AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

Microemulsions as Enhanced Drug Delivery Carrier: An Overview

Akruti S. Khodakiya*[1], J. R. Chavada[2], N. P. Jivani[1], Bimal N. Patel[1], Moorti S. Khodakiya[3], Ankit P. Ramoliya[4]

1. C. U. Shah College of Pharmacy and Research, Wadhwan City, Gujarat, India.
2. B. K. Modi Government Pharmacy College, Rajkot, Gujarat, India.
3. B. Pharmacy College, Navalgadh, Gujarat, India.
4. College of Professional Studies, Northeastern University, Boston, MA, USA.

ABSTRACT

Microemulsions are clear, thermodynamically stable, isotropic mixtures of oil, water and surfactant, frequently in combination with a co-surfactant. They offer numerous advantages like improved solubilization of both hydrophilic and lipophilic drugs, better bioavailability, prolong and targeted release, enhanced permeation across biological membranes, protection against oxidation, better stability and ease of manufacturing as well as processing. These systems are currently of interest to the pharmaceutical scientist because of their unique characteristics and considerable potential to act as drug delivery carrier by incorporating a wide range of drug molecules. In order to appreciate the potential of microemulsions as delivery carrier, this review gives an overview of the microemulsion properties, formulation, phase behaviour, characterization and application of microemulsions as a drug delivery carrier.

Keywords: Microemulsion, solubilization, bioavailability, prolong and target release, phase behaviour, drug delivery carrier

*Corresponding Author Email: akruti.pharma@gmail.com

Received 19 June 2012, Accepted 4 July 2012

Please cite this article in press as: Khodakiya AS *et al.*, Microemulsions as Enhanced Drug Delivery Carrier: An Overview. American Journal of PharmTech Research 2012.

INTRODUCTION

Currently, microemulsions are being extensively investigated as drug delivery carriers. Much of the interest in the use of microemulsions as drug delivery carrier arises from their unique physical properties, particularly, their thermodynamic stability and ease of preparation. The development in therapeutic Microemulsion formulations has been stimulated by the introduction of a very successful oral microemulsions pre-concentrate formulation of cyclosporin called Neoral®, in Europe and America by Sandoz (Basel, Switzerland).[1]Although, presently only few microemulsion formulations are on the market, it is widely anticipated that there will be further more microemulsion, or microemulsion-based, drug delivery systems in the very near future. The objective of this review is to describe basic concepts about Microemulsion that will be useful in designing an efficient therapeutic Microemulsion system. This review also highlights potential of Microemulsion as a drug delivery carrier on the basis of various research works on Microemulsion based system.

History, definitions and concepts

Hoar and Schulmanhad already noticed in 1943 that by titrating a milky emulsion (a mixture of water, oil, and surfactant) with hexanol, a clear single-phase and stable solution was formed.[2]Schulman and associates also coined the term microemulsion that holds up to this day.[3] The definition has changed slightly through the years, but the general concepts are still intact. Most scientists use a general and broad definition for microemulsion as ‘‘a system of water, oil, and one or more surfactant (or amphiphile) which is a single optically isotropic and thermodynamically stable solution.’’ It is well established today that microemulsions can appear in at least three major microstructures: water-in-oil (w/o), oil-in-water (o/w) and bicontinuous structure (Figure 1).

Microemulsions have very high surface areas and, therefore, it is obvious that they can incorporate, in their core or at the interface, large quantities of molecules that are usually insoluble in the continuous phase. The molecules that are incorporated at the interface are solubilized rather than dissolved, and, therefore, Microemulsion efficiency is measured based on the solubilization capacity of guest molecules (i.e. drug(s)). For a microemulsion to exhibit drug delivery properties, the existence of microstructures in the mixture must be clearly demonstrated. The choice of type of Microemulsion for particular therapy depends on the route of administration and intended target organ.

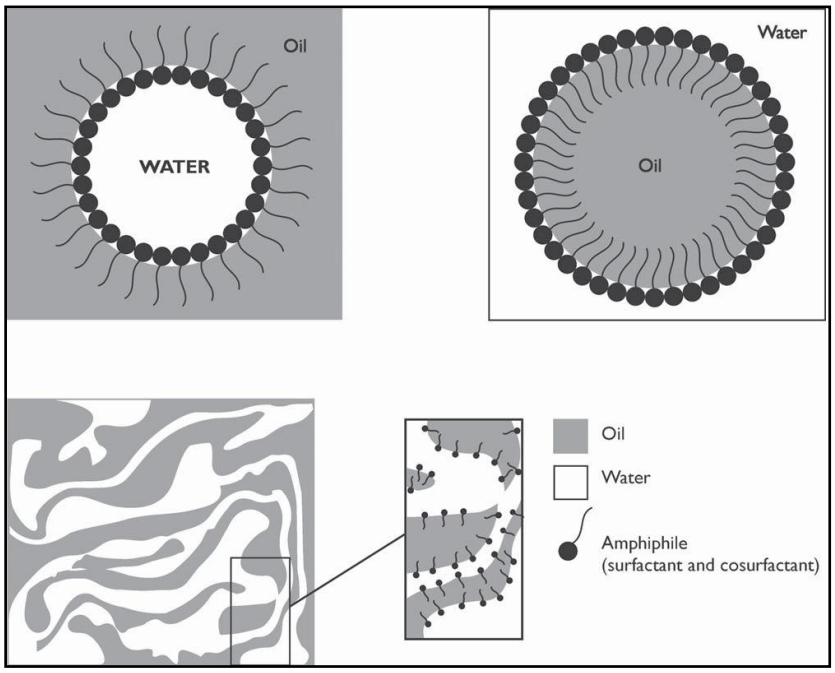

Figure 1: Diagrammatic representation of different types of Microemulsion systems: (a) w/o ME, (*b*) o/w ME, and (*c*) Bicontinuous ME.

It is very important to have understanding of differences between emulsions, microemulsions and nanoemulsions. The main difference between emulsions and microemulsions lies in their size and shape of the droplets that are dispersed in the continuous phase(Table 1). 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 are not nanoemulsions

The main difference between microemulsions and nanoemulsions is that microemulsions are self-assembling nano-scale emulsions whereas nanoemulsions are nano-scale emulsions formed by energy input, generally from mechanical devices or from the chemical potential of the components.[4]

Microemulsions are isotropic solutions of oil and water and are prepared using a high surfactant concentration of around 40 percent under gentle stirring or shaking. Microemulsions form spontaneously without mechanical shear.[5]An extremely high concentration of surfactants ensures self-assembling with particle size at the nano-scale level.

Nano-emulsion generating processes are divided into two groups. The first gathers together the 'high-energy' processes which use high mechanical shear to reach very small droplet sizes, whereas the second 'low-energy' process benefits from the intrinsic physico-chemical properties of surfactants for generating nano-emulsions.[6]

Unlike microemulsions, nanoemulsions are thermodynamically unstable systems as the interfacial tension between oil and water phase is high. It has high kinetic stability against creaming or sedimentation and a large interfacial area.[4]

Table 1: Difference between Microemulsion and Macroemulsion[7]

S.no	Property	Microemulsion	Macroemulsion
1	Appearance	Transparent	Cloudy
2	Optical Isotropy	Isotropic	Anisotropic
3	Interfacial tension	Ultra low	High
4	Microstructure	Dynamic (interface is continuously and spontaneously fluctuating)	Static
5	Droplet size	20-200 nm	> 500 nm
6	Stability	Thermodynamically stable, long shelf-life	Thermodynamically unstable (kinetically stable), will eventually phase separate
7	Phases	Monophasic	Biphasic
8	Preparation	Facile preparation, relatively lower cost for commercial production	Require a large input of energy, higher cost
9	Viscosity	Low viscosity	Higher viscosity

Formulators have to carefully select the surfactant and the nature of the two phases so that the interfacial tension will always be close to zero. If such selection is made, the destabilization effect because of the gain in surface area will be minimal, and the gain in entropy will be maximal. Such microemulsions will be formed spontaneously (self-associate or self-aggregate)and will be thermodynamically stable. The co-surfactant helps to achieve flexible and fluid interfacial layer and further reduces interfacial tension of the oil/water interface.

Another important consideration in the formation of microemulsions is related to the packing parameter. It is based solely on geometric considerations. Accordingly, if the volume of the surfactant is *v*, its head group surface area *a*, and its length *l*, it follows that when the critical packing parameter (CPP = *v/al)* has values between 0 and 1, o/w MEs are likely to be formed. On other hand, when CPP is greater than 1, w/o MEs are favoured. When using surfactants with critical packing parameters close to unity (CPP ≈ 1) and at approximately equal volumes of water and oil, the mean curvature of the interfacial film approaches zero and droplets may merge into a bi-continuous structure.[8]

The ratio of hydrophilic and hydrophobic groups of the surfactant molecules, that is, their hydrophile-lipophile balance (HLB), is also important in determining interfacial film curvature and consequently the structure of the ME. The HLB system has been used for the selection of

surfactants to formulate MEs and accordingly the HLB of the candidate surfactant blend should match the required HLB of the oily component for a particular system. In brief, a match in the lipophilic part of the surfactant used with the oily component should be favourable.[9, 10]

THEORY OF MICROEMULSION FORMATION AND STABILITY

Interfacial tension in microemulsions

A simple picture for describing microemulsion formation is to consider a subdivision of the dispersed phase into very small droplets. Then the configurational entropy change, ΔS_{conf}, canbe approximately expressed as:[11]

$$\Delta \mathbf{S_{conf}} = -\mathbf{nk_B}\left[\ln \emptyset + \left\{\frac{1-\emptyset}{\emptyset}\right\}\ln(1-\emptyset)\right] \quad (1.1.1)$$

Where, n is the number of droplets of dispersed phase, k_B is the Boltzmann constant and $\emptyset$ is the dispersed phase volume fraction. The associated free energy change can be expressed as a sum of the free energy for creating new area of interface, $\Delta A\gamma_{12}$, and configurational entropy in the form:[12]

$$\Delta \mathbf{G_{form}} = \Delta \mathbf{A\gamma_{12}} - \mathbf{T\Delta S_{conf}} \quad (1.1.2)$$

Where, ΔA is the change in interfacial area A (equal to $4\pi r^2$ per droplet of radius r) and γ_{12} is the interfacial tension between phases 1 and 2 (e.g., oil and water) at temperature T (Kelvin). Substituting Eq. 1.1.1 into 1.1.2 gives an expression for obtaining the maximum interfacial tension between phases 1 and 2. On dispersion, the droplet number increases and $\Delta S_{conf}$is positive. If the surfactant can reduce the interfacial tension to a sufficiently low value, the energy term in Eq. 1.1.2 ($\Delta A\gamma_{12}$) will be relatively small and positive, thus allowing a negative (and hence favourable) free energy change, that is, spontaneous microemulsification.

In surfactant free oil-water systems, $\gamma_{o/w}$ is of the order of 50 mN m^{-1}, and during microemulsion formation the increase in interfacial area (ΔA) is very large, typically a factor of 10^4 to 10^5. Therefore in the absence of surfactant, the second term in Eq. 2.1.2 is of the order of 1000 k_BT, and in order to fulfil the condition $\Delta A\gamma_{12} \leq T\Delta S_{conf}$, the interfacial tension should be very low (approximately 0.01 mN m^{-1}). Some surfactants (double chain ionics and some non-ionics[13]can produce extremely low interfacial tensions typically 10^{-2} to 10^{-4} mN m^{-1}, but in most cases, such low values cannot be achieved by a single surfactant since the CMC is reached before a low value of $\gamma_{o/w}$ is attained. An effective way to further decrease $\gamma_{o/w}$ is to include a second surface-

active species (either a surfactant or medium-chain alcohol), that is a co-surfactant. This can be understood in terms of the Gibbs equation extended to multicomponent systems.[14] It relates the interfacial tension to the surfactant film composition and the chemical potential, μ, of each component in the system, i.e,

$$\mathbf{d\gamma_{o/w} = -\sum_i (\Gamma_i d\mu_i) \approx -\sum_i (\Gamma_i RTd \ln C_i)} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (1.1.3)$$

Where, C_i is the molar concentration of component i in the mixture, and Γ_i the surface excess (mol m^{-2}). Assuming that surfactants and co-surfactants, with concentration C_s and C_{co} respectively, are the only adsorbed components (i.e., $\Gamma_{water} = \Gamma_{oil} = 0$), Eq. 1.1.3 becomes:

$$\mathbf{d\gamma_{o/w} = -\Gamma_s RTd \ln C_s - \Gamma_{co} RTd \ln C_{co}} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (1.1.4)$$

Integration of Eq. 1.1.4 gives:

$$\mathbf{\gamma_{o/w} = \gamma^{\circ}_{o/w} - \int_0^{C_s} \Gamma_s RTd \ln C_s - \int_0^{C_{co}} \Gamma_{co} RTd \ln C_{co}} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots (1.1.5)$$

Eq. 1.1.5 shows that $\gamma^{\circ}_{o/w}$ is lowered by two terms, both from the surfactant and co-surfactant (of surface excesses Γ_s and Γ_{co} respectively) so their effects are additive. However, the surfactant and co-surfactant molecules should be of completely different chemical nature such that they adsorbed simultaneously and should not interact with each other. This prevents lowering of their respective activities and mixed micellisation.

Kinetic instability

Internal contents of the microemulsion droplets are known to exchange, typically on the millisecond time scale.[15,16] They diffuse and undergo collisions. If collisions are sufficiently violent, then the surfactant film may rupture thereby facilitating droplet exchange, which means that droplets are kinetically unstable. This dynamic process occurs continuously, resulting in an overall equilibrium. However, if one disperses emulsions sufficiently small droplets (< 500 Å), the tendency to coalesce will be counteracted by energy barrier and the system will remain dispersed and transparent for a long period of time (months).[17] Such an emulsion is said to be kinetically stable. In any case, an equilibrium droplet shape and size is always maintained and this can be studied by different techniques.[18]

PHARMACEUTICAL FORMULATION OF MICROEMULSIONS

Components of Microemulsion Formulations

A large number of oils and surfactants are available which can be used as components of

microemulsion systems but their toxicity, irritation potential and unclear mechanism of action limit their use. One must choose formulation components that are biocompatible, non-toxic, and clinically acceptable. Again the use of those formulation components is limited to acceptable concentration range. The emphasis is, therefore, on the use of generally regarded as safe (GRAS) excipients.

The surfactant

The amount of surfactant in emulsions is very small, 0.1% to 1.0% of the total emulsion weight. The amount of surfactant in a microemulsion is a minimum of 10% of the total ME weight. Such large surfactant levels are essential because of the large increase in interface area between the aqueous and oil phase.

Selection of a proper surfactant is the key to the formation of any Microemulsion.[19]In general, hydrophobic surfactants will be suitable for the formation of w/o microemulsions (ME), and the hydrophilic surfactants will form o/w ME. In industrial applications, it is common to use inexpensive ionic surfactants but in food, pharmaceutical, and cosmetic applications, the ionic surfactant toxicity limits their use. The most common anionic surfactants are the sodium di-isooctylsulfosuccinate (AOT) and the sodium dodecylsulfate (SDS). Nonionic surfactants are very often used in pharmaceutical microemulsion formation.

Tweens (ethoxylatedsorbitan esters) are well known and widely used. They are water-soluble and have high HLB values and, therefore, are used mainly for making o/w microemulsions. Ethoxylated (with up to 40 EO units castor oil, ECO-40) and hydrogenated ethoxylated castor oil (HECO) with 8 to 40 EO group attached to the hydroxyl group on the side chain of the triglyceride are regarded a svery efficient surfactants. In ethoxylated fatty acids and fatty alcohols (Myrj andBrij, respectively) and also in polyethylene glycols (PEG of up to 200 EO units) or Poloxamers, polyoxyethylene glycol blocks appear in some of the formulations.[20]Amphoteric surfactants like lecithin are of low toxicity and are considered as natural ingredients. There are many commercial lecithin products in the market with various degrees of purity and with a large variation in internal phospholipid compositions among which egg lecithin and soy lecithin are widely documented.

The Co-surfactant

Co-surfactants play a very important role in microemulsions. They help the surfactant reduce the interfacial tension to very low values to achieve thermodynamic stability. They both modify the curvature of the interface by incorporating additional polar groups and provide more fluidity to the film, preventing crystallization of the tails of the surfactants, which could result in the

formation of lyotropic liquid crystals. Co-surfactants are considered to be liquid crystal structure breakers. They are of less help to surfactants with unsaturated (double) bonds in their tails. However, they are especially essential when the surfactant has a saturated tail.

In most cases, the co-surfactants are short (ethanol) and medium-chain (propanolto octanol) alcohols. In some pharmaceutical applications (transdermal, ocular), we use mostly those that do not present irritation. Other molecules, such as amino acids and short organic acids, have also been utilized.

The Oil or the Organic Phase

For drugs that cannot be formulated as an aqueous solution, emulsions and microemulsion shave typically been cost-effective and provided for ease of administration. Hydrocarbons pack well within the surfactant tails and, therefore, they are the most recommended compounds for making large w/o and o/w MEs for pharmaceutical applications. Too long tails are not good oily phases because of lack of solubility.

Other common oil phases include esters of fatty acids or fatty alcohol, depending on the nature of the application. The oil that typically comes to mind for pharmaceutical applications consists of digestible oils from the family of triglycerides, including soybean oil, sesame seed oil, cotton seed oil, and safflower oil. These oils are inexpensive and compatible with most surfactants, but are not stable for high temperature treatment or filtration sterilization because of either heat-induced destabilization of the ME or hydrolysis of the triglycerides.

Triglycerides seem to be excellent oils for making MEs, but it was shown that making an ME of o/w from vegetable oils, such as soy, Canola, corn, and many others, is a very difficult task. These oils, although they look somewhat polar from their chemical structure, are actually too bulky, with very high molecular volume fractions, and form curved interfaces with difficulty, and their solubility (solvation) around the surfactant tails is limited. Thus, MEs made of vegetable oils are limited in their isotropic regions.

METHOD OF PREPARATION

Phase Titration Method

Microemulsions are prepared by the spontaneous emulsification method (phase titration method) and can be depicted with the help of phase diagrams. Construction of phase diagram is a useful approach to study the complex series of interactions that can occur when different components are mixed. Microemulsions are formed along with various association structures (including emulsion, micelles, lamellar, hexagonal, cubic, and various gels and oily dispersion)depending

on the chemical composition and concentration of each component. The understanding of their phase equilibriums and demarcation of the phase boundaries are essential aspects of the study.

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 microemulsion zone, in which each corner of the diagram represents 100% of the particular component (Figure 2). The region can be separated into w/o or o/w microemulsion 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. The methodology has been comprehensively discussed by Shafiq-un-Nabi*et al.*[21]

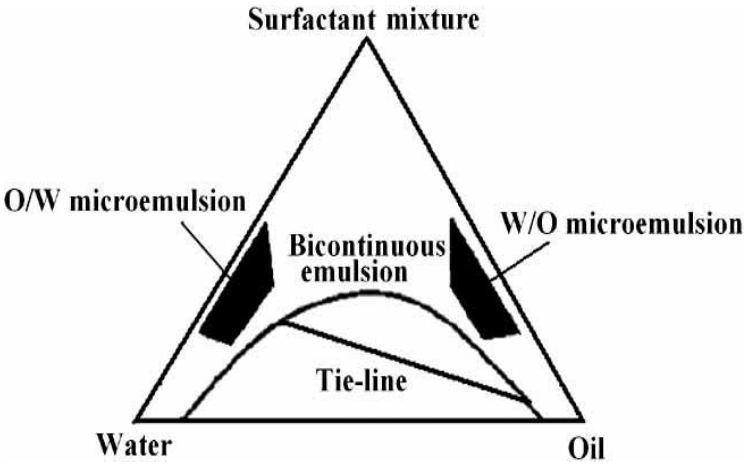

Figure 2: Pseudoternary phase diagram of oil, water and surfactant showing microemulsion region.

Phase Inversion Method

Phase inversion of microemulsions occurs upon addition of excess of the dispersed phase or in response to temperature. During phase inversion drastic physical changes occur including changes in particle size that can affect drug release both *in vivo* and *in vitro*. These methods make use of changing the spontaneous curvature of the surfactant. For non-ionic surfactants, this can be achieved by changing the temperature of the system, forcing a transition from an o/w microemulsion at low temperatures to a w/o microemulsion at higher temperatures (transitional phase inversion). During cooling, the system crosses a point of zero spontaneous curvature and minimal surface tension, promoting the formation of finely dispersed oil droplets. This method is referred to as phase inversion temperature (PIT) method. Instead of the temperature, other parameters such as salt concentration or pH value may be considered as well instead of the temperature alone.

Additionally, a transition in the spontaneous radius of curvature can be obtained by changing the water volume fraction. By successively adding water into oil, initially water droplets are formed in a continuous oil phase. Increasing the water volume fraction changes the spontaneous curvature of the surfactant from initially stabilizing a w/o microemulsion to an o/w microemulsion at the inversion locus. Short-chain surfactants form flexible monolayer's at the o/w interface resulting in a bicontinuous microemulsion at the inversion point.

Phase Behavior Studies

Before a ME can be used as a drug delivery vehicle, the phase behavior of the particular combination of the candidate ingredients should be established. This is necessary due to the diverse range of colloidal and coarse dispersions that could be obtained when oil, water, and an amphiphile blend are mixed. Coarse emulsions, vesicles, lyotropic liquid crystals, and micellar systems are some examples. A variety of multiphase systems may coexist and the demarcations of the regional boundaries become important. One of the most suitable methods to study the phase behavior of such systems is to construct a ternary phase diagram using a Gibbs triangle (Figure 3). A ternary phase diagram can be constructed by two methods: [22]

- Titrating a mixture of two components with the third component
- Preparing a large number of samples of different composition

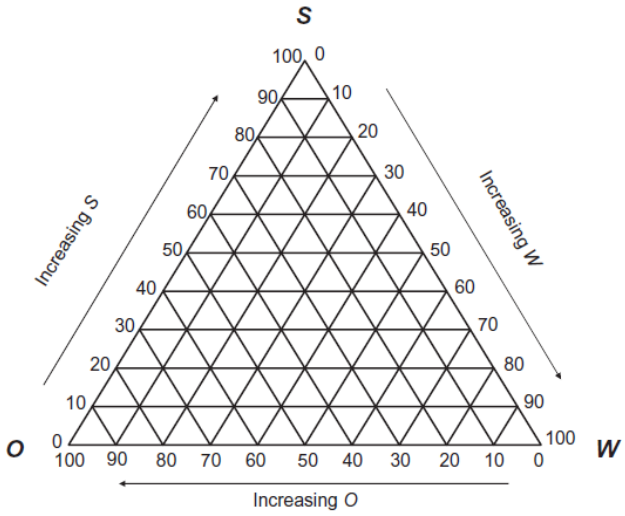

Figure 3:Ternary phase diagram used to elucidate ME formation regions. Each of the three corners represents 100% of the individual components. Apex *S* = 100% w/w surfactant (0% oil and water), apex *W* = 100% w/w water (0% oil and surfactant), and apex *O* = 100% w/w oil (0% water and surfactant). The three lines joining the corner points represent two component systems. The area within the triangle represents all possible combinations of the three components.

If all mixtures reach equilibrium rapidly, both methods give identical results. For mixtures that do not reach equilibrium quickly, the second method is recommended, as with the titration method the change in the ratio of components during titration may occur too fast, not allowing sufficient time to visually recognize phase changes.[22]

As the formulation may contain more than three components, the complete phase behavior cannot be fully represented using a triangular diagram. However, the phase behavior of a four component mixture at fixed pressure and temperature can be represented using a tetrahedron. Full characterization of such systems is a tedious task requiring a large number of experiments.[23]

One acceptable approach for representing such systems is by fixing the mass ratio of two components (such as the two amphiphiles) and as such considered a single component. Such an approach, although regarded by many as an oversimplification of the systems, is yet acceptable for the purpose of phase behavior studies. Such systems are described as "pseudo ternary" as they comprise more than three components (four or possibly five) yet are represented using a Gibbs triangle, which is a used to describe the phase behavior of a three - component system.

A novel approach to reduce the experimental effort associated with constructing pseudo ternary phase diagrams is by using expert systems to predict the phase behavior of multicomponent ME - forming systems. Artificial neural networks have been investigated and were shown to be promising in phase behavior studies [24,25,26]as well as in the process of ingredient selection.[27]

CHARACTERIZATION OF MICROEMULSION SYSTEMS

The characterization of these systems is highly challenging due to their small droplet size with fluctuating boundaries and complex structure. The physicochemical and analytical techniques used to characterize MEs and related systems could be categorized into those used to (1) Elucidate the microstructure and monitor phase behaviour changes; (2) Determine the droplet size of the disperse phase; (3) Local molecular arrangements, interactions and dynamics.

Among these properties, particle size, interactions, and dynamics are of fundamental importance since they control many of the general properties of microemulsions. In particular, the size distributions of microemulsions give essential information for a reasonable understanding of the mechanism governing both the stability and penetration into the membrane.[28, 29]

The choice of a particular technique is limited by factors such as availability, feasibility, and the nature of the information sought. Pharmaceutical scientists are more focused on the usefulness of a particular ME system for a drug delivery application and the influence of the microstructure on that, rather than on the fundamental understanding of aspects such as microstructure and phase behaviour.

Polarized light microscopy is a readily available technique that could be used at the early formulation development stage to differentiate between isotropic and anisotropic systems. Transmission electron microscopy (TEM) is another available technique that has been shown to provide micro structural as well as size-related information on droplet and bicontinuous ME systems. The main disadvantages of TEM applications (such as freeze fracture and cryo-TEM) are the lengthy and sophisticated experimental procedures associated with sample preparation and the possibility of creating artefacts during sample preparation.

Other readily available and more user friendly techniques are electrical conductivity and viscosity measurements. Electrical conductivity measurements are widely used for their simplicity, feasibility, and sensitivity to structural changes in systems with increasing water content, particularly systems undergoing percolation transitions. Viscosity measurements, on the other hand, require more sophisticated instrumentation yet provide useful information on changes in the flow properties associated with structural changes of the systems.

Many technologies like dynamic light scattering (DLS)[30,31], small angle neutron scattering(SANS)[32,33,34]and small angle X-ray scattering (SAXS)[35,36]as well as cryo transmission electron microscopy[37,38,39,40]and pulsed field gradient spin echo (self-diffusion)NMR [41,42,43,44,45]have been in growing use in particle size characterization. Other methods, e.g. electrokinetic chromatography, conductance, viscosity, electrical birefringence, infrared spectroscopy and calorimetry are also employed for investigating the internal physicochemical states ofmicroemulsions.[46,47,48,49,50,51]

Viscosity measurement can indicate the presence of rodlikeor worm-like reverse micelles while conductivity measurement provides a means of determining whether microemulsion is oil-continuous or water-continuous as well provide a means of monitoring phase inversion phenomena.[52]Dielectric measurements are a powerful means of probing both the structural and dynamic features of Microemulsion systems. Pulsed field gradient NMR is also used extensively to measure self-diffusion coefficients of the various components and yields information on the mobility and microenvironment.

Microemulsion as Drug Delivery Carrier

During the last two decades, microemulsions have been extensively researched because of their tremendous potential in many applications. The role of microemulsions in drug delivery is major concern for pharmaceutical development.

Oral delivery

Microemulsions 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. Microemulsions 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, non polar 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[53]and enhance the membrane permeability.[54] Presently, SandimmuneNeoral® (Cyclosporine A), Fortovase® (Saquinavir), Norvir® (Ritonavir), etc. are the commercially available oral SMEDDS formulations.

Parenteral 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[55]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.[55,56,57,58,59,60,61,62] Microemulsions can also be used as intravenous delivery systems for the fat soluble vitamins and lipids in parenteral nutrition.[62]

Topical delivery

Microemulsions have been reported to enhance the transdermal permeation of drugs significantly compared to conventional formulations such as solutions, gels or creams.[63,64]They are able to incorporate both hydrophilic (5-fluorouracil, apomorphine hydrochloride, diphenhydramine hydrochloride, tetracaine hydrochloride, methotrexate etc.) and lipophilic drugs (estradiol, finasteride, ketoprofen, meloxicam, felodipine, triptolide etc.) and enhance their permeation.[65,66,67,68,69,70,71,72]

The advantages of microemulsion for the transdermal delivery of a drug are: 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,[73]the permeation rate of the drug from microemulsion may be increased, since the affinity of a drug to the internal phase in microemulsion can be easily modified to favour partitioning into stratum corneum, using different internal phase, changing its portion in microemulsion,[74]the surfactant and co surfactant

in the microemulsions may reduce the diffusional barrier of the stratum corneum by acting as penetration enhancers,[71] the percutaneous absorption of drug will also increase due to hydration effect of the stratum corneum if the water content in microemulsion is high enough.

Ophthalmic delivery

Microemulsions offer a promising alternative in ocular drug delivery. In point of view of production and sterilization, microemulsions are simple and inexpensive. Moreover, they are comprised of aqueous and oily components and therefore can accommodate both hydrophilic as well as lipophilic drugs. Water-in-oil microemulsions may be of value as vehicles for ocular drug delivery of irritant hydrophilic compounds as they appear to have a protective effect.[75]

Microemulsions could become especially favourable for water-continuous ophthalmological carrier systems because of their aqueous consistence, their transparency and thermodynamical stability. Further advantages result from a possible improvement of solubility and stability of drugs with a potential increase in bioavailability, especially for poorly soluble drugs. In addition, no impairment of visibility can be expected in comparison with eye oils. Because of these circumstances the compliance to the patient could be improved.[76]The most used surfactants in the preparation of ophthalmic microemulsions are the poloxamers, polysorbates, tyloxapol, polyethylene glycol and their derivatives.[77]

Periodontal delivery

The periodontium, which anchors the teeth to the jaws, consists of the gingiva, periodontal ligament, cementum and alveolar bone.[78]It is normally in a balanced state with the periodontal microbiota in the dental plaque. Human periodontal diseases (i.e. gingivitis and periodontitis) result from heterogenousetiologies, including changes to the complex biofilm in the subgingivial microenvironment, social and behavioural modulations, and genetic or epigenetic traits of the host's immune and inflammatory responses. Periodontitis is a chronic inflammatory disease that is characterized by destructive inflammatory processes affecting the supporting structures of the teeth, causing resorption of alveolar bone and formation of periodontal pockets.[79]It is a major cause of tooth loss. The microemulsion formulation comprising local anaesthetic in oil form, surfactant, water and optionally a taste masking agent could be used as a local anaesthetic for pain relief within the oral cavity in conjunction with periodontal scaling and root planning.[80] The formulation can overcome the problem with the existing topical products (jelly, ointment or spray) such as lack of efficacy due to inadequate depth of penetration, too short duration and difficulties in administration due to spread, taste etc. Microemulsion alone or in conjunction with in situ gelling system is promising tool for drug delivery in periodontitis.

Nasal delivery

Microemulsions are now being studied as a delivery system to enhance penetration/uptake across nasal mucosa. Addition of a mucoadhesive polymer helps in prolonging the residence time on the mucosa. Nasal route for administration of diazepam microemulsion might be a useful approach for the rapid onset of action during the emergency treatment of status epilepticus due to better penetration and improved bioavailability.[81]

CONCLUSION

It is clear that microemulsions and their related formulations offer considerable potential as a carrier for the delivery of therapeutic agents. To date microemulsions have been shown to be able to protect labile drug, control drug release, increase bioavailability and reduce patient variability. Furthermore, it has proven possible to formulate preparations suitable for most routes of administration. There is still however a considerable amount of fundamental work characterizing the physico-chemical behaviour of microemulsions that needs to be performed before they can live up to their potential as multipurpose drug delivery carriers.

REFERENCES

1. Lawrence MJ, Rees GD. Microemulsion - based media as novel drug delivery systems. Advance Drug Delivery Review 2000; 45(1): 89-121.
2. Hoar TP, Schulman JH. Transparent water-in-oil dispersions: the oleopathichydromicelle. Nature 1943; 152:102–104.
3. Schulman JH, Stoeckenius W, Prince LM. Mechanism of formation and structure of microemulsions by electron microscopy. J Phys Chem 1959; 63:1677–1680.
4. Maria JGC, Nuria S, Conxita S, Nuria, A. Studies on the formation of O/W nano-emulsions by low-energy emulsification methods suitable for pharmaceutical applications. Eur J Pharma Sci 2005; 26: 438-445.
5. Mason TG, Wilking JN, Meleson, K., Chang CB, Graves, SM. Nanoemulsions: formation, structure, and physical properties. J physics: condensed matter 2006; 18: 635-666.
6. Anton N. Reverse micelle-loaded lipid nano-emulsions: New technology for nano-encapsulation of hydrophilic materials. Int J Pharma 2010.
7. Talegaonkar, S, Azeem, A, Ahmad, FJ, Khar, RK, Pathan, SA. and Khan, ZI. Microemulsions: A Novel Approach to Enhanced Drug Delivery. Recent Patents on Drug Delivery & Formulation 2008; 2: 238-257.

8. Mitchell D, Ninham W. Micelles vesicles and microemulsions. J Chem Soc Faraday Trans 1981; 77(2): 601-629.
9. Prince LM. Microemulsions: Theory and Practice. New York: Academic; 1977.
10. Alany RG, Wen J. Pharmaceutical manufacturing handbook- Production and Processes. Wiley-Inter science; 2008.
11. Overbeek, J. Th. G. Faraday Discuss. Chem. Soc. 1978; 65: 7.
12. Tadros, Th. F. Vincent B. in 'Encyclopaedia of Emulsion Technology'.Becher, P. Ed., Vol. 1, Marcel Dekker, New York; 1980.
13. Kunieda H, Shinoda KJ. Colloid and Interface Science. New Delhi: Pallab Ghosh; 1980; 75: 601.
14. Hunter RJ. Introduction to Modern Colloid Science. Oxford University Press, Oxford; 1994.
15. P. D. I. Fletcher, A. M. Howe, and B. H. Robinson. The Kinetics of Solubilisate Exchange between Water Droplets of a Water-in-Oil Microemulsion. J. Chem. Soc. 1987; 83: 985
16. S. Clark, P. D. I. Fletcher, and X. L. Ye. Inter droplet Exchange-Rates of Water-in-Oil and Oil-in-Water Microemulsion Droplets Stabilized by C12e5. Langmuir 1990; **6**:1301-1309.
17. Biais J, Bothorel P, Clin B, Lalanne P. Theoretical behavior of microemulsions: geometrical aspects and dilution properties. J. Colloid Interface Sci. 1981; 80: 136-145.
18. Friberg S, Mandell L, Larson M. Mesamorphous Phases, a factor of importance for the properties of emulsions. J. Colloid Interface Sci. 1969; 29: 155 - 156.
19. Garti N, Aserin A, Ezrahi S, Wachtel E. Water solubilization and chain-length compatibility in nonionic microemulsions. J Colloid Interface Sci 1995; 169:428–436.
20. Hofland HEJ, Van der Geest R, Bodde HE, Junginger HE, Bouwstra JA. Estradiol permeation from nonionic surfactant vesicles through human stratum corneum in vitro. Pharm Res 1994; 11:659–664.
21. Shafiq-un-Nabi S, Shakeel F, Talegaonkar S, et al. Formulation development and optimization using nanoemulsion technique: A technical note. AAPS Pharm Sci Tech 2007; 8(2): E1-E6.
22. Bhargava, H. N., Narurkar, A., and Lieb, L. M. Using microemulsions for drug delivery.Pharm. Technol., 1987; 11: 46.

23. Bourrel, M., and Schechter, R. S. The R - ratio, in Bourrel, M., and Schechter, R. S. Eds., Microemulsions and Related Systems. Marcel Dekker, New York. 1988; 1 – 30.
24. Agatonovic - Kustrin S, Glass BD, Wisch MH and Alany RG. Prediction of a stable microemulsion formulation for the oral delivery of a combination of antitubercular drugs using ANN methodology. Pharm. Res. 2003; 20 (11): 1760 – 1765.
25. Alany, R. G., Davies, N. M.,Tucker, I. G., and Rades, T. Characterizing colloidal structures of pseudoternary phase diagrams formed by oil/water/amphiphile systems.Drug Dev. Ind. Pharm. 2001; 27 (1): 33 – 41.
26. Alany, R. G., Agatonovic - Kustrin, S., Rades, T., and Tucker, I. G. Use of artificial neural networks to predict quaternary phase systems from limited experimental data. J. Pharm. Biomed. Anal. 1999; 19 (3): 443 – 452.
27. Richardson CJ, Mbanefo A, Aboofazeli R, Lawrence MJ, and Barlow DJ. Prediction of phase behavior in microemulsion systems using artificial neural networks. J. Colloid Interface Sci. 1997; 187 (2): 296 – 303.
28. Constantinides PP, Yiv SH. Particle size determination of phase inverted water-in-oil microemulsions under different dilution and storage conditions. Int J Pharm 1995; 115: 225-234.
29. Mueller BW, Mueller RH. Particle size distributions and particle size alterations in microemulsions. J Pharm Sci 1984; 73: 919-922.
30. Kang BK, Chon SK, Kim SH, et al. Controlled release of paclitaxel from microemulsion containing PLGA and evaluation of antitumour activity in vitro and in vivo. Int J Pharm 2004; 286: 147- 156.
31. Porras M, Solans C, Gonzalez, C, Martinez A, Guinart A, Gutierrez, JM. Studies of formation of w/o nanoemulsions. Colloid Surf A: Physicochem Eng Asp 2004; 249: 115-118.
32. Burnett GR, Rees GD, Steytler DC, Robinson BH. Fluorescence correlation spectroscopy of water-in-oil microemulsions: an application in specific characterization of droplets containing biomolecules. Colloids Surf A: Physicochem Eng Asp 2004; 250: 171-178.
33. Silas JA, Kaler EW. Effect of multiple scattering on SANS spectra from bicontinuous microemulsions. J Colloid Interface Sci 2003; 257: 291-298.
34. Pedersen JS. Analysis of small-angle scattering data from micelles and microemulsions: Free-form approaches and model fitting. CurrOpin Colloid Interface Sci 1999; 4: 190-196.

35. Kawakami K, Yoshikawa T, Moroto Y, et al. Microemulsion formulation for enhanced absorption of poorly soluble drugs: I. Prescription design. J Control Release 2002; 81: 65-74.
36. Kumar P, Mittal KL. Microemulsions in foods; In: Handbook of Microemulsion Science and Technology. New York, Marcel Dekker 1999; 789.
37. Danino D, Gupta R, Satyavolu J, Talmon Y. Direct Cryogenic temperature transmission electron microscopy imaging of phospholipids aggregates in soybean oil. J Colloid Interface Sci 2002; 249: 180-186.
38. Danino D, Talmon Y, Zana R. Cryo-TEM of thread like micelles: on the grid microstructural transformations induced during specimen preparation Colloid Surf A: Physicochem Eng Asp 2002; 169: 67-73.
39. Jian X, Ganzuo L, Zhiqiang Z, Guowei Z, Kejian J. A study of the microstructure of CTAB/1-butanol/octane/water system by PGSENMR, conductivity and cryo-TEM. J Colloid Surf A: Physicochem Eng Asp 2001; 191: 269-278.
40. Magdassi S, Ben Moshe M, Talmon Y, Danino D. Microemulsion based on anionic Gemini surfactant. Colloid Surf A: Physicochem Eng Asp 2003; 212: 1-7.
41. Andersson M, Lofroth J-E. Small particles of a heparin/chitosan complex prepared from a pharmaceutically acceptable microemulsion. Int J Pharm 2003; 257: 305-309.
42. Kreilgaard M, Pedersen EJ, Jaroszewski JW. NMR characterization and transdermal drug delivery potential microemulsion systems. J Control Release 2000; 69: 421-433.
43. Lopez F, Cinelli G, Ambrosone L, Colafemmina G, Ceglie A, and Palazzo G. Role of the cosurfactant in water-in-oil microemulsion: interfacial properties tune the enzymatic activity of lipase. Colloid Surf A: PhysicochemEng Asp 2004; 237: 49-59.
44. Koa CJ, Kob YJ, Kim DM, Park HJ. Solution properties and PGSE-NMR self-diffusion study of C18:1 E10/oil/water system. Colloid Surf A: PhysicochemEng Asp 2003; 216: 55-63.
45. Fanun M, Wachtel E, Antalek B, Aserin A, Hoffman RE, Garti N. A study of the microstructure of four-component sucrose ester microemulsions by SAXS and NMR. Colloid Surf A: PhysicochemEng Asp 2001; 180: 173-186.
46. Kreuter J. Microemulsions; In: Colloidal drug delivery systems. New York: Marcel Dekker 1994; 31-71.
47. Kumar P, Mittal KL. Microemulsions in foods; In: Handbook of Microemulsion Science and Technology. New York, Marcel Dekker 1999; 789.

48. Djordjevic L, Primorac M, Stupar M, Krajisnik D. Characterization of caprylocaproylmacrogolglycerides based microemulsion drug delivery vehicles for an amphiphilic drug. Int J Pharm 2004; 271: 11-19.
49. Mrestani Y, El-Mokdad N, Ruttinger HH, Neubert RHH. Characterization of partitioning behavior of cephalosporin using microemulsion and micellar electrokinetic chromatography. Electrophoresis 1998; 19: 2895-2899.
50. Mrestani Y, Neubert RHH, Krause A. Partition behaviour of drugs in microemulsions measured by electrokinetic chromatography. Pharm Res 1998; 15: 799-801.
51. Moulik SP, Paul BK. Structure, dynamics and transport properties of microemulsions. Adv Colloid Interface Sci 1998; 78: 99-195.
52. Lawrence MJ, Rees GD. Microemulsion based media as novel drug delivery systems. Adv Drug Del Rev 2000; 47: 89-121.
53. Sariciaux, M.J., Alan, L. and Sado, P.A. Using microemulsion for drug delivery of therapeutic peptides. Int J Pharma1995; 12: 127-136.
54. Swenson, E.C. and Curatolo, W. Intestinal permeability enhancement for proteins, peptides and other polar drugs: mechanism and potential toxicity. Advance Drug Delivery Review 1992; 8: 39-42.
55. Shaw JM. Lipoproteins as carriers of pharmacological agents. New York: Marcel Dekker; 1991.
56. Kyung-Mi, P. and Chong-Kook, K. Preparation and evaluation of flurbiprofen-loaded microemulsion for parenteral delivery. Int J Pharma1999; 181: 173-179.
57. Lee, J.M., Park, K.M., Lim, S.J., Lee, M.K. and Kim, C.K. Microemulsion formulation of clonixic acid: solubility enhancement and pain reduction. J Pharm Pharmacol 2002; 54: 43-49.
58. Rhee, Y.S., Park, C.W., Nam, T.Y., Shin, Y.S., Chic, S.C. and Park, E.S. Formulation of parenteral microemulsion containing itraconazole. Archives of Pharmacal Research 2007; 30: 114-123.
59. Ryoo, H.K., Park, C.W., Chi, S.C. and Park, E.S. 'Development of propofol loaded microemulsion systems for parenteral delivery. Archives of Pharmacal Research 2005; 28: 1400-1404.
60. Hwang, S.R., Lim, S.J., Park, J.S. and Kim, C.K. Phospholipid based microemulsion formulation for all-trans-retinoic acid for parenteral administration. Int J Pharma 2004; 276: 175-183.

61. Zhao, X., Chen, D., Gao, P., Ding, P. and Li, K. Synthesis of Ibuprofen eugenol ester and its microemulsion formulation for parenteral delivery. Chemical and Pharmaceutical Bulletin 2005; 53: 1246-1250.
62. Jumma, M. and Muller, B.W. The effect of oil components and homogenization conditions on the physicochemical properties and stability of parenteral fat emulsions. Int J Pharma 1998; 163: 81-89.
63. Kriwet, K. and Muller-Goymann, C.C.Diclofenac release from phospholipid drug systems and permeation through excised human stratum corneum. Int J Pharma 1995; 125: 231-242.
64. Trotta, M. Influence of phase transformation on indomethacin release from microemulsions.Journal of Control Release 1999; 60: 399-405.
65. Schmalfuß, U., Neubert, R. and Wohlrab, W. Modification of drug penetration into human skin using microemulsions. J Control Release 1997; 46: 279-285.
66. Alvarez-Figueroa, M.J. and Blanco-Mendez, J. Transdermal delivery of methotrexate: iontophoretic delivery from hydrogels and passive delivery from microemulsions. Int J Pharma 2001; 125: 57-65.
67. Trotta, M., Morel, S. and Gasco, M.R. Effect of oil phase composition on the skin permeation of felodipine from w/o microemulsions. Pharmazie 1997; 52: 50-53.
68. Chen, H., Chang, X., Weng, T., Zhao, X., Gao, Z., Yang, Y., Xu, H. and Yang, X. A study of microemulsion systems for transdermal delivery of triptolide. J Control Release 2004; 98: 427-436.
69. Gupta, R.R., Jain, S.K. and Varshney, M. Water-in-oil microemulsions as a penetration enhancer in transdermal drug delivery of 5-fluorouracil.Colloids Surfaces B: Biointerfaces 2005; 41: 25-32.
70. Elena, P., Paola, S. and Maria, R.G. Transdermal permeation of apomorphine through hairless mouse skin from microemulsions. Int J Pharma 2001; 226: 47-51.
71. Rhee, Y.S., Choi, J.G., Park, E.S. and Chi, S.C. Transdermal delivery of ketoprofen using microemulsions.International Journal of Pharmaceutics 2001; 228: 161-170.
72. Yuan, Y., Li, S.M., Mo, F.K. and Zhong, D.F. Investigation of microemulsion system for transdermal delivery of meloxicam. Int J Pharma 2006; 321: 117-123.
73. Hua, L., Weisan, P.,Jiayu, L. and Ying, Z. Preparation, evaluation and NMR characterization of vinpocetine microemulsion for transdermal delivery. Drug DevInd Pharm 2004; 30: 657-666.

74. Kreilgaard, M. Influence of microemulsion on cutaneous drug delivery.Advance Drug Delivery Review 2002; 54: 77-98.
75. Alany R, Rades T, Nicoll J, Tucker IG, Davies NM. W/O microemulsions for ocular delivery: Evaluation of ocular irritation and precorneal retention. J Controlled Release 2006; 111: 145-152.
76. Keipert, S. and HaBe, A. Development and characterization of microemulsions for ocular application. Eur J Pharma Biopharma1997; 43: 179-183.
77. Vandamme TF. Microemulsions as ocular drug delivery systems: recent developments and future challenges. Progress in Retinal and Eye Research 2002; 21: 15-34.
78. Newman, M.G., Takei, H. and Carranza, F.A .Clinical Periodontology, 9th edition, Philadelphia: WB Saunders; 2002.
79. Houshmand, B, Rafiei A, Hajilooi M, Mani-Kashani K, Gholami, L.E-selectin and L-selectin polymorphisms in patients with periodontitis. J Periodont Research 2009; 44: 88-93.
80. Talegaonkar, S, Azeem, A. Ahmad FJ, Khar RK, Pathan SA, Khan ZI. Microemulsions: A Novel Approach to Enhanced Drug Delivery. Recent Patents on Drug Delivery & Formulation 2008; 2: 238-257.
81. Lianly IL, Nandi I, Kim, KH. Development of an ethyl laurate based microemulsion for rapid onset of intranasal delivery of diazepam. Int J Pharma 2002; 237: 77-85.