REVIEWS

Microemulsions—Modern Colloidal Carrier for Dermal and Transdermal Drug Delivery

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ABSTRACT: Microemulsions are modern colloidal drug carrier systems. They form spontaneously combining appropriate amounts of a lipophilic and a hydrophilic ingredient, as well as a surfactant and a co-surfactant. Due to their special features, microemulsions offer several advantages for pharmaceutical use, such as ease of preparation, long-term stability, high solubilization capacity for hydrophilic and lipophilic drugs, and improved drug delivery. The article summarizes the level of research with respect to dermal and transdermal application. A large number of *in vitro* as well as some *in vivo* studies demonstrated that drugs incorporated into microemulsions penetrate efficiently into the skin. The enhancing activity seems to be attributable to a variety of factors depending on the composition and the resulting microstructure of the formulations. However, an extended use in practice depends on the choice of well-tolerated ingredients, mainly surfactants, and the restriction of their amounts in order to guarantee skin compatibility. © 2007 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 97:603–631, 2008

Keywords: microemulsion; colloidal carrier; dermal drug delivery; characterization; microstructure; compatibility; skin; surfactants; solubilization; penetration; permeation

INTRODUCTION AND DEFINITION

Human skin is an important target site for the application of drugs. In the treatment of local diseases topical drug delivery is an appropriate strategy to restrict the therapeutic effect to the affected area and to reduce systemic incrimination. On the other hand, systemic availability is the aim in transdermal delivery, which can be used to minimize the first-pass-effect.

In order to reach therapeutic drug concentrations in certain skin layers or in the blood circulation, the uppermost barrier, the stratum corneum (SC), has to be overcome. This process is affected by various factors, e.g., the

Abbreviations: AOT, sodium bis(2-ethyl hexyl)sulfosuccinate; AP, ascorbyl palmitate; APG, alkyl polyglycoside; Cs A, cyclosporine A; DDA, diclofenac diethylamine; DLS, dynamic light scattering; DMSO, dimethyl sulfoxide; DPH, diphenhydramine; DSC, differential scanning calorimetry; FF-TEM, freeze fracture-transmission electron microscopy; IPM, isopropyl myristate; IPP, isopropyl palmitate; ME, microemulsion; MCT, medium chain triglycerides; MTX, methotrexate; NMP, N-methyl pyrrolidone; NMR, nuclear magnetic resonance; o/w, oil-in-water; PEG, polyethylene glycol; PG, propylene glycol; R_h, hydrodynamic radius; SANS, small angle neutron scattering; S/CoS, surfactant/cosurfactant; SDS, sodium dodecyl sulfate; SLN, solid lipid nanoparticle; TEM, transmission electron microscopy; TEWL, transepidermal water loss; THCl, tetracaine hydrochloride; w/o, water-in-oil.

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physicochemical properties of the drug and the vehicle used for administration.

Modern drug carriers are microemulsions (ME). These systems form spontaneously combining appropriate amounts of a lipophilic and a hydrophilic ingredient, as well as a surfactant and a co-surfactant. What are the characteristics of microemulsions? They are single optically isotropic, transparent or slightly opalescent solutions of low viscosity. Very special about them are the thermodynamic properties. Microemulsions are thermodynamically stable and form without any energy input.[1–3] According to the Gibbs-Helmholtz equation, such spontaneously running processes are characterized by a negative free energy ΔG. In our case, the equation can be written as:

$$\Delta G = \gamma \Delta A - T\Delta S,$$

where ΔG is the free energy of formation, γ the interfacial tension, ΔA the change in interfacial area during the formation process, ΔS the change in entropy, and T is the temperature.

The formation of a microemulsion is accompanied by a significant increase in the interfacial area A. Since the interfacial tension γ decreases remarkably (but remains positive all the time), a negative free energy is achieved when the interfacial energy (γA) is compensated by a dramatic change in the entropy of the system, which is mainly dispersion entropy.[4,5] The required very low interfacial tension cannot be realized by only one surfactant. The additionally used co-surfactant penetrates the amphiphilic interfacial layer and increases its curvature and fluidity.[5,6] For this purpose, short or medium chain alcohols and, for reasons of compatibility in humans, preferably non-ionic surfactants are used.

The resulting systems show a number of different microstructures—submicroscopic regions of either aqueous or oleic nature, separated by the interfacial layer. Basically two types of microemulsions are differentiated: bicontinuous ones and microemulsions with droplet like structure. Bicontinuous means that both water and oil form continuous domains separated by surfactant-rich interfaces. They are likely to occur when similar amounts of oil and water are present. Otherwise, droplet structures are formed. Depending on the major compound water-in-oil (w/o) and oil-in-water (o/w) microemulsions are described. The size of the colloidal phase is typically in the range of 10–100 nm.

The common feature of all the appearing microstructures in microemulsions is that they are highly dynamic, undergoing continuous and spontaneous fluctuations. According to Lam et al. two classes of change are considered: inversions (fluctuations in which the system reverts locally from water to oil continuity and back) and superimposed on that, based on the droplet model: variations in droplet size.[7] Although microemulsions do not consist of static phases according to the definition of Gibbs, throughout the literature, occurring water- or oil-rich domains are referred to as "phases."

The term "microemulsion" itself is sometimes used in a misleading way. On the one hand, various homogeneous surfactant-containing solutions were named like this and on the other hand, the expression itself implies emulsion-like properties with droplet sizes in the submicron-range. Therefore, Danielsson and Lindman suggested a definition giving some including and excluding criteria in order to minimize the confusion.[2] For example, the concept does not cover aqueous surfactant solutions without added solubilizate, liquid crystalline systems, and normal emulsions. Table 1 summarizes the main differences between micro- and "macro-" emulsions. However, a clear-cut distinction from other colloidal structures like solubilized micellar systems is missing since there is no well-defined

Table 1. Differences between Microemulsions and Emulsions

Microemulsion	Property	Emulsion
Transparent/translucent	Appearance	Milky
Stable	Thermodynamic stability	Unstable (kinetically stabilized)
Spontaneous	Formation	Energy input
Towards 0 mN m^{-1}	Interfacial tension	$\sim$50 mN m^{-1}
Dynamic (fluctuating surfaces)	Microstructure	Static (until coalescence)
Yes	Optical isotropy	No
10–100 nm	Droplet size of the colloidal phase	>500 nm (nanoemulsions: >50 nm)