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Microemulsions as drug delivery systems

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The concept of microemulsion was first introduced by Hoar and Schulman in 1943 (1) ; they prepared the first microemulsions by dispersing oil in an aqueous surfactant solution and adding an alcohol as a co-surfactant, leading to a transparent, stable formulation.

The existence of this theoretical structure was later confirmed by use of various technologies, and we can today adopt the definition given by Attwood (2) : “a microemulsion is a system of water, oil, and amphiphilic compounds (surfactant and co-surfactant) which is a transparent, single optically isotropic, and thermodynamically stable liquid”.

The main difference between emulsions and microemulsions lies in the size — and shape — of the particles dispersed in the continuous phase : these are at least an order of magnitude smaller in the case of microemulsions (10 – 200 nm) than those of conventional emulsions (1 – 20 μm). Also, whereas emulsions consist of roughly spherical droplets of one phase dispersed into the other, microemulsions constantly evolve between various structures ranging from droplet-like swollen micelles to bicontinuous structures, making the usual “oil in water” and “water in oil” distinction sometimes irrelevant (3).

Microemulsions are formed when and only when (i) the interfacial tension at the oil/water interface is brought to a very low level and (ii) the interfacial layer is kept highly flexible and fluid. These two conditions are usually met by a careful and precise choice of the components and of their respective proportions, and by the use of a “co-surfactant” which brings flexibility to the oil/water interface.

These conditions lead to a thermodynamically optimised structure, which is stable — as opposed to conventional emulsions — and does not require high input of energy (i.e. through agitation) to be formed.

Because the size of the particles is much smaller than the wavelength of visible light, microemulsions are transparent and their structure cannot be observed through an optical microscope.

Microemulsions have been used in a wide range of industries, starting with enhanced oil recovery in the 70's, expanding to a wide range of chemicals and entering the pharmaceutical and cosmetic formulation area a decade ago.

Because of their unique solubilization properties, microemulsions have attracted increasing attention as potential drug delivery systems, either as vehicles for topical applications or as bioavailability enhancers for poorly water soluble active pharmaceutical ingredients (API).

In topical formulations, microemulsions have been proved to increase the cutaneous absorption of both lipophilic and hydrophilic API's when compared to conventional vehicles (emulsions, pure oils, aqueous solutions, etc.). In an extensive review of this type of applications, Kreilgaard et. al. (3) attribute this performance to a generally higher solubility of the API's in microemulsions, generating an increased concentration gradient towards the skin. The role of penetration enhancers played by the amphiphilic components of the microemulsion and the internal mobility of the drug within the vehicle also contribute to the overall performance of microemulsions in dermal or transdermal drug delivery.

Many topical formulations currently marketed are based on microemulsions:

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The dog shampoo "Allermyl" marketed by Virbac is, to our knowledge, the first application of microemulsions to a therapeutic cleansing product ; the use of microemulsion allowed the addition of a higher content of essential fatty acids to the formula.

Solvium is a topical Ibuprofen gel marketed by Chefaro (Akzo). In this case, microemulsion has been used to formulate a poorly soluble active at a dose of 5% into a perfectly transparent gel. But the most promising potential in microemulsions comes from the advantage they bring to oral route formulations.

Microemulsions enhance the bioavailability of poorly soluble drugs by maintaining them in molecular dispersion in the GI tract and extending the absorption window available in the GI lumen.

This lead to a faster absorption allowing a more rapid onset of drug action. But microemulsions also overcome food effect and reduce subject to subject variability by levelling the differences in digestive capabilities.

Many examples of microemulsion based formulations are now on the market ; Among them, the performances of microemulsions are well demonstrated in the reformulation of Cyclosporin A by Novartis into a microemulsion based formulation marketed under the trade mark Neoral® : this has increased the bioavailability nearly by a factor 2. In addition, Neoral shows a much faster onset of action than the earlier version Sandimmune®, a reduced inter/intra-subject variability and a much lower impact of food intake on cyclosporin pharmacokinetics.

Further promising development have been brought by Self Micro Emulsifying Drug Delivery Systems (SMEDDS .), patented by Gattefossé in the 90's (5): these are "latent" microemulsions in the form of a stable, water-free combination of surfactants, co-surfactants and lipophilic phase, which creates a microemulsion when diluted in water or body fluids. Such systems combine the advantages of microemulsions with a water-free formulation protecting sensitive API from the chemical degradation they would undergo in an aqueous medium.

The performance of SMEDDS has been demonstrated by Gattefossé on Simvastatin, a well known anti-hyperlipidemic drug marketed by Merck (Zocor), which is subject to extensive hepatic first pass metabolism. The use of a SMEDDS formulation gives a spectacular (four fold) increase in bioavailability in dogs (6).

Microemulsions are powerful formulation tools for poorly soluble API's, both for the oral and topical administration routes. The availability of efficient, non toxic surfactants and co-

surfactant now makes them a very attractive and feasible option to overcome the bioavailability problems frequently encountered in the development of modern drugs.

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3. Kreilgaard M. "Influence of microemulsions on cutaneous drug delivery". in Bulletin Technique Gattefossé N°95 : 79 – 100, 2002
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