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Microemulsions: A Paradigm Shift in Drug Delivery Systems

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ABSTRACT
A microemulsion is a transparent or nearly transparent, quasi-homogeneous, thermodynamically stable mixture of two immiscible liquid stabilized by surfactant (or mixture of surfactant). As pharmaceuticals drug delivery systems, microemulsion have unique properties, including clarity, high stability and ease of preparation. Due to their physicochemical properties, microemulsion often advantages over traditional topical and transdermal drug delivery systems. Moreover, microemulsion dispersion are promising candidates as means for controlled drug delivery, and as drug carriers for oral, topical, and parenteral administration furthermore, microemulsion have been shown to process promising potential in the fields of cosmetic and various consumer products. A brief overview regarding the preparation, characterization and application of microemulsion has been given in this review article.

Keywords: Microemulsion, Advantages, Novel drug delivery system, Application.

I. INTRODUCTION

Emulsions are heterogeneous system in which one immiscible liquid is dispersed as droplets in another liquid. Such a thermodynamically unstable system is kinetically stabilized by addition of one further component or mixture of components that exhibit emulsifying properties. One emulsion that is further dispersed into another continuous phase is called double emulsion, multiple emulsion or emulsified emulsion. The droplet-size distribution of emulsion droplets is 0.5-50.0µm. The inner droplet size distribution of w/o emulsion in multiple emulsions is usually smaller than 0.5µm, where as the outer, external multiple emulsions is quite large and can exceed 10µm. Another emulsion system is "microemulsion" and can define a system of water, oil and amphiphile, which is a single optically isotropic. The droplets in a microemulsion are in the range of 0.1-1.0µm [1]. The existence of this theoretical structure was later confirmed by use of various technologies and we can today adopt the definition given by Attwood as follows : "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" [2].Microemulsion is homogenous, thermodynamically stable dispersion of water and oil stabilized by relatively large amounts of surfactant(s) frequently in combination with cosurfactant(s) [3-8].Microemulsion shows diverse structural organization due to the use of wide range of surfactant concentration, water-oil ratios, temperature etc. (Lawrence et al., 2005). In case of emulsion, it contains three components, namely oil, water and surfactant; whereas microemulsions generally require a forth component i.e. cosurfactants, which include linear alcohols of medium chain length that is miscible with water. The combination of surfactant and co-surfactant promotes the generation of extensive interfaces through the spontaneous dispersion of oil in water, or vice-versa. The large interfacial area between oil and water consists of a mixed interfacial film containing both surfactant and cosurfactant molecules. The interfacial tension at the oil-water interfaces in emulsions approaches zero, which also contributes to their spontaneous formation. Microemulsions are regarded as micelles extensively swollen by large amounts of solubilized oil [9,10].

Three types of microemulsions are most likely to be formed depending on the composition:

1. Oil in water (O/W) microemulsions wherein oil droplets are dispersed in the continuos aqueous phase.

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2. Water in oil (W/O) microemulsions wherein water droplets are dispersed in the continuous oil phase;
3. Bi-continuous microemulsions wherein microdomains of oil and water are interdispersed within the system.

In all the three types of microemulsions, the interface is stabilized by an appropriate combination of surfactants and/or co-surfactants [11].

Microemulsion displays a rich behavior regarding the release of solubilized material. Also, one can reach sustained release if the interactions between drug and surfactant and/or partitioning of drug between oil and water phase strongly affect the drug release [12]. O/W microemulsion is also formulated as aqueous vehicles for oil-soluble drug to be administered by the percutaneous, oral or parenteral routes.

Microemulsion components are classified into oils, surfactants and co-surfactants. Oils are moderate to large alkyl hydrocarbons (140-900 Da) that might contain ester or carboxylic acid moieties. Surfactant are complex mixture of phospholipids characterized with molecular weight range of 500-700 Da and two structurally distinct part of opposite lipophilicity/hydrophilicity properties are small (60-190 Da) mono or multi-hydroxy alcohols or carboxylic acids that might contain ether linkages. The co-surfactant is also added to stabilize microemulsion, which is also amphiphillic with an affinity for both oil and aqueous phases and partitions to an applicable extent into the surfactant interface. A wide variety of molecules can function as co-surfactant including non-ionic surfactant, alcohol, alkanoic acids, alkanoids and alkylamines [13].

In order to investigate a drug delivery potential of microemulsion vehicle, it is necessary to characterize their microstructure as well as a microstructure of drug loaded microemulsion. The formulation process and gradual change in microemulsion microstructure can be monitored quantitatively by measuring the electrical conductivity and rheological properties of the system [1]. A part from the microemulsion structure and composition, the incorporated drug molecules participate in the microstructure of the system and may influenced it due to molecular interactions, especially if the drug possesses amphiphilic and/or mesogenic properties [14].

Comparison between emulsion and microemulsion

Emulsions and microemulsions are both stable dispersions of oil-in-water or water-in-oil. In emulsion systems, the structures are large enough to scatter light and as such they appear as cloudy colloidal solutions in comparison. The gross physical differences between microemulsion and emulsion systems can be determined by visual examination i.e. microemulsions show no tendency to phase separate and are usually optically transparent, whereas emulsions are opalescent or turbid and the phases inevitably separate (Table 1).

Advantages of microemulsion based system

1. Microemulsions act as super solvents of drug. They can solubilize hydrophilic and lipophilic drugs including drugs that are relatively insoluble in both aqueous and hydrophobic solvents. This is due to existence of microdomains of different polarity within the same single-phase solution.
2. Microemulsions are thermodynamically stable system and the stability allows self-emulsification of the system whose properties are not dependent on the process followed.
3. Microemulsion based system has long self life.
4. The use of microemulsion as delivery systems can improve the efficacy of a drug, allowing the total dose to be reduced and thus minimizing side effects.
5. The formation of microemulsion is reversible. They may become unstable at low or high temperature but when the temperature returns to the stability range, the microemulsion reforms [15].

Disadvantages of microemulsion based systems

1. Use of a large concentration of surfactant and co-surfactant necessary for stabilizing nano droplets.
2. Limited solubilizing capacity for high-melting substances.
3. The surfactant must be nontoxic for using pharmaceutical applications.
4. Microemulsion stability is influenced by environmental parameters such as temperature and pH. These parameters change upon microemulsion delivery to patients [16].

PREPARATION OF MICROEMULSION

It is well established that large amounts of two immiscible liquids (e.g. water and oil) can be brought into a single phase (macroscopically homogeneous but microscopically heterogeneous) by the addition of an appropriate surfactant or a surfactant mixture. Microemulsions can have

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characteristic properties such as ultralow interfacial tension, large interfacial area and capacity to solubilize both aqueous and oil-soluble compounds. Microemulsions can be prepared by controlled addition of lower alkanols (butanol, pentanol and hexanol) to milky emulsions to produce transparent solutions comprising dispersions of either water-in-oil (W/O) or oil-in-water (O/W) in nanometer or colloidal dispersions (~100nm). The lower alkanols are called cosurfactants; they lower the interfacial tension between oil and water sufficiently low. The miscibility of oil, water and amphiphile (surfactant plus cosurfactant) depends on the overall composition which is system specific. Ternary and quaternary phase diagrams can describe the phase manifestations and are essential in the study of microemulsions.

The knowledge on the phase manifestations of the pseudo-ternary (water/amphiphile/oil) or explicitly quaternary (water/surfactant/cosurfactant/oil) mixtures has been systematized. At low surfactant concentration, there is a sequence of equilibria between phases, commonly referred to as Winsor phases (Winsor, 1954), which are **Winsor I (A-1)**: With two phases, the lower (oil/water) microemulsion phase in equilibrium with the upper excess oil; **Winsor II (A-2)**: with two phases, the upper microemulsion phase (water/oil) in equilibrium with excess water; **Winsor III (A-3)**: With three phases, middle microemulsion phase (O/W plus W/O, called bicontinuous) in equilibrium with upper excess oil and lower excess water; **Winsor IV (A 4)**: In single phase, with oil, water and surfactant homogeneously mixed. Inter-conversion among the above mentioned phases can be achieved by adjusting proportions of the constituents. Simultaneous presence of two microemulsion phases, one in contact with water and the other in contact with oil, is also possible. This may be considered as an extension of Winsor's classification forming the fifth category. A composite representation of the above-mentioned features of microemulsion forming systems is depicted in Figure 1 [17].

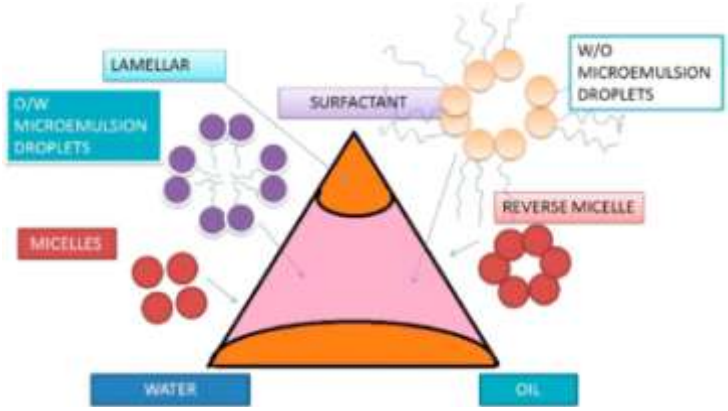

FIGURE 1. Phase diagram of a microemulsion system.

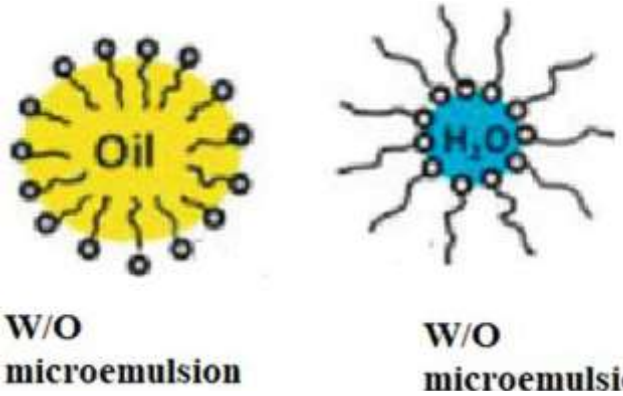

FIGURE 2. Representation of different types of microemulsions.

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CHARACTERIZATION OF MICROEMULSION

In contrast to their ease of production, microemulsions are very difficult to characterize principally because of their wide variety of structures. For this reason, the use of several techniques is often required in order to characterize microemulsion systems. An understanding of the properties of the vehicle is an important requirement for optimizing drug delivery. Additionally, factors affecting drug release, stability, and structure need to be understood in order to establish the potential, and also limitations of microemulsion formulations. A variety of techniques, such as NMR spectroscopy, electrical conductivity, self-diffusion, small-angle neutron scattering, quasi-elastic light scattering, and fluorescence spectroscopy, have been employed to characterize these systems.

Microscopy

Although polarizing microscopy confirms the optical isotropy of the microemulsion system, conventional optical microscopy cannot be used for studying microemulsion systems because of the small droplet size diameter which is typically less than 150 nm. However, transmission electron microscopy (TEM) combined with freeze fracture techniques have been successfully applied for the study and characterization of microemulsions [18]. The sensitivity of microemulsion structure to temperature and the potential introduction of experimental artifacts during manipulation are of some concern with this approach. Other problems are: (1) high microemulsionvapour pressure, which is not compatible with low pressures used in microscopy, (2) electrons may induce chemical reactions, thus, altering microemulsion structure, and (3) lack of contrast between the microemulsion structure and its environment. The introduction of controlled environmental chambers as well as improvements in thermal fixation now permit very fast sample cooling rates to be achieved without crystal formation. The techniques of Cryo-TEM and freeze fracture-TEM, which have evolved from these advances, permit direct visualization of the microemulsion structure with fewer problems of artifactual results [19].

NMR

Self-diffusion is the random movement of a molecule in the absence of any concentration gradient, and this movement reflects the environment where the molecule is localized. If a molecule is confined in a close aggregate, such as micelles, its self-diffusion will be two or three orders of magnitude lower than the expected self-diffusion coefficient from a pure solvent. Therefore, in w/o microemulsions, the self-diffusion of water molecules is slow, whereas,the diffusion of the oil molecules is high. Conversely, for O/W microemulsions the reverse is found. In bicontinuous structures, both oil and water molecules exhibit high self-diffusion coefficients. Microemulsion structure has been characterized as using self-diffusion measurements of the components, obtained by proton Fourier transform pulse-gradient spin-echo NMR (PGSE NMR) [20].

Conductivity and viscosity

The nature of the microemulsion and detection of phase inversion phenomena can be determined using classical rheological methods and by conductivity determination. Viscosity determination also provide useful information on how the colloidal systems may influence drug release. The likely systems present are, for example, vesicles with multilamellar layers, rod-like or worm-like reverse micelles. Water-continuous microemulsions display high conductivity values, whereas oil-continuous systems should have poor or no conductivity [21]. Previously, it has been demonstrated that microemulsions may also exhibit percolation phenomena at certain volume fractions of water (Φp) termed the percolation threshold [22]. When the water fraction is below Φp, the system behaves as an insulator, whereas the effective conductivity increases sharply at values of the water fraction slightly higher than Φp[23]. According to the percolation concept, these electrical properties result from the attractive interactions between water globules, characteristic of bicontinuous structures [24].

Fluorescence spectroscopy

Fluorescence spectroscopy measures the ease of movement of the fluorescent probe molecules in the microemulsions. This is controlled by diffusion, which varies inversely with the viscosity of the medium and with the microemulsion type. In water-continuous microemulsions, the propagation of the excitation is inhibited because of the slow diffusion of the water-insoluble fluorescent (e.g. pyrene) molecules. On the other hand, oil continuous microemulsions should produce a similar excimer formation to that of the pure oil [25].

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Interfacial tension

The formation and the properties of microemulsion can be studied by measuring the interfacial tension. Ultralow values of interfacial tension are correlated with phase behavior, particularly,the existence of surfactant phase or middle-phase microemulsions in equilibrium with aqueous and oil phases. Spinning-drop apparatus can be used to measure the ultralow interfacial tension. Interfacial tensions are derived from the measurement of the shape of a drop of the low-density phase, rotating it in cylindrical capillary filled with high-density phase. To determine the nature of the continuous phase and to detect phase inversion phenomena, the electrical conductivity measurements are highly useful. A sharp increase in conductivity in certain W/O microemulsion system was observed at low volume fractions and such behavior was interpreted as an indication of a "percolative behavior" or exchange of ions between droplets before the formulation of bi-continuous structures. Dielectric measurements are a powerful means of probing both structure and dynamic feature of microemulsion systems [15].

APPLICATIONS OF MICROEMULSION

Microemulsion in pharmaceuticals

Parenteral administration: Parenteral administration (especially via the intravenous route) of drugs with limited solubility is a major problem in the pharmaceutical industry because of the extremely low amount of drug actually delivered to a targeted site. Microemulsion formulations have distinct advantages over macroemulsion systems when delivered parenterally because of the fine particle, microemulsion is cleared more slowly than the coarse particle emulsion and, therefore, have a longer residence time in the body. Both O/W and W/O microemulsion can be used for parenteral delivery.

Oral administration: Oral administration of microemulsion formulations offer several benefits over conventional oral formulation including increased absorption, improved clinical potency, and decreased drug toxicity [27]. Therefore, microemulsion has been reported to be an ideal delivery of drugs such as steroids, hormones, diuretic and antibiotics.

Pharmaceutical drugs of peptides and proteins are highly potent and specific in their physiological functions. However, most are difficult to administer orally. With on oral bioavailability in conventional (i.e. non-microemulsion based) formulation of less than 10%, they are usually not therapeutically active by oral administration. Because of their low oral bioavailability, most protein drugs are only available as parenteral formulations. However, peptide drugs have an extremely short biological half life when administered by parenteral route, so require multiple dosing [28].

Topical administration: Topical administration of drugs can have advantages over other methods for several reasons, one of which is the avoidance of hepatic first pass metabolism of the drug and related toxicity effects. Another is the direct delivery and targetability of the drug to the affected area of the skin or eyes [29].

Ocular and pulmonary delivery: Ocular and pulmonary delivery for the treatment of eye diseases, drugs are essentially delivered topically. O/W microemulsions have been investigated for ocular administration, to dissolve poorly soluble drugs, to increase absorption and to attain prolong release profile.

For instance microemulsions containing pilocarpine were formulated using lecithin, propylene glycol and PEG 200 as co-surfactant and iso-propyl myristate (IPM) as the oil phase. The formulations were of low viscosity with a refractive index lending to ophthalmologic applications.

Microemulsions in biotechnology

Many enzymatic and biocatalytic reactions are conducted in pure organic or aqua-organic media. Biphasic media are also used for these types of reactions. The use of a pure polar media causes the denaturation of biocatalysts. The use of water-proof media is relatively advantageous. Enzymes in low water content display and have:

1. Increased solubility in non-polar reactants.
2. Possibility of shifting thermodynamic equilibria in favour of condensations .
3. Improvement of thermal stability of the enzymes, enabling reactions to be carried out at higher temperatures.

Many enzymes, including lipases, esterases, dehydrogenases and oxidases often function in the cells in microenvironments that are hydrophobic in nature. In biological systems many enzymes operate at the interface between hydrophobic and hydrophilic domains and these usually interfaces are stabilized by polar lipids and other natural amphiphiles. Enzymatic catalysis in microemulsions has been used for a variety of reactions, such as synthesis of esters, peptides and

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sugar acetals transesterification; various hydrolysis reactions and steroid transformation. The most widely used class of enzymes in microemulsion-based reactions is of lipases [30].

Solubilization of drug in microemulsion

Microemulsion possesses interesting physicochemical properties, i.e. transparency, low viscosity, thermodynamic stability, high solubilization power. Because of these specific properties of microemulsion can be useful as a drug delivery system. Different categories of drugs can be solubilized in microemulsion systems for their better therapeutic efficacy [26].

Microemulsions as coatings and textile finishing

The coating application area is a very promising and rapidly-growing field of microemulsion technology, because the microemulsified resins overcome many of the shortcomings of the more traditional water-based systems without creating the health and pollution problems and flammability hazards of the solvent-based coatings. Due to their stability and small droplet size, microemulsions are ideal, where stability and homogeneity of the finished product is desired. Paint formulations using microemulsions have shown higher scrub resistance, better colour intensity and more stain resistance than those prepared by emulsions.

A microemulsion as fuels

A microemulsion-based fuel in the presence of water is one of the advantages of stable microemulsion and they are successfully used to reduce soot formation. When the water is vaporized during the combustion, this will lower the heat released and the combustion temperature. As a direct consequence, the emission rate of gases like nitrogen oxides (NOx) and carbon monoxide (CO) will decrease.

The presence of water is also supposed to cause improved fuel atomization, minimization of particulate emission and sooting, and improved fuel economy in terms of price and miles/volume of the fuel. Another interesting feature of microemulsion-based fuel is their capacity to increase the octane number of gasoline and the corresponding octane number for diesel oils. Octane number improvers include formamide, glycols, urea, etc. In diesel fuels, many problems are overcome due to the high combustion temperatures (160–325°C). It is normal that diesel microemulsions contain watersoluble cetane number improvers [33].

Microemulsions as lubricants, cutting oils and corrosion inhibitors

Microemulsions or reverse micellar solutions are in use as lubricants, cutting oils and corrosion inhibitors for several decades. The presence of surfactant in microemulsion causes corrosion inhibition and the increased water content compared to pure oil leads to higher heat capacity. On one hand the corrosive agents, because of solubilization in microemulsion cannot react with the metal surface and on the other, the metal surface is protected by the adsorbed hydrophobic surfactant film. However, solubilization is selective, and in some cases, other mechanisms might play a role in corrosion prevention. In microemulsions, water with much higher thermal conductivity, imparts higher heat capacity to the system. Such formulations can be used in cutting oil; the oil lubricates the cutting surface, and the water helps to remove the frictional heat generated during the cutting process.

Microemulsions in cosmetics

In many cosmetic applications such as skin care products, emulsions are widely used with water as the continuous phase. It is believed that microemulsion formulation will result in a faster uptake into the skin. Cost, safety (as many surfactants are irritating to the skin when used in high concentrations), appropriate selection of ingredients (i.e. surfactants, cosurfactants, oils) are key factors in the formulation of microemulsions [34].

Unique microemulsions as hair care products have been prepared. They contain an amino-functional polyorganosiloxane (a nonionic surfactant) and an acid and/or a metal salt. Solubilization of fragrance and flavored oils can be achieved in microemulsions. Cosmetic microemulsions (transparent and translucent) of silicone oils, produced by emulsion polymerization have been reported. They are, however, not thermodynamically stable products because of low solubility of silicone oil in the surfactants. Ultra fine emulsions prepared by condensation method have some advantages in cosmetic and medical products, as they have excellent stability and safety and their droplet size can be readily controlled. Ultrafine emulsions can be regarded as thermodynamically unstable microemulsions, as they are O/W emulsions with droplet size similar to microemulsion. Cosmetic formulations for skin care products using commercial nonionic

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surfactants and oils usually used in cosmetics are also investigated [35].

Microemulsions in food

Certain foods contain natural microemulsions. Microemulsions as a functional state of lipids have been, therefore, used in the preparation of foods. Microemulsions form in the intestine during the digestion and absorption of fat. The possibility of producing microemulsion on purpose and using them as tools in food production is, however, a neglected field in food technology. Excellent component solubilization, enriched reaction efficiency and extraction techniques have considerable potential in the area of food technology. An important application of microemulsion is to provide improved antioxidation effectiveness because of the possibility of a synergistic effect between hydrophilic and lipophilic antioxidants. It is known that soybean oil is effectively protected when contained within an L2- phase produced by the addition of monoglycerides (sunflower oil monoglycerides) to water. An approximately 1:5 ratio of monoglycerides to triglycerides is needed to get enough water into the L2-phase (about 5 wt %). In such a system, 200 ppm of tocopherol in the oil and 5% ascorbic acid in the reverse micelles give a dramatic antioxidant effect compared to conventional methods of dissolving or dispersing antioxidants in oils. In fish oils, the same microemulsion-based method to achieve an antioxidant protective effect has also been used. Glycerol has been used instead of water for further improvement of the protectivity [36].

Table 1. Comparison between Emulsion and Microemulsion

Sr. No.	Emulsion	Microemulsion
1.	Emulsions are thermodynamically unstable, they may remain stable for long periods of time, will ultimately undergo phase separation on standing to attain a minimum in free energy.	Microemulsions are thermodynamically stable, it can have essentially infinite lifetime assuming no change in composition, temperature and pressure, and do not tend to separate.
2.	They are lyophobic.	They are on the borderline between lyophobic and lyophilic colloids.
3.	Most emulsions are opaque (white) because bulk of their droplets is greater than wavelength of light and most oils have higher refractive indices than water.	Microemulsions are transparent or translucent as their droplet diameter are less than ¼ of the wavelength of light, they scatter little light.
4.	Emulsions consist of roughly spherical droplets of one phase dispersed into the other.	They constantly evolve between various structures ranging from droplet like swollen micelles to bi-continuous structure.
5.	Droplet diameter 1–20mm.	Droplet diameter 10–100nm.
6.	Inefficient molecular packing	Efficient molecular packing
7.	Direct oil/water contact at the interface.	No direct oil/water contact at the interface.

II. CONCLUSION

In the recent years microemulsions have attracted a great deal of attention not because of there importance in industrial application but also their intrinsic interest. Microemulsions are an attractive technology platform for the pharmaceutical formulators as it has excellent solubilization properties, transparency and the relativelysimple formulation process. There is still a considerable amount of fundamental work characterizing the physico-chemical behaviors of microemulsions that need to be performed before they can live to their potential as multipurpose drug delivery vehicle. Although the number of microemulsions for cosmetic application of highly biocompatible for transdermal delivery system.

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