



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification ⁵ : A61K 31/66, 31/685, 31/20</p>	<p>A1</p>	<p>(11) International Publication Number: WO 94/05298 (43) International Publication Date: 17 March 1994 (17.03.94)</p>
<p>(21) International Application Number: PCT/US93/00044 (22) International Filing Date: 5 January 1993 (05.01.93)</p> <p>(30) Priority data: 102984 28 August 1992 (28.08.92) IL 103907 27 November 1992 (27.11.92) IL</p> <p>(71) Applicant: PHARMOS CORPORATION [US/US]; 599 Lexington Avenue, New York, NY 10022 (US).</p> <p>(72) Inventors: AVIV, Haim ; 9 Habrosh Street, Rehovot (IL). FRIEDMAN, Doron ; 33 Alon Street, Carmei Yossef (IL). BAR-ILAN, Amir ; 14 Tamar Street, Neve Mons- son (IL). VERED, Micha ; 11 Weizmann Street, Rehovot (IL).</p>		<p>(74) Agents: TERZIAN, Berj, A. et al.; Pennie & Edmonds, 1155 Avenue of the Americas, New York, NY 10036 (US).</p> <p>(81) Designated States: AT, AU, BB, BG, BR, CA, CH, DE, DK, ES, FI, GB, HU, JP, KR, LK, LU, MG, MN, MW, NL, NO, NZ, PL, RO, RU, SD, SE, UA, European pa- tent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG).</p> <p>Published <i>With international search report.</i></p>
<p>(54) Title: SUBMICRON EMULSIONS AS OCULAR DRUG DELIVERY VEHICLES</p> <p>(57) Abstract</p> <p>An ocular drug delivery vehicle of an oil-in-water submicron emulsion comprising about 0.5 to 50 % of a first component of an oil, about 0.1 to 10 % of a second component of an emulsifier, about 0.05 to 5 % of a non-ionic surfactant and an aqueous component, with the mean droplet size being in the submicron range, i.e., below about 0.5 μm and preferably between about 0.1 and 0.3 μm. Also, topical pharmaceutical compositions containing a drug such as an anti-glaucoma drug, beta adrenergic blocker or other autonomic system drug, a local anesthetic, a steroid, a non-steroidal anti-inflammatory drug, an antibiotic drug, an anti-fungal drug, an antiviral drug or combinations thereof and the vehicle described above. Methods of administering such vehicles or compositions to the eye of a patient while reducing irritation thereof and providing increased bioavailability of the drug.</p>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FR	France	MR	Mauritania
AU	Australia	GA	Gabon	MW	Malawi
BB	Barbados	GB	United Kingdom	NE	Niger
BE	Belgium	GN	Guinea	NL	Netherlands
BF	Burkina Faso	GR	Greece	NO	Norway
BG	Bulgaria	HU	Hungary	NZ	New Zealand
BJ	Benin	IE	Ireland	PL	Poland
BR	Brazil	IT	Italy	PT	Portugal
BY	Belarus	JP	Japan	RO	Romania
CA	Canada	KP	Democratic People's Republic of Korea	RU	Russian Federation
CF	Central African Republic	KR	Republic of Korea	SD	Sudan
CG	Congo	KZ	Kazakhstan	SE	Sweden
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovak Republic
CM	Cameroon	LU	Luxembourg	SN	Senegal
CN	China	LV	Latvia	TD	Chad
CS	Czechoslovakia	MC	Monaco	TG	Togo
CZ	Czech Republic	MG	Madagascar	UA	Ukraine
DE	Germany	ML	Mali	US	United States of America
DK	Denmark	MN	Mongolia	UZ	Uzbekistan
ES	Spain			VN	Viet Nam
FI	Finland				

**SUBMICRON EMULSIONS AS
OCULAR DRUG DELIVERY VEHICLES**

5 **FIELD OF THE INVENTION**

The present invention relates to the field of drug delivery and, particularly, to the administration of various pharmaceutical agents to a patient through the eye by application of the innovative compositions of these agents in a non-irritating submicron
10 emulsion.

BACKGROUND OF THE PRESENT INVENTION

The primary problem associated with topical
15 applications of drugs to the eye is that the human eye is a very sensitive organ and any substance which is not compatible with it causes irritation and pain. This evokes blinking and reflex-tearing, which is a physiological reaction intended for removal of the
20 irritating substance from the ocular surface. Irritation is a major cause of poor patient compliance with many ophthalmic drugs. This phenomenon is aggravated by the need to include relatively high concentrations of a drug in such ophthalmic
25 compositions in order to obtain a therapeutic effect, since bioavailability of topically applied ophthalmic drugs is generally very poor. Thus, there is no doubt that a reduction in the irritating effect of a drug will enable increased ocular drug bioavailability, increased patient compliance with the drug, and
30 enhanced therapeutic efficacy of the drug.

Currently, aqueous solutions are by far the most
common vehicles for ophthalmic drugs. Such vehicles
have a serious drawback, however, in that the ocular
35 bioavailability of drugs administered thereby is generally very poor due to rapid drainage and tear turnover. See Fitzgerald et al. (1987) J. Pharm.

Pharmacol. 39:487-490. A typical dose of ophthalmic solution is in the range of about 50-100 μ l, which far exceeds the normal lachrymal volume of about 7-10 μ l. Thus, the portion of the dose that is not
5 eliminated by spillage from the pulberal fissure is quickly drained. Furthermore, lachrymation and physiological tear turnover, which in humans is about 16% per minute under normal conditions, increases
10 after the introduction of the solution, resulting in rapid dilution of the remaining amount of drug that has not been spilled or drained. As a consequence, the contact time with the absorbing surfaces of the eye (i.e., the cornea and sclera) of drugs which are applied to the eye via liquid aqueous compositions is
15 less than about two minutes.

Another drawback of aqueous vehicles is that many drugs which may potentially be used in eye therapy are hydrophobic and their delivery into the eye by such aqueous vehicles is not possible. While such
20 hydrophobic drugs may potentially be administered to the eye in conjunction with various organic solvents, the use of such solvents usually causes irritation and inflammatory reactions. See Harmia et al. (1987) Pharm. Acta Helv. 62:322-332.

25 Attempts have been made to develop various delivery vehicles in which the drug residence time in the eye is increased. The most direct approach for achieving this goal is by an increase in the viscosity of the vehicle. Thus, various viscous vehicles, such
30 as hydrogels or ointments, have been attempted, some of which also enable delivery of hydrophobic drugs into the eye. Additionally, many attempts to use various non-conventional carriers, such as liposomes, micellar solutions and nanoparticles, as vehicles of
35 ophthalmic drugs have also been made. While the use of such delivery systems may provide limited success in prolonging the residence time of drugs in the eye

and hence some enhancement of the ocular bio-availability, such carriers also produce various deleterious side effects. See Harmia et al., supra., Saettone et al. (1988) J. Pharm. 43:67-70 and Meisner et al. (1989) Int. J. Pharm. 55:105-113.

Emulsions have also been suggested as vehicles for delivery of drugs to the eye in references such as EP 391,369, Ellis et al. (1987) J. Ocular Pharmacol. (U.S.) 3:121-128, and Shell (1984) Surv. Ophthalmol. 29:177-178. Nevertheless, the practical inability to realize the potential of emulsion systems for ocular drug delivery stems predominantly from two problems. First, ocular drug formulations must be comfortable to the patient as well as safe, due to the sensitivity of the delicate eye tissues involved. Second, emulsions are generally metastable dispersions of immiscible fluids and these instability problems must be overcome.

An emulsion is a dispersion of oil in water ("o/w"), and can be defined as either a macroemulsion or a microemulsion. A macroemulsion is a cloudy turbid composition having an oil-droplet size of 0.5 to 100 μm and is generally thermodynamically unstable. In comparison, a microemulsion is a translucent to transparent composition having a droplet size of 0.005 to 0.5 μm , is thermodynamically stable and is generally self emulsifying. See, e.g., Friberg et al. (1987) Microemulsions Structure and Dynamics, CRC Press Inc., Boca Raton, FL, pp. 154. Also, the proportion of surfactants to oil required to generate microemulsions is generally much higher than in macroemulsions.

Emulsions developed specifically for ophthalmic use have attempted to solve the problem of inherent instability through the use of microemulsions or the addition of stabilizing polymers to classical emulsions. In several instances, specific drugs have

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.