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A Mini-Review : Microemulsion as the Novel Carrier for Topical Drug Delivery

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Abstract
In the designing of topical formulations of highly lipophilic drugs the clinical efficacy is compromised by their low aqueous solubility resulting in poor drug penetration through skin. Among the different innovative approaches that have been suggested for enhancing the penetration of lipophilic drugs through topical administration, microemulsions have shown better results. The microemulsion is a promising vehicle due to powerful ability to deliver drug through skin and large solubilizing capacities of lipophilic, hydrophilic and amphiphilic drug candidates. A microemulsion one of the pharmaceutical interests for new drug delivery is normally composed of oil, water surfactant and cosurfactant. Microemulsion can be defined as a transparent and clear solution obtained by titrating a normal coarse emulsion with medium chain alcohols to the point of clarity.

Keywords : Microemulsion, Percutaneous, Phase diagram, Pseudo-ternary, Topical

Introduction
Operationally microemulsion may be defined as dispersion of insoluble liquid in a second liquid that appears clear and homogenous to the naked eyes. Microemulsions are frequently called solubilized systems because on a macroscopic basis they seem to behave as true solutions. Careful examination of this complex system has shown that clear emulsions can exist in several differentiable forms. Microemulsions appear to represent a state intermediate between the thermodynamically stable solubilized solutions and ordinary emulsions, which are relatively unstable. Microemulsion contain droplets of oil in water phase (o/w) or droplets of water in oil phase (o/w) with diameter of about 10-200 nm and the volume fraction of dispersed phase may vary from 0.2 to 0.5 [1]. A microemulsion one of the pharmaceutical interests for new drug delivery is normally composed of oil, water surfactant and cosurfactant [1-5]. Schulman and coworkers were first to introduce the term microemulsion, which they defined as a transparent and clear solution obtained by titrating a normal coarse emulsion with medium chain alcohols to the point of clarity [2, 6]. The short to medium chain alcohols are generally considered as cosurfactants in the microemulsion system. The presence of surfactant and cosurfactant in the system makes the interfacial tension very low therefore the microemulsion is thermodynamically stable and forms spontaneously without any significant energy input in the form of shear or heat treatment. Microemulsions are readily distinguished from normal emulsions by their transparency low, viscosity and more fundamentally their thermodynamic stability [2]. Depending on the concentration and nature of components used is formulation microemulsion can be o/w, w/o or bicontinuous type. Currently there is considerable interest in colloidal delivery systems (liposomes, nanoparticles, microspheres, macromolecular drug complexes) for the purpose of drug targeting, controlled release and the protection of drug substances.[3] Liposomes in particular have been

extensively investigated over the last decade as potential carriers for polar and non-polar drugs, but only with limited success as they are relatively unstable and tend to be leaky and have low drug carrying capacity [2]. Microemulsion on the other hand have advantages over both the colloidal system currently under investigation and conventional emulsion, suspension and micellar solution and may provide alternative drug carrier. Microemulsion systems have extensive interfacial, aqueous and oily domains, so are capable of dissolving considerable quantities of oil soluble, water-soluble and amphiphilic materials. They form spontaneously without high shear equipment or significant energy input, and their microstructure are independent of the order of addition of the excipients. Optical transparency and low viscosity of microemulsions ensure their good appearance, easy to handle and pack and long shelf life. Microemulsion systems represent a promising prospect for the development of formulation suitable for the incorporation of poorly water-soluble drugs due to high solubilization capacity as well as the potential for enhanced absorption. In addition, the solution like feature of microemulsion could provide advantages such as spray ability and dose uniformity. In recent years microemulsion has been extensively studied for transdermal, parenteral and oral delivery of drugs [7]. Since microemulsions are thermodynamically stable, the properties of the formulation would not be dependent upon process and the phase separation in the product does not occurs provided temperature and pressure conditions remain reasonably constant. In addition to increased physical stability, microemulsion often function as super solvent for certain compounds. Thus, these clear fluids may dramatically increase the solubility/solubilization of poorly soluble drugs. While microemulsions have significant potential as drug delivery vehicles only few well-characterized surfactant systems have been systemically studied [8]. Recent increasing attention has focused on microemulsions for transdermal delivery of drugs. The transdermal delivery of ketoprofen, apomorphine, estradiol and lidocaine using microemulsions has been reported to show better drug availability over conventional formulations [9]. Beside other lipophilic compounds microemulsions of poorly water-soluble antifungal agents were successfully developed with in vitro release rate comparable to that of gel formulations [6].

A useful strategy for improving the percutaneous flux is to improve the concentration of drug or choose an appropriate vehicle for the drug delivery across the skin. The microemulsion should be a promising vehicle due to powerful ability to deliver drug through skin and large solubilizing capacities of lipophilic, hydrophilic and amphiphilic drug candidates [9, 2].

A topical treatment of several diseases is often limited by the poor percutaneous permeation through the human skin. For this reason, the realization of topical formulations which are able to improve the percutaneous drug permeation can be of particular importance for the success of topical therapeutic approaches. The common methods to improve drug permeation through the skin is to use permeation enhancers i.e., organic solvents and fatty acids. Penetration enhancers can change the structure of skin lipids and alter the skin barrier function. The compounds, even if they increase the transdermal flux of several drugs often generate skin irritation. Other methods that have been proposed to increase the permeability of drugs through the skin i.e., iontophoresis and ultrasound, are frequently not used due to the requirement of qualified staff for their application. Recently some methods have proposed the use of substances endowed with low toxicity, i.e., phospholipid as penetration enhancers. These substances present a notable affinity with cellular membranes thus leading to an increased absorption of several drugs [10]. Various lipid based topical formulations have been proposed as dermal and transdermal drug delivery systems i.e., liposomes and microemulsions [2,10].

The success in the field of drug delivery across the skin depends on the ability of drug molecules to penetrate the skin. This is in spite of the inherent protective function of stratum corneum, which is considered to form a primary rate-limiting barrier to the permeation of the drug molecules across the skin. [11]. Despite the obvious interference of stratum corneum transdermal delivery system provide rate controlled continuous supply of the drug during a predetermined time interval and drug so delivered diffuses through the skin, bypassing the liver .[6-10, 12]

Phase behavior

The phenomenological approach using phase diagrams has been extensively studied and has yielded a comprehensive knowledge of how to formulate microemulsions.[6] The phase diagram characterizes Microemulsions. The amount of oil, water and surfactant- cosurfactant mixture can be determined by plotting pseudo-ternary phase diagrams.[13,14] Quaternary diagrams, are time consuming to prepare and often difficult to interpret[2]. In practice it is therefore more usual to investigate by plotting a two-dimensional triangular diagram (pseudo-ternary phase diagram) by either keeping the composition of one component fixed and varying the other three or by using a constant ratio of two components, generally the surfactant and the cosurfactant. The microemulsion domains that may be single phase or multiphase regions are in areas containing comparatively large amounts of surfactant. This introduces a major problem for their pharmaceutical use. Because high concentrations of most surfactants are irritant and toxic[12-22].

Microemulsions can also exist in equilibrium with excess water, excess oil or both. The multiphase microemulsion domains, which can be, located in two and three phase regions of the phase diagrams are also of practical importance. These equilibria systems are referred to as type I, type II, and type III systems, after their original description by Winsor. The Winsor type I system consists of a lower phase o/w microemulsion in aqueous phase. This This does not favors the ultra-low interfacial tension with surfactants. In a Winsor type II system, the surfactant forms a water-in-oil emulsion in the oil phase. this leads to surfactant retention in the oil phase. The type III system forms when the surfactants are concentrated in a surfactant rich bicontinuous middle phase, which coexists with both oil and water. This situation is ideal to achieve ultralow interfacial.
Both phase equilibria are driven by the bending stress of the interfacial film. The type of equilibria depends on concentration and chemical nature of the surfactant(s), oil and any solubilized substances. Transitions between the differ ypes and between the single-phase microemulsion can be readily induced by a change in temperature, a change in salinity (i.e., ionic strength), or by modifying the surfactant to co surfactant ratio [2,4].

Theoretical aspects of microemulsion formulation and stability

Various theories have been proposed so far but pioneering description by Schulman of o/w microemulsion invoked a droplet model and was based on interfacial film and ultra-low interfacial tension. The spontaneous formation of microemulsion droplets was considered to be due to formation, complex film at the oil-water interface by surfactant and co surfactant molecules. This causes a reduction in oil-water interfacial tension to very low values (from close to 0 to –ve). The mixed interfacial film in equilibrium with both oil and water was considered to be liquid and duplex in nature (showing deferent properties at oil and water sides) with a two-dimensional spreading pressure (π) which determine the interfacial tension at droplet solvent interface

$$\gamma_1 = \gamma_{o/w} - \pi \qquad \text{--- eq. (1)}$$

Where $\gamma_{o/w}$ is interfacial tension without presence of film. When large amounts of surfactant and co surfactant are adsorbed to form the interface, the spreading pressure (π) may become larger then $\gamma_{o/w}$. A negative interfacial tension results and energy is available to increase the interfacial area, effectively reducing droplet sizes. This negative interfacial tension produced by mixing of components is transient phenomenon and at equilibrium it becomes 0 or very small positive value. The conditions for stability of microemulsion is $\gamma = 0$

Surfactant co surfactant contributes to spreading pressure. Co surfactant and oil penetrate the interface affecting its curvature rendering it more disordered and flexible.

Ruckenstien and Chi using surface tension concept included the dispersion entropy of droplet and reduction of chemical potential of surfactant and cosurfactant in bulk phase by adsorption at interface, the later form negative contribution may exceed the positive free energy arising from the lower interfacial tension produced by using cosurfactant and lead to thermodynamically stable emulsion[2,4].

Structure and dynamics of microemulsion

Microemulsion are not static, impenetrable structures but very labile systems where rapid changes of individual components between the various environments as well as spontaneous fluctuations of the interfacial film occur continuously. Investigations into the structure and dynamics of these fluids transparent system using a variety of experimental techniques are currently an area of enormous interest. The current view is that the composite micro droplet model first proposed by Schulman and coworkers is a satisfactory basis for a structural description of specific hydrocarbon rich or water rich microemulsions. When the concentrations of oil and water are more equal, the curvature of the film approaches zero and the droplets may merge and fuse into various equilibrium discontinuous structure in which both the oil and the water domains extend over macroscopic distances. Although early investigations of microemulsion focused on the droplet phases and used classical colloidal technique such as light scattering, ultra-centrifugation, conductivity, viscosity etc. to determine the characteristic dimensions of the structure and develop static models, today attention is directed more on the dynamic aspects of microstructure with particular given to the bicontinuous phase and nonionic systems[19-25,27-5,27-34].

Droplet phase

At high water concentrations microemulsion consist of small oil droplets dispersed in water whereas at water concentrations the situation is reversed and the system consists of water droplets dispersed in oil. In each phase the oil and water are separated by a surfactant rich film. In general w/o systems can be prepared at higher disperse phase concentrations than o/w systems, especially when ionic surfactants are used. The oil droplets into the external phase form a considerable distance (up to 100nm), depending on the electrolyte concentration. Thus, the hard sphere volume of the droplets is generally considerably greater than that of the oil core volume, which creates a strong osmotic (repulsive) force at relatively low disperse phase concentrations.

Droplet interaction can take place at relatively short distances of separation where the tails of the hydrocarbon chains can interpenetrate with each other. This allows a great increase in the droplet number concentration before a strong osmotic force is felt. Currently w/o systems are the topic of much interest because of the

emerging number of potential biotechnological application. Normally the term-reverse micelle is formed when the molar ratio of water to surfactant (designated by the symbol w_o or R) is less than 15 and that of microemulsion for systems containing greater amounts of water, the difference between two categories however is not sharp and the term reverse micelle is used by custom for both types of w/o systems. The size and shape of reverse micelles and microemulsions are critically dependent on the amount of incorporated water. This water generally referred to as the water pool, is different from that of bulk water, the difference becoming progressively less as the water content in the system increases. At low water to surfactant ratio, the water is highly immobilized in the reverse micelle, whereas at the high ratio found in microemulsion its mobility approaches that of bulk water. When droplets collide with one another as a result of Brownian movement most encounters are elastic, although a small number of such collisions may result in the formation of "transient dimmer" with a communication channel that permits the exchange of water or oil pools and any solubilized material on breakdown of this reactions[21].

Bicontinuous phases

In many cases it is possible to affect a gradual transition from o/w to w/o microemulsion simply by changing the volume fraction of oil and water. The intermediate region, which contains approximately equal volumes of oil and water, is currently the subject of intense investigation. This region is often composed of lamellar phases or bicontinuous structures. Where both the oil and water domains extend over macroscopic distances and the surfactant forms an interface of rapidly fluctuating curvature, but in which the net curvature is near zero.

Formulation and preparation of microemulsion

Microemulsions are usually developed empirically since no adequate theory exists to predict from which material they are formed. Their formulation usually involves a combination of there of five components, an oil phase an aqueous phase, a primary surfactant and in many cases, a secondary surfactant (co surfactant), and sometimes an electrolyte. These isotropic systems are usually more difficult to formulate than ordinary emulsions because their formation is a highly specific process involving spontaneous from these components at a particular temperature depends not only on the chemical nature of each component but also on their relative concentrations. Thus, it is essential for a systematic study of microemulsion composition to establish phase diagrams for the system under investigation. From these the extent of the microemulsion region can be identified and its relation to other phases established. Without this approach. It is possible to miss a part or even the whole extent of the microemulsion region.

Choice of Components

Although there are no strict rules for choosing the appropriate microemulsion components. There are a number of general guidelines based on empirical observations. A crucial step lies in the choice of surfactant and (if necessary) cosurfactant for the particular oil. The surfactant (s) chosen must.

Lower interfacial tension to a very small value to aid dispersion processes during the preparation of the microemulsion.

Provide a flexible film that can readily deform round small droplets and

Be of the appropriate hydrophilic-lipophilic character to provide the correct curvature at the interfacial region for the desired microemulsion type, o/w, w/o, or bicontinuous.
These conditions have been achieved in several ways, for example, by using a combination of an anionic or cationic surfactant of high HLB with a co surfactant of lower HLB: a double – chained surfactant of the appropriate molecular composition: or a single chained nonionic surfactant of the polyethylene glycol alkyl ether type at appropriate temperature.

Selection of surfactants

The formulation of microemulsion is still an art, hence understanding the interaction at a molecular level, at the oil and water sides of the interface is far being achieved. The hydrophilic lipophilic balance (HLB) system has been used for the action of surfactants for microemulsions[5]. The concept is based on the relative percentage of hydrophilic to lipophilic groups in the surfactant molecule. W/o microemulsions are formed using emulsion within the HLB range of 3 to 6 while o/w microemulsions are formed using emulsifier within HLB range of 8 to 18. For given oil to be emulsified, the formulator should first determine the required HLB number, then find the chemical type of emulsifier that can best matches the oil.

Role of Cosurfactant

A cosurfactant is usually a medium chain fatty alcohol, acid or amine. Usually, role of the cosurfactant together with the surfactant is to lower the interfacial tension to a very small even transient negative value. At this value the interface would expand to from fine dispersed droplets, and subsequently adsorb more surfactant and surfactant/cosurfactants until their bulk condition is depleted enough to make Interfacial tension positive again. This process known as "spontaneous emulsification", forms the microemulsion. However, the use of cosurfactant in microemulsion is not mandatory for many nonionic surfactants. Microemulsions can also form at low surfactant concentration without cosurfactants when the temperature of the system is at the phase inversion temperature (PIT) as suggested by Shinoda and coworkers[11]. The selection of surfactant and cosurfactant is crucial not only to the formation of microemulsion, but also to solubilization in microemulsions. Other variables such as the chemical nature of oil, salinity, and temperature are also expected to influence the curvature of the interfacial film. Thus, many parameters are available for manipulation in the design and formulation of microemulsions.[4]

Double – chained Surfactants, Lecithin

Microemulsion sometimes from with double- chain surfactants, such as anionic Aerosol OT or cationic DDAB in the absence of a cosurfactant or salt. These surfactants, which have relatively small head groups and bulky hydrophobic portions, are already of the required HLB to form w/o form w/o microemulsion spontaneously. Unfortunately, these widely investigated surfactants are too toxic oils and for general pharmaceutical or biotechnological application, systems containing nontoxic oils and natural double – chained phospholipid surfactants, such as the lecithin are an obvious area for further study. More recent studies indicate that pharmaceutically acceptable microemulsion can be prepared from double –chained solution properties phospholipids with an appropriate choice of cosurfactant.

The characteristic solution properties of lecithin that must be taken into account when formulating microemulsion include

1. A strong nonpolar portion due to the two long hydrocarbon chains;
2. A strong polar portion due to the zwi tter ionic polar head groups that are

strongly hydrated.

3. A close balance between the polar and nonpolar regions, although slightly biased toward the lipophilic side; and.
4. A strong tendency to form lamellar liquid crystal.

Lecithin is too lipophilic to spontaneously form the zero mean curvature lipid layers needed for balanced microemulsions with hexadecane as the oil. But upon addition of the short chain polar alcohols ethanol or propanol as co surfactants, microemulsion form[2].

Construction of pseudo-ternary phase diagrams

In order to find out the construction range of components for the existing range of microemulsions pseudo-ternary phase diagrams are constructed using titration method at an ambient temperature. The coarse emulsions are formed by mixing oil with water. These coarse emulsions are then titrated with the combination of surfactant and co surfactant until the clear transparent microemulsions are formed and the volumes of surfactant-cosurfactant combinations used are recorded. The pseudo-ternary phase diagrams were proposed by plotting the amounts of water phase, oil phase and surfactant / co surfactants combination used[4].

Preparation of microemulsion

Once the microemulsion region in the phase diagrams at different surfactant and co surfactant ratios for a particular oil is identified, the microemulsion formulations are selected at different component ratios. In order to prepare microemulsion, the oil phase the aqueous phase, surfactant and co surfactant are taken together in required amounts and stirred up to the formation of transparent clear fluid system at room temperature.

Microemulsion characterization

Type of emulsion weather w/o or o/w type of microemulsion can be determined by dye solubilization, dilution test or electrical conductivity measurement method.

The nano-range of droplet size is the key feature in formulation and stability of microemulsion system. For proper characterization, techniques like Zetasizer, scanning electron microscopy and Quasi Dynamic Light scattering techniques are used.

Microemulsions are also characterized for viscosity and drug loading, and permeation studies. XRD and FTIR are used to rule out any possible interaction among the components and with the drug.

Stability of microemulsion

The physical stability of microemulsion is studied via clarity and phase separation.

Microemulsions are stored at 5, 15, 25, 37 ^{0}C in the dark for three months or more. Then the clarity and phase separation are investigated to judge the optimal storage temperature.
The centrifuge tests are also carried out to assess the physical stability of microemulsions. In order to determine the metastable microemulsion system the selected microemulsion vehicles are centrifuged at 5000 rpm for 10 minutes. Stable formulations do not show phase separation and turbidity.

Applications of topical microemulsions

There has been a revolution in the last two decades in the utilization of microemulsion systems in a variety of pharmaceutical, chemical, industrial processes etc. Microemulsion in pharmaceutical Liquid crystalline, miceller and emulsion forming systems are widely used in pharmaceutical preparations. The easy formation, remarkable environment independent stability, excellent solubilization capacity, etc. favour microemulsions to be a better proposition over other compartmentalized systems.

The dispersed phase, lipophilic or hydrophilic (o/w or w/o type) can act as a potential reservoir of lipophilic or hydrophilic drugs that can be partitioned between the dispersed and the continuous phases. Coming in contact with a semipermeable membrane, such as skin or mucous 45 membrane, the drug can be transported through the barrier. Both lipophilic and hydrophilic drugs can be administered together in the same preparation.

It is believed that microemulsion formulation will result in a faster uptake into the skin. Cost, safety, appropriate selection of ingredients are key factors in the formulation of microemulsions. Skin care microemulsions contain, sodium alkyl sulfate, tetraethylene glycol monododecyl ether, lecithin, dodecyl oligoglucoside, alkyl dimethyl amine oxide, propanol,hexadecane, isopropyl myristate have been used as surfactants, cosurfactants and oils respectively. Hair care microemulsions contain an amino-functional polyorganosiloxane (a nonionic surfactant) and an acid and/or a metal salt.

Ultrafine 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.

Conclusion.

Topical microemulsions play important role to overcome the problems of poor aqueous solubility of highly lipophilic drugs and provide high, more consistent and reproducible percutaneous drug permeability. These formulations can be easily manufactured and are cost-effective in terms of commercial production. In the modern era topical products may be produced using the microemulsion technology. Microemulsions can also be used as transdermal drug delivery systems and to achieve drug targeting. Recent research work is focused on the production of safe, efficient and more compatible microemulsion systems that will further enhance the utility of these novel vehicles. Microemulsions today can act as potential novel carrier for topical delivery of pharmaceuticals.

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