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Pharmaceutical Considerations of Microemulsion as a Drug Delivery System

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ABSTRACT

Microemulsions were recognized after the work of Hoar and Schulman in 1943, which revealed the use of strong surface-active agent leading to spontaneous emulsification; however, it was in 1959 when Schulman first used the term "microemulsion" for such emulsion system. Microemulsions are optically transparent, thermodynamically stable colloidal systems, 10–100 nm diameters that form spontaneously upon mixing of oil, water, and emulsifier. After its discovery in 1943 to till date, more than 1200 publications have been reported and development of O/W type of microemulsions has been the priority for the researchers, mostly using non-ionic surfactants. Although microemulsions seem to be one of the most promising candidates in pharmaceuticals because of relative ease in the formulation and distinct characteristics when compared to other dispersion systems, its commercial success as a drug delivery system has been very little. Much of the time after its discovery has been exhausted in failure to understand correct formulation requisites or confusing it with other similar systems. In the face of increasing the number of publication year after year, its formulation has been generally based on trial-and-error. Efficient strategies for excipient selection and detailed understanding of microstructures contributing to its formulation is still required which may serve as the foundation for attaining greater success in this field.

Keywords: Microemulsion, Surfactants. Spontaneous emulsification, Solubilization.

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INTRODUCTION

It may be required to formulate a drug as Oral liquids for new molecules as well as for existing molecules. However, it might not be feasible to formulate such liquid systems by simple solution, may be due to limiting factors such as poor mixability, stability issues,etc. In such cases, formulations like emulsions, suspensions, colloidal systems, etc. may be used. Formulations based on conventional colloidal dispersions have been been used from many years, recently giving way to novel version of these colloidal dispersions.[1] Microemulsion is one such novel system which is transparent, isotropic and thermodynamically stable liquid mixture. Microemulsions are usually prepared by using correct proportions of oil phase, aqueous phase, surfactant system (combination of surfactant and co-surfactant). The aqueous phase may contain salt(s) and/or other ingredients, and the "oil" may actually be a complex mixture of different hydrocarbons and olefins. In contrast to ordinary emulsions, microemulsions form upon simple mixing of the components and do not require the high shear conditions generally used in the formation of ordinary emulsions. The two basic types of microemulsions are direct (oil dispersed in water, o/w) and reversed (water dispersed in oil, w/o). [2-4]

In ternary systems such as microemulsions, where two immiscible phases (water and 'oil') are present with a surfactant, the surfactant molecules may form a monolayer at the interface between the oil and water, with the hydrophobic tails of the surfactant molecules dissolved in the oil phase and the hydrophilic head groups in the aqueous phase. As in the binary systems (water/surfactant or oil/surfactant), self-assembled structures of different types can be formed, ranging, for example, from (inverted) spherical and cylindrical micelles to lamellar phases and bi-continuous microemulsions, which may coexist with predominantly oil or aqueous phases.

In principle, microemulsions can be used to deliver drugs to the patients via several routes, but the topical application of microemulsions has gained increasing interest. The three main factors determining the transdermal permeation of drugs are the mobility of drug in the vehicle, release of drug from the vehicle, and permeation of drug into the skin. These

factors affect either the thermodynamic activity that drives the drug into the skin or the permeability of drug in the skin, particularly stratum corneum.

Microemulsions improve the transdermal delivery of several drugs over the conventional topical preparations such as emulsions[5] and gels[6]. Mobility of drugs in microemulsions is more facile[7], as compared to the microemulsion with gel former which will increase its viscosity and further decrease the permeation in the skin.[8] The superior transdermal flux from microemulsions has been shown to be mainly due to their high solubilization potential for lipophilic and hydrophilic drugs.

This generates an increased thermodynamic activity towards the skin. Microemulsions may affect the permeability of drug in the skin. In this case, the components of microemulsions serve as permeation enhancers.[9-11] Several compounds used in microemulsions have been reported to improve the transdermal permeation by altering the structure of the stratum corneum.[12-14] For example, short chain alkanols are widely used as permeation enhancers.[15] It is known that oleic acid, a fatty acid with one double bond in the chain structure, perturbs the lipid barrier in the stratum corneum by forming separate domains which interfere with the continuity of the multilamellar stratum corneum and may induce highly permeable pathways in the stratum corneum.

Isopropyl myristate (IPM) is used as a permeation enhancer in transdermal formulations, but the mechanism of its action is poorly understood. Nonionic surfactants are widely used in topical formulations as solubilizing agents but some recent results indicate that they may affect also the skin barrier function.[16] It is of interest to explore the effects of these components in the organized microemulsion structures. The aim of the present study was to investigate the potential of several microemulsion formulations in transdermal delivery of lipophilic drugs. A unique attempt was made to emulsify coconut oil with the help of polyoxyethylene 2-cetyl ether (Brij 52) and isopropanol or ethanol, forming stable isotropic dispersion thus paving way for use of plant and vegetable oil to be used as oil phase in microemulsion.[17]

HISTORICAL BACKGROUND

The combination of water and oil, made into a single-phase system with the aid of a third component (surfactant), was patented in mid 1930's. However, it was not until 1943 when the first academic studies were performed.[18] Hoar and Schulman showed, with the help of a strong surface-active agent, it is possible to induce spontaneous emulsification.[19] This is now attributed to microemulsion formation, owing to very low interfacial tensions promoted by the surfactants. According to Winsor (1948) there are four types of microemulsions: (i) Type I- biphasic with an upper excess oil phase and lower O/W emulsion, (ii) Type II- biphasic with an upper W/O emulsion and lower excess water phase, (iii) Type III- triphasic with upper excess oil phase, middle bicontinuous microemulsion and lower excess water phase, (iv) Type IV- monophasic, single microemulsion phase. Depending on the emulsifier used, microemulsions can transition between each type quite easily. A simple change in temperature, in the case of a non-ionic surfactant or salinity, S, in the case of an ionic surfactant can result in transition from a Type I → III → II microemulsion. An increase in surfactant concentration can also induce a transition from any of these microemulsion types to a Type IV microemulsion, within temperature or salinity constraints.[18]

In 1959, Schulman *et al.*,[19] titrated a multiphase system (consisting of water, oil and surfactant) with alcohol and obtained a transparent solution which they termed 'a microemulsion'. At that early stage some researchers preferred to identify these systems with 'swollen micelles'[20], others used the term 'micellar emulsion'.[21] Nevertheless, the term 'microemulsion' is a commonly used name nowadays. A detailed historical background of microemulsions can be found elsewhere. [22]

Microemulsions were confused with Nanoemulsions in the past, primarily due to comparable characteristics of having nannomter size range as well as similar preparation technique. A number studies have been published to delineate between both the systems.[23]

Table 1 Summarising general differences between Nanoemulsion and Microemulsion

Property	Nanoemulsions	Microemulsions
Types	Oil in Water and Water in Oil type	Type I :- Two phased, O/W type Type II :- Two phased, W/O type Type III :- Three phase system Type IV :- Single phase system
Droplet Size	10 nm to 300 nm	>100 nm
Preparation	Usually, High Energy methods and also Low Energy methods	Low Energy Methods
Stability	Kinetically stable	Thermodynamically stable
Interfacial tension	High interfacial tension	Very low interfacial tension
Micellar Structures	Spherical nano-sized micelles	Structures such as; spherical, continuous, hexagonal, cylindrical, cubic, lamellar, etc. (depending upon formulation variables)
Structural Variations	Do not show deformation on slight changes temperature and composition	Temperature and compositional variation induces deformation of micellar structure

ADVANATGES AND DISADVANATGES OF MICROEMULSION BASED SYSTEMS

Advantages:

Microemulsions possess a number of unique characteristics that render them suitable for drug delivery. Unfortunately, their complex nature does not always make them a viable option for drug delivery. Understanding the key advantages and disadvan- tages of microemulsion drug delivery systems is essential in making informed decisions regarding the delivery of the active pharmaceutical ingredient (API) in question. Advantages Microemulsions are uniquely equipped for drug delivery. In particular, microemulsions are able to:

i) administer APIs in liquid form,

ii) improve bioavailability and stability via small droplet sizes,

iii) solubilize and delivery both hydrophilic and lipophilic drugs,

iv) form spontaneously with relatively simple starting ingredients.[24]

Disadvantages

Some factors limit the use of microemulsion in pharmaceutical applications.

i) The need of pharmaceutically acceptable ingredients limits the choice of microemulsion components (e.g., oil, surfactant and cosurfactants) leading to difficulties in formulation.

ii) The concentration of surfactants and co-surfactants used must be kept low for toxicological reasons.

iii) Microemulsion also suffers from limitations of phase separation.

iv) For intravenous use, the demand of toxicity on the formulation is rigorous and very few studies have been reported so far.

v) The major limitation is the toxicity of excipients i.e. surfactant/ co-surfactants. Exploration of safe excipients and evaluation of the toxicity parameters of available excipients may help in further expansion of research in this field. [25]

DEVELOPMENT OF MICROEMULSIONS

Role of Phase Diagrams:

The microemulsion region is usually characterized by constructing ternary-phase diagrams. Three components are the basic requirement to form a microemulsion: an oil phase, an aqueous phase and a surfactant. If a cosurfactant is used, it may sometimes be represented at a fixed ratio to surfactant as a single component, and treated as a single "pseudo-component". The relative amounts of these three components can be represented in a ternary phase diagram. Gibbs phase diagrams can be used to show the influence of changes in the volume fractions of the different phases on the phase behavior of the system. [26]

The three components composing the system are each found at an apex of the triangle, where their corresponding volume fraction is 100%. Moving away from that corner reduces the volume fraction of that specific component and increases the volume fraction of one or both of the two other components. Each point within the triangle represents a possible composition of a mixture of the three components or pseudo-components, which may consist (ideally, according to the Gibbs' phase rule) of one, two or three phases. These points combine to form regions with boundaries between them, which represent the "phase behavior" of the system at constant temperature and pressure.[27]

The Gibbs phase diagram, however, is an empirical visual observation of the state of the system and may, or may not express the true number of phases within a given composition. Apparently clear single phase formulations can still consist of multiple iso-tropic phases (e.g. the apparently clear heptane/AOT/water microemulsions consist multiple phases). Since these systems can be in equilibrium with other phases, many systems, especially those with high volume fractions of both the two immiscible phases, can be easily destabilized by anything that changes this equilibrium e.g. high or low temperature or addition of surface tension modifying agents.[28]

However, examples of relatively stable microemulsions can be found. It is believed that the mechanism for removing acid build up in car engine oils involves low water phase volume, water-in-oil (w/o) microemulsions. Theoretically, transport of the aqueous acid droplets through the engine oil to micro-dispersed calcium carbonate particles in the oil should be most efficient when the droplets are small enough to transport a single hydrogen ion (the smaller the droplets, the greater the number of droplets, the faster the neutralization). Such microemulsions are probably very stable across a reasonably wide range of elevated temperatures.[29]

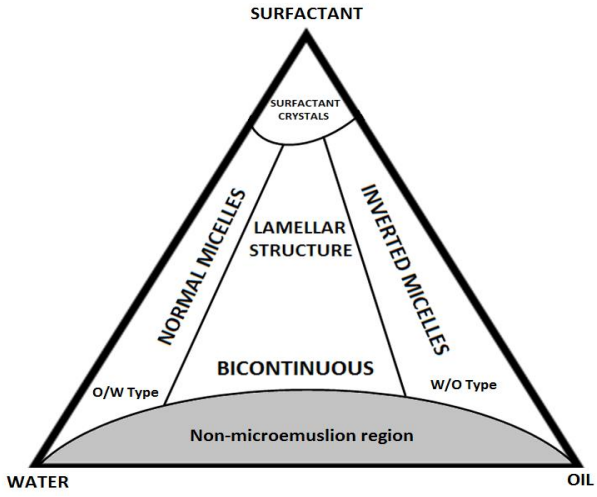

Figure 1: Illustration of microemulsion region in a Pseudoternary Phase Diagram showing composition of various micellar structures above Non-microemulsion region.

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

- Oil in water microemulsions wherein oil droplets are dispersed in the continuous aqueous phase
- Water in oil microemulsions wherein water droplets are dispersed in the continuous oil phase;
- Bi-continuous microemulsions wherein micro-domains of oil and water are inter-dispersed within the system.

In all three types of microemulsions, the interface is stabilized by an appropriate combination of the surfactants and/or co-surfactants. The key difference between emulsions and microemulsions are that the former, whilst they may exhibit excellent kinetic stability, are

fundamentally thermodynamically unstable and phases will eventually separate. Another important difference concerns their appearance; emulsions are cloudy while microemulsions are clear or translucent. In addition, there are distinct differences in their method of preparation, since emulsions require a large input of energy while microemulsions do not. The latter point has obvious implications when considering the relative cost of commercial production of the two types of system.[3]

Theory of Microemulsion Formulation:

Various theories concerning microemulsion formation, stability and phase behavior have been proposed over the years. For example, one explanation for their thermodynamic stability is that the oil/water dispersion is stabilized by the surfactant present and their formation involves the elastic properties of the surfactant film at the oil/water interface, which involves as parameters, the curvature and the rigidity of the film. These parameters may have an assumed or measured pressure and/or temperature dependence (and/or the salinity of the aqueous phase), which may be used to infer the region of stability of the microemulsion, or to delineate the region where three coexisting phases occur, for example. Calculations of the interfacial tension of the microemulsion with a coexisting oil or aqueous phase are also often of special focus and may sometimes be used to guide their formulation.

Microemulsion formation and stability can be explained on the basis of a simplified thermodynamic rationalization. The free energy of microemulsion formation can be considered to depend on the extent to which surfactant lowers the surface tension of the oil–water interface and the change in entropy of the system such that [30],

$$DG_f = \gamma DA - T\,DS$$

Where, DG_f =free energy of formation, γ = Surface tension of the oil–water interface DA =Change in interfacial area on microemulsification, DS = Change in entropy of the system which is effectively the dispersion entropy, and T = Temperature.

It should be noted that when a microemulsion is formed, the change in DA is very large due to the large number of nanodroplets are formed. It is seen that while the value of γ is positive at all times, it is very small (of the order of fractions of mN/m), and is offset by the entropic component. The dominant favorable entropic contribution is the very large dispersion entropy arising from the mixing of one phase in the other in the form of large numbers of nanodroplets. However, favorable entropic contributions also arise from other dynamic processes such as surfactant diffusion in the interfacial layer and monomer-micelle surfactant exchange.

Thus, a negative free energy of formation is achieved when large reductions in surface tension are accompanied by significant favorable entropic change. In such cases, microemulsification is spontaneous and the resulting dispersion is thermodynamically stable.Though, it has been know that several factors determine whether a w/o or o/w microemulsion system will be formed but in general it could be summarized that the most likely microemulsion would be that in which the phase with the smaller volume fraction forms.[31]

Surfactants, co-surfactants and oil used in microemulsion formulation:

- Surfactants- used to stabilize the system; -non-ionic, zwitter ion, cationic or anionic.
- Co-surfactant- decrease the interfacial tension; -and increase the microemulsion region; -alcohols, amines, and cholesterol
- Oils- hydrocarbon oils such as heptane or -cyclic oils like cyclohexane the droplets i.e., internal phase.

Attempts have been made to rationalize surfactant behavior in terms of the hydrophilic- lipophilic balance (HLB) [32], as well as the critical packing parameter (CPP)[29,30]. Both approaches are fairly empirical but can be a useful guide to surfactant selection. The HLB takes into account the relative contribution of hydrophilic and hydrophobic fragments of the surfactant molecule. It is generally accepted that low HLB (3-6) surfactants are favored for the formation of w/o microemulsions whereas surfactants with high HLBs (8-18) are preferred for the formation of o/w microemulsion systems. Ionic surfactants such as sodium dodecyl sulphate which have HLBs greater than 20, often require the presence of a co-surfactant to reduce their effective HLB to a value within the range required for microemulsion formation. In contrast, the CPP relates the ability of surfactant to form particular aggregates to the geometry of the molecule itself.

A combination of these, particularly ionic and non-ionic, can be very effective at increasing the extent of the microemulsion region. Examples of non-Ionics include polyoxyethylene surfactants such as Brij 35($C_{12}E_{35}$) or sugar esters such as sorbitan monooleate (Span 80). Phospholipids are a notable example of zwitter ionic surfactants and exhibit excellent biocompatibility. Lecithin preparations from a variety of sources including soybean and egg are available commercially and contain diacylphosphatidylcholine as its major constituent.[33-36]

Quaternary ammonium alkyl salts form one of the best known classes of cationic surfactants, with hexadecyltrimethyl ammonium bromide (CTAB), and the twin-tailed surfactant didodcecylammonium bromide (DDAB) are amongst the most well known. The most widely studied anionic surfactant is probably sodium bis-2-ethylhexylsulphosuccinate (AOT) which is twin-tailed and is a particularly effective stabiliser of w/o microemulsions.[37]

Table 2: Common excipients used to formulate Microemulsions in recent years

Oil Phase	Surfactant	Co-surfactant
Caprylic Acid	Tween 80	Transcutol P
Oleic acid	Transcutol	PEG 400
Capmul MCM	Cremophor RH 40	Ethanol
Isopropyl Myristate	Cremophor EL	Poloxamer 407
Capryol 90	Labrasol	Propylene glycol

CONCLUSION

Although after discovery, it took time for researchers to understand the potential of microemulsion as a drug delivery system but, in recent times, a lot of studies from the field of pharmaceutics have targeted microemulsions. The number of hydrophobic, labile drugs with poor release characteristics have been formulated as microemulsion to increase solubility and bioavailability of drugs used. However, a considerable amount of fundamental work characterizing the physico-chemical behavior of microemulsions that needs to be performed before they can live up to their potential as multipurpose drug delivery vehicles.Recently, several research papers have been published for the improvement of drug delivery, but still there is a need to put an emphasis on its characterization

part including in vitro evaluation. Besides this, research papers shows higher percentage of surfactant (much higher than CMC level) used for the formation of microemulsion, irrespective of different routes of administration, but there is a lack of toxicological evaluation of the prepared microemulsion, which can be a broad research area in future.

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