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(54) Title: SUBMICRON EMULSIONS AS OCULAR DRUG DELIVERY VEHICLES

(57) Abstract

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 antifungal 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.

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SUBMICRON EMULSIONS AS OCULAR DRUG DELIVERY VEHICLES

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 emulsion.

BACKGROUND OF THE PRESENT INVENTION

The primary problem associated with topical 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 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 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 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 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 μl, which far exceeds the normal lachrymal volume of about 7-10 μl. Thus, the portion of the dose that is not 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 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 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 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.

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 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 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 Pharmcol. (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

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