



Review on: Microemulsion a Novel Approach for Drug Delivery

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ABSTRACT

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 molecule. Now a day Microemulsion is an emerging trade and having worldwide importance in a variety of technological applications. These applications include enhanced oil recovery, combustion, cosmetics, pharmaceuticals, agriculture, metal cutting, lubrication, food, enzymatic catalysis, organic and bio-organic reactions, chemical synthesis of nanoparticles etc. This review article deals with feature and application of microemulsion. a brief introduction and definition, structure, type, formation characteristics, stability, phase behavior and the effect of additives, pressure, temperature on the phase behavior of microemulsion.

Keywords: Microemulsion, Surfactant, Delivery System.

INTRODUCTION

Micro emulsion is Dispersion made of water, oil, and surfactant(s) that is anisotropic and thermodynamically stable system with dispersed domain diameter varying approximately from 1 to 100 nm, usually 10 to 50 nm.¹ Micro emulsions are clear, thermodynamically stable, isotropic liquid mixtures of oil, water and surfactant, frequently in combination with a 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.² The term of micro emulsion applies to a mixture with at least three components; an oily phase, an aqueous phase and a surface active species, so called surfactants. Sometimes the forth component i.e., co-surfactant can/must be present. Depending on the ratios between the components, in the two extremes the microstructure of the micro emulsions vary from a very tiny water droplets dispersed in oil phase (w/o micro emulsion) to a oil droplets dispersed in water phase (o/w micro emulsion). The microstructure of the mixture changes continuously from one to another extreme, namely, from a spherical to cylindrical, tubular and interconnected continuous oil and water phases separated with a very thin layer of surfactant molecules, in the middle, which is defined as discontinues micro emulsion. The micro emulsions of each kind are thermodynamically stable and transparent solutions. There are main differences between emulsions and micro emulsions in terms of structure and stability. In contrast to the micro emulsions, the emulsions are unstable systems and without agitation, phase separation will occur in them. The other difference is that the size of droplets in emulsions are in the range of micrometers,

while in micro emulsions the size of micelles are in the range of 5-100 nm, depending on the some parameters such as surfactant type and concentration, the extent of dispersed . Hence, sometimes the micro emulsion term is misleading, because it doesn't reflect the size of dispersed phase droplets in the system which, are in the nanometer range. Depending on the type of the surfactants employed in the preparation of the micro emulsion, another important parameter that affects the main characteristics of a micro emulsion is the presence of electrolytes in the aqueous phase.²

History and Terminology

Micro emulsions were not really recognized until the work of Hoar and Schulman in 1943, who reported a spontaneous emulsion of water and oil on addition of a strong surface-active agent. The term "micro emulsion" was first used even later by Schulman et al.³ in 1959 to describe a multiphase system consisting of water, oil, surfactant and alcohol, which forms a transparent solution.⁴ There has been much debate about the word "micro emulsion" to describe such systems Although not systematically used today, some prefer the names "micellar emulsion" or "swollen micelles".⁵ Micro emulsions were probably discovered well before the studies of Schulmann: Australian housewives have used since the beginning of last century water/eucalyptus oil/soap flake/white spirit mixtures to wash wool, and the first commercial micro emulsions were probably the liquid waxes discovered by Rodawald in 1928. Interest in micro emulsions really stepped up in the late 1970's and early 1980's when it was recognized that such systems could improve oil recovery and when oil prices reached levels where tertiary recovery methods became profit earning.⁶ Nowadays this is no longer the case, but 60



other micro emulsion applications were discovered, e.g., catalysis, preparation of submicron particles, solar energy conversion, liquid-liquid extraction (mineral, proteins, etc.). Together with classical applications in detergency and lubrication, the field remains sufficiently important to continue to attract a number of scientists. From the fundamental research point of view, a great deal of progress has been made in the last 20 years in understanding micro emulsion properties. In particular, interfacial film stability and micro emulsion structures can now be characterized in detail owing to the development of new and powerful techniques such as small-angle neutron scattering. The following sections deal with fundamental micro emulsion properties, i.e., formation and stability, surfactant films, classification and phase behavior.

Structure of Micro Emulsion

Micro emulsions or Micellar emulsion are dynamic system in which the interface is continuously and spontaneously fluctuating.⁷ 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.⁸The mixture oil water and surfactants are able to form a wide variety of structure and phase depending upon the proportions of component.

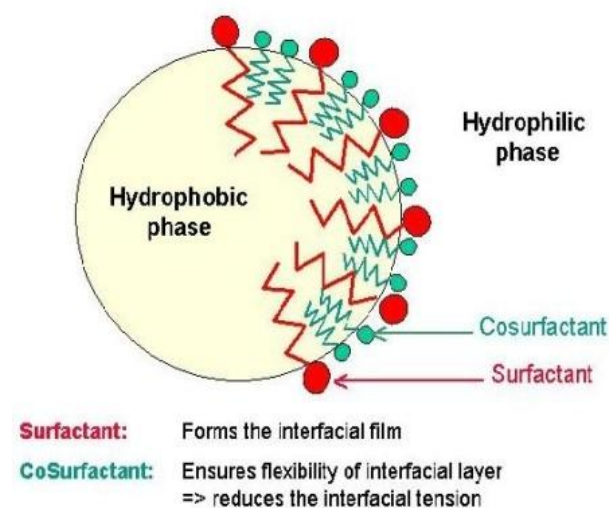


Figure 1: Structure of Microemulsion

Characteristics

If a surfactant possessing balanced hydrophilic and lipophilic properties is used in the right concentration, a different oil and water system will be produced. The system remains an emulsion, but exhibits some characteristics that are different from the milky emulsions discussed earlier. These new systems are “micro emulsions”. The interfacial tension between phases, amount of energy required for formation, droplet sizes,

and visual appearance are only a few of the differences seen when comparing emulsions to micro emulsions. Water-in-oil micro emulsions are also known as reverse micelles. These systems have the ability to solubilise both hydrophilic and hydrophobic substances. Micro emulsions usually exhibit low viscosities and Newtonian flow characteristics. Their flow remains constant when subjected to a variety of shear rates. Discontinuous formulations may show some non-Newtonian flow and plasticity. Micro emulsion viscosity is close to that of water, even at high droplet concentrations. The microstructure constantly changes, making them very dynamic systems with reversible droplet coalescence. A variety of techniques are employed to characterize different properties of micro emulsions. Light scattering, X-ray diffraction, ultracentrifugation, electrical conductivity, and viscosity measurements have been widely used.⁹

Classification of Micro Emulsion^{10,11,12}

According to Winsor, there are four types of micro emulsion phases exists in equilibrium, these phases are referred as Winsor phases.¹⁰⁻¹³ they are:

- Winsor I (two phase system): upper oil layer exists in equilibrium with lower (o/w) micro emulsion phase
- Winsor II (two phase system): the upper (w/o) micro emulsion exists in equilibrium with lower excess water.
- Winsor III (three phase system): middle bi-continuous phase of o/w and w/o called) exists in equilibrium with upper phase oil and lower phase water.
- Winsor IV (single phase system): it forms homogenous mixture of oil, water and surfactant

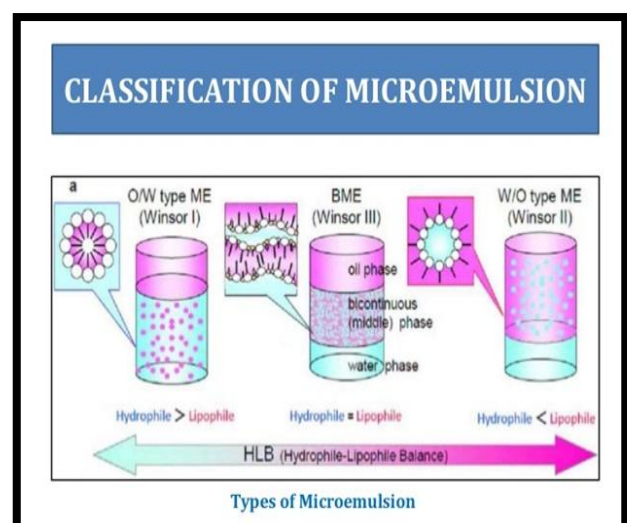


Figure 2: classification of micro emulsion

The R-ratio is one of the characterization concepts which were first proposed by Winsor to explain the influence of amphiphiles and solvents on interfacial curvature. R-ratio compares the affinity for an amphiphile to disperse into oil, to its affinity to dissolve in water. If one phase is

avored, the interfacial region forms a definite curvature. Thus, if $R > 1$, the interface increases its area of contact with oil while decreasing its area of contact with water. Thus oil becomes the continuous phase and the

Formation of Micro Emulsion¹³

corresponding characteristic system is type II (Winsor II). Similarly, a balanced interfacial layer is represented by $R = 1$.

The following steps involved in micro emulsion-



Figure 3: steps involved in micro emulsion formulation

Ternary Phase Diagram

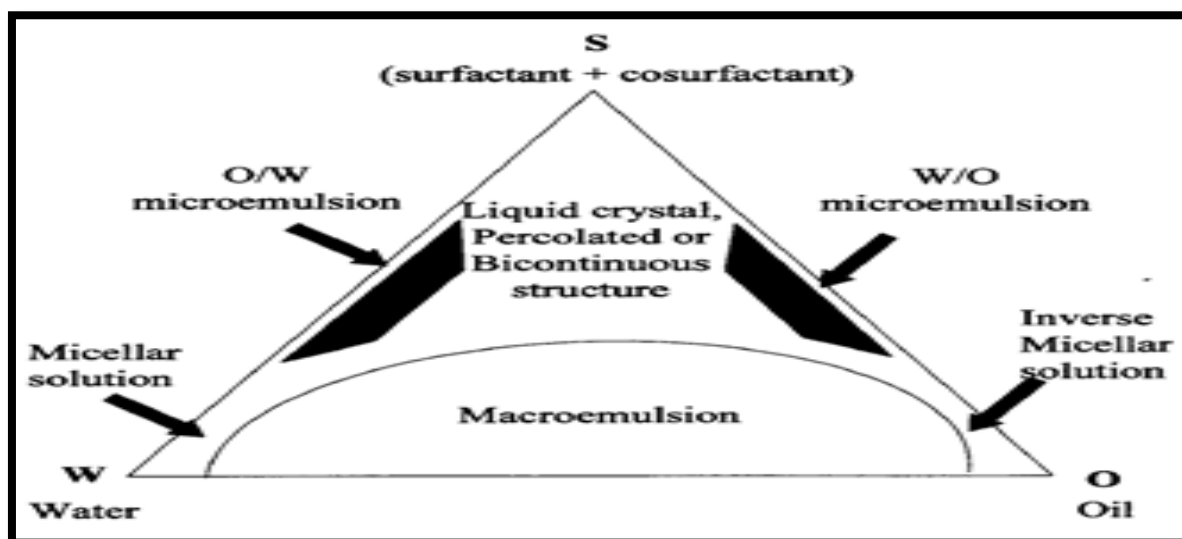


Figure 4: ternary phase diagram

Ternary phase diagrams at constant temperature and pressure, the ternary phase diagram of a simple three-component micro emulsion is divided into two or four regions. In each case, every composition point within the single-phase region above the demising line corresponds to a micro emulsion. Composition points below this line correspond to multiphase regions comprising in general micro emulsions in equilibrium with either an aqueous or an organic phase or both, i.e., Winsor type systems.

Any system whose overall composition lies within the two-phase region will exist as two phases whose compositions are represented by the ends of the "tie-line", i.e., a segment formed by phase's m and n. Therefore, every point on a particular tie-line has identical coexisting phases (m and n) but of different relative volumes.

If three phases coexist (Figure 4), i.e., corresponding to WIII, the system at constant temperature and pressure is, according to the phase rule, invariant. Then, there is a

region of the ternary diagram that consists of three phase systems having invariant compositions and whose boundaries are tie lines in the adjacent two-phase regions that surround it. This region of three phase invariant compositions is therefore triangular in form and called "tie85 triangle"

Phases Involved

Water phase

Depending upon the amount of water present in the system, water may form water pool or work as a dispersion medium in micro-emulsion system.

Oil phase

The oil phase must be chosen appropriately, since it governs the selection of the other ingredients for the micro emulsion and there are two main factors that need be considered before selecting the appropriate oil phase.

Firstly, the solubilizing potential of the oil for the selected substance must be seen and secondly, the chosen must be 103 such that the micro emulsion forming region is enhanced. Oils with shorter hydrocarbon chains are easier to micro-emulsify as compared to oils with long hydrocarbon chains. An oils ability to solubilizing lipophilic groups is directly proportional to the chain length of the oil. Thus, the selected oil should be such that it is capable of solubilizing the API, and facilitating the formation of micro emulsions with desired characteristics

Composition¹⁴⁻²³

The Major component in micro emulsion system are-

- 1) Oil phase
- 2) Surfactant (primary surfactant)
- 3) Co-surfactant (secondary surfactant)
- 4) Co-solvent

Table 1: Component of Microemulsion System:

Component	Example
Oil	1)-saturated fatty acid- lauric acid, capric acid 2)unsaturated fatty acid-oleic acid, linolic acid, linolenic acid 3)fatty acid ester-ethyl or methyl ester of lauric, oleic acid and myristic acid
Surfactant	1-polyoxyethylene/polysorbate/tween 20,40,60,80 2-sorbitan monolaurate, eggs lecithin 3-sodium dodecyl sulphate
Co-surfactant	1-ethanol, proranol, butanol, isopropanol, pentanol, hexanol 2-polyoxyethylene-10-oelyl ether 3-sodium monoethyl phosphate 4-cinnamic alcohol, cinamic alcohol

Preparation Method of Micro-Emulsion^{24,25}

Following are the method used for the preparation of the micro emulsion:

- 1) Phase titration method:
- 2) Phase inversion method:

Phase Titration Method

Micro emulsions 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. Micro emulsions 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 equilibrium and demarcation of the phase boundaries are essential aspects of the study. As quaternary phase diagram (four component system) is time consuming and difficult to

interpret, pseudo ternary phase diagram is often constructed to find the different zones including micro emulsion zone, in which each corner of the diagram represents 100% of the particular component. The region can be separated into w/o or o/w micro emulsion by simply considering the composition that is whether it is oil rich or water rich. Observations should be made carefully so that the metastable systems are not included.

Phase Inversion Method

Phase inversion of micro emulsions occurs as a result of addition of 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 micro emulsion at low temperatures to a w/o micro emulsion 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 phase inversion temperature (PIT) method. Instead of the temperature, other parameters such as salt concentration or pH value may be considered as well instead of the temperature alone. Additionally, a transition in the spontaneous radius of curvature can be obtained by changing the water volume fraction. By successively adding water into oil, initially water droplets are formed in a continuous oil phase. Increasing the water volume fraction changes the spontaneous curvature of the surfactant from initially stabilizing a w/o micro emulsion to an o/w micro emulsion at the inversion locus. Short-chain surfactants form flexible monolayer at the o/w interface resulting in a discontinuous micro emulsion at the inversion.

Theories of Micro Emulsion Formation^{26, 27}

Historically, three approaches have been used to explain micro emulsion formation and stability. They are as follows-

- 1- Interfacial or mixed film theories.
- 2- Solubilization theories
- 3- Thermodynamic treatments

The free energy of micro emulsion formation can be considered to depend on the extent to which surfactant lowers the surface tension of the oil water interface and change in entropy of the system such that,

$$G_f = \gamma a - TS$$

Where,

G_f = free energy of formation

A = change in interfacial area of micro emulsion

S = change in entropy of the system

T = temperature

γ = surface tension of oil water interphase.

When micro emulsion is formed the change in A is very large due to the large number of very small droplets formed. In order for a micro emulsion to be formed (transient) negative value was required, it is recognized that while value of A is positive at all times, it is very small and it is offset by the entropic component. The dominant favorable entropic contribution is very large dispersion entropy arising from the mixing of one phase in the other in the form of large number of small droplets. However there are also expected to be favorable entropic contributions arising 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, micro emulsion is spontaneous and the resulting dispersion is thermodynamically stable.

Factor affecting Microemulsion^{28, 29, 30}

Factor affecting the micro-emulsion are as follows

- Packing ratio
- Property of surfactant
- Property of oil phase
- Temperature
- Chain length
- Nature of co-surfactant

Application of Microemulsion

The application of micro-emulsion is given as follows

- Oral delivery system
- Parental delivery system
- Ophthalmic delivery system
- micro-emulsion in detergency
- micro-emulsion in cosmetics
- micro-emulsion in food

CONCLUSION

Microemulsion is drug delivery systems for the delivery of more than one medicament simultaneously. Microemulsion protect labile drug, control drug release, increase drug solubility, increase bioavailability and reduce patient variability also it has proven possible to formulate preparations suitable for most routes of administration. The role of microemulsion in providing novel solutions to overcome the problems of poor aqueous solubility of highly lipophilic drug compounds and provide high, more consistent and reproducible bioavailability. The drug delivery through the microemulsion is a promising area for the continued research with the aim of achieving the controlled release with enhanced bioavailability and for drug targeting to various sites of the body.

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