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(54) **COMPOSITIONS AND METHODS OF DELIVERY OF PHARMACOLOGICAL AGENTS**

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(57) **ABSTRACT**

The present invention relates to a pharmaceutical composition comprising a pharmaceutical agent and a pharmaceutically acceptable carrier, which carrier comprises a protein, for example, human serum albumin and/or deferoxamine. The human serum albumin is present in an amount effective to reduce one or more side effects associated with administration of the pharmaceutical composition. The invention also provides methods for reducing one or more side effects of administration of the pharmaceutical composition, methods for inhibiting microbial growth and oxidation in the pharmaceutical composition, and methods for enhancing transport and binding of a pharmaceutical agent to a cell.

12 Claims, No Drawings

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COMPOSITIONS AND METHODS OF DELIVERY OF PHARMACOLOGICAL AGENTS

CROSS-REFERENCE TO RELATED PATENT APPLICATIONS

This patent application is a continuation of patent application Ser. No. 10/731,224, which claims the benefit of U.S. Provisional Patent Application No. 60/432,317 filed Dec. 9, 2002, U.S. Provisional Patent Application 60/526,544 filed Dec. 3, 2003, U.S. Provisional Patent Application 60/526,773 filed Dec. 4, 2003, and U.S. Provisional Patent Application 60/527,177 filed Dec. 5, 2003.

FIELD OF THE INVENTION

This invention pertains to pharmaceutical compositions comprising pharmaceutically active agents for parenteral or other internal use, which have the effect of reducing certain undesirable side effects upon administration when compared with available formulations of similar drugs.

BACKGROUND OF THE INVENTION

It is well recognized that many drugs for parenteral use, especially those administered intravenously, cause undesirable side effects such as venous irritation, phlebitis, burning and pain on injection, venous thrombosis, extravasation, and other administration related side effects. Many of these drugs are insoluble in water, and are thus formulated with solubilizing agents, surfactants, solvents, and/or emulsifiers that are irritating, allergenic, or toxic when administered to patients (see, e.g., Briggs et al., *Anesthesis* 37, 1099 (1982), and Waugh et al., *Am. J. Hosp. Pharmacists,* 48, 1520 (1991)). Often, the free drug present in the formulation induces pain or irritation upon administration. For example, phlebitis was observed in 50% of patients who received peripheral vein administration of ifosfamide and vinorelbine as first-line chemotherapy for advanced non-small cell lung carcinoma. (see, e.g., Vallejo et al., *Am. J. Clin. Oncol.,* 19(6), 584-8 (1996)). Moreover, vancomycin has been shown to induce side effects such as phlebitis (see, e.g., Lopes Rocha et al., *Braz. J. Infect. Dis.,* 6(4), 196-200 (2002)). The use of cisplatin, gemcitabine, and SU5416 in patients with solid tumors has resulted in adverse events such as deep venous thromboses and phlebitis (see, e.g., Kuenen et al., *J. Clin. Oncol.,* 20(6), 1657-67 (2002)). In addition, propofol, an anesthetic agent, can induce pain on injection, burning and vein irritation, particularly when administered as a lecithin-stabilized fat emulsion (see, e.g, Tan et al., *Anathesia,* 53, 468-76, (1998)). Other drugs that exhibit administration-associated side effects include, for example, Taxol (paclitaxel) (see, e.g., package insert for Taxol I.V.), codarone (amiodarone hydrochloride) (see, e.g., package insert for Codarone I.V.), the thyroid hormone T3 or liothyronine (commercially available as Triostat), thiotepa, bleomycin, and diagnostic radiocontrast agents.

Another problem associated with the manufacture of drugs for injection, particularly water insoluble drugs, is the assurance of sterility. Sterile manufacturing of drug emulsions/dispersions can be accomplished by absolute sterilization of all the components before manufacture, followed by absolutely aseptic technique in all stages of manufacture. However, such methods are time consuming and expensive. In addition, the oxidation of drug formulations by exposure to air during manufacture or storage can lead to, for example,

reduced pH, drug degradation, and discoloration, thereby destabilizing the drug formulation and/or reducing shelf life.

To circumvent the problems associated with administration-related side effects of drug formulations, alternate formulations have been attempted. With respect to propofol, for example, methods for reducing propofol-induced pain include increasing the fat content of the solvent (e.g., long chain triglycerides (LCT)), premedication, pretreatment with non-steroidal drugs, local anaesthetics, opioids, the addition of lidocaine, the addition of cyclodextrin, and microfiltration (see, e.g., Mayer et al., *Anaesthesist,* 45(11), 1082-4 (1996), Davies, et al. *Anaesthesia,* 57, 557-61 (2002), Doenicke, et al., *Anaesth. Analg.,* 82, 472-4 (1996), Larsen et al., *Anaesthesitis* 50, 842-5 (2001), Lilley et al., *Anaesthesia,* 51, 815-8 (1996), Bielen et al., *Anesth. Analg.,* 82(5), 920-4 (1996), and Knibbe et al., *Br. J. Clin. Pharmacol.,* 47(6), 653-60 (1999)). These formulations, however, induce other side effects (e.g., cardiovascular complications), or cause destabilization of propofol emulsions.

To overcome the problem of bacterial contamination, propofol formulations have been developed with antibacterial agents, such as an EDTA equivalent (e.g., edetate), pentetate, or sulfite-containing agents, or they have been have been formulated with a lower pH (see, e.g., U.S. Pat. Nos. 5,714,520, 5,731,355, 5,731,356, 6,028,108, 6,100,302, 6,147,122, 6,177,477, 6,399,087, 6,469,069, and International Patent Application No. WO 99/39696). Since edetate and pentetate are metal ion chelators, however, they have the potential to be dangerous by scavenging the essential metal ions from the body system. Moreover, the addition of sulphites to drug formulations presents potential adverse effects to the pediatric population and for those in the general population who are allergic to sulphur.

Thus, there remains a need for a composition and method that reduce or eliminate the side effects associated with the parenteral or in vivo administration of drugs. There also is a need for a pharmaceutical composition that is sterile, and methods of preparing such a composition. In addition, there is a need for a pharmaceutical composition and method that reduce or eliminate oxidation of pharmaceutical formulations to prevent drug destabilization.

The invention provides such compositions and methods. These and other advantages of the invention, as well as additional inventive features, will be apparent from the description of the invention provided herein.

BRIEF SUMMARY OF THE INVENTION

The invention provides various embodiments of pharmaceutical compositions. One, some, or all of the properties of the various embodiments can be found in different embodiments of the invention and still fall within the scope of the appended claims.

The invention provides a pharmaceutical composition comprising a pharmaceutical agent and a pharmaceutically acceptable carrier, wherein the pharmaceutically acceptable carrier comprises a protein, such as albumin, more preferably human serum albumin, in an amount effective to reduce one or more side effects of administration of the pharmaceutical composition into a human, and wherein the pharmaceutically acceptable carrier comprises deferoxamine in an amount effective to inhibit microbial growth in the pharmaceutical composition. The invention also provides a pharmaceutical composition comprising a pharmaceutical agent and a pharmaceutically acceptable carrier, wherein the pharmaceutically acceptable carrier comprises a protein, such as albumin, in an amount effective to reduce one or more side effects of

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