Biocompatible Microemulsions and Their Prospective Uses in Drug Delivery

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ABSTRACT: Efficacy of lipophilic drugs is often hindered due to their poor aqueous solubility leading to low absorption after *in vivo* administration. A part of the administered dose is absorbed and reaches the pharmacological site of action and the remainder causes toxicity and undesirable side effects due to unwanted biodistribution. Enhancement in drug efficacy and lowering of drug toxicity could be achieved through encapsulation and delivery of the lipophilic drugs in aqueous based delivery systems. Microemulsions are macroscopically homogeneous pseudoternary and ternary colloidal assemblies having polar and nonpolar micro domains. Their dispersed phases in nanodimension have good shelf-life (due to thermodynamic stability), large surface area, low viscosity (in some compositions), and ultraslow surface tension. These properties qualify them to be prospective drug delivery systems provided they are composed of biocompatible excipients. Due to the existence of polar, nonpolar, and interfacial microdomains, encapsulation of different kinds of drugs is possible. The review entails reports on development and characterization of biocompatible microemulsion systems and their evaluation as probable vehicles for encapsulation, stabilization, and delivery of bioactive natural products and prescription drugs. © 2007 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 97: 22–45, 2008

Keywords: microemulsion; ternary; pseudoternary; drug delivery; surfactants; cosurfactants; *in vitro*; *in vivo*

INTRODUCTION

The concept of drug delivery system has emerged to minimize the toxic side effects of drugs, to broaden their application, to expand modes of their administration and to solve absorption problems. The twentieth century has witnessed a remarkable growth in drug development and the newly developed drugs are mostly lipophilic compounds with poor aqueous solubility, which limits their efficacy and bioavailability. Solubilization, encapsulation, and delivery of these drugs using aqueous based and biocompatible systems are likely to furnish better absorption, by way of lower dose, reduced frequency of administration, and improved therapeutic index.

During the last two decades, colloidal vehicles[1–10] (liposomes, niosomes, microemulsions, organogels, and nanocapsules) have been explored and they have emerged as prospective systems for drug delivery. These self-organizing systems often lead to improvement in the therapeutic index of the lipophilic drugs through increased solubilization and modification of their pharmacokinetic

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profiles. For fruitful uses of these systems in pharmacy, tolerance towards additives, stability over a wide temperature range, low viscosity, small size, biodegradability, and easy elimination from the body are some of the essential criteria. Also, the size of the encapsulated particles needs to be controlled to avoid capillary blockage and hence submicron-sized entities are preferred. Development, characterization and biological studies on "biocompatible microemulsion" as potential vehicles for drug delivery[11–19] have become a thrust area of research as they satisfy most of the required criteria.[20–29]

Microemulsions are spontaneously forming single-phase colloidal dispersions of either oil-in-water (o/w) or water-in-oil (w/o) stabilized by an interfacial film of surfactant(s) and cosurfactant(s) (optional) (Fig. 1). Systems devoid of cosurfactants are the "ternary systems" and those requiring cosurfactants are the "pseudoternary" systems (where the surfactant and cosurfactant are together taken as a single-phase) The surfactants are amphphilic molecules with a polar head and a nonpolar (hydrophobic) tail, and the cosurfactants can be short chain alcohols, amines and similar substances. The dispersions are formed when oil, water, and surfactant/cosurfactant are mixed in appropriate proportions.[30–32] These self-assembled dispersions have low viscosity, ultraslow interfacial tension, enormous interfacial area, good shelf-life (stability with time), high solubilizing capacity, macroscopic homogeneity, and microscopic heterogeneity (microdomains). Depending on composition and type of amphiphiles, there may be dispersion of oil droplets in water continuum (o/w microemulsion) or *vice versa* (w/o microemulsion). Phase inversion of microemulsion upon addition of an excess of the dispersed phase or in response to temperature variation is another interesting property[1] when a transition from w/o to o/w microemulsion can occur through a bicontinuous state (Fig. 2) wherein the swollen micelles and swollen reverse micelles constantly interchange between themselves forming interspersed regions of oil and water with undefined structures. While it is true that an increase in solubility of drugs in microemulsion system is an important factor in their performance, another important factor is their small droplet size, resulting in large surface area from which the drug can partition and be absorbed or permeate through membranes, and the dissolution route is no longer limiting. The encapsulated drugs in the microdomains are also offered protection from enzymatic degradation by the interfacial layer[33] and their membrane permeability is facilitated due to the presence of surfactants and cosurfactants.[34] Some microemulsion systems undergo phase separation on dilution and transition to a micellar solution,[35] hence knowledge of their kinetics of dilution is essential.

Oil-in-water microemulsions have been proposed as aqueous based vehicles for delivery of a range of drugs.[36–42] Systems for topical, dermal, and transdermal[43–45] administration are relatively well studied than those for oral, parenteral, and other modes of delivery.

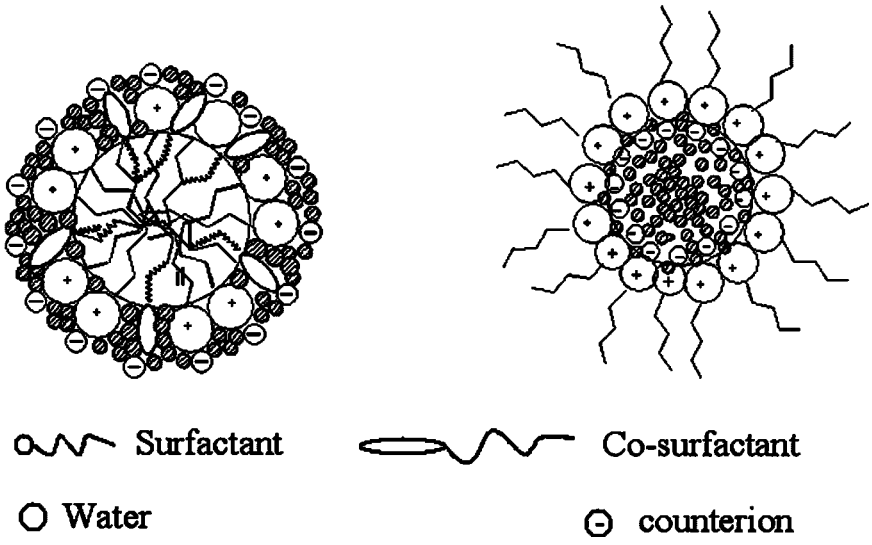

Figure 1. Microemulsion, with a positively charged surfactant as example.