



A REVIEW ON MICROEMULSION FOR ANTIFUNGAL ACTIVITY

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ABSTRACT

Microemulsion is clear, stable, isotropic mixtures of oil, water and surfactant, frequently in combination with a co-surfactant. Microemulsions act as potential drug carrier systems for oral, topical, and parenteral administration. They offer the advantage of spontaneous formation, ease of manufacturing and scale-up, thermodynamic stability, and improved drug solubilization and bioavailability. Preparing a pharmaceutically acceptable dosage form demands a clear understanding of the micro-emulsion structure, phase behavior, factors leading to its thermodynamic stability and the potential uses and limitations of the microemulsion system. Knowledge of the various methods available to thoroughly characterize a microemulsion system is essential. While microemulsion is used in several fields, in this review the pharmaceutical applications are emphasized.

KEYWORDS: Microemulsion, topical, bioavailability, antifungal.

INTRODUCTION

The term “microemulsion” refers to a thermodynamically stable isotropically clear dispersion of two immiscible liquids, such as oil and water, stabilized by an interfacial film of surfactant molecules. A microemulsion is considered to be a thermodynamically or kinetically stable liquid dispersion of an oil phase and a water phase, in combination with a surfactant. The dispersed phase typically comprises small particles or droplets, with a size range of 5 nm-200 nm, and has very low oil/water interfacial tension. Because the droplet size is less than 25% of the wavelength of visible light, microemulsion are transparent. The microemulsion is formed readily and sometimes spontaneously, generally without high-energy input. In many cases a co-surfactant or co-solvent is used in addition to the surfactant, the oil phase and the water phase.

Superficial fungal infections like deep skin mycoses are better treated when drug is administered topically than any other route. It minimizes the deleterious effects of drug and produces the local action at the site of application more effectively. Antifungal agents are basically lipophilic in nature easily formulated in topical vehicles. It is advantageous to choose microemulsion as topical vehicle for antifungal agents since ease of preparation due to spontaneous formation, thermodynamic stability, transparent and elegant

appearance, increased drug loading, enhanced penetration through the biological membranes, increased bioavailability compared to conventional dosage forms like gel, cream etc. It has been observed that solubility of fluconazole in ethylolate-lecithin reverse micellar system was almost 3 folds higher than that in ethylolate. Organogel formed from reverse micelle containing 300 mM of lecithin showed the higher drug release and have better consistency. The histopathological data showed that organogels were safe enough for the topical purpose. El-Hadidy developed topical microemulsion of voriconazole using polyoxyethylene (10) oleyl ether (Brij 97) as surfactant and jojoba oil.^[38] Oleic acid and sodium deoxycholate were also incorporated as permeability enhancer in drug loaded microemulsions. It has been concluded that drug loaded microemulsion showed better antifungal activity against candida albicans than voriconazole supersaturated solution. Junyaprasert et al developed w/o and o/w novel aerosolized topical formulations of clindamycin phosphate consisting of isopropyl myristate and 1-butanol microemulsion.^[39] The drug permeation from oil-in-water (o/w) microemulsion was relatively higher than that from water-in-oil (w/o) microemulsion. Esposito et al formulated monoglyceride based topical microemulsion of amphotericin B.^[42] It has been shown that solubility of amphotericin in formulations was increased up to 20-fold with respect to the single oil and aqueous phases of microemulsion alone. Patel et al

reported lauryl alcohol based microemulsions emulsified with labrasol/ethanol with enhanced solubility of ketoconazole to several folds which may result in high drug permeation across skin.^[44] Histopathological investigation of rat skin revealed the safety of microemulsion formulations for topical use. Hashem et al formulated topical clotrimazole microemulsion using two different microemulsion bases made from either lemon oil/Tween 80/n butanol/water or isopropyl myristate/Tween 80/n butanol/water.^[43] Microemulsion formulations achieved significantly higher skin retention of drug than cream base. The efficacy and tolerability of microemulsion preparations in the treatment of various topical candida albicans infections were clinically proved. Chudasma et al studied the permeation of itraconazole from microemulsion based transdermal system. Aggrawal et al studied the topical delivery of griseofulvin from microemulsion base.

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 (1). However, it was not until 1943 when the first academic studies were performed². Hoar and Schulman showed, with the help of a strong surface active agent, it is possible to induce spontaneous emulsification. This is now attributed to microemulsion formation, owing to very low interfacial tensions promoted by the surfactants. Five years later, Win so studied the phase behavior of water-oil-surfactant mixtures in the presence of different additives and classified four types of phase equilibrium.

Type I: Surfactant-rich water phase (lower phase) coexists with surfactant-poor oil phase (Winsor I).

Type II: Surfactant-rich oil phase (the upper phase) coexists with surfactant-poor water phase (Winsor II).

Type III: Surfactant rich middle-phase coexists with both water (lower) and oil (upper) surfactant-poor phases (Winsor III).

Type IV: Single phase homogeneous mixture.

In 1959, Schulman et al., (3) 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' (4), others used the term 'micellar emulsion' (5). Nevertheless, the term 'microemulsion' is a commonly used name nowadays. A detailed historical background of microemulsion can be found elsewhere (6).

Advantages^[7-12]

1. Microemulsion are easily prepared and require no energy contribution during preparation this is due to better thermodynamic stability.
2. 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.

3. Microemulsion are thermodynamically stable system and allows self-emulsification of the system.
4. Microemulsion have low viscosity compared to emulsions.
5. Microemulsion act as super solvents for drug, can solubilise both hydrophilic and lipophilic drugs including drugs that are insoluble in both aqueous and hydrophobic solvents.
6. Having the ability to carry both lipophilic and hydrophilic drugs.
7. The dispersed phase, lipophilic or hydrophilic (O/W, or W/O microemulsion) can act as a potential reservoir of lipophilic or hydrophilic drugs, respectively.
8. 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.

Disadvantages^[13-15]

1. Having limited solubilizing capacity for high-melting substances.
2. Require large amount of Surfactants for stabilizing droplets.
3. Microemulsion stability is influenced by environmental parameters such as temperature and pH.

Limitations of the micro-emulsion system^[16-18]

There are certain reasons which limit the utilization of the micro emulsion systems within the medicinal submissions:

- There is a common problem of phase separation seen in the case of micro-emulsions.
- For toxicity reasons, the concentrations of the co-surfactants and the surfactants must be kept low.
- The micro-emulsion systems are not that much suitable for the intravenous use due to the toxicity of the formulation and till now only a very few studies have been reported on them.
- To reduce the toxicity of the micro-emulsion systems, the surfactants which are to be used are to be of "Generally Regarded-as-Safe" (GRAS) class.

Characterization of Micro-Emulsion

There are various techniques by which micro-emulsions are characterized. Because the micro-emulsions are very complex, they have various components involved in their systems, they have a very large variety of structures and also there are various limitations attached to their methods of characterization, it is very difficult to characterize micro-emulsions, but their characterization data is very much important used for their viable manipulation.

For physic -chemical characterization of micro-emulsion the basic components are:

The dimension and the microstructure of the microemulsion., Phase behavior and phase stability, The local molecular rearrangement, The surface features like

charge distribution and the specific area, Shape, Interface and changing aspects.

From these assets, Interface and changing aspects and the particle size are very much important as many general properties of the micro-emulsions are governed by them. There are various parameters on which the drug release from the micro-emulsions depends such as droplet size, Oil liquid section magnitude relation.

Structure of Microemulsion

Micro emulsions or Micellar emulsion are dynamic system in which the interface is continuously and

spontaneously fluctuating.^[21] Structurally, they are divided in to oil in water (o/w), water in oil (w/o) and bi-continuous micro emulsions. In w/o micro emulsions, water droplets are dispersed in the continuous oil phase while o/w micro emulsions are formed when oil droplets are dispersed in the continuous aqueous phase. In system where the amounts of water and oil are similar, the bi-continuous micro emulsions may result.^[22] The mixture oil water and surfactants are able to form a wide variety of structure and phase depending upon the proportions of component.

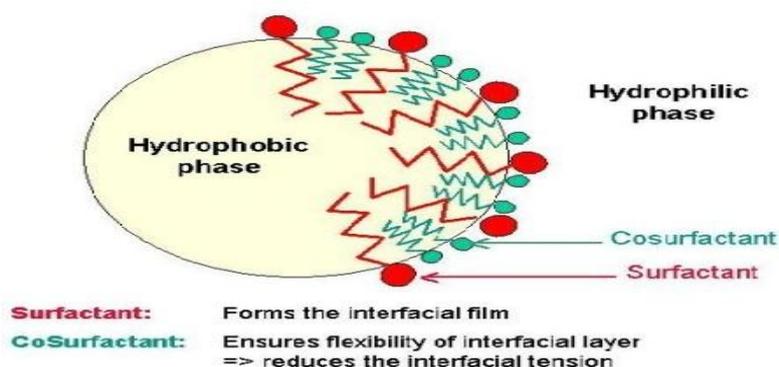


Figure: Microemulsion Skeletal Structure.

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 co-surfactant is used, it may sometimes be represented at a fixed ratio to surfactant as a single component, and treated as a single "pseudocomponent". 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.^[23] 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. 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 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.

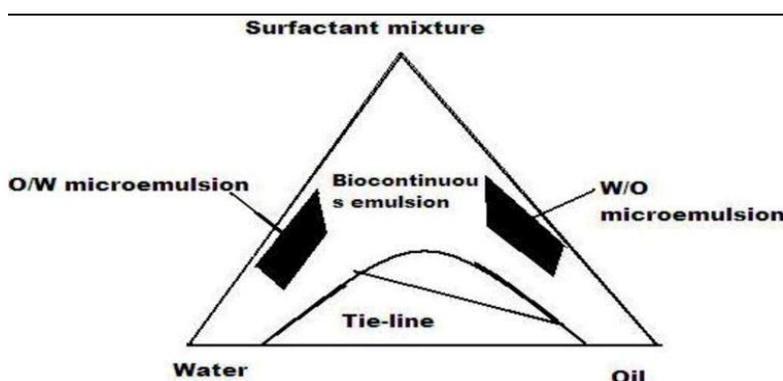


Fig. 2: Schematic Representation of Pseudo Ternary Phase Diagram Showing Microemulsion Region.^[24]

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

1. Oil in water microemulsion wherein oil droplets are dispersed in the continuous aqueous phase.
2. Water in oil microemulsion wherein water droplets are dispersed in the continuous oil phase.
3. Bi-continuous microemulsion wherein micro domains of oil and water are inter-dispersed within the system.

Basic Differences Between Macroemulsion And Microemulsion.^[25-27]

S. No	MACROEMULSION	MICROEMULSION
1	They are lyophobic in nature.	They are the border between lyophilic and lyophobic.
2	Droplet diameter 1 to 20 nm.	Droplet diameter 10 to 100 nm.
3	Macroemulsion droplets exist as individual entities.	Microemulsion droplets disappear within fraction of seconds.
4	Emulsion droplets are roughly spherical droplets of one phase dispersed into the other phase.	Microemulsion are the structures of various droplets like bi-continuous to swollen micelles.
5	Macroemulsion requires quick agitation for their formation.	Microemulsion are obtained by gentle mixing of ingredients
6	Most of the emulsions are opaque (white) in appearance.	Microemulsion are transparent or translucent in nature.

Types of Microemulsions^[28-31]

Microemulsion are thermodynamically stable, but are only found under carefully defined conditions. According to Winsor, there are four types of microemulsion phases exists in equilibrium, these phases are also referred as Winsor phases. They are-

1. Oil- in- water microemulsion or winsor I
2. Water – in oil microemulsion or winsor II
3. Bi-continuous microemulsion or winsor III
4. Single phase homogeneous mixture or winsor IV

Oil- in- water microemulsion or winsor I

In Oil-in-water type of microemulsion droplets of oil is surrounded by a surfactant (and may be co-surfactant) film that forms the internal phase distributed in water, which is the continuous phase. This type of microemulsion generally has a larger interaction volume than the w/o microemulsion.

Water - in - oil microemulsion or winsor II

In Water-in-oil type of microemulsion droplets of water surrounded by a continuous oil phase. These are

Microemulsion in Topical Delivery

Table: Microemulsion based topical and transdermal formulations.

Name of drug	Surfactant	Cosurfactant	Oil
Fluconazole	Tween 80	Labrafac lipophile	Olive oil
voriconazole	Cremophor RH 40	Transcutol P	Cinnamon oil
ketoconazole	Tween 80	PEG 400	Olive oil
Itraconazole	Tween 80	PEG 400	Castor oil
Amphotericin B	Tween 20	Propylene glycol	Lemon oil

CONCLUSION

Microemulsion are optically isotropic and thermodynamically stable liquid solutions of oil, water and amphiphile. Microemulsion are readily distinguished from normal emulsions by their transparency, low viscosity and more fundamentally their thermodynamic stability. Drug delivery through microemulsion is a promising area for continued research with the aim of achieving controlled release with enhanced

bioavailability and for drug targeting to various sites in the body. Despite the increasing number of reports regarding advances in antifungal therapy, the number of cases of infection and antifungal resistance are still alarmingly high, and control of antifungal disease is far from being achieved.

Bi-continuous microemulsion or winsor III

In bi-continuous microemulsion system the amount of water and oil present are similar, In this case, both water and oil exist as a continuous phase. An irregular channel of oil and water are combined, and looks like a “sponge-phase”. Transitions from o/w to w/o microemulsion may pass through this bi-continuous state. Bi-continuous microemulsion may show non-Newtonian flow and plasticity. These properties make them especially useful for topical delivery of drugs or for intravenous administration.

Single phase homogeneous mixture or winsor IV

In single phase homogeneous mixture or winsor IV the oil, water and surfactants are homogeneously mixed.

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