on the ready-to-use solutions were carried out by means of high performance liquid chromatography (HPLC), at the following experimental conditions:

Liquid chromatograph	:	Varian model 5010
Spectrophotometric detector	:	Knauer model 8700
Integrating recorder	:	Varian model CDS 401
Injection valve	:	Rheodyne model 7125 fitted with a 10 mcl sample loop
Chromatographic column	:	Waters μ-Bondapak C18 (length = 300 mm; inner diameter = 3.9 mm; average particle size = 10 mcm)
Column temperature	:	ambient (about 22°C ± 2°C)
Mobile phase	:	water : acetonitrile (69:31 v/v) adjusted to pH 2 with phosphoric acid, filtered (sintered glass filter, 1 mcm or finer porosity) and deaerated
Mobile phase flow rate	:	1.5 ml/min
Analytical wavelength	:	254 ± 1 nm

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Integrating recorder sensitivity : 512
Chart speed : 1 cm/min

At these conditions, the peak of the anthracycline glycoside showed a retention time of about 6 minutes.

The obtained results are reported in the Tables accompanying the examples.

The extrapolation of the analytical data in order to determine the time when the 90% of the initial assay could be expected (t_{90} value) was made following an Arrhenius plot.

This procedure of analytical data treatment is well known and widely used and described in the art: see, e.g., Chemical Stability of Pharmaceuticals, Kennet A. Connors, Gordon L. Amidon, Lloyd Kennon, Publ.John Wiley and Sons, New York, N.Y., 1979.

The term "teflon" refers to "Teflon" (Registered Trade Mark).

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Example 1

Composition	for 80 vials	(for 1 vial)
Doxorubicin.HCl	0.8 g	(10 mg)
Hydrochloric acid 0.1N q.s. to	pH = 3	(pH = 3)
Water for injections q.s. to	0.4 l	(5 ml)

Doxorubicin.HCl (0.8 g) was dissolved in 90 percent of the amount of water for injections, de-aerated by nitrogen bubbling. The hydrochloric acid was then added dropwise to adjust the pH of the solution to 3. Further de-aerated water for injections was then added to bring the solution to its final volume (0.4 l).

The solution was filtered through a 0.22 μ microporous membrane under nitrogen pressure. Volumes of 5 ml of the solution were distributed into type I-colourless glass vials having 5/7 ml capacity. The vials were then closed with chlorobutyl teflon-faced rubber stoppers and sealed with aluminium caps.

The stability of the solutions in the vials was tested. The vials were stored at temperatures of 55°C, 45°C and 35°C (accelerated stability controls) and at 4°C for up to 3 weeks (55°C), 4 weeks (45°C and 35°C) and 12 weeks (4°C).

The stability data obtained, using high performance liquid chromatography (HPLC) for the determination of potency, are reported in the following Table 1:

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Table 1

INITIAL VALUES
Concentration: 1.992 mg/ml pH = 3.0
Relative % Assay: 100.0

TIME (weeks)	TEMPERATURE							
	4° C		35°C		45°C		55° C	
	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay
1	1.995	100.2	1.952	98.0	1.919	96.3	1.493	75.0
2			1.889	94.8	1.851	92.9	1.036	51.9
3			1.876	94.2	1.565	78.6	0.730	36.7
4	1.979	99.4	1.808	90.8	1.393	69.9		
8								
12	1.972	99.0						

t_{go} (days) extrapolated according to Arrhenius equation:
t_{go} at 4°C = 3970 days
t_{go} at 8°C = 2000 days

Similar stability data can be observed also for analogous solutions containing either doxorubicin hydrochloride at 5 mg/ml concentration, or 4'-epi-doxorubicin, 4'-desoxy-doxorubicin, 4'-desoxy-4'-iodo-doxorubicin, daunorubicin or 4-demethoxy-daunorubicin, as hydrochloride salts, at both 2 mg/ml and 5 mg/ml concentration.

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Example 2

Composition	for 80 vials	(for 1 vial)
Doxorubicin.HCl	8.0 g	(100 mg)
Hydrochloric acid 0.1N q.s. to	pH = 3	(pH = 3)
Water for injections q.s. to	0.4 l	(5 ml)

Doxorubicin.HCl (8.0 g) was dissolved in 90 percent of the amount of water for injections, de-aerated by nitrogen bubbling. The hydrochloric acid was then added dropwise to adjust the pH of the solution to 3. Further de-aerated water for injections was then added to bring the solution to its final volume (0.4 l).

The solution was filtered through a 0.22 μ microporous membrane under nitrogen pressure. Volumes of 5 ml of the solution were distributed into type I-colourless glass vials having 5/7 ml capacity. The vials were then closed with chlorobutyl teflon-faced rubber stoppers and sealed with aluminium caps.

The stability of the solutions in the vials was tested. The vials were stored at temperatures of 55°C, 45°C and 35°C (accelerated stability controls) and at 4°C for up to 3 weeks (55°C), 4 weeks (45°C and 35°C) and 12 weeks (4°C).

The stability data obtained, using high performance liquid chromatography (HPLC) for the determination of potency, are reported in the following Table 2:

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Table 2

INITIAL VALUES
Concentration: 20.06 mg/ml pH = 2.95
Relative % Assay: 100.0

TIME (weeks)	TEMPERATURE							
	4°C		35°C		45°C		55°C	
	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay
1	20.06	100.0	19.56	97.5	17.84	88.9	12.31	61.4
2			18.87	94.1	15.61	77.8	7.09	35.3
3			18.24	90.9	13.41	66.8	3.13	15.6
4	19.91	99.2	17.51	87.3	11.07	55.2		
8								
12	19.80	98.7						

t_{90} (days) extrapolated according to Arrhenius equation:
t_{90} at 4°C = 3700 days
t_{90} at 8°C = 1780 days

Similar stability data can be observed for analogous solutions containing 4'-epi-doxorubicin or 4'-desoxy-doxorubicin, as hydrochloride salts, at the same 20 mg/ml concentration.

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Example 3

Composition	for 80 vials	(for 1 vial)
Doxorubicin.HCl	0.800 g	(10.00 mg)
N,N-Dimethylacetamide	0.060 l	(0.75 ml)
Propylene glycol	0.048 l	(0.60 ml)
Ethanol	0.012 l	(0.15 ml)
Hydrochloric acid 0.1N q.s. to	pH = 3	(pH = 3)
Water for injections q.s. to	0.400 l	(5.00 ml)

Doxorubicin.HCl (0.800 g) was dissolved in 90 percent of the amount of water for injections, de-aerated by nitrogen bubbling. N,N-dimethylacetamide, propylene glycol and ethanol were subsequently added under stirring and nitrogen bubbling. The hydrochloric acid was then added dropwise to adjust the pH of the solution to 3. Further de-aerated water for injections was then added to bring the solution to its final volume (0.400 l).

The solution was filtered through a 0.22 μ microporous membrane under nitrogen pressure. Volumes of 5 ml of the solution were distributed into type I-colourless glass vials having 5/7 ml capacity. The vials were then closed with chlorobutyl teflon-faced rubber stoppers and sealed with aluminium caps.

The stability of the solutions in the vials was tested. The vials were stored at temperatures of 55°C, 45°C and 35°C (accelerated stability controls) and at 4°C for up to 3 weeks (55°C), 4 weeks (45°C and 35°C) and 8 weeks (4°C).

The stability data obtained, using high performance liquid chromatography (HPLC) for the determination of potency, are reported in the following Table 3:

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Table 3

INITIAL VALUES
Concentration: 2.000 mg/ml pH = 3.03
Relative % Assay: 100.0

TIME (weeks)	TEMPERATURE							
	4°C		35°C		45°C		55°C	
	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay
1			1.892	94.6	1.735	86.7	1.495	74.7
2	1.993	99.7	1.927	96.4	1.624	81.2	1.212	60.6
3			1.908	95.4	1.432	71.6	1.032	51.6
4	2.00	100.0	1.863	93.2	1.266	63.3		
8	1.960	98.0						

t_{go} (days) extrapolated according to Arrhenius equation:
t_{go} at 4°C = 4360 days
t_{go} at 8°C = 2200 days

Similar stability data can be observed also for analogous solutions containing either doxorubicin hydrochloride at 5 mg/ml concentration, or 4'-epi-doxorubicin, 4'-desoxy-doxorubicin, 4'-desoxy-4'-iodo-doxorubicin, daunorubicin or 4-demethoxy-daunorubicin, as hydrochloride salts, at both 2 mg/ml and 5 mg/ml concentration.

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Example 4

Composition	for 80 vials	(for 1 vial)
Doxorubicin.HCl	0.8 g	(10.0 mg)
Polyvinylpyrrolidone	20.0 g	(250.0 mg)
Hydrochloric acid 0.1N q.s. to	pH = 3	(pH = 3)
Water for injections q.s. to	0.4 l	(5.0 ml)

Doxorubicin.HCl (0.8 g) was dissolved in 90 percent of the amount of water for injections, de-aerated by nitrogen bubbling. Polyvinylpyrrolidone was added and dissolved under stirring and nitrogen bubbling. The hydrochloric acid was then added dropwise to adjust the pH of the solution to 3. Further de-aerated water for injections was then added to bring the solution to its final volume (0.4 l).

The solution was filtered through a 0.22 μ microporous membrane under nitrogen pressure. Volumes of 5 ml of the solution were distributed into type I-colourless glass vials having 5/7 ml capacity. The vials were then closed with chlorobutyl teflon-faced rubber stoppers and sealed with aluminium caps.

The stability of the solutions in the vials was tested. The vials were stored at temperatures of 55°C, 45°C and 35°C (accelerated stability controls) and at 4°C for up to 3 weeks (55°C), 4 weeks (45°C and 35°C) and 8 weeks (4°C).

The stability data obtained, using high performance liquid chromatography (HPLC) for the determination of potency, are reported in the following Table 4;

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Table 4

INITIAL VALUES
Concentration: 1.973 mg/ml pH = 2.71
Relative % Assay: 100.0

TIME (weeks)	TEMPERATURE							
	4°C		35°C		45°C		55°C	
	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay
1	2.028	102.8	1.944	98.5	1.791	90.8	1.477	74.9
2			1.885	95.5	1.582	80.2	0.972	49.3
3			1.840	93.2	1.402	71.0	0.632	32.0
4	1.913	97.0	1.853	93.9	1.273	64.5		
8	1.972	99.9						

t_{90} (days) extrapolated according to Arrhenius equation:
t_{90} at 4°C = 5560 days
t_{90} at 8°C = 2670 days

Similar stability data can be observed also for analogous solutions containing either doxorubicin hydrochloride at 5 mg/ml concentration, or 4'-epi-doxorubicin, 4'-desoxy-doxorubicin, 4'-desoxy-4'-iodo-doxorubicin, daunorubicin or 4-demethoxy-daunorubicin, as hydrochloride salts, at both 2 mg/ml and 5 mg/ml concentration.

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Example 5

Composition	for 80 vials	(for 1 vial)
Doxorubicin.HCl	8.00 g	(100.0 mg)
N,N-Dimethylacetamide	0.12 l	(1.5 ml)
Hydrochloric acid 0.1N q.s. to	pH = 3	(pH = 3)
Water for injections q.s. to	0.40 l	(5.0 ml)

Doxorubicin.HCl (8.00 g) was dissolved in 90 percent of the amount of water for injections, de-aerated by nitrogen bubbling. N,N-dimethylacetamide was added under stirring and nitrogen bubbling. The hydrochloric acid was then added dropwise to adjust the pH of the solution to 3. Further de-aerated water for injections was then added to bring the solution to its final volume (0.40 l).

The solution was filtered through a 0.22 μ microporous membrane under nitrogen pressure. Volumes of 5 ml of the solution were distributed into type I-colourless glass vials having 5/7 ml capacity. The vials were then closed with chlorobutyl teflon-faced rubber stoppers and sealed with aluminium caps.

The stability of the solutions in the vials was tested. The vials were stored at temperatures of 55°C, 45°C and 35°C (accelerated stability controls) and at 4°C for up to 3 weeks (55°C), 4 weeks (45°C and 35°C) and 8 weeks (4°C).

The stability data obtained, using high performance liquid chromatography (HPLC) for the determination of potency, are reported in the following Table 5:

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Table 5

INITIAL VALUES
Concentration: 19.32 mg/ml pH = 2.96
Relative % Assay: 100.0

TIME (weeks)	TEMPERATURE							
	4°C		35°C		45°C		55°C	
	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay
1	20.1	103.5	19.14	99.1	17.34	89.8	15.57	80.6
2			19.20	99.4	15.77	81.6	12.94	67.0
3			18.06	93.5	14.85	76.9	11.61	60.1
4	20.03	103.7	17.81	92.2	13.78	71.3		
8	19.99	103.5						

t_{90} (days) extrapolated according to Arrhenius equation:
t_{90} at 4°C = 1310 days
t_{90} at 8°C = 770 days

Similar stability data can be observed for analogous solutions containing 4'-epi-doxorubicin or 4'-desoxy-doxorubicin, as hydrochloride salts, at the same 20 mg/ml concentration.

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Example 6

Composition	for 80 vials	(for 1 vial)
Doxorubicin.HCl	0.80 g	(10.0 mg)
Ethanol	0.12 l	(1.5 ml)
Hydrochloric acid 0.1 N q.s. to	pH = 3	(pH = 3)
Water for injections q.s. to	0.40 l	(5.0 ml)

Doxorubicin.HCl (0.80g) was dissolved in 90 percent of the amount of water for injections, de-aerated by nitrogen bubbling. Ethanol was added under stirring and nitrogen bubbling. Hydrochloric acid 0.1 N was then added dropwise to adjust the pH of the solution to 3. De-aerated water for injections was finally added to bring the solution to its final volume (0.40 l).

The solution was filtered through a 0.22 μ microporous membrane under nitrogen pressure. Volumes of 5 ml of the solution were distributed into type I-colourless glass vials having 5/7 ml capacity. The vials were then closed with chlorobutyl teflon-faced rubber stoppers and sealed with aluminium caps.

The stability of the solutions in the vials was tested. The vials were stored at temperatures of 55°C, 45°C and at 35°C (accelerated stability controls) and at 4°C for up to 3 weeks (55°C), 4 weeks (45°C and 35°C) and 12 weeks (4°C).

The stability data obtained, using high performance liquid chromatography (HPLC) for the determination of potency, are reported in the following Table 6 .

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Table 6

INITIAL VALUES

Concentration: 1.979 mg/ml **pH = 3.11**

Relative % Assay: 100.0

TIME (weeks)	TEMPERATURE							
	4°C		35°C		45°C		55°C	
	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay
1	2.010	101.6	1.965	99.3	1.947	98.4	1.750	88.4
2			1.957	98.9	1.910	96.5	1.645	83.1
3			1.895	95.8	1.737	87.8	1.356	68.5
4	1.927	97.3	1.818	91.9	1.678	84.8		
12	1.939	97.9						

t_{90} (days) extrapolated according to Arrhenius equation:

t_{90} at 4°C = 1270 days

t_{90} at 8°C = 780 days

Similar stability data can be observed also for analogous solutions containing either doxorubicin hydrochloride at 5mg/ml concentration, or 4'-epi-doxorubicin, 4'-desoxy-doxorubicin, 4'-desoxy-4'-iodo-doxorubicin, daunorubicin or 4-demethoxy-daunorubicin, as hydrochloride salts, at both 2 mg/ml and 5 mg/ml concentration.

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Example 7

Composition	for 80 vials	(for 1 vial)
Doxorubicin.HCl	8.000 g	(100.00 mg)
N,N-Dimethylacetamide	0.060 l	(0.75 ml)
Propylene glycol	0.048 l	(0.60 ml)
Ethanol	0.012 l	(0.15 ml)
Hydrochloric acid 0.1N q.s. to	pH = 3	(pH = 3)
Water for injections q.s. to	0.400 l	(5.00 ml)

Doxorubicin.HCl (8.000 g) was dissolved in 90 percent of the amount of water for injections, de-aerated by nitrogen bubbling. N,N-dimethylacetamide, propylene glycol and ethanol were subsequently added under stirring and nitrogen bubbling. The hydrochloric acid was then added dropwise to adjust the pH of the solution to 3. Further de-aerated water for injections was then added to bring the solution to its final volume (0.400 l).

The solution was filtered through a 0.22 μ microporous membrane under nitrogen pressure. Volumes of 5 ml of the solution were distributed into type I-colourless glass vials having 5/7 ml capacity. The vials were then closed with chlorobutyl teflon-faced rubber stoppers and sealed with aluminium caps.

The stability of the solutions in the vials was tested. The vials were stored at temperatures of 55°C, 45°C and 35°C (accelerated stability controls) and at 4°C for up to 3 weeks (55°C), 4 weeks (45°C and 35°C) and 8 weeks (4°C).

The stability data obtained, using high performance liquid chromatography (HPLC) for the determination of potency, are reported in the following Table 7:

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Table 7

INITIAL VALUES
Concentration:20.07 mg/ml pH = 2.99
Relative % Assay: 100.0

TIME (weeks)	TEMPERATURE							
	4°		35°		45°		55°	
	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay
1			19.14	95.4	17.81	88.7	14.84	73.9
2	19.97	99.5	19.07	95.0	16.27	81.1	12.36	61.6
3			18.08	90.1	14.62	72.9	10.04	50.0
4	20.06	99.9	18.03	89.8	13.20	65.8		
8	19.69	98.1						

t_{90} (days) extrapolated according to Arrhenius equation :
t_{90} at 4°C = 846 days
t_{90} at 8°C = 505 days

Similar stability data can be observed for analogous solutions containing 4'-epi-doxorubicin or 4'-desoxy-doxorubicin, as hydrochloride salts, at the same 20 mg/ml concentration.

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Example 8

Composition	for 80 vials	(for 1 vial)
Doxorubicin.HCl	8.0 g	(100.0 mg)
Polyvinylpyrrolidone	20.0 g	(250.0 mg)
Hydrochloric acid 0.1N q.s. to	pH = 3	(pH = 3)
Water for injections q.s. to	0.4 l	(5.0 ml)

Doxorubicin.HCl (8.0 g) was dissolved in 90 percent of the amount of water for injections, de-aerated by nitrogen bubbling. Polyvinylpyrrolidone was added and dissolved under stirring and nitrogen bubbling. The hydrochloric acid was then added dropwise to adjust the pH of the solution to 3. Further de-aerated water for injections was then added to bring the solution to its final volume (0.4 l).

The solution was filtered through a 0.22 μ microporous membrane under nitrogen pressure. Volumes of 5 ml of the solution were distributed into type I-colourless glass vials having 5/7 ml capacity. The vials were then closed with chlorobutyl teflon-faced rubber stoppers and sealed with aluminium caps.

The stability of the solutions in the vials was tested. The vials were stored at temperatures of 55°C, 45°C and 35°C (accelerated stability controls) and at 4°C for up to 3 weeks (55°C), 4 weeks (45°C and 35°C) and 8 weeks (4°C).

The stability data obtained, using high performance liquid chromatography (HPLC) for the determination of potency, are reported in the folllowing Table 8:

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Table 8

INITIAL VALUES
Concentration: 19.57 mg/ml pH = 2.62
Relative % Assay: 100.0

TIME (weeks)	TEMPERATURE							
	4°C		35°C		45°C		55°C	
	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay
1	19.54	99.9	19.11	97.6	16.88	86.2	12.48	63.8
2			18.43	94.2	14.13	72.2	6.00	30.7
3			18.02	92.1	11.57	59.1	2.61	13.3
4	19.58	100.1	17.36	88.7	9.23	47.2		
8	19.34	98.8						

t_{90} (days) extrapolated according to Arrhenius equation:
t_{90} at 4°C = 2540 days
t_{90} at 8°C = 1290 days

Similar stability data can be observed for analogous solutions containing 4'-epi-doxorubicin or 4'-desoxy-doxorubicin, as hydrochloride salts, at the same 20 mg/ml concentration.

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Example 9.

Composition	for 80 vials	(for 1 vial)
Doxorubicin.HCl	0.80 g	(10.0 mg)
N,N-Dimethylacetamide	0.12 l	(1.5 ml)
Hydrochloric acid 0.1N q.s. to	pH = 3	(pH = 3)
Water for injections q.s. to	0.40 l	(5.0 ml)

Doxorubicin.HCl (0.80 g) was dissolved in 90% of the amount of water for injections, de-aerated by nitrogen bubbling. N,N-Dimethylacetamide was added under stirring and nitrogen bubbling. Hydrochloric acid 0.1N was then added dropwise to adjust the pH of the solution to 3. De-aerated water for injections was finally added to bring the solution to its final volume (0.40 l).

The solution was filtered through a 0.22 μ microporous membrane under nitrogen pressure. Volumes of 5 ml of the solution were distributed into type I-colourless glass vials having 5/7 ml capacity. The vials were then closed with chlorobutyl teflon-faced rubber stoppers and sealed with aluminium caps.

The stability of the solutions in the vials was tested. The vials were stored at temperatures of 55°C, 45°C and 35°C (accelerated stability controls) and at 4°C for up to 3 weeks (55°C), 4 weeks (45°C and 35°C) and 8 weeks (4°C).

The stability data obtained, using high performance liquid chromatography (HPLC) for the determination of potency, are reported in the following Table 9:

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Table 9

INITIAL VALUES
Concentration: 1.826 mg/ml pH = 3.14
Relative % Assay: 100.0

TIME (weeks)	TEMPERATURE							
	4°C		35°C		45°C		55°C	
	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay
1	1.830	100.2	1.812	99.2	1.784	97.7	1.605	87.9
2	1.818	99.6	1.781	97.5	1.554	85.1	1.292	70.8
3			1.743	95.4	1.409	77.2	1.018	55.7
4	1.823	99.8	1.734	95.0	1.369	75.0		
8	1.792	98.2						

t_{90} (days) extrapolated according to Arrhenius equation:
t_{90} at 4°C = 5815 days
t_{90} at 8°C = 2920 days

Similar stability data can be observed also for analogous solutions containing either doxorubicin hydrochloride at 5 mg/ml concentration, or 4'-epi-doxorubicin, 4'-desoxy-doxorubicin, 4'-epi-desoxy-4'-iodo-doxorubicin, daunorubicin or 4-demethoxy-daunorubicin, as hydrochloride salts, at both 2 mg/ml and 5 mg/ml concentration.

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Example 10

Composition	for 80 vials	(for 1 vial)
Doxorubicin.HCl	0.80 g	(10.0 mg)
Propylene glycol	0.12 l	(1.5 ml)
Hydrochloric acid 0.1N q.s. to	pH = 3	(pH = 3)
Water for injections q.s. to	0.40 l	(5.0 ml)

Doxorubicin.HCl (0.80 g) was dissolved in 90% of the amount of water for injections de-aerated by nitrogen bubbling. Propylene glycol was added under stirring and nitrogen bubbling. Hydrochloric acid 0.1 N was then added dropwise to adjust the pH of the solution to 3. De-aerated water for injections was finally added to bring the solution to its final volume (0.40 l).

The solution was filtered through a 0.22 μ microporous membrane under nitrogen pressure. Volumes of 5 ml of the solution were distributed into type I-colourless glass vials having 5/7 ml capacity. The vials were then closed with chlorobutyl teflon-faced rubber stoppers and sealed with aluminium caps.

The stability of the solutions in the vials was tested. The vials were stored at temperatures of 55°C, 45°C and 35°C (accelerated stability controls) and at 4°C for up to 3 weeks (55°C), 4 weeks (45°C and 35°C) and 4 weeks (4°C).

The stability data obtained, using high performance liquid chromatography (HPLC) for the determination of potency, are reported in the following Table 10:

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Table 10

INITIAL VALUES
Concentration: 1.982 mg/ml pH = 3.11
Relative % Assay: 100.0

TIME (weeks)	TEMPERATURE							
	4°C		35°C		45°C		55°C	
	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay
1	1.972	99.5	1.934	97.6	1.889	95.3	1.705	86.0
2			1.952	98.5	1.795	90.6	1.483	74.8
3			1.935	97.6	1.699	85.7	1.153	58.2
4	2.056	103.7	1.788	90.2	1.460	73.7		

t_{90} (days) extrapolated according to Arrhenius equation:

t_{90} at 4°C = 1794 days

t_{90} at 8°C = 1025 days

Similar stability data can be observed also for analogous solutions containing either doxorubicin hydrochloride at 5 mg/ml concentration, or 4'-epi-doxorubicin, 4'-desoxy-doxorubicin, 4'-desoxy-4'-iodo-doxorubicin, daunorubicin or 4-demethoxy-daunorubicin, as hydrochloride salts, at both 2 mg/ml 5 mg/ml concentration.

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Example 11

Composition	for 80 vials	(for 1 vial)
Doxorubicin.HCl	0.80 g	(10.0 mg)
Polyethylene glycol 400	0.12 l	(1.5 ml)
Hydrochloric acid 0.1N q.s. to	pH = 3	(pH = 3)
Water for injections q.s. to	0.40 l	(5.0 ml)

Doxorubicin.HCl (0.80 g) was dissolved in 90% of the amount of water for injections, de-aerated by nitrogen bubbling. Polyethylene glycol 400 was added under stirring and nitrogen bubbling. Hydrochloric acid 0.1 N was then added dropwise to adjust the pH of the solution to 3. De-aerated water for injections was finally added to bring the solution to its final volume (0.40 l).

The solution was filtered through a 0.22 μ microporous membrane under nitrogen pressure. Volumes of 5 ml of the solution were distributed into type I-colourless glass vials having 5/7 ml capacity. The vials were then closed with chlorobutyl teflon-faced rubber stoppers and sealed with aluminium caps.

The stability of the solutions in the vials was tested. The vials were stored at temperatures of 55°C, 45°C and 35°C (accelerated stability controls) and at 4°C for up to 3 weeks (55°C), 4 weeks (45°C and 35°C) and 4 weeks (4°C).

The stability data obtained, using high performance liquid chromatography (HPLC) for the determination of potency, are reported in the following Table 11:

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Table 11

INITIAL VALUES

Concentration: 1.907 mg/ml pH = 3.07

Relative % Assay: 100.0

TIME (weeks)	TEMPERATURE							
	4°C		35°C		45°C		55°C	
	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay
1	1.871	98.1	1.797	94.2	1.668	87.5	1.484	77.8
2			1.710	89.7	1.608	84.3	1.237	64.9
3			1.739	91.2	1.551	81.3	1.007	52.8
4	1.873	98.2	1.693	88.8	1.453	76.2		

t_{90} (days) extrapolated according to Arrhenius equation:

t_{90} at 4°C = 1130 days

t_{90} at 8°C = 680 days

Similar stability data can be observed also for analogous solutions containing either doxorubicin hydrochloride at 5mg/ml concentration, or 4'-epi-doxorubicin, 4'-desoxy-doxorubicin, 4'-desoxy-4'-iodo-doxorubicin, daunorubicin or 4-demethoxy-daunorubicin, as hydrochloride salts, at both 2 mg/ml and 5 mg/ml concentration.

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Example 12

Composition	for 80 vials	(for 1 vial)
Doxorubicin.HCl	0.8 g	(10 mg)
Hydrochloric acid 0.1N q.s. to	pH = 3	(pH = 3)
Water for injections q.s. to	0.4 l	(5 ml)

Doxorubicin.HCl (0.8 g) was dissolved in 90 percent of the amount of water for injections, de-aerated by nitrogen bubbling. The hydrochloric acid was then added dropwise to adjust the pH of the solution to 3. Further de-aerated water for injections was then added to bring the solution to its final volume (0.4 l).

The solution was filtered through a 0.22 μ microporous membrane under nitrogen pressure. Volumes of 5 ml of the solution were distributed into type I-colourless glass vials having 5/7 ml capacity. The vials were then closed with chlorobutyl teflon-faced rabber stoppers and sealed with aluminium caps.

The stability of the solutions in the vials was tested. The vials were stored at temperatures of 4°C and 8°C for up to 6 months.

The stability data obtained, using high performance liquid chromatography (HPLC) for the determination of potency, are reported in the following Table 12:

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INITIAL VALUES
Concentration: 2.039 mg/ml pH = 3.06
Relative % Assay: 100.0

TIME (months)	TEMPERATURE			
	4°C		8°C	
	Conc. mg/ml	Rel.% Assay	Conc. mg/ml	Rel.% Assay
1	1.983	97.3	1.959	96.1
3	1.984	97.3	1.983	97.3
6	2.012	98.7	2.002	98.2

At the same conditions,similar stability data can be generally observed also for the other solutions mentioned in the preceding examples.

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CLAIMS

1. An injectable, ready-to-use, sterile, pyrogen-free, anthracycline glycoside solution which consists essentially of 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 5.0 solely with a physiologically acceptable acid, the said acid being selected from hydrochloric, sulfuric, phosphoric, acetic, succinic, tartaric, ascorbic, citric, glutamic, methanesulphonic or ethanesulphonic acid.

2. A solution according to claim 1 having a pH of from 2.62 to 3.14.

3. An injectable, ready-to-use, sterile, pyrogen-free, anthracycline glycoside solution which consists essentially of 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 about 3 solely with a physiologically acceptable acid, the said acid being selected from hydrochloric, sulfuric, phosphoric, acetic, succinic, tartaric, ascorbic, citric, glutamic,

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methanesulphonic or ethanesulphonic acid.

4. A solution according to any one of the preceding claims, wherein the acid is hydrochloric acid.

5. A solution according to any one of the preceding claims wherein the anthracycline glycoside is chosen from the group consisting of doxorubicin, 4'-epi-doxorubicin, 4'-desoxy-doxorubicin, 4'-desoxy-4'-iodo-doxorubicin, daunorubicin and 4-demethoxy-daunorubicin.

6. A solution according to claim 5 wherein the anthracycline glycoside is doxorubicin.

7. A solution according to any one of the preceding claims wherein the physiologically acceptable salt of the anthracycline glycoside is the salt with an acid chosen from hydrochloric, hydrobromic, sulfuric, phosphoric, succinic, tartaric, ascorbic, citric, methanesulfonic and ethanesulfonic acids.

8. A solution according to claim 7 wherein the physiologically acceptable salt of the anthracycline glycoside is the salt with hydrochloric acid.

9. A solution according to any one of the preceding claims wherein the solvent is water or a mixture of water and one or more of ethanol, polyethyleneglycol and dimethylacetamide.

10. A solution according to any one of claims 1 to 7, wherein the solvent is physiological saline.

11. A solution according to any one of the preceding claims which also contains one or more additional

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components selected from a cosolubilizing agent, a tonicity adjustment agent and a preservative.

12. A solution according to claim 11, which contains a tonicity adjustment agent selected from dextrose, lactose and mannitol.

13. A solution according to any one of the preceding claims, suitable for inhibiting the growth of a tumour selected from sarcomas, carcinomas, lymphomas, neuroblastomas, melanomas, myelomas, leukemias and Wilms tumour.

14. A solution according to claim 13, wherein the tumour is selected from Moloney Sarcoma Virus, Sarcoma 180 Ascites, Solid Sarcoma 180, gross transplantable leukemia, L 1210 leukemia and lymphocytic P388 leukemia.

15. A solution according to any one of the preceding claims in a sealed container.

16. A solution according to any one of the preceding claims, wherein the anthracycline concentration is from 1 to 20 mg/ml.

17. An injectable, ready-to-use, sterile, pyrogen-free, doxorubicin solution which consists essentially of a physiologically acceptable salt of doxorubicin dissolved in a physiologically acceptable aqueous solvent therefor at a concentration of doxorubicin of from 2 mg/ml to 20 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, the said acid being

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selected from hydrochloric, sulfuric, phosphoric, acetic, succinic, tartaric, ascorbic, citric, glutamic, methanesulphonic or ethanesulphonic acid.

18. A solution according to claim 17 having a pH of from 2.62 to 3.14.

19. An injectable, ready-to-use, sterile, pyrogen-free, doxorubicin solution which consists essentially of a physiologically acceptable salt of doxorubicin dissolved in a physiologically acceptable aqueous solvent therefor at a concentration of doxorubicin of from 2 mg/ml to 20 mg/ml, which has not been reconstituted from a lyophilizate and the pH of which has been adjusted to about 3 solely with a physiologically acceptable acid, the said acid being selected from hydrochloric, sulfuric, phosphoric, acetic, succinic, tartaric, ascorbic, citric, glutamic, methanesulphonic or ethanesulphonic acid.

20. A solution according to any one of claims 17 to 19, wherein the acid is hydrochloric acid.

21. A solution according to any one of claims 17 to 20, wherein the physiologically acceptable salt of doxorubicin is the salt with a physiologically acceptable acid chosen from hydrochloric, hydrobromic, sulfuric, phosphoric, succinic, tartaric, ascorbic, citric, methanesulfonic and ethanesulfonic acids.

22. A solution according to claim 21 wherein the physiologically acceptable salt of doxorubicin is the salt with hydrochloric acid.

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23. A solution according to any one of claims 17 to 22, wherein the solvent is water or a mixture of water and one or more of ethanol, polyethyleneglycol and dimethylacetamide.

24. A solution according to any one of claims 17 to 22 wherein the solvent is physiological saline.

25. A solution according to any one of claims 17 to 24 wherein the concentration of doxorubicin is 2 mg/ml or 5 mg/ml.

26. A solution according to any one of claims 17 to 25 which also contains one or more additional components selected from a cosolubilizing agent, a tonicity adjustment agent and a preservative.

27. A solution according to claim 26, which contains a tonicity adjustment agent selected from dextrose, lactose and mannitol.

28. A solution according to any one of claims 17 to 27, in a sealed container.

29. A solution according to any one of claims 17 to 28, suitable for inhibiting the growth of a tumour selected from sarcomas, carcinomas, lymphomas, neuroblastomas, melanomas, myelomas, leukemias and Wilms tumour.

30. A solution according to claim 29, wherein the tumour is selected from Moloney Sarcoma Virus, Sarcoma 180 Ascites, Solid Sarcoma 180, gross transplantable leukemia, L 1210 leukemia and lymphocytic P388 leukemia.

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31. A process for producing a solution according to any one of the preceding claims; which process comprises dissolving the physiologically acceptable salt of the anthracycline glycoside, which salt is not in the form of a lyophilizate, in the physiologically acceptable aqueous solvent therefor; adding solely the physiologically acceptable acid to adjust the pH within the said range as desired; optionally, adding an additional component selected from a co-solubilizing agent, a tonicity adjustment agent and a preservative to the solution; and then passing the resulting solution through a sterilising filter.

32. An injectable, ready-to-use, sterile, pyrogen-free anthracycline glycoside solution substantially as hereinbefore described in any one of Examples 1 to 12.

33. A process for producing an injectable, ready-to-use, sterile, pyrogen-free anthracycline glycoside solution, said process being substantially as hereinbefore described in any one of Examples 1 to 12.

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