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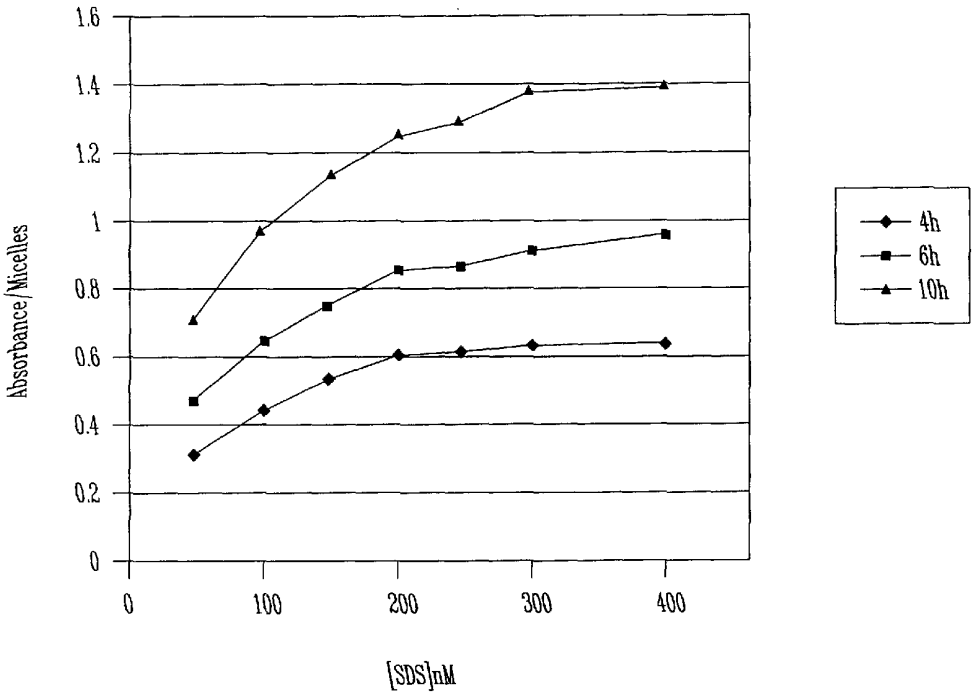
(54) Title: NOVEL MICROEMULSION AND MICELLE SYSTEMS FOR SOLUBILIZING DRUGS



(57) Abstract: A microemulsion delivery system for water insoluble or sparingly water soluble drugs that comprise a long polymer chain surfactant component and a short fatty acid sufractant component, with the amount of each being selected to provide stable microemulsion or micellar systems.

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TITLE: NOVEL MICROEMULSION AND MICELLE SYSTEMS FOR SOLUBILIZING DRUGS

FIELD OF THE INVENTION

This invention relates to compositions and a method for making microemulsion delivery systems for water insoluble or sparingly soluble drugs.

BACKGROUND OF THE INVENTION

Dissolving water insoluble agents into aqueous solutions appropriate for human use (e.g., oral, topical application, intravenous injection, intramuscular injection, subcutaneous injection) represents a major technological hurdle for pharmaceutical delivery systems. Previous attempts have resulted in a number of serious side effects caused not by the drugs, but by the carrier agents used to dissolve the drug. These complications include significant hypotension during intravenous injection (e.g., amiodarone), painful injection with subsequent phlebitis (e.g., valium), anaphylaxis (e.g., propofol in Cremaphor), postoperative infections (e.g., propofol in Intralipid), and others. Clearly, an approach aimed at improving the solubilization of these drugs and avoiding the complications of solubilizing agents would enhance the quality of health care to patients. For many drugs, a major technological barrier for their routine clinical use is very poor solubility in the aqueous phase. For such drugs, oil/water macroemulsions have been commonly used in the pharmaceutical industry to "dissolve" a drug to its desired concentration. For example, the anesthetic propofol is supplied to the health care industry as Baxter PPI propofol (Gensia Sicor, Inc.) or Diprivan (AstraZeneca Pharmaceuticals, Inc.), as a macroemulsion of propofol in soybean oil (100 mg/mL), glycerol (22.5 mg/mL), egg lecithin (12 mg/mL), and disodium edetate (0.005%) or metabisulfite; with sodium hydroxide to adjust pH to 7.0-8.5. However, the stability of such macroemulsions is relatively poor, and the oil and water components separate into distinct phases over time. In addition, the droplet size of the macroemulsion increases with time. Macroemulsions

are defined as formed by high shear mixing and normally having particles of 1 micron to 10 microns in size.

In contrast to macroemulsion systems, microemulsion systems consisting of oil, water, and appropriate emulsifiers can form spontaneously and are therefore thermodynamically stable. For this reason, microemulsion systems theoretically have an infinite shelf life under normal conditions in contrast to the limited life of macroemulsions (e.g., two years for Baxter PPI propofol). In addition, the size of the droplets in such microemulsions remains constant and ranges from 100-1000 angstroms (10-100 nm), and has very low oil/water interfacial tension. Because the droplet size is less than 25% of the wavelength of visible light, microemulsions are transparent. Three distinct microemulsion solubilization systems that can be used for drugs are as follows:

1. oil in water microemulsions wherein oil droplets are dispersed in the continuous aqueous phase;

2. water in oil microemulsions wherein water droplets are dispersed in the continuous oil phase;

3. bi-continuous microemulsions wherein microdomains of oil and water are interdispersed within the system. In all three types of microemulsions, the interface is stabilized by an appropriate combination of surfactants and/or co-surfactants.

It can be seen from the above description that there is a real and continuing need for the development of new and effective drug delivery systems for water insoluble or sparingly soluble drugs. One such approach might be pharmaceutical microemulsions. However, one must choose materials that are biocompatible, non-toxic, clinically acceptable, and use emulsifiers in an appropriate concentration range, and form stable microemulsions. This invention has as its objective the formation of safe and effective pharmaceutical microemulsion delivery systems.

The delivery system described herein has been found particularly useful for propofol, but is not exclusively limited thereto. It is presented here as an example of a state of the art drug, normally poorly soluble in its present

delivery form, but when properly delivered in a pharmaceutical microemulsion carrier, the current problems can be solved. Such current problems in the case of propofol stem directly from its poor solubility in water. These include significant pain during injection, and post-operative infections in some patients who, for example, receive a macroemulsion of propofol for surgery or sedation.

In an attempt to lower health care costs, there has been an explosive growth in the number of surgical procedures being done on an outpatient basis in the United States. In the outpatient setting, the use of short acting anesthetics allows for prompt emergence from anesthesia and provides expeditious discharge of patients to their home. Propofol (2,6-diisopropylphenol, molecular weight 178.27) is an organic liquid similar to oil, has very little solubility in the aqueous phase (octanol/water partition coefficient 6761:1 at a pH 6.0-8.5), and is a short-acting intravenous anesthetic that meets the criteria of rapid anesthetic emergence with minimal side effects. Currently, propofol is supplied as a macroemulsion, an opaque dispersion using biocompatible emulsifiers such as phospholipids, cholesterol, and others. In addition, a number of other drawbacks cause significant limitations and risk to some patients.

Most of the disadvantages of propofol relate to its commercial formulation and physical properties. That is, propofol is a liquid at room temperature and is extremely insoluble in water. The inherent lipophilicity of propofol makes dissolution in saline or phosphate buffer problematic. In the early 1980's, Cremaphor was used as a solvent, but subsequently abandoned because of its propensity to cause life threatening anaphylactic reactions. Since that time, propofol is suspended in a macroemulsion consisting of 10% Intralipid, a milky white solution of soybean oil and other additives as specified previously. The current commercial formulation of propofol has several major disadvantages. First, use of propofol in Intralipid has been implicated as the causative agent contributing to several cases of postoperative infection in human patients as detailed by the Center for Disease Control and

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