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(54) **Title**: PHARMACEUTICAL SOLUTIONS AND METHOD FOR SOLUBILIZING THERAPEUTIC AGENTS

(57) **Abstract**: Pharmaceutical solutions containing hydrophobic or lipophilic therapeutic agents and methods for producing the same are provided. Pharmaceutical solutions of the invention are produced by dissolving the therapeutic agent in one or more to-

PHARMACEUTICAL SOLUTIONS AND METHOD FOR SOLUBILIZING THERAPEUTIC AGENTS

This patent application claims the benefit of priority from U.S. Application Serial No. 61/040,281, filed March 28, 2008, teachings of which are herein incorporated by reference in their entirety.

Background of the Invention

A vast number of potential therapeutic agents are discovered each year, many of which are water insoluble or poorly water soluble. For such hydrophobic compounds, direct injection may be impossible or highly dangerous, and can result in hemolysis, phlebitis, hypersensitivity, organ failure and/or death. Such compounds are termed by pharmacists as "lipophilic", "hydrophobic", or in their most insoluble form, "amphiphobic".

A few examples of therapeutic agents in these categories are ibuprofen, diazepam, griseofulvin, cyclosporin, cortisone, proleukin, etoposide and paclitaxel. (Kagkadis et al. *PDA J. Pharm. Sci. Tech.* 1996 50(5):317-323; Dardel *Anaesth. Scand.* 1976 20:221-24; Sweetana and Akers *PDA J. Pharm. Sci. Tech.* 1996 50(5):330-342).

Administration of chemotherapeutic agents is particularly problematic. Most of these agents are poorly soluble and thus are difficult to deliver in aqueous solvents and to supply at therapeutically effective levels. Further, water-soluble, chemotherapeutic agents are generally taken up by both cancer and non-cancer cells, making such agents non-specific and oftentimes unacceptably toxic.

For therapeutic agents that cannot be formulated as an aqueous solution, emulsions have oftentimes provided a cost-effective and therapeutically acceptable alternative. However, it is difficult to render emulsions sterile and/or

endotoxin free for intravenous injection. Oils typically used for pharmaceutical emulsions include saponifiable oils from the family of triglycerides, for example, soybean oil, sesame seed oil, cottonseed oil, safflower oil and the like (Hansrani, et al. *J. Parenter. Sci. Technol.* 1983 37:145-150). One or more surfactants are used to stabilize the emulsion, and excipients are added to render the emulsion more biocompatible, stable and less toxic. Lecithin from egg yolks or soybeans is a commonly used surfactant. Sterile manufacturing can be accomplished by sterilization of all the components before manufacture, followed by aseptic technique in all stages of manufacture. Improved ease of manufacture and assurance of sterility is obtained by terminal sterilization following sanitary manufacture, either by heat or by filtration. However, terminal sterilization by heat or filtration treatments is not suitable for all emulsions.

Vitamin E emulsions have been disclosed. For example, injectable vitamin E emulsions are described by Hidiroglou and Karpinski (*Brit. J. Nutrit.* 1988 59:509-518) for dietary supplementation in sheep and for research on the pharmacokinetics of vitamin E and its derivatives. An injectable form of vitamin E for mice was prepared by Kato et al. (*Chem. Pharm. Bull.* 1993 41(3):599-604). Micellar solutions were formulated with TWEEN 80, BRIJ 58 and HCO-60. Isopropanol was used as a co-solvent, and was then removed by vacuum evaporation; the residual oil glass was then taken up in water with vortexing as a micellar suspension. An emulsion was also prepared by dissolving vitamin E with soy phosphatidycholine (lecithin) and soybean oil. Water was added and the emulsion prepared with sonication. Ethanol-free emulsions of alpha-tocopherol, stabilized by biocompatible surfactants, as a vehicle or carrier for

therapeutic drugs is also disclosed in U.S. Patent Nos. 6,667,048 and 6,660,286.

E-Ferol, a vitamin E emulsion for vitamin E supplementation and therapy in neonates was also disclosed by Alade et al. (*Pediatrics* (1986) 77(4):593-597). The surfactant mixture used to emulsify the 25 mg/mL vitamin E in E-Ferol was composed of 9% TWEEN 80 and 1% TWEEN 20. However, this supplement was not safe.

An alternative means of solubilizing low solubility compounds is direct solubilization in a non-aqueous milieu, for example, alcohols (such as ethanol), dimethylsulfoxide, and/or triacetin. For example, WO 95/11039 describes the use of vitamin E (100 mg), lecithin (20 mg), ethanol (100 mg) and EUTANOL (500 mg) as an injectable formulation of the immunosuppressant molecule cyclosporine (50 mg). U.S. Patent No. 5,689,846 discloses various alcohol solutions of paclitaxel. U.S. Patent No. 5,573,781 discloses the dissolution of paclitaxel in ethanol, butanol and hexanol and an increase in the antitumor activity of paclitaxel when delivered in butanol and hexanol as compared to ethanol.

WO 95/31217 discloses that tocopherols can be used as solvents and/or emulsifiers of drugs that are substantially insoluble in water, in particular for the preparation of topical formulations. The use of vitamin E-TPGS as an emulsifier in formulations containing high levels of α-tocopherol is mentioned and formulations for topical administration composed of a lipid layer (α-tocopherol), the drug and vitamin E-TPGS as an emulsifier in quantities of less than 25% w/w of the formulation.

WO 97/03651 discloses lipid vehicle drug delivery compositions that contain at least five ingredients: a therapeutic drug, vitamin E, an oil in which the drug and vitamin E are dissolved, a stabilizer (either phospholipid,

a lecithin, or a poloxamer which is a polyoxyethylene-polyoxypropylene copolymer) and water.

Similarly, U.S. Patent No. 6,962,691 teaches topical compositions composed of at least ten ingredients: alendronate sodium, povidone, povidone vinyl acetate, vitamin E, menthol, dimethyl isosorbide, acetone, ethanol, tetrafluroroethane and, dichlorodifluoromethane.

U.S. Patent No. 4,393,073 also suggests vitamin E as an active ingredient in pharmaceutical compositions containing ethanol.

Summary of the Invention

An aspect of the present invention relates to a pharmaceutical solution comprising a therapeutic agent dissolved in one or more natural or synthetic tocopherols or tocotrienols, or any combination thereof and one or more alcohols or glycols, or any combinations thereof. In some embodiments, the tocopherol(s) and/or tocotrienol(s) is in an amount from about 30% to about 99% (w/w) and the alcohol(s) and/or glycol(s) is in an amount from about 1% to about 70% (w/w).

Another aspect of the present invention relates to methods for producing these pharmaceutical solutions.

Another aspect of the present invention relates to methods of treatment of a patient with these pharmaceutical solutions.

Detailed Description of the Invention

The present invention is directed to the use of one or more tocopherols and/or tocotrienols and one or more alcohols and/or glycols as pharmaceutically acceptable solvents for solubilizing therapeutic agents, in particular hydrophobic or lipophilic therapeutic agents. Advantageously, the resulting pharmaceutical solution is not

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