# REVIEW ARTICLE - MICROEMULSION: NOVEL DRUG DELIVERY SYSTEM

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***Abstract*: Microemulsions are one of the best candidates as novel drug delivery system because of their long shelf life, improved drug solubilization with ease of preparation and administration. Microemulsions are thermodynamically stable and optically isotropic liquid solutions of oil, water and amphiphile they have emerged as novel vehicles for drug delivery which allow controlled or sustained release for ocular, percutaneous, topical, oral, transdermal, and parenteral administration of medicaments. Microemulsions can be easily distinguished from normal emulsions by their low viscosity, transparency and more accurately their thermodynamic stability.**

***Keywords*: Microemulsion, Surfactant, Co-surfactant, Ternary phase diagram, Thermodynamically stable.**

## 1. Introduction:

The most preferred route of drug administration is oral route due to its ease, patient compliance and low production cost. The drug must be presented in solution form for absorption through gastrointestinal tract (GIT) when given orally. In the case of poorly soluble drugs, solubility is an important parameter and dissolution is the rate limiting step in absorption process.1About 60% of pharmaceutical actives exhibit poor systemic exposure upon oral ingestion owing to poor dissolution or limited absorption across the gastro intestinal membrane (BCS class II, III and IV drugs). Poorly water-soluble drugs involve many difficulties in the development of pharmaceutical dosage forms for oral delivery systems due to their low bioavailability. It has been established that the active ingredient in a solid dosage form must undergo dissolution before it is available for absorption from the gastrointestinal tract. The rate of absorption of a poorly water-soluble drug, formulated as an orally administered solid dosage form, is controlled by its dissolution rate in the fluid present at the absorption site, i.e., the dissolution rate is often the rate-determining step in drug absorption. Therefore, the solubility and dissolution behavior of a drug are the key determinants of oral bioavailability. Various techniques have been published in the scientific literature to enhance the dissolution profile and also the absorption efficiency and bioavailability of water-insoluble and/or liquid lipophilic drugs.

• Reduction of the particle size via micronization or nanonization

• Co-grinding

• Adsorption on porous structures

• Inclusion of active pharmaceutical ingredients into cyclodextrin

• Solid dispersion

• Self-emulsification and self-micro emulsification

• Microencapsulation

### 1.1 Micronization

It is the method for increasing surface area of the drug. Micronized drugs have tendency to aggregate due to electrostatic charge and hydrophobicity.

### 1.2 Co-grinding

Co-grinding of poorly soluble drug with different excipients may also result in an amorphization of the drug and thus improved dissolution characteristics.

### 1.3 Adsorption on porous structure

Adsorption of poorly soluble drug on hydrophilic silica aerogel was found to enhance drug dissolution, but drug adsorption is dependent upon the selected drug and sometimes only low drug loading is achieved. Another problem with this system is the complex manufacturing process.

### 1.4 Inclusion complexation with beta cyclodextrin

Complexes of lipophilic drug with cyclodextrin can be formulated by mixing the drug with carrier. Beta cyclodextrin act as a solubilizer and stabilizer, but the maximum possible drug load of this system is relatively low and the inclusion complexation only works with drugs that fit into the cavities of the cyclodextrin molecule.

### 1.5 Solid dispersion

Solid dispersion has gained an active research interest for improving drug dissolution in the past few decades, however its commercial application is very limited and only a few products, such as Kaletra® and Gris-PEG® have become commercially available. The reason mainly lies on its poor stability during storage and lack of understanding of its solid-state structure.

### 1.6 Self-emulsifying drug delivery system

Self-emulsifying drug delivery system (SEDDS) is an isotropic mixture of oil, surfactant, co-solvent and drug, which emulsify spontaneously to produce oil in water emulsion when introduced into aqueous phase under gentle agitation. Generally, SEDDS are either administered as liquid dosage forms or as soft gelatin capsules. Basically, solid dosage forms are preferred over liquid preparations for many reasons including ease of manufacture, patient compliance, dosage uniformity, and stability. Formulating soft gelatin capsules is another widely used approach, whereas it is costly and requires sophisticated technologies. All the above mentioned techniques impart many advantageous effects in the formulation development. But usually these approaches show lack of stability and decreasing success rate over a period of storage. One of the remarkable demerits of solid dispersions, eutectic mixtures and inclusion complexes is formation of sticky and hygroscopic mass resulting in the poor flow characteristics. Due to the set-back, industrial feasibility of the final dosage form becomes very difficult.

## 2. TYPES

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

### 2.1 Winsor I (two phase system):

Upper oil layer exists in equilibrium with lower (o/w) micro emulsion phase

### 2.2 Winsor II(two phase system):

The upper(w/o) micro emulsion exists in equilibrium with lower excess water.

### 2.3 Winsor III (three phase system):

Middle bi-continuous phase of o/w and w/o called) exists in equilibria with upper phase oil and lower phase water.

### 2.4 Winsor IV (single phase system):

It forms homogenous mixture of oil, water and surfactant

The R-ratio is one of the characterisation 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 favoured, 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 corresponding characteristic system is type II (Winsor II). Similarly, a balanced interfacial layer is represented by $R = 1$.

**Table 1 Difference between Emulsion & Microemulsion**

| **Property** | **Emulsion** | **Microemulsion** |
|---|---|---|
| **Appearance** | Cloudy | Transparent |
| **Optical isotropy** | Anisotropic | Isotropic |
| **Interfacial tension** | High | Ultra low |
| **Microstructure** | Static | Dynamic |
| **Droplet size** | >500nm | 20-200nm |
| **Stability** | Thermodynamically unstable | Thermodynamically stable |
| **Phases** | Biphasic | Monophasic |
| **Preparation** | Require a large input of energy | Facile preparation |
| **Viscosity** | High viscosity | Low viscosity |
| **Turbidity** | Turbid | Transparent |
| **Co-surfactant used** | No | Yes |

| | | |
|---|---|---|
| **Surfactant concentration** | 0.5-5µ | <0.1µ |
| **Molecular packing** | Inefficient | Efficient |

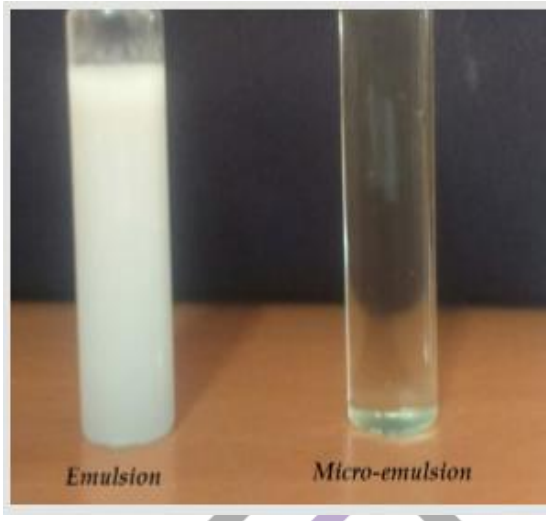


Fig.1 Difference between Emulsion & Microemulsion

## 3. PREPARATION METHODS

### 3.1 Phase titration method:

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 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 microemulsion zone, in which each corner of the diagram represents 100% of the particular component Fig. (2) The region can be separated into w/o or o/w microemulsion 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.21-25

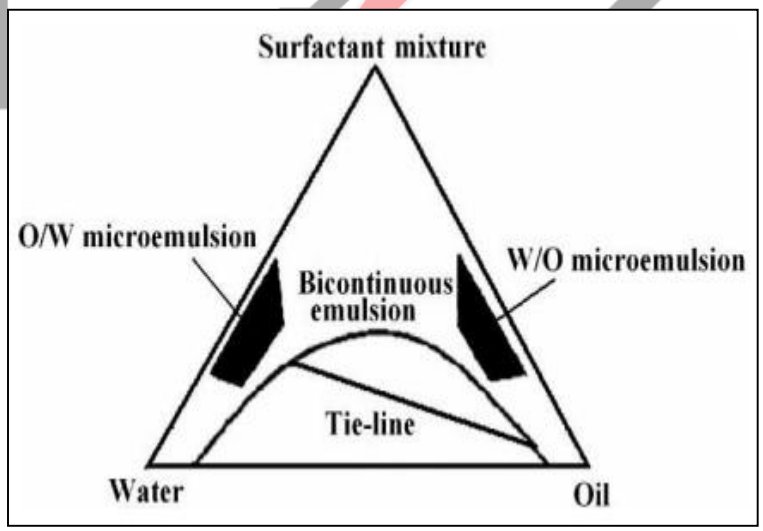


Fig.2 Pseudoternary phase diagram of oil, water and surfactant showing microemulsion region.

### 3.2 Phase inversion temperature method (PIT):

Phase inversion of microemulsions 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 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 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 microemulsion to an o/w microemulsion at the inversion locus. Short-chain surfactants form flexible monolayers at the o/w interface resulting in a bicontinuous microemulsion at the inversion point (Figure 3).

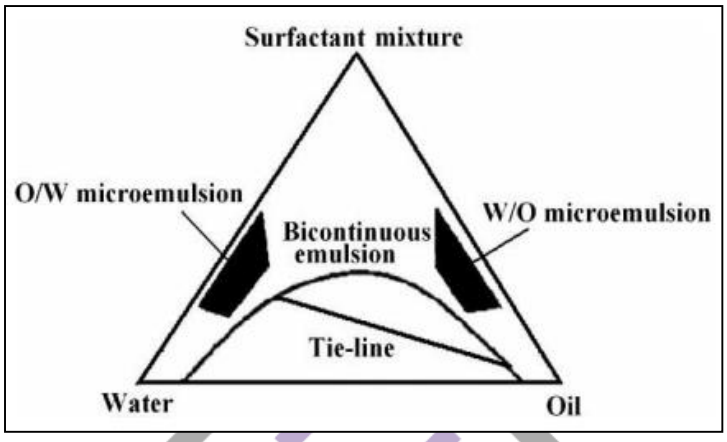


Fig.3 Phase inversion temperature method (PIT)

Hypothetical Phase Diagram

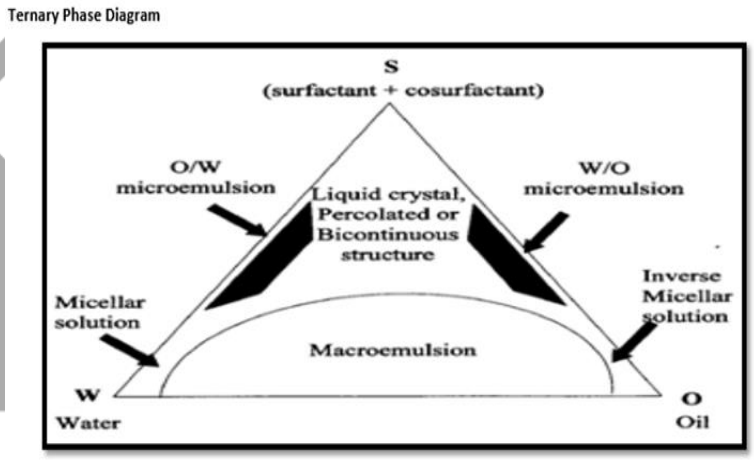


Fig. 4 Ternary Phase diagram based on solubilisation theory.

From Figure 4, we can see that,

• When there is high concentration of oil, surfactant forms reverse micelles capable of solubilizing more water molecules in their hydrophilic interior.

• Continued addition of water in this system may result in theformation of W/O microemulsion in which water exists as droplets surrounded and stabilized by interfacial layer of the surfactant / co-surfactant mixture. At a limiting water content, the isotropic clear region changes to a turbid, birefringent one.

• Upon further dilution with water, a liquid crystalline region may be formed in which the water is sandwiched between surfactant double layers.

• Finally, as amount of water increases, this lamellar structure will break down and water will form a continuous phase containing droplets of oil stabilized by a surfactant / cosurfactant (O/W microemulsions).

## 4. COMPOSITION

The major components of micro emulsion system are:

1) Oil phase

2) Surfactant (Primary surfactant)

3) Co-surfactant (Secondary surfactant)

4) Co-Solvent

### 4.1 Oil phase

Oil phase is second most important vehicle after water due to its properties to solubilise lipophilic drug molecules and improve absorption through lipid layer present in body. Oil has unique property of penetrating cell wall and hence very useful for lipophilic active drug delivery. Swelling of tail group region of the surfactant is influence by oil phase. Such penetration is to greater extent in case of short chain alkanes as compared to long chainalkanes.

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.

### 4.2 Surfactants

During the preparation of the microemulsion, 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,

Nature of surfactants helps in deciding stability of microemulsion. Dipole and hydrogen bond interactions stabilize non-ionic surfactant and electrical double layer stabilizes ionic surfactants.

Ionic surfactants are also affected by salt concentration. Hence ionic surfactants being sensitive in stability issues and due to toxicity concern, are generally nor preferable. But non-ionic surfactants can produce nontoxic pharmaceutical dosage forms and hence more popular. Surfactants with HLB values3-6 are useful in preparation of W/O micro emulsion and surfactants with higher HLB values8-18 are useful in preparation of O/W micro emulsion. Surfactants with more than 20 HLB values are acts as co-surfactant to reduce concentrations of surfactants to a acceptable limit and micro emulsion formation.

Examples of non-ionic surfactants:

• Polyoxyl 35 castor oil (Cremophor EL)

• Polyoxyl 40 hydrogenated castor oil (Cremophor RH 40)

• Polysorbate20(Tween20)

• Polysorbate80(Tween80)

### 4.3 Co-surfactants

It is studied that high concentrations of single-chain surfactants are required to reduce the O/W interfacial tension to a level to enable a spontaneous formation of a microemulsion. However, if cosurfactants are added then with minimum concentration of surfactants different curvatures of interfacial film can be formed to generate stable micro emulsion composition. Co surfactants raises the fluidity of the interface due to presence of fluidizing groups like unsaturated bonds, then demolishes liquid crystalline or gel structure and alters the HLB value in such way to cause spontaneous formation of micro emulsion.

Example:

• Short chain alcohols like ethanol to butanol

• Short chain glycols like propylene glycol

• Medium chain alcohols like amines or acids

(Ethanol, propanol, Isopropanol, butanol, pentanol, hexanol, sorbitol, n–pentanoic acid, n–hexanoic acid, n–butylamine, sec, butylamine, 2-aminopentane, 1,2-butanediol, Propylene glycol.)

**4.4 Co-solvents**

Co-solvents are organic solvents like ethanol, propylene glycol (PG), and polyethylene glycol (PEG) which helps to dissolve relatively high concentrations of surfactants as well as lipid soluble drugs. Hence co-solvents are also considered as co-surfactants.

**5. APPLICATION OF MICROEMULSION**

During the last two decades, microemulsions have been promisingly used as drug delivery system for its advantages include their thermodynamic stability, optical clarity and ease of penetration. The role of microemulsion as drug delivery system shall be discussed herein.

Oral delivery

Topical delivery

Parentral delivery

Nasal delivery

Ocular delivery

Pulmonar delivery

Periodontal delivery

**6. ADVANTAGE & DISADVANTAGE**

**6.1 ADVANTAGES**

It is very easy to prepare and scale up due to spontaneous formation ability.

It is very good system to raise rate of absorption as well as bioavailability by eliminating interfering variations.

It able to improve solubility of lipophilic drugs.

It is thermodynamically more stable system as compared to conventional system and hence suitable for long term use.

It can be preferred to develop sustained and controlled releases drug system.

It is best system to minimize first pass metabolism.

**6.2 DISADVANTAGES**

Additional use of excess amount of surfactant and co-surfactant increases cost.

Excess concentration of surfactants can lead to mucosal toxicity.

**7. EVALUATION OF MICROEMULSION**

**7.1 Visual inspection**

Visual inspection was made after each addition of water to the oil and surfactant and co-surfactant mixture. The samples were identified as microemulsion, emulsion or gel formation by visual observation.

**7.2 Thermodynamic stability**

To overcome the problem of metastable formulation, thermo-dynamic stability tests were performed.

a) Centrifugation

The formulation was centrifuged at 3500 rpm for 30 min to ensure physical stability.

b) Stress test

These tests were done to optimize the best microemulsion formulation under extreme conditions. Stress was carried out at 4 °C and 45 °C for 48 h each for a period of six cycles, followed by 25 °C and 21 °C for 48 h for about three cycles. The samples were checked for coalescence, cracking or phase separation.

**7.3 Measurement of pH**

The pH values of the optimized formulation were measured by immersing the electrode directly into the dispersion using a calibrated pH meter (Digital Potentiometer Model EQ-601 Equip-Tronics).

**7.4 Viscosity measurements**

The viscosity of the optimized formulation was determined as such without dilution using Brookfield Viscometer (DV-E Brookfield Viscometer Model-LVDVE).

**7.5 Zeta potential determination**

Zeta potential of samples was measured by Zeta sizer. Samples were placed in clear disposable zeta cells and results were recorded. Before putting the fresh sample, cuvettes were washed with methanol and rinsed using the sample to be measured before each experiment.

**7.6 Particle size determination**

The mean particle size and particle size distribution of drug loaded microemulsion were determined by Horiba SZ-100 nanoparticle analyzer, at 28°C. It measures the fluctuation of the intensity of the scattered light which is caused by particle movement. Each sample was measured in triplicate.

**7.7 Drug content estimation**

Microemulsion containing 100 mg drug was dissolved in 100 ml 0.1N HCl taken in volumetric flask. Then the solvent was filtered, 1 ml was taken in 50 ml volumetric solution and diluted up to the mark with 0.1N HCl and analyzed spectrometrically at 295 nm. The concentration of drug in mg/ml was obtained by using standard calibration curve of the drug. Drug content studies were carried out in triplicate for each formulation batch.

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