

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
7 February 2002 (07.02.2002)

PCT

(10) International Publication Number
WO 02/09671 A2

(51) International Patent Classification⁷: A61K 9/107

Box 115500, Gainesville, FL 32611-5500 (US). **SHAH, Dinesh** [US/US]; P.O. Box 115500, Gainesville, FL 32611-5500 (US).

(21) International Application Number: PCT/US01/24167

(22) International Filing Date: 31 July 2001 (31.07.2001)

(74) Agent: **SEASE, Edmund, J.**; Zarley, McKee, Thomte, Voorhees & Sease, Suite 3200, 801 Grand Avenue, Des Moines, IA 50309-2721 (US).

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/630,237 1 August 2000 (01.08.2000) US

(81) Designated States (*national*): AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

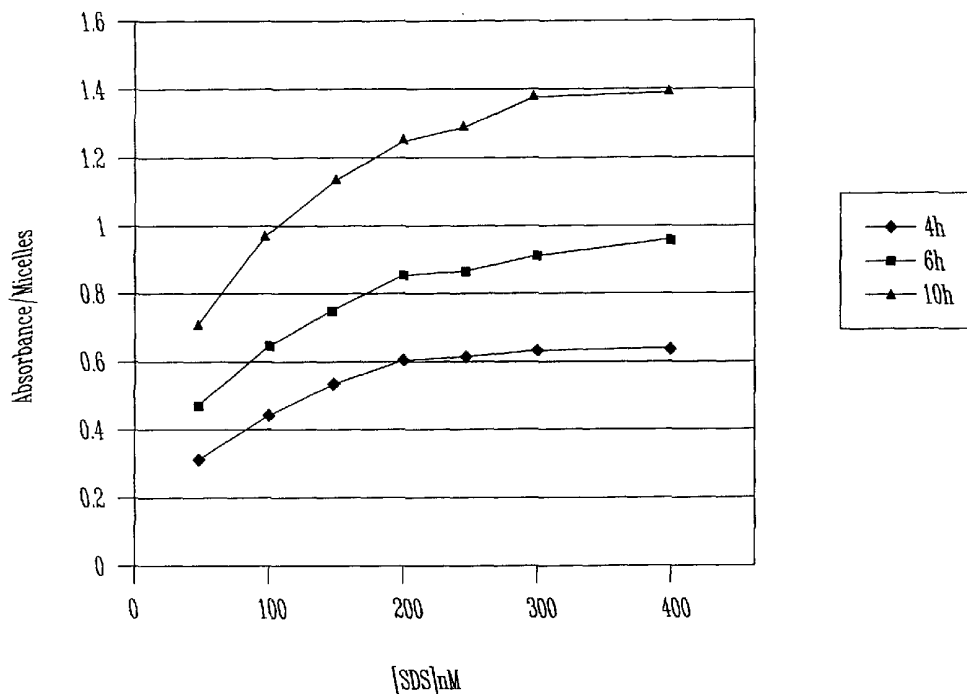
(72) Inventors; and

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(75) Inventors/Applicants (*for US only*): **DENNIS, Donn, M.** [US/US]; P.O. Box 115500, Gainesville, FL 32611-5500 (US). **GRAVENSTEIN, Nikolaus** [US/US]; P.O. Box 115500, Gainesville, FL 32611-5500 (US). **MODELL, Jerome, H.** [US/US]; P.O. Box 115500, Gainesville, FL 32611-5500 (US). **MOREY, Timothy, E.** [US/US]; P.O. Box 115500, Gainesville, FL 32611-5500 (US).

[Continued on next page]

(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 surfactant component, with the amount of each being selected to provide stable microemulsion or micellar systems.



WO 02/09671 A2



Published:

— without international search report and to be republished upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

TITLE: NOVEL MICROEMULSION AND MICELLE SYSTEMS FOR
SOLUBILIZING DRUGS

FIELD OF THE INVENTION

5 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
10 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
15 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
20 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
25 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
30 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;
- 15 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

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.