



Prospective and Challenges of Micro-Emulsion as a Novel Carrier for Drug Delivery

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Abstract

Micro-emulsions are isotropic, thermodynamically stable transparent (or translucent) systems of oil, water, and surfactant with a droplet size usually in the range of 20-200 nm. Micro-emulsions are currently of great technological and scientific importance to the researchers because of their potential to incorporate a wide range of drug molecules (hydrophilic and hydrophobic) due to the presence of both lipophilic and hydrophilic domains. These delivery systems provide protection against oxidation, enzymatic hydrolysis and improve the solubilization of lipophilic drugs and hence enhance their bioavailability. In addition to oral and intravenous delivery, they are amenable for sustained and targeted delivery through ophthalmic, dental, pulmonary, vaginal, and topical routes. They have been used to improve the oral bioavailability of various poorly soluble drugs. Furthermore, they can be employed for challenging tasks such as carrying chemotherapeutic agents to neo-plastic cells and oral delivery of insulin. In order to appreciate the potential of micro-emulsions as delivery vehicles, this review gives an overview of the formation and characterization of microemulsions. The use of microemulsions and closely related micro-emulsion-based systems as drug delivery vehicles is reviewed, with particular emphasis being placed on recent developments and future directions.

Keywords: Microemulsion, characterization, solubilization, bioavailability, targeted drug delivery

Introduction

Micro-emulsion is homogeneous, transparent, thermodynamically stable dispersions of water and oil, stabilized by a surfactant, usually in combination with a co-surfactant. In this type of system, the two liquids tend to separate out in two layers,¹⁻⁵ and to avoid this, a third substance called as an emulsifier is added which is, in general, surface-active agent or surfactant. Surfactant molecules contain both a polar and a nonpolar group. So they exhibit a very peculiar behavior, first, they tend to adsorb at interface, where they can fulfill their dual affinity with hydrophilic groups located in aqueous phase and hydrophobic groups in oil or air. Second, they reduce the mismatch with solvent through a specific kind of aggregation process known as micellization.

The micro-emulsion concept was introduced as early as the 1940s by Hoar and Schulman who generated a clear single-phase solution by titrating a milky emulsion with hexanol.⁶ Schulman and coworkers (1959) subsequently coined the term micro-emulsion,⁷ and it has since been defined and indeed redefined on many occasions. In practice, the key difference between emulsions and micro-emulsions are that the former, whilst they may exhibit excellent kinetic stability, are fundamentally thermodynamically unstable, and will eventually solphase separate.⁸⁻⁹ Another important difference concerns their appearance; emulsions are cloudy while microemulsions are clear or translucent. In addition,

there are distinct differences in their method of preparation, since emulsions require a large input of energy while microemulsions do not. The latter point has obvious implications when considering the relative cost of commercial production of the two types of system.

Advantages of Microemulsion

Microemulsions are potential drug carrier systems for various routes of administration.⁶ These are having advantages when compare to the other dosage forms.

- These are thermodynamically stable and require minimum energy for formation.
- Ease of manufacturing and scale-up
- Improved drug solubilisation and bioavailability.
- This system is reckoned advantageous because of its wide applications in colloidal drug delivery systems for the purpose of drug targeting and controlled release.
- Liquid dosage form increases patient compliance.
- Provides protection from hydrolysis and oxidation as drug in oil phase in O/W microemulsion is not exposed to attack by water and air.

- Various routes like topical, oral and intravenous can be used to deliver the product.
- Provides a aqueous dosage form for water insoluble drugs.
- Less amount of energy requirement.
- Increase the rate of absorption.
- Microemulsion is having wide applications in colloidal drug delivery systems for the purpose of drug targeting and controlled release.

Theory of Microemulsion Formation

Historically, three approaches have been proposed to explain microemulsion formation and stability. These are (a) interfacial or mixed film theory; (b) solubilisation theory; and (c) thermodynamic treatments.

An in depth discussion of these theories are beyond the scope of this review but has been addressed by others.¹⁰ However, an admittedly simplified thermodynamic rationalization is presented below. The free energy of micro-emulsion formation can be considered to depend on the extent to which surfactant lowers the surface tension of the oil–water interface and the change in entropy of the system such that,

$$\Delta GF = \gamma \Delta A - T \Delta S$$

Where, ΔGF = free energy of formation; γ = surface tension of oil-water interface; ΔA = the change in interfacial area on microemulsion; ΔS = change in entropy; T = temperature.

It should be noted that when a micro-emulsion is formed the change in ΔA is very large due to the large number of very small droplets formed. Originally workers proposed that in order for a micro-emulsion to be formed a negative value of γ was required, it is now recognized that while value of γ is positive at all times, it is very small and is offset by the entropic component. The dominant favorable entropic contribution is the very large dispersion entropy arising from the mixing of one phase in the other in the form of large numbers of small droplets. However, there are also expected to be favorable entropic contributions arising from other dynamic processes such as surfactant diffusion in the interfacial layer and monomer-micelle surfactant exchange. Thus a negative free energy of formation is achieved when large reductions in surface tension are accompanied by significant favorable entropic change. In such cases, micro-emulsification is spontaneous and the resulting dispersion is thermodynamically stable.

Characterization

In contrast to their ease of preparation, it is a far from trivial matter to characterize the microstructure of a micro-emulsion, yet such knowledge is essential for their successful commercial exploitation. For example, it has been shown that the rate of

release of sodium salicylate from lecithin-based micro-emulsions is dependent upon their microstructure.¹¹ The micro-emulsions are evaluated/characterized by the following techniques:

Phase behavior studies

Visual observations, phase contrast microscopy, and freeze fracture transmission electron microscopy can be used to differentiate micro-emulsions and coarse emulsions. Clear isotropic one-phase systems are identified as micro-emulsions whereas opaque systems showing birefringence when viewed by cross polarized light microscopy may be taken as liquid crystalline system. Solubilisation and interfacial properties of micro-emulsions depend upon pressure, temperature and also on the nature and concentration of the components. Several types of phase diagram can be identified depending on the number of variables involved. In using an adequate mode of representation, it is possible to describe not only the limits of existence of the single and multiphase regions, but also to characterize equilibrium between phases. As quaternary phase diagram (four component system) is time consuming and difficult to interpret, pseudo ternary phase diagram is often constructed to find the different zones including micro-emulsion zone, in which each corner of the diagram represents 100% of the particular component Fig. 1. The region can be separated into w/o or o/w micro-emulsion by simply considering the composition that is whether it is oil rich or water rich. Observations should be made carefully so that the metastable systems are not included.

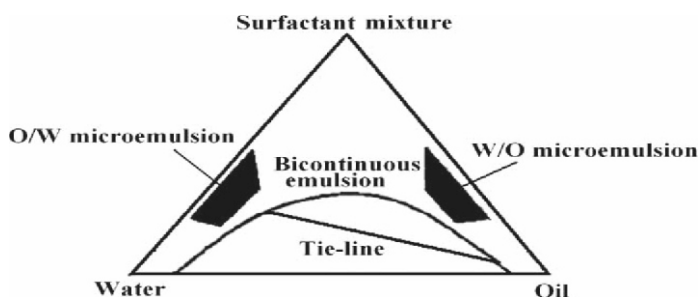


Fig.1: Schematic representation of a two-arm randomized clinical trial of new and existing anti-HT treatments in HT patients with one or more additional risk factors

Determination of internal structure

Transmission (TEM) and scanning (SEM) techniques have been used to study internal and surface mesophase nanostructure. The general approach to TEM analysis is to prepare a sample as a thin film, such that an electron beam can pass through it. The image is collected with contrast resulting from differential absorption and scattering of electrons from different regions of the sample. As with all electron microscope based techniques, imaging artefacts due to sample preparation and dehydration are a major consideration. This has led to the development of cryogenic

preparation (cryo-TEM) and freeze-fracture (FFEM) techniques.¹²

Viscosity measurement

The rheological properties of micro-emulsions depend on the type, shape and number density of aggregates present, as well as the interactions between these aggregates. Hence, microstructural changes such as sphere-rod or discontinuous to bicontinuous transitions are reflected in micro-emulsion rheology. Bicontinuous microemulsions exhibit a Newtonian behavior (constant viscosity) at low to medium shear rates but shear thinning is observed at high shear rates, probably due to fragmentation of the bicontinuous structure. Discontinuous microemulsions on the other hand show Newtonian behavior over a wider range of shear rates. However, differentiation of the types of microemulsions or identification of the structure of the microemulsion cannot be done purely on the basis of rheological data, because this macroscopic property is not sensitive enough to detect subtle microstructural changes such as the transformation of microemulsion to a wormlike micellar phase induced by temperature. Hence, rheometry has most often been used in combination with other techniques in the characterization of microemulsions.

Electrical conductivity measurement

Electrical conductivity remains a simple and inexpensive technique for microemulsion characterization. It primarily reveals whether an aqueous or oil phase or both phases are continuous. The conductivity measurement technique has been used to determine the type of microemulsion, and to estimate phase boundaries resulting from changes in composition or temperature

In-vitro drug release study

The diffusion study can be carried out on a modified Franz diffusion

cell. The receptor compartment was filled with buffer. The donor compartment was fixed with cellophane membrane containing the micro-emulsion formulation. At predetermined time intervals samples were withdrawn from the receptor compartment and analyzed for drug content, using a UV spectrophotometer at specific wavelength.

Ex-vivo drug release study

Ex-vivo drug release into buffer was studied using intestinal membrane within a Franz diffusion cell. Micro-emulsion formulation was placed in the donor compartment of two separate diffusion cells and the temperature of each cell was maintained at $37 \pm 2^\circ\text{C}$. The amount of drug released from the micro-emulsion formulation can be estimated spectrophotometrically at specific wavelength, by withdrawing samples from the receptor compartment at predetermined time intervals.¹³

Development of microemulsion drug delivery system

Oral drug delivery system

The development of the effective oral delivery systems has always been the main goal because drug efficacy can be severely limited by instability or poor solubility in the gastrointestinal fluid. Biopharmaceutical Classification System (BCS) is a useful guidance and it takes into account contributions of three major factors, dissolution, solubility, and intestinal permeability, which affect oral drug absorption. According to the BCS, drug substances are classified as follows:¹⁴ Class I - High Permeability, High Solubility; Class II - High Permeability, Low Solubility; Class III - Low Permeability, High Solubility; Class IV - Low Permeability, Low Solubility. Various approaches of solubility enhancement are shown in Fig. 2.

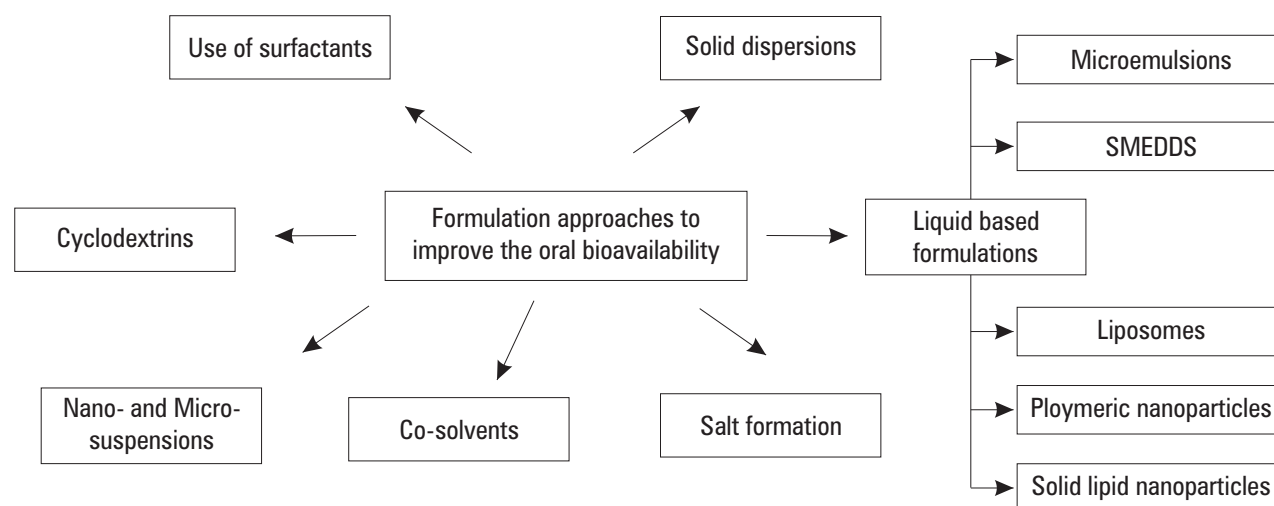


Fig. 2: Some of the formulation approaches to improve the oral bioavailability of poorly water soluble drugs

Micro-emulsions have the potential to enhance the solubilization of the poorly soluble drugs and overcome the dissolution related bioavailability problems. This is particularly important for the BCS class II or class IV drugs. The successful formulation of such drugs is highly dependent on the performance of the formulated product. Micro-emulsions act as super solvent of these drugs and can be optimized to ensure consistent bioavailability. In addition, they can be used for the delivery of hydrophilic drugs including macromolecules such as proteins and peptides. This is due to the existence of polar, nonpolar, and interfacial domains which allow encapsulation of drugs with varying solubility. Moreover, these systems have been reported to protect the incorporated drugs against oxidation, enzymatic degradation and enhance the membrane permeability.

Parenteral drug delivery

The formulation of lipophilic and hydrophobic drugs into parenteral dosage forms has proven to be difficult. O/w microemulsions are beneficial in the parenteral delivery of sparingly soluble drugs where the administration of suspension is not desirable. They provide a means of obtaining relatively high concentration of these drugs which usually requires frequent administration. Other advantages are that they exhibit a higher physical stability in plasma than liposomes or other vesicles and the internal oil phase is more resistant against drug leaching. Several sparingly soluble drugs have been formulated into o/w microemulsion for parenteral delivery.¹⁵⁻¹⁸ Microemulsions can also be used as intravenous delivery systems for the fat soluble vitamins and lipids in parenteral nutrition.¹⁹ Dennis *et al.* studied an intravenous microemulsion delivery system for water insoluble or sparingly water soluble drugs that comprised an oil phase comprising the drug, a long polymer chain surfactant (e.g. lecithin, gelatin casein, tweens, macrogol ethers, etc.) component and a short fatty acid surfactant (e.g. stearic acid, glyceryl monostearate, sorbitan esters, etc.) component and an aqueous phase.²⁰ The droplet size ranged from 10-100 nm.

According to the invention of the Wretling *et al.* parenteral administration of water-insoluble active agents was enhanced when the agents were administered in the lipid phase of a carrier microemulsion.²¹ The microemulsion comprised of a finely dispersed lipid in an aqueous phase with a mean particle size below 1 micron. Higher concentration of the agent (diagnostic or therapeutic) could be achieved and hence a lower dose whereby a rapid onset of the pharmacological effect was accompanied by a reduced incidence of injury to body tissues. As the agents were present in a dissolved state in the hydrophobic phase, there was no need of affecting the pH or the osmotic pressure of the aqueous phase. Because of this, the method of administration according to the invention would cause a lower occurrence of injuries to the body tissues.

Pulmonary drug delivery system

Very few emulsions or micro-emulsions have been studied to administer drugs by the pulmonary route. However, these dosage forms show numerous advantages compared to other drug targeting systems: easiness to be manufactured and maximum of drug to be incorporated. Indeed, the drug being soluble into one phase, this one will be located preferentially into this phase, leading to an encapsulation close to 100%. Due to their physicochemical characteristics, reverse emulsions and micro-emulsions should allow solubilization of a large amount and a lot of hydrophilic drugs.²² Several aerosol formulations designed with an external phase constituted of a propellant have been described. As example, one can cite water-in-chlorofluorocarbon reverse micelles including proteins and peptides stabilized by lecithin.²³ Even if this dosage form is stable and is able to deliver peptides and proteins efficiently by pulmonary route, its use should be limited since the Montreal protocol (1987) recommended stopping the production and the use of chlorofluorocarbons. Propellants like hydrofluoroalkanes or propane have been suggested. Reverse micro-emulsions stabilized by lecithin and using propane and dimethylether as propellants have been also described.²⁴ These micro-emulsions, characterized by mean geometric diameters ranged between 1 and 5 μm and by a respirable fraction up to 36%, showed high stability during more than 4 weeks at room temperature. Pulmonary drug delivery having very negligible side effects since rest of body is not exposed to drug. Onset of action is very quick with pulmonary drug delivery. Degradation of drug by liver is avoided in pulmonary drug delivery. In asthma and diabetes requires long term treatment if it is given by pulmonary drug delivery safety is maximal because rest of body is not exposed to drug.

Ocular drug delivery system

Eye drops account for 90% of the available ophthalmic formulations due to their simplicity and convenience. However, rapid precorneal loss caused by drainage and high tear fluid turnover is amongst the major problems associated with topical ophthalmic drug delivery. Only 5% of the applied drug in eye drops penetrates the cornea and reaches the intraocular tissues with the rest of the dose undergoing transconjunctival absorption or drainage via the nasolacrimal duct before transnasal absorption. This results in loss of drug into the systemic circulation and provides undesirable systemic side effects. Accordingly, microemulsions provided a promising alternative with improved ocular retention, increased corneal drug absorption and reduced systemic side effects whilst maintaining the simplicity and convenience of the dosage form as eye drops. The development and characterization of o/w micro-emulsions designed for ocular use has recently been reported.²⁵ The micro-emulsions containing pilocarpine were formulated using lecithin, propylene glycol and PEG 200 as co-surfactants.

The formulations were low viscosity fluids with a refractive index lending them to ophthalmological application. The test micro-emulsions were non-irritant in rabbit eyes or hen egg membrane. A prolonged pharmacological effect was observed *in vivo* compared to the drug administered as a simple aqueous solution. This may have been related to increased bioavailability or enhanced retention or both. However, prolonged release was not observed *in vitro* using a cellulose membrane as permeability barrier.

Transdermal drug delivery system

Several plausible mechanisms have been proposed to explain the advantages of micro-emulsion for the transdermal delivery of a drug:

- A large amount of drug can be incorporated in the formulation due to the high solubilizing capacity that might increase thermodynamic activity towards the skin.
- The permeation rate of the drug from micro-emulsion may be increased, since the affinity of a drug to the internal phase in micro-emulsion can be easily modified to favor partitioning into stratum corneum, using different internal phase, changing its portion in micro-emulsion.
- The surfactant and co surfactant in the micro-emulsions may reduce the diffusional barrier of the stratum corneum by acting as penetration enhancers.
- The percutaneous absorption of drug will also increase due to hydration effect of the stratum corneum if the water content in micro-emulsion is high enough.

A number of recent reports detail microemulsion formulations designed for transdermal applications. Both o/w and a w/o microemulsions have been evaluated in a hairless mouse model for the delivery of prostaglandin E1. The microemulsions were based on oleic acid or Gelucire as the oil phase and were stabilized by a mixture of Labrasol and Plurol as surfactant.²⁶ Although enhanced delivery rates were observed in the case of the o/w microemulsion, the authors concluded that the penetration rates were inadequate for practical use from either system.

The delivery of the hydrophilic diphenhydramine hydrochloride through excised human has been investigated from a w/o type microemulsion. The formulation was based on combinations of Tween 80 and Span 20 with isopropylmyristate. However, two additional formulations were tested containing cholesterol and oleic acid, respectively. Cholesterol increased drug penetration whereas oleic acid had no measurable effect, but the authors clearly demonstrated that penetration characteristics can be modulated by compositional selection.²⁷

Protein drug delivery system

Numerous peptide and proteins have been identified for use as

novel therapeutic agents. With increase in the understanding of their structure and mechanism, recent research has shifted to biotechnological products.²⁸ Changing scenario and increased market competitiveness is pressurizing companies to address significant protein delivery issues already at late discovery and early development stages. However, in spite of tremendous advances in peptide and protein development, their delivery is limited to systemic route. This is due to their low oral bioavailability which can be ascribed to their inactivation by gastrointestinal enzymes and poor permeability of the intestinal mucosa. To circumvent this, micro-emulsions have been developed as smart systems and patented for the oral delivery of protein and peptide drugs.

One preferred embodiment of the invention of Burnside *et al.* comprised of a micro-emulsion containing an oil phase (such as a long chain carboxylic acid or ester or alcohol thereof), a surface active agent (such as a poloxamer) and an aqueous phase containing the insulin.²⁹ They had attempted to increase the intestinal absorption of the hormone which had met with only limited success earlier. The hydrophobic material formed the continuous phase and the hydrophilic material formed the discontinuous phase in which the hydrophilic material was emulsified (w/o). A large amount of polar solutes could be dissolved in an overall oily environment by using w/o micro-emulsion thereby creating an oral delivery system for insulin.

Owen *et al.* provided a highly stable w/o micro-emulsion which readily converted to an o/w emulsion by the addition of aqueous fluid.³⁰ Proteins and peptides could be stored for long periods of time at room temperature and above by using the w/o micro-emulsion. When required for use aqueous fluid was added which converted the micro-emulsion to an o/w emulsion and released the protein.

Nasal drug delivery system

Micro-emulsions are now being studied as a delivery system to enhance uptake across nasal mucosa. Addition of a mucoadhesive polymer helps in prolonging the residence time on the mucosa. Nasal route for administration of diazepam might be a useful approach for the rapid onset of action during the emergency treatment of status epilepticus. For this micro-emulsion were formulated comprising of ethyl laurate, Tween 80, propylene glycol, ethanol, and water. The nasal absorption of diazepam was found to be fairly rapid with maximum drug plasma concentration reached within 2-3 min. The bioavailability (0-2 h) after nasal spray compared to IV injection was about 50%.³¹

Conclusion

To date micro-emulsions have been shown to be able to protect labile drug, control drug release increase drug solubility, increase

bioavailability, and reduce patient variability. Furthermore, it has proven possible to formulate preparations suitable for most routes of administration. The use of micro-emulsion as drug delivery vehicles is an exciting and attractive area of research, offering not only many challenges to be overcome but also many potentially extraordinary benefits. There is still however a considerable amount of fundamental work characterizing the physicochemical behavior of microemulsions that needs to be performed before they can live up to their potential as multipurpose drug delivery vehicles.

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