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PHARMACEUTICAL COMPOSITIONS CONTAINING ANTHRACYCLINE GLYCOSIDES

The present invention relates to lyophilised preparations comprising an anthracycline glycoside, or a pharmaceutically acceptable salt thereof, as the active drug substance, and to the use of said preparations in the treatment of tumours.

It is currently known that reconstitution with sterile physiological saline solution is preferable, rather than reconstitution with sterile water, in order to obtain isotonic reconstituted injectable solutions, i.e. solutions having a tonicity more compatible with that of the blood.

It is also known that solubility problems are sometimes encountered in reconstitution, particularly with physiological saline solution, of certain anthracycline glycoside-containing freeze-dried preparations, because the lyophilized cake dissolves somewhat slowly and complete dissolution may require prolonged shaking.

The problem is of particular relevance in view of the recognised toxicity of drugs of the anthracycline glycoside family. It has now been found that the presence of a suitable cosolubilising agent in a lyophilised anthracycline glycoside-containing preparation enhances to a great extent the solubility of the drug so that upon reconstitution, particularly with physiological saline solution but also

with sterile water, complete dissolution is achieved in a few seconds without any difficulty.

Accordingly, the present invention provides a stable lyophilised preparation which on reconstitution is rapidly solubilised into a sterile solution suitable for injection, which preparation comprises:

(i) an anthracycline glycoside, or a pharmaceutically acceptable salt thereof, and

(ii) a cosolubilising agent which is a hydroxy-, mercapto- or amino-substituted benzoic acid or an alkali metal salt thereof or a C_1-C_4 alkyl ester thereof, or a ring-halogenated methyl-substituted phenol or an amino acid, or two or more of said compounds;

with the proviso that component (i) is not doxorubicin hydrochloride when 4 parts by weight of p-hydroxy-benzoic acid methyl ester and 1 part by weight of p-hydroxy-benzoic acid propyl ester are present together as co-solubilising agents.

The anthracycline glycoside active drug substance in the preparations of the invention may be any anthracycline glycoside, for example one of those disclosed in the UK Patent Specifications Nos. 1161278, 1217133, 1457632, 1467383, 1500421 and 1511559. In particular, the said anthracycline glycoside is, for example, doxorubicin, 4'-epi-doxorubicin (i.e. epirubicin), 4'-desoxy-doxorubicin (i.e. esorubicin), daunorubicin and 4-demethoxy-daunorubicin

(i.e. idarubicin).

The cosolubilising agent used as solubility enhancer in the preparation of the invention is a compound selected from the group consisting of a hydroxy-, mercapto- or amino-benzoic acid, for example p-hydroxy- or o-hydroxy- or p-amino-benzoic acid, an alkali-metal salt thereof, for example a sodium or potassium salt, a C_1-C_4 alkylester thereof, for example a methyl-, ethyl-, propyl-, or butyl ester, a ring-halogenated methyl-substituted phenol, for example 3-methyl-4-chlorophenol or 3,5-dimethyl-4-chlorophenol; an amino acid, in particular a neutral amino acid, for example a neutral aliphatic amino acid such as e.g. glycine, alanine, leucine and the like, a neutral thioaliphatic amino acid such as e.g. cysteine or methionine, a neutral aromatic amino acid such as e.g.phenylalanine or tyrosine or a neutral heterocyclic amino acid such as e.g. proline or hydroxyproline; or two or more of the above said compounds.

Some of the above cosolubilising agents are known to be used as preservatives/bacteriostatics in pharmaceutical formulations but there is nothing known about their possible role as solubility enhancers in reconstitution of lyophilised preparations, e.g. anthracycline glycoside-containing preparations. For example, K.P. Flora et al (J. Pharm. Pharmacol. 1980, 32:577) report about freeze-drying of adriamycin (i.e. doxorubicin) hydrochloride formulations

containing 4 parts by weight of p-hydroxy-benzoic acid methyl ester and 1 part by weight of p-hydroxy-benzoic acid propyl ester as a preservative, but not a single indication is given there of a possible role of said preservatives in improving the solubility of the freeze-dried preparation.

Furthermore there isn't any evidence in the article of Flora et al that the solutions used for the freeze-drying process may be suitable for injection. As is known, in fact, solutions for injection must be sterile, in particular aqueous solutions are obtained from a lyophilised prparation by dissolving it in sterile, pyrogen-free water for injection, while this does not result in the case of the Flora's solutions.

The preferred cosolubilising agent is either a compound selected from the group consisting of p-hydroxy-benzoic acid and the methyl ester thereof, p-amino-benzoic acid and the methyl ester thereof, o-hydroxy-benzoic acid and the methyl ester thereof, 3-methyl-4-chlorophenol and 3,5-dimethyl-4-chlorophenol, or two or more of said compounds. A particularly preferred cosolubiliser is p-hydroxy-benzoic acid methyl ester.

In the preparations of the invention the pharmaceutically acceptable salt of the anthracycline glycoside may be either a salt with inorganic acid such as, for instance, hydrochloric, hydrobromic, sulphuric or phosphoric acid, or a salt with an organic acid such as, for

example, acetic, benzoic, maleic, fumaric, succinic, tartaric, citric, oxalic, glyoxylic, methanesulphonic, ethanesulphonic or benzenesulphonic acid. A particularly preferred salt is the salt with hydrochloric acid.

The lyophilised preparations of the invention are stable and on reconstitution are rapidly solubilised into a sterile solution suitable for injection. The terms "pharmaceutical", "pharmaceutically" and the like are meant to refer to applications in both the human and the veterinary field. The terms "lyophilised" and "freeze-dried" are used without distinction.

While the main components of the lyophilised formulations of the invention are the anthracycline glycoside active drug substance and the above described cosolubilising agent, an inert excipient is usually present as a further component and it is, for example, lactose, mannitol, sorbitol or maltose, preferably lactose, in a suitable amount.

According to a particularly preferred feature of the invention a stable lyophilised preparation is provided which on reconstitution is rapidly solubilised into a sterile solution suitable for injection and which comprises doxorubicin hydrochloride as the active drug substance, p-hydroxy-benzoic acid methyl ester as the cosolubilising agent and lactose as the inert excipient.

The relative proportions of the active drug substance and cosolubilising agent in the preparations of the invention are such that for 10 parts by weight of active drug substance about 0.1-10, preferably 0.5-2 parts by weight of cosolubilising agent may be present; a particularly preferred weight ratio between the cosolubiliser and the active drug substance is 1:10. The lyophilised formulations of the invention may contain the active drug substance in different amounts; typical formulations contain, for example, 5, 10, 20, 25 or 50 mg of anthracycline glycoside.

As already said, the presence of the cosolubilising agent in the lyophilised preparations of the invention enhances to a great extent the solubility of the drug so that the dissolution times in reconstitution. e.g. with physiological saline solution, are greatly reduced, even from about 2 minutes (for reconstitution of lyophilised formulations not containing solubility-enhancer) to 10-30 seconds or less.

The lyophilised formulations of the invention may be prepared in a conventional way following the usual freeze-drying techniques while taking, however, all precautions required in manipulation of toxic substances such as anthracycline glycosides. Thus, for example, the cosolubiliser, the anthracycline glycoside and the inert excipient are successively made to dissolve under stirring

in a suitable amount of deaerated water for injections and then further water is added to reach the desired final volume. The resulting solution is clarified and filtered under sterile conditions and distributed in sterile containers (vials) of desired capacity. Freezing of the solution, e.g. at -40° to -50°C for about 4 to 5 hours, and drying, e.g. at a final temperature of 40°-50°C for about 6 to 7 hours, is then performed and the vials are sealed under sterile conditions according to usual procedure.

The dry unopened vials are completely stable for at least 3 months at 40°C. Also the reconstitution of the freeze-dried preparations, e.g with sterile physiological saline solution, is carried out in conventional manner. Thus, for example, the physiological saline solution (0.9% sodium chloride aqueous solution) is used in a volume which may vary depending on the kind and on the amount of the active principle contained in the lyophilised cake: volumes from 5 ml to 25 ml of physiological saline solution may be, e.g., used for reconstituting amounts from 5mg to 50 mg of anthracycline glycoside.

The reconstituted solutions of the invention have a pH which may vary between about 3 and about 6.5, depending particularly on the nature of the cosolubilising agent. Still further objects of the invention are the sterile solutions containing the anthracycline glycoside or salt thereof and the cosolubilising agent used for

lyophilisation, (i.e. the solutions leading, by a freeze-drying process, to the lyophilised preparations of the invention) and the sterile injectable solutions obtained after reconstitution, particularly with physiological saline solution, of the lyophilised preparations of the invention.

The invention additionally provides a method of producing a sterile injectable solution of an anthracycline glycoside, which method comprises dissolving, in a solution suitable for injection, a lyophilised preparation comprising
(i) the anthracycline glycoside, or a pharmaceutically acceptable salt thereof, and
(ii) a cosolubilising agent which is a hydroxy-, mercapto- or amino-substituted benzoic acid or an alkali metal salt thereof or a C_1-C_4-alkyl ester thereof, or a ring-halogenated methyl-substituted phenol or an amino acid, or two or more of said compounds.

Also the invention provides a method of improving the solubility of an anthracycline glycoside, or a pharmaceutically acceptable salt thereof, in an injectable solution, which method comprises successively dissolving a cosolubilising agent which is a hydroxy-, mercapto- or amino-substituted benzoic acid or an alkali metal salt thereof or a C_1-C_4- alkyl ester thereof, or a ring-halogenated methyl-substituted phenol or an amino acid, or two or more of said compounds, and the anthracycline glycoside or salt thereof under stirring in a suitable amount of deaearated water for injections, adding further water to reach the desired final volume, clarifying and filtering the resulting solution under sterile conditions, distributing the solution in sterile vials of the desired capacity, and freezing the solution and sealing the vials under sterile conditions.

Owing to the well-known anti-tumour activity of the anthracycline glycoside active drug substance the pharmaceutical compositions of the invention are useful for

treating tumours in both human and animal hosts.

Accordingly, the invention further provides a stable lyophilised preparation for use in treating a tumour in a human or animal host and which on reconstitution is rapidly solubilised into a sterile solution suitable for injection, which preparation comprises

(i) an anthracycline glycoside, or a pharmaceutically acceptable salt thereof, and

(ii) a cosolubilising agent which is a hydroxy-, mercapto- or amino-substituted benzoic acid or an alkali metal salt thereof or a C_1-C_4-alkyl ester thereof, or a ring-halogenated methyl-substituted phenol or an amino acid, or two or more of said compounds.

Examples of tumours 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, Wilms tumour, 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.

The injectable reconstituted solutions of the invention 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 28 days.

Suitable dosages of 4'-epi-doxorubicin and 4'-deoxy-doxorubicin may be, for instance, of 75 to 90

mg/m^2 and, respectively, of 25-35 mg/m^2 given in a single infusion to be repeated at 21 days.

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 also for daunorubicin.

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

EXAMPLE 1

Doxorubicin lyophilised formulations were prepared by the procedure reported below. The relative proportions of the various components employed in preparation were as hereinbelow indicated (amounts are per vial):

doxorubicin.HCl	10.00 mg
lactose.H_2O	52.63 mg (equivalent to 50 mg of anhydrous lactose)
p-hydroxy benzoic acid methyl ester	0.50 mg
water for injections	q.s.to 2.50 ml

The p-hydroxy-benzoic acid methyl ester, the doxorubicin.HCl and the lactose were subsequently dissolved under stirring into water for injections, deaerated by

nitrogen bubbling (about 90% of the finally required water volume). Deaerated water for injections was then added to get the final volume. The solution was clarified through a fibre-glass pre-filter and a 0.45 μ microporous membrane, and then filtered under sterile conditions through a 0.22 μ microporous membrane; the filtrate was directly collected in sterile area. Volumes of 2.5 ml of solution were automatically distributed, under sterile conditions, in sterile type III-colourless glass vials having 8/10 ml capacity.

The solutions were freezed in the vials at a temperature of -40° to -45°C for 4 to 5 hours. Lyophilisation was then carried out, drying the product in the final stage at a 43°-45°C temperature for 6 to 7 hours. Vials were closed with sterile chlorobutyl rubber stoppers and sealed with aluminium sterile caps.

By an analogous procedure, doxorubicin lyophilised formulations containing 20 mg of active drug substance were prepared from:

doxorubicin.HCl	20.00 mg
lactose.H_2O	105.26 mg
p-hydroxy-benzoic acid methyl ester	2.00 mg
water for injections	q.s. to 3.00 ml

Freeze-drying was carried out in type III-glass vials of 20/26 ml capacity.

Again by an analogous procedure, doxorubicin freeze-dried formulations containing 50 mg of active drug substance were prepared from:

doxorubicin.HCl		50.00 mg
lactose.H_2O		263.15 mg
p-hydroxy-benzoic acid methyl ester		5.00 mg
water for injections	q.s. to	5.00 ml

Freeze-drying was carried out in type III-glass vials of 50/57 ml capacity.

Doxorubicin lyophilised formulations analogous to those described above but containing p-hydroxy-benzoic acid or, respectively, p-amino-benzoic acid, or salicylic acid, or 3-methyl-4-chlorophenol or 3,5-dimethyl-4-chlorophenol or glycine, or cysteine or phenylalanine or proline, instead of p-hydroxy-benzoic acid methyl ester, were also prepared by analogous procedures. In particular, for example, formulations as follows were freeze-dried:

10 mg formulation

doxorubicin.HCl		10.00 mg
lactose.H_2O		52.63 mg
3-methyl-4-chlorophenol		1.00 mg
water for injections	q.s. to	2.50 ml

20 mg formulation

doxorubicin.HCl		20.00mg
lactose.H_2O		105.26 mg
p-hydroxy-benzoic acid		2.00 mg
water for injections	q.s. to	3.00 ml

Freeze-drying of these formulations was performed as reported before in this Example for formulations of same doxorubicin dosage.

The amounts indicated above and in the following Examples for the various components are amounts per vial.

EXAMPLE 2

Operating in analogous fashion as described in Example 1, 4'-epi-doxorubicin lyophilised formulations were prepared containing 10, 20 and 50 mg of active drug substance. The relative proportions of the various components employed in preparation were as indicated below.

	10 mg formulation	20mg formulation	50 mg formulation
4'-epi-doxorubicin.HCl	10.00 mg	20.00 mg	50.00 mg
lactose.H_2O	52.63 mg	105.26 mg	263.15 mg
p-hydroxy-benzoic acid methyl ester	1.00 mg	2.00 mg	5.00 mg
water for injections	q.s.to 2.50 ml	q.s.to 3.00 ml	q.s.to 5.00 ml

The three above formulations were freeze-dried as described in Example 1 in type III-glass vials having, respectively, 8/10 ml, 20/26 ml and 50/57 ml capacity.

Similar 4'-epi-doxorubicin freeze-dried formulations were also prepared, in analogous way, but containing a cosolubiliser chosen from p-hydroxy-benzoic acid, p-amino-benzoic acid, salicylic acid, 3-methyl-4-chlorophenol, 3,5-dimethyl-4-chlorophenol or glycine, or cysteine or phenylalanine or proline instead of p-hydroxy-benzoic acid methyl ester.

EXAMPLE 3

Following a procedure analogous to that described in Example 1, 4'-desoxy-doxorubicin lyophilised formulations were prepared containing 5 and 25 mg of active drug substance. The relative proportions of the various components employed in preparation were as indicated below:

	5 mg formulation	25 mg formulation
4'-desoxy-doxorubicin.HCl	5.00 mg	25.00 mg
lactose.H_2O	52.63 mg	263.15 mg
p-hydroxy-benzoic acid methyl ester	0.50 mg	2.50 mg
water for injections	q.s. to 2.00 ml	q.s. to 5.00 ml

The two formulations were freeze-dried in accordance with the procedure of Example 1 in type III-glass vials having 8/10 ml and, respectively, 50/57 ml capacity.

Analogous lyophilised formulations were also prepared containing, however, p-hydroxy-benzoic acid or p-amino-benzoic acid or salicylic acid or 3-methyl-4-chlorophenol or 3,5-dimethyl-4-chlorophenol or glycine or cysteine or phenylalanine or proline, instead of p-hydroxy-benzoic acid methyl ester.

EXAMPLE 4

Proceeding in analogous fashion as reported in Example 1, lyophilised formulations containing daunorubicin (20 and, respectively, 50 mg of active drug substance) or 4-demethoxy-daunorubicin (5 and, respectively, 10 mg of active drug substance) were prepared. The relative proportions of the components in the various formulations were as reported below:

	20 mg formulation	50 mg formulation
daunorubicin.HCl	20.00 mg	50.00 mg
mannitol	100.00 mg	250.00 mg
p-hydroxy-benzoic acid methyl ester	2.00 mg	5.00 mg
water for injections	q.s. to 3.00 ml	q.s. to 7.5 ml

	5 mg formulation	10 mg formulation
4-demethoxy-daunorubicin.HCl	5.00 mg	10.00 mg
lactose.H_2O	52.63 mg	105.26 mg
p-hydroxy-benzoic acid methyl ester	0.50 mg	1.00 mg
water for injections	q.s. to 2.00 ml	q.s.to 3.00 ml

Freeze-drying was performed in type I-glass vials for daunorubicin-containing formulations: vials of 10/14 ml capacity for 20 mg formulations and, respectively, vials of 50/57 ml capacity for 50 mg formulations were used. Type III-glass vials were used for freeze-drying 4-demethoxy-daunorubicin formulations: capacity of vials was 8/10 ml for 5 mg formulations and 20/26ml for 10 mg formulations.

Analogous lyophilised preparations but containing p-hydroxy-benzoic acid or p-amino-benzoic acid or salicylic acid or 3-methyl-4-chlorophenol or 3,5-dimethyl-4-chlorophenol or glycine or cysteine or phenylalanine or proline instead of p-hydroxy-benzoic acid methyl ester, were also prepared.

EXAMPLE 5

Each lyophilised formulation obtained in the preceding Examples was reconstituted with physiological saline solution in the conventional manner. The volume of physiological saline solution used in reconstitution was

dependent on the kind and on the amount of the active drug substance in the freeze-dried preparations. Thus, for example, freeze-dried preparations containing 10 mg of doxorubicin.HCl or 10 mg of 4'-epi-doxorubicin.HCl, as well as those containing 5 mg of 4'-desoxy-doxorubicin.HCl or 5 mg of 4-demethoxy-daunorubicin.HCl, were reconstituted with 5 ml of physiological saline solution.

Freeze-dried preparations containing 20 mg of doxorubicin.HCl or 20 mg of 4'-epi-doxorubicin.HCl or 10 mg of 4-demethoxy-daunorubicin.HCl or 20 mg of daunorubicin.HCl were reconstituted with 10 ml of physiological saline solution, while a volume of 25 ml of physiological saline solution was used to reconstitute lyophilised formulations containing 50 mg of doxorubicin.HCl or 50 mg of 4'-epi-doxorubicin.HCl or 50 mg of daunorubicin.HCl or 25 mg of 4'-desoxy-doxorubicin.HCl.

In all cases the reconstitution time was very short in that complete dissolution was observed in about 5-20 seconds, and, in any case, it did not require more than 30 seconds.

CLAIMS

1. A stable lyophilised preparation which on reconstitution is rapidly solubilised into a sterile solution suitable for injection, which preparation comprises:

(i) an anthracycline glycoside, or a pharmaceutically acceptable salt thereof, and

(ii) a cosolubilising agent which is a hydroxy-, mercapto- or amino-substituted benzoic acid or an alkali metal salt thereof or a C_1-C_4 alkyl ester thereof, or a ring-halogenated methyl-substituted phenol or an amino acid, or two or more of said compounds;

with the proviso that component (i) is not doxorubicin hydrochloride when 4 parts by weight of p-hydroxy-benzoic acid methyl ester and 1 part by weight of p-hydroxy-benzoic acid propyl ester are present together as co-solubilising agents.

2. A preparation according to claim 1 wherein the anthracycline glycoside is chosen from doxorubicin, 4'-epi-doxorubicin, 4'-desoxy-doxorubicin, daunorubicin and 4-demethoxy-daunorubicin.

3. A preparation according to claim 1 or 2 wherein the salt of the anthracycline glycoside is the hydrochloride.

4. A preparation according to any one of the preceding claims wherein the cosolubilising agent is either

a compound selected from the group consisting of p-hydroxy-benzoic acid and the methyl ester thereof, p-amino-benzoic acid and the methyl ester thereof, o-hydroxy-benzoic acid and the methyl ester thereof, 3-methyl-4-chlorophenol and 3,5-dimethyl-4-chlorophenol, or two or more of said compounds.

5. A preparation according to claim 4 wherein the cosolubilising agent is p-hydroxy-benzoic acid methyl ester.

6. A preparation according to any one of the preceding claims comprising an inert excipient.

7. A preparation according to claim 6 wherein the inert excipient is lactose.

8. A stable lyophilised preparation which on reconstitution is rapidly solubilised into a sterile solution suitable for injection, which preparation comprises doxorubicin hydrochloride, p-hydroxy-benzoic acid methyl ester and lactose.

9. A preparation according to any one of claims 1 to 8 for use in treating a tumour in a human or animal host.

10. A stable lyophilised preparation for use in treating a tumour in a human or animal host and which on reconstitution is rapidly solubilised into a sterile solution suitable for injection, which preparation comprises (i) an anthracycline glycoside, or a pharmaceutically acceptable salt thereof, and
(ii) a cosolubilising agent which is a hydroxy-, mercapto-

or amino-substituted benzoic acid or an alkali metal salt thereof or a C_1-C_4-alkyl ester thereof, or a ring-halogenated methyl-substituted phenol or an amino acid, or two or more of said compounds.

11. A preparation according to claim 10, wherein the anthracycline glycoside is chosen from doxorubicin, 4'-epi-doxorubicin, 4'-desoxy-doxorubicin, daunorubicin and 4-demethoxy-daunorubicin.

12. A preparation according to claim 10 or 11 wherein the pharmaceutically acceptable salt of the anthracycline glycoside is the hydrochloride.

13. A preparation according to any one of claims 10 to 12 wherein the cosolubilising agent is p-hydroxy-benzoic acid methyl ester.

14. A preparation according to any one of claims 10 to 13, comprising an inert excipient.

15. A preparation according to claim 14, wherein the inert excipient is lactose.

16. A preparation according to any one of claims 10 to 15 for use in inhibiting the growth of a tumour selected from sarcomas, carcinomas, lymphomas, neuroblastoma, leukemias and Wilms tumour.

17. A preparation according to claim 16 wherein the tumour is seleccted from Moloney Sarcoma Virus, Sarcoma 180 Ascites, Solid Sarcoma 180, gross transplantable leukemia, L 1210 leukemia and lymphocytic P388 leukemia.

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18. A sterile solution which can be freeze-dried to give a lyophilised preparation according to any one of claims 1 to 8.

19. A sterile solution which can be freeze-dried to give a lyophilised preparation according to any one of claims 10 to 17.

20. A sterile injectable solution obtained upon reconstitution of a lyophilised preparation according to any one of claims 1 to 8.

21. A sterile injectable solution obtained upon reconstitution of a lyophilised preparation as defined in any one of claims 10 to 17.

22. A sterile injectable solution according to claim 20 or 21 obtained upon reconstitution with physiological saline solution.

23. A sterile injectable solution according to any one of claims 20 to 22 for use in treating a tumour in a human or animal host.

24. A method of producing a sterile injectable solution of an anthracycline glycoside, which method comprises dissolving, in a solution suitable for injection, a lyophilised preparation comprising

(i) the anthracycline glycoside, or a pharmaceutically acceptable salt thereof, and

(ii) a cosolubilising agent which is a hydroxy-, mercapto- or amino-substituted benzoic acid or an alkali metal salt

thereof or a C_1-C_4-alkyl ester thereof, or a ring-halogenated methyl-substituted phenol or an amino acid, or two or more of said compounds.

25. A method accoding to claim 24 wherein the solution suitable for injection is physiological saline solution.

26. A method of improving the solubility of an anthracycline glycoside, or a pharmaceutically acceptable salt thereof, in an injectable solution, which method comprises successively dissolving a cosolubilising agent which is a hydroxy-, mercapto- or amino-substituted benzoic acid or an alkali metal salt thereof or a C_1-C_4-alkyl ester thereof, or a ring-halogenated methyl-substituted phenol or an amino acid, or two or more of said compounds, and the anthracycline glycoside or salt thereof under stirring in a suitable amount of deaerated water for injections, adding further water to reach the desired final volume, clarifying and filtering the resulting solution under sterile conditions, distributing the solution in sterile vials of the desired capacity, and freezing the solution and sealing the vials under sterile conditions.

27. A lyophilised formulation substantially as hereinbefore described in any one of Examples 1 to 4.