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A comprehensive review on microemulsions: a potential novel drug delivery system

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Abstract

Microemulsions are excellent candidates as potential drug delivery systems because of their improved drug solubilization, long shelf life, and ease of preparation and administration. The formulation of microemulsion for pharmaceutical use requires a thorough understanding of the properties uses, and limitations of the microemulsion. Three distinct microemulsions – oil external, water external and middle phase can be used for drug delivery, depending upon the type of drug delivery upon the type of drug and the site of action. In this article, Since the term micro emulsion' was first coined almost fifty years ago to describe clear, isotropic, thermodynamically stable systems composed of oil, water, surfactant and cosurfactant, numerous and varied reports of the applications of microemulsions have appeared in the literature. Reports of the use of microemulsions in separation science began to appear in the literature in the early 1990s when they were first used as mobile phases for HPLC and as carrier electrolytes for CE separations, particularly for pharmaceutical applications.

Keywords: Micelle, Thermodynamics, Co-solvents, Transparent, Coarse.

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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 [1, 2]. Because the droplet size is less than 25% of the wavelength of visible light, microemulsions are transparent. The microemulsion is formed readily and sometimes spontaneously, generally without high-energy input. In many cases a cosurfactant or cosolvent is used in addition to the surfactant, the oil phase and the water phase [3, 4].

Three types of microemulsions are most likely to be formed depending on the composition [5, 6, and 7]:

- Oil in water microemulsions wherein oil droplets are dispersed in the continuos aqueous phase
- Water in oil microemulsions wherein water droplets are dispersed in the continuous oil phase;
- Bi-continuous microemulsions wherein microdomains of oil and water are interdispersed within the system. In all three types of microemulsions, the interface is

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stabilized by an appropriate combination of surfactants and/or co-surfactants.

Structure of Micro Emulsion

In a structure split into oil into water (o/w), oil-water (w/o) and bilateral microemulsions. microemulsions or micellar emulsions are dynamic systems in which the interface is fluctuated constantly and spontaneously [7]. Water droplets are distributed in the continuous oil phase in w / w of micro-emulsions during the continuous aqueous phase of the oil droplets. The two-continuous microemulsions may occur in systems with comparable quantities of water and oil [8]. The combination of oil-water and surfactants can create a broad range of phases and structures depending on the component quantities [8, 9].

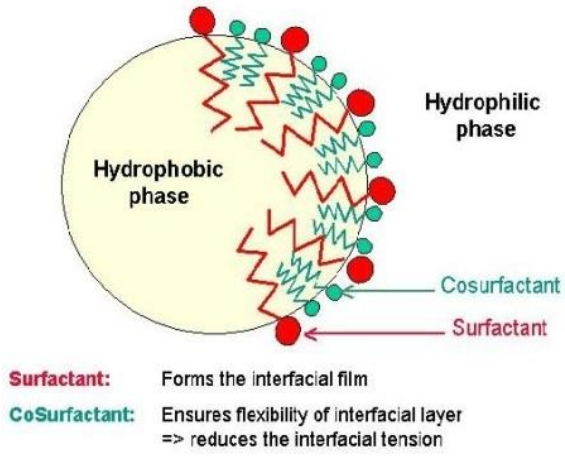

Figure 1: Structure of Microemulsion

Difference between emulsions and microemulsions

The main difference between emulsions and microemulsions lies in the size and shape of the particles that are dispersed in the continuous phase: these are at least an order of magnitude smaller in the case of microemulsions (10–200 nm) than those of conventional emulsions (1–20 μm) [10]. 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 [11]. Also, whereas emulsions consist of roughly spherical droplets of one phase dispersed into the other, microemulsions constantly evolve between various structures ranging from droplet-like swollen micelles to bicontinuous structures, making the usual "oil in water" and "water in oil" distinction sometimes irrelevant [12].

Advantages [13, 14, and 15]

a. Thermodynamically stable and require minimum energy for formation.
b. compatibility in manufacturing
c. Enhanced drug solubilization and improved bioavailability.
d. Micro emulsion are having wide applications in colloidal drug delivery systems for the purpose of drug targeting and controlled release.

Construction of Phase Diagram

Pseudo-ternary phase diagrams of oil, water, and cosurfactant/surfactant mixtures are constructed at fixed cosurfactant/surfactant weight ratios. Phase diagrams are obtained by mixing the ingredients, which shall be preweighed into glass vials and titrated with water and stirred well at room temperature. The formation of the monophasic/biphasic system is confirmed by visual inspection. In case turbidity appears followed by phase separation, the samples shall be considered biphasic. In case monophasic, clear and transparent mixtures are visualized after stirring, the samples shall be marked as points in the phase diagram [16].

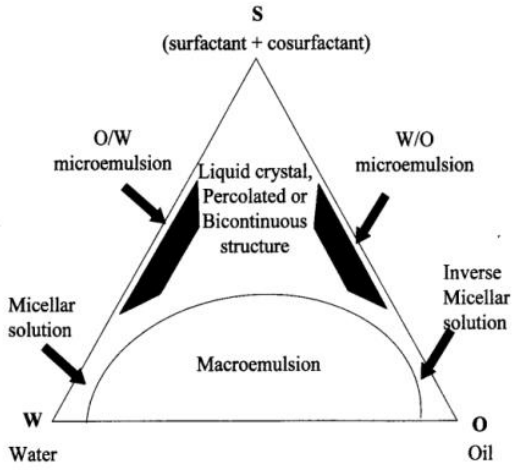

Figure 1: Hypothetical phase regions of microemulsion system of oil (O), water (W), and surfactant + cosurfactant (S)

Composition [17, 18]

The major components of microemulsion system are:

1. Oil phase
2. Surfactant (Primary surfactant)
3. Co-surfactant (Secondary surfactant)
4. Co-Solvent

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1. Oil phase

Oil segment Oil section is 2nd most vital automobile after water due to its house to solubilise lipophilic drug molecules and improve absorption through the lipid layer current in the body [6]. Oil has the special property of penetrating phone walls and therefore very useful for lipophilic active drug delivery. The swelling of the tail crew place of the surfactant is influenced by means of the oil phase. Such penetration is to a greater extent in the case of brief chain alkanes as in contrast to long-chain alkanes [19, 20].
Examples

Saturated fatty acids: lauric, myristic and capric acid

Unsaturated fatty acids: oleic acid, linoleic acid and linolenic acid

Fatty acid esters: ethyl or methyl esters of lauric, myristic and oleic acid Surfactants During the instruction of the microemulsion, the surfactant must be able to reduce the interfacial tension nearest to zero to facilitate dispersion of all components. These surfactants can be:
Non-ionic, Anionic, Cationic Zwitterionic. The nature of surfactants helps in determining the steadiness of microemulsion. Dipole and hydrogen bond interactions stabilize non-ionic surfactant and the electrical double layer stabilizes ionic surfactants. Ionic surfactants are also affected by salt concentration. Hence ionic surfactants being sensitive to steadiness issues and due to toxicity concerns, are generally not preferable. But non-ionic surfactants can produce nontoxic pharmaceutical dosage forms and therefore greater popular [21,22].

Examples of non-ionic surfactants:

Polyoxyl 35 castor oil (Cremophor EL)

Polyoxyl forty hydrogenated castor oil (Cremophor RH 40)

Polysorbate20(Tween20)

Polysorbate80(Tween80)

Co-surfactants

It is studied that excessive concentrations of single-chain surfactants are required to minimize the O/W interfacial anxiety to a level to enable a spontaneous formation of a microemulsion. However, if co-surfactants are delivered then with minimum attention of surfactants one of a kind curvatures of interfacial movie can be formed to generate steady micro emulsion composition [11-16]. Co surfactants raises the fluidity of the interface due to presence of fluidizing groups like unsaturated bonds, then demolishes liquid crystalline or gel shape and alters the HLB cost in such a way to cause the spontaneous formation of the microemulsion. Example: Short-chain alcohols like ethanol to butanol. Short-chain glycols like propylene glycol [24,25].

Classification of microemulsion [26,27,28].

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

i. **Oil in water microemulsions** wherein oil droplets are dispersed in the continuous aqueous phase.
ii. **Water in oil microemulsions** wherein water droplets are dispersed in the continuous oil phase.
iii. **Bi-continuous microemulsions** wherein microdomains of oil and water are interspersed within the system.

Theories of microemulsion formation [29,30]

Historically, three approaches have been used to explain microemulsion formation and stability. i. Interfacial or mixed film theories.
ii. Solubilization theories.
iii. Thermodynamic treatments.
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 changes in entropy of the system such that,

$$Gf = \gamma a - T S$$

Where Gf = free energy of formation
A = change in the interfacial area of microemulsion
S = change in entropy of the system
T = temperature
γ = surface tension of oil-water interphase
It should be noted that when a microemulsion has formed the change in A is very large due to the large number of very small droplets formed.

Method of Preparation

1. Phase Titration Method [22, 23]

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

and demarcation of the phase boundaries are essential aspects of the study.

2. Phase Inversion Method

Phase inversion of microemulsions occurs upon the addition of an excess of the dispersed phase or in response to temperature. During phase inversion, drastic physical changes occur including changes in particle size that can affect drug release both in vivo and in vitro. These methods make use of changing the spontaneous curvature of the surfactant. For non-ionic surfactants, this can be achieved by changing the temperature of the system, forcing a transition from an o/w microemulsion at low temperatures to a w/o microemulsion at higher temperatures (transitional phase inversion). During cooling, the system crosses a point of zero spontaneous curvature and minimal surface tension, promoting the formation of finely dispersed oil droplets. This method is referred to as the phase inversion temperature (PIT) method [24, 25].

Evaluation of microemulsion

Physical appearance

For a Physical look, microemulsion can be investigated visually for homogeneity, fluidity and optical clarity.

2. Scattering Techniques

Scattering strategies such as small-angle neutron scattering, small perspective X-ray scattering and mild scattering have determined purposes in the research of microemulsion structure, mainly in the case of dilute monodisperse spheres, when polydisperse or concentrated systems such as those frequently considered in microemulsions [26].

3. Limpidity Test (Percent Transmittance)

The limpidity of the microemulsion is often measured spectrophotometrically by exploitation photometer27.

4. Drug stability

The optimized microemulsion was unbroken beneath cold conditions (4-8°C), temperature and at elevated temperature (50 ± two °C). Once every two months, the microemulsion will be analyzed for section separation, nothing transmission, orb size and a couple of assays [28].

5. Globule size and zeta potential measurements

The orb size and letter potential of the microemulsion are often determined by dynamic lightweight scattering, employing a Zetasizer HSA 3000.

6. Assessment of the Rheological Properties (viscosity measurement)

The physical science properties play a very important role in stability. It is often determined by Brookfield digital measuring system. Modification within the physical science characteristics facilitates in deciding the microemulsion [29].

Electrical conductivity

The water part was an additional drop informed a combination of oil, chemical agent and co-surfactant and also the electrical conduction of developed samples is measured by employing a conductometer at close temperature and at a continuing frequency of one cycle per second30.

8. Drug solubility

The drug was added in excess to the optimized microemulsion formulation similarly to every individual ingredient of the formulation. once continuous stirring for twenty-four h at temperature, samples were withdrawn and centrifuged at a 6000 rate for ten min. quantity the number} of soluble drug within the optimized formulation similarly as every individual ingredient of the formulation was calculated by subtracting the drug gift within the sediment from the whole amount of drug added. The solubility of the drug in microemulsion was compared in relation to its individual ingredients [11].

9. In-vitro drug release

The diffusion study is allotted on a changed Franz diffusion cell, at intervals volume of 20mL. The receptor compartment was crammed with buffer. The donor compartment was mounted with a plastic wrap membrane, containing the microemulsion formulation and also the plain drug the resolution, separately. At present time intervals, samples were withdrawn from the receptor compartment and analyzed for drug content, employing an ultraviolet light photometer at a specific wavelength [12].

Application of Microemulsion The application of microemulsion is given as follows ¬

Parenteral Delivery

Parenteral administration (especially via the intravenous route) of drugs with limited solubility is a major problem in 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 the fine particle microemulsion is cleared more slowly than the coarse particle emulsion and, therefore, has a longer residence time in the body [13].

Oral Delivery

Microemulsion formulations offer several benefits over conventional oral formulations including increased

absorption, improved clinical potency, and decreased drug toxicity. Therefore, microemulsions have been reported to be ideal for the delivery of drugs such as steroids, hormones, diuretics and antibiotics [22].

Topical delivery

Topical administration of drugs can have advantages over other methods for several reasons, one of which is the avoidance of hepatic first-pass metabolism, salivary and degradation of the drug in the stomach and related toxicity effects. Another is the direct delivery and targetability of the drug to affected areas of the skin or eyes [19].

Conclusion

To date, microemulsions have been shown to be able to protect labile drugs, control drug release, increase drug solubility, increase bioavailability and reduce patient variability. Furthermore, it has proven possible to formulate preparations suitable for most routes of administration. There is still however a considerable amount of fundamental work characterizing the physicochemical behaviour of microemulsions that needs to be performed before they can live up to their potential as multipurpose drug delivery vehicles.

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