

Microemulsion

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Introduction

- ❖ Microemulsion is an isotropic mixture of oil, surfactant, Cosurfactant and drug.
- ❖ Upon **mild agitation followed by dilution in aqueous media**, such as gastrointestinal (GI) fluids, the **systems can form fine oil in water (O/W) Microemulsions** which usually have a **droplet size less than 100 nm**.
- ❖ Microemulsion have been successfully used to **improve the solubility, chemical stability, and oral bioavailability of many poorly water soluble drugs**.
- ❖ They have characteristic properties such as a **low interfacial tension, large interfacial area** and capacity to **solubilize both aqueous and oil-soluble compounds**.

Microemulsion

Microemulsion

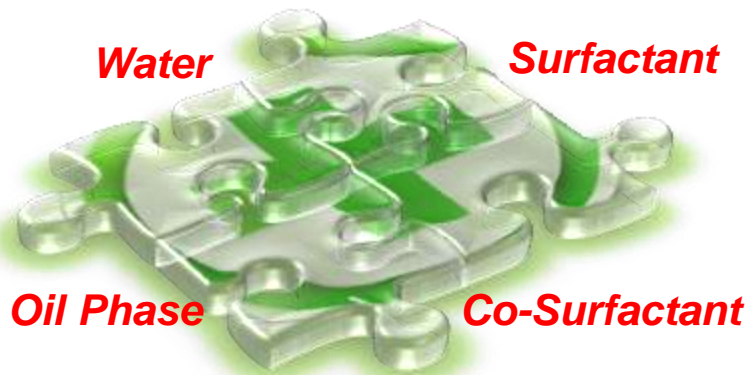


Figure 1: Isotropic mixture of oil, Smix and water

Definition

Microemulsion is defined as isotropic mixtures of natural or synthetic oils , surfactants and Cosurfactant”.

History

The Microemulsion concept was introduced as early as 1940s by Hoar and Schulman who generated a clear single-phase solution by titrating a milky emulsion with hexanol. Schulman and co-worker (1959) subsequently coined the term microemulsion The Microemulsion definition provided by Danielson and Lindman in 1981 will be used as the point of reference.

Difference between Microemulsion and Macroemulsion

Microemulsion

Macroemulsion

Thermodynamically Stable

Kinetically Stable

Droplet size 10 - 100 nm (transparent)

1-10 μm (opaque)

High surface area: 200 m^2/g

Low surface area: 15 m^2/g

Clear and translucent

Cloudy

W/O, O/W and Bicontinuous types

W/O or O/W types

Comparison between emulsion and microemulsion

Emulsion	Microemulsions
1. Emulsions consist of roughly spherical droplets of one phase dispersed into the other.	1. They constantly evolve between various structures ranging from droplet like swollen micelles to bicontinuous structure.
2. Droplet diameter: 1 – 20 μm .	2. 10 – 100 nm.
3. Most emulsions are opaque (white) because bulk of their droplets is greater than wavelength of light and most oils have higher refractive indices than water.	3. Microemulsions are transparent or translucent as their droplet diameter are less than $\frac{1}{4}$ of the wavelength of light, they scatter little light.
4. Ordinary emulsion droplets, however small exist as individual entities until coalescence or Ostwald ripening occurs.	4. Microemulsion droplet may disappear within a fraction of a second whilst another droplet forms spontaneously elsewhere in the system.
5. They may remain stable for long periods of time, will ultimately undergo phase separation on standing to attain a minimum in free energy. They are kinetically stable thermodynamically unstable	5. More thermodynamically stable than emulsions and can have essentially infinite lifetime assuming no change in composition, temperature and pressure, and do not tend to separate.
6. They are lyophobic.	6. They are on the borderline between lyophobic and lyophilic colloids.

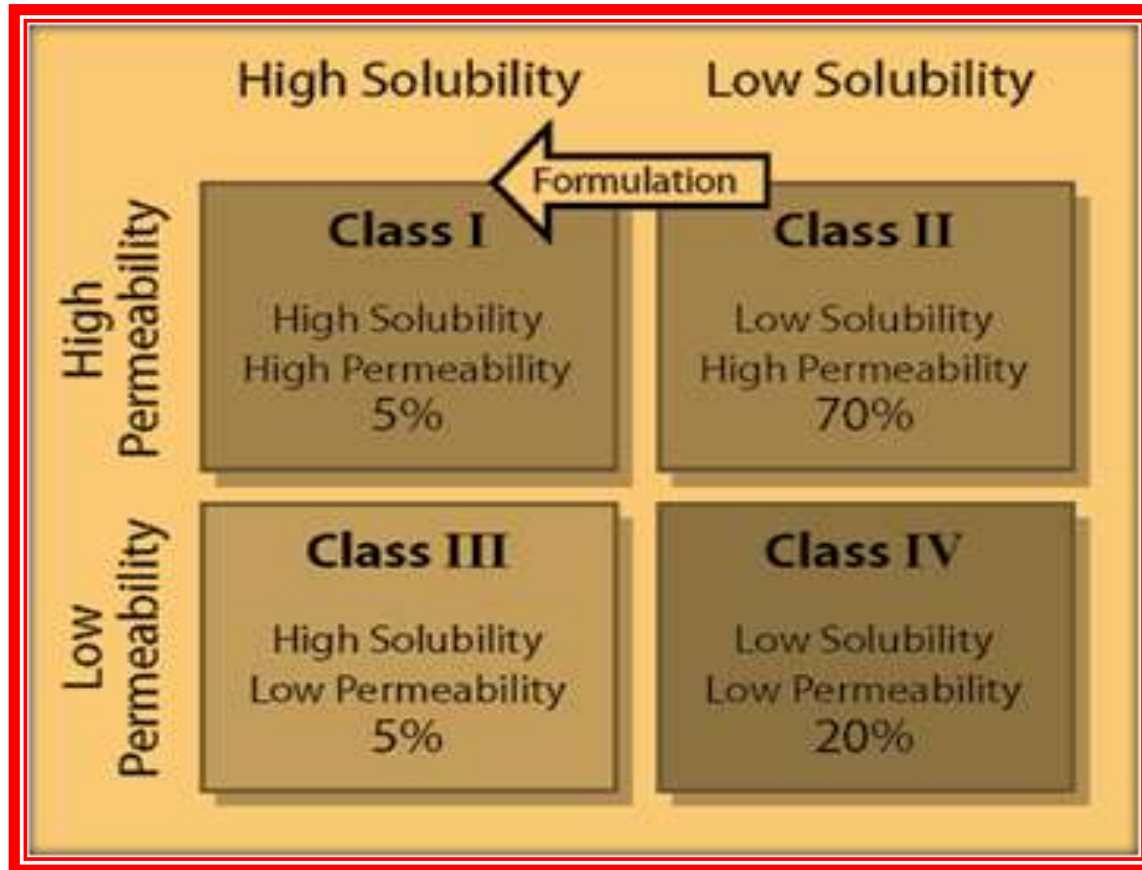
Difference between SEDDS And SMEDDS

Sr.no.	SEDDS	SMEDDS
1	It is a mixture of Oil, Surfactant and Drug	It is a mixture of Oil, Surfactant, Co-surfactant and Drug
2	Droplet size is 100 – 300 nm	Droplet size is less than 100 nm
3	It is a Turbid in nature	It is Transparent in nature
4	It is Thermodynamically not Stable	It is Thermodynamically Stable
5	Ternary Phase Diagrams are used to optimized	Pseudo Ternary Phase Diagrams are used to optimized

Difference between SMEDDS And SNEDDS

SMEDDS	SNEDDS
It is Self-Micro emulsifying drug delivery system	It is Self Nano emulsifying drug delivery system
It is turbid in nature	It is transparent in nature
Large amount of energy is required for preparation as compare to nanoemulsion	Less energy required for preparation
Droplet size is 100-300nm	Droplet size is less than 100nm
It is thermodynamically stable	It is thermodynamically and kinetically stable
It is optimized by ternary phase diagram	It is optimized by Pseudoternary phase diagram

Bio-pharmaceutical classification system



Microemulsion is important approach for BCS class II, IV drugs to improve the Solubility of poorly water soluble drugs and increases Bioavailability of drugs.

Advantages

- ❖ **Enhanced oral bioavailability and stability of drugs which show low bioavailability.**
- ❖ **Reduction of inter-subject and intra subject variation.**
- ❖ **Ease of manufacturing and scale up.**
- ❖ **Less amount of energy requirement.**
- ❖ **Ability to deliver peptides that are prone to Enzymatic hydrolysis in GIT.**
- ❖ **They are used for both liquid and solid dosage forms.**
- ❖ **Useful in topical application.**

Disadvantages

One of the obstacles for the development of Microemulsion and other lipid-based formulations is the lack of good predicative in vitro models for assessment of the formulation. Traditional dissolution methods do not work because these formulations potentially are dependent on digestion prior to release of the drug. To mimic this, in vitro model simulating the digestive processes of the duodenum has been developed. This in vitro model needs further development and validation before its strength can be evaluated. Further development will be based on invitro in-vivo correlations and therefore different prototype lipid based formulations need to be developed and tested in vivo in a suitable animal model.

Theories of Microemulsion Formation

1. Interfacial/Mixed Film Theories

- ❖ They considered that the spontaneous formation of microemulsion droplets was due to the formation of a complex film at the oil-water interface by the surfactant and co-surfactant.
- ❖ This caused a reduction in oil-water interfacial tension to very low values (from close to zero to negative)

❖ equation

$$\gamma_i = \gamma_{o/w} - \pi_i$$

Where,

$\gamma_{o/w}$ = Oil-water interfacial tension without the film present

π_i = Spreading pressure

γ_i = Interfacial tension

Mechanism of curvature of a duplex film

- ❖ The interfacial film should be curved to form small droplets to explain both the stability of the system and bending of the interface.
- ❖ A flat duplex film would be under stress because of the difference in tension and spreading of pressure on either side of it.
- ❖ Reduction of this tension gradient by equalizing the two surface tensions is the driving force for the film curvature.
- ❖ It is generally easier to expand the oil side of an interface than the water side and hence W/O microemulsion can be formed easily than O/W microemulsion.

Solubilization Theories

- ❖ Illustrated the relationship between reverse micelles and W/O microemulsion with the help of phase diagrams.
- ❖ The inverse micelle region of ternary system i.e. water, pentanol and sodium dodecyl sulphate (SDS) is composed of water solubilized reverse micelles of SDS in pentanol.
- ❖ Addition of O-xylene up to 50% gives rise to transparent W/O region containing a maximum of 28% water with 5 % pentanol and 6% surfactant (i.e. microemulsions).
- ❖ These four component systems could be prepared by adding hydrocarbon directly to the inverse micellar phase by titration.

Thermodynamic theory

- ❖ The process of formation of oil droplets from a bulk oil phase is accompanied by an increase in the interfacial area ΔA , and hence an interfacial energy ΔG .
- ❖ The entropy of dispersion of the droplets is equal to $T \Delta S$ and hence the free energy of formation of the system is given by the expression.

$$\Delta G_f = \gamma \Delta a - T \Delta S$$

Where,

ΔG_f = free energy of formation

ΔA = change in interfacial area of microemulsion

ΔS = change in entropy of the system

T = temperature

γ = surface tension of oil water interphase

- ❖ When the interfacial tension is made sufficiently low that the interfacial energy becomes comparable to or even lower than the entropy of dispersion.
- ❖ 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.
- ❖ The free energy of formation of the system becomes zero or negative.
- ❖ This explains the thermodynamic stability of micro emulsions.
- ❖ The co-surfactant along with surfactant lower the interfacial tension to a very small even transient negative value.

Components of SMEDDS

Surfactants

Surfactants are wetting agents that lower the interfacial tension between two immiscible liquid.

Types of Surfactants

Anionic - Examples - Sodium Lauryl Sulphate

Cationic - Example Quaternary ammonium Halide

Zwitterionic (amphoterics) - Example - Sulfobetaines

Non-ionic - Example - Polysorbates

HLB System

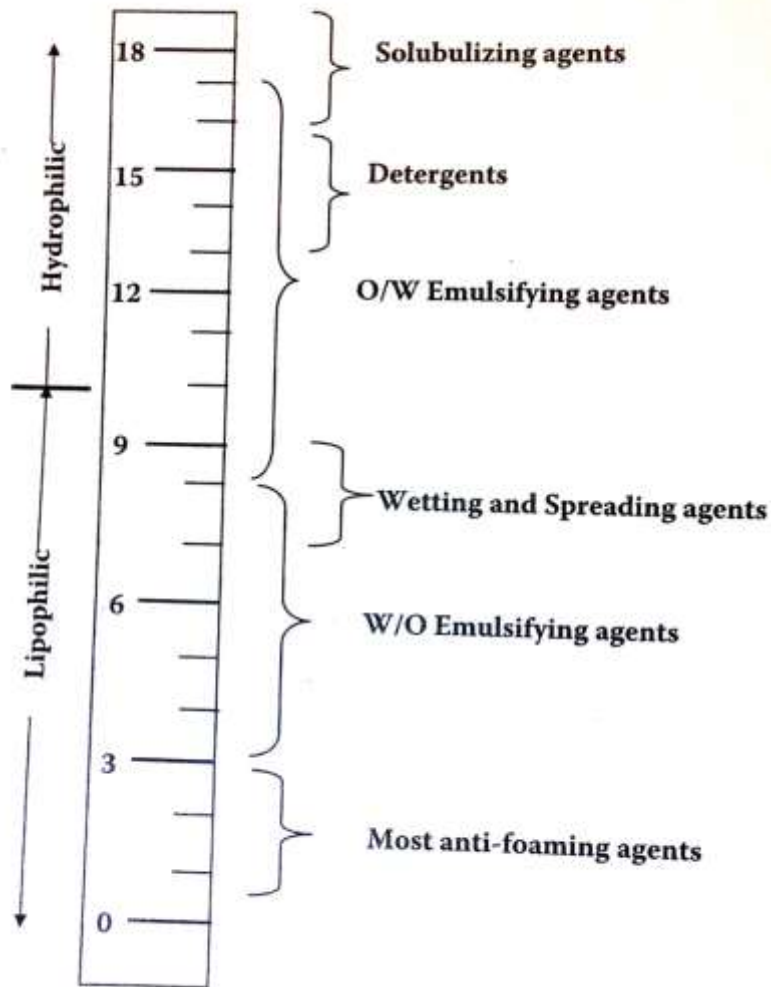


Figure 2: HLB System

1.HLB value – **If high** > more polar > **more hydrophilic.**

E.g. polyoxyethylene derivatives

2.HLB value- **If low** > less polar > **more lipophilic.**

E.g. sorbitan esters

▪ **Types of emulsion** formation whether o/w or w/o depends on the emulsifying agents used.

▪ **O/W-** HLB **9-12** – surfactant **Soluble** in water

▪ **W/O** – HLB **3-6** – surfactant **Insoluble** in water

Oil

The oil represents the most important excipient in the Microemulsion formulation. It can solubilize the amount of the poorly water soluble drug. Both long-chain triglyceride (LCT) and medium chain triglyceride (MCT) oils with different degrees of saturation have been used in the design of Microemulsion.

It can not only solubilize large amount of lipophilic drugs but also enhance the fraction of lipophilic drug transported via intestinal lymphatic system, thereby increase its absorption from GIT.

E.g. - Corn oil, olive oil, soybean oil, hydrolysed corn oil.

Co-surfactant

In SMEDDS, generally co-surfactant of HLB value [10-14] is used. Such as hexanol, pentanol and octanol which are known to reduce the oil water interface and allow the spontaneous formulation of micro emulsion, are used in formulation of SMEDDS.

Preparation of Microemulsion

- Following are the different methods are used for the preparation of microemulsion:

1. Phase titration method
2. Phase inversion method

1. Phase titration method

1. dilution of an oil-surfactant mixture with water.(w/o)
2. dilution of a water-surfactant mixture with oil.(o/w)
3. mixing all components at once. In some systems, the order of ingredient addition may determine whether a microemulsion forms or not. *e.g.(w/o)*
4. soybean oil, ethoxylated mono- and di-glycerides as surfactants and a mixture of sucrose and ethanol as the aqueous phase.
5. Transparent Microemulsions resulted from dilution of the oil-surfactant mixtures with water along several regions in the pseudo-ternary phase diagram.

Phase inversion method

- ❖ **Phase Inversion Temperature (PIT)**, *i.e.*, the temperature range in which an o/w microemulsion inverts to a w/o type or *vice versa*.
- ❖ **using non-ionic surfactants**, polyoxyethylene are very susceptible to temperature since surfactant solubility (in oil or water) strongly depends on temperature. With increasing temperature, the polyoxyethylene group becomes dehydrated, altering the critical packing parameter which results in phase inversion.
- ❖ **For ionic surfactants**, increasing temperatures increase the electrostatic repulsion between the surfactant head groups thus causing reversal of film curvature.
- ❖ Hence the effect of temperature is opposite to the effect seen with non-ionic surfactants.

General method of Preparation

- ❖ **Drug has to dissolve in to oil phase (lipophilic part) of microemulsion.**
- ❖ **Water phase is combined with the surfactant and then Cosurfactant is added slowly with constant stirring until the system is become transparent.**
- ❖ **The amount of surfactant and co-surfactant to be added and the parent oil phase that can be incorporated is determined with the help of pseudo ternary phase diagram.**

Mechanism of Microemulsion

- ❖ **Self-Microemulsification** occurs when **the entropy change that favours dispersion is greater than the energy required to increase the surface area of the dispersion.** So, **The free energy of the conventional emulsion is a direct function of the energy required to create a new surface between the oil and water phases.**
- ❖ In emulsification process **the free energy (ΔG) associated** is given by the equation:

$$\Delta G = \sum_i N_i \pi r_i^2 \sigma$$

where,

ΔG = free energy associated with the process

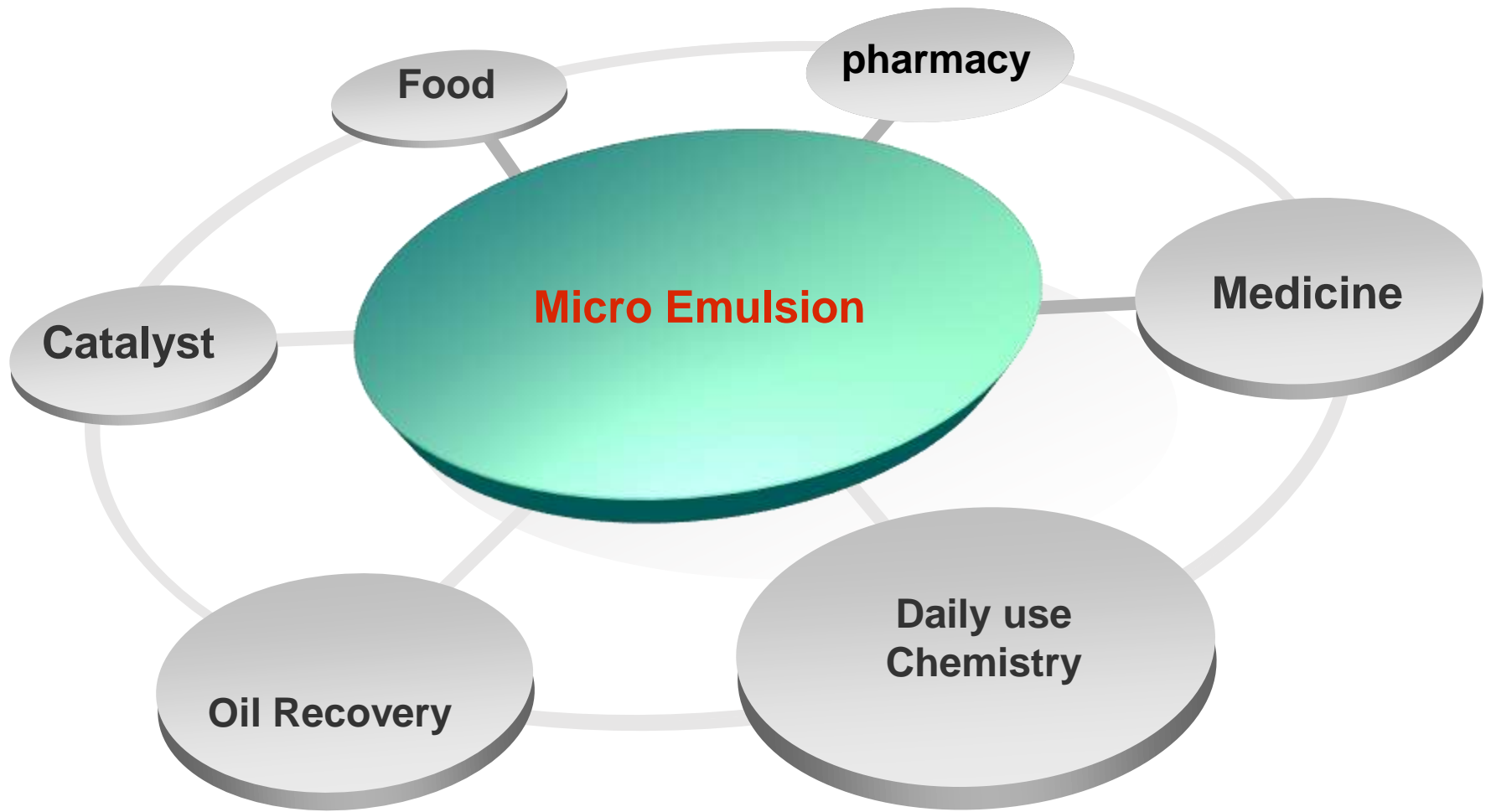
N = number of droplets

r = Radius of droplets

σ = interfacial energy

- ✓ **The two phases of emulsion** tend to **separate** with time to **reduce the interfacial area**, and subsequently, the **emulsion is stabilized by emulsifying agents.**

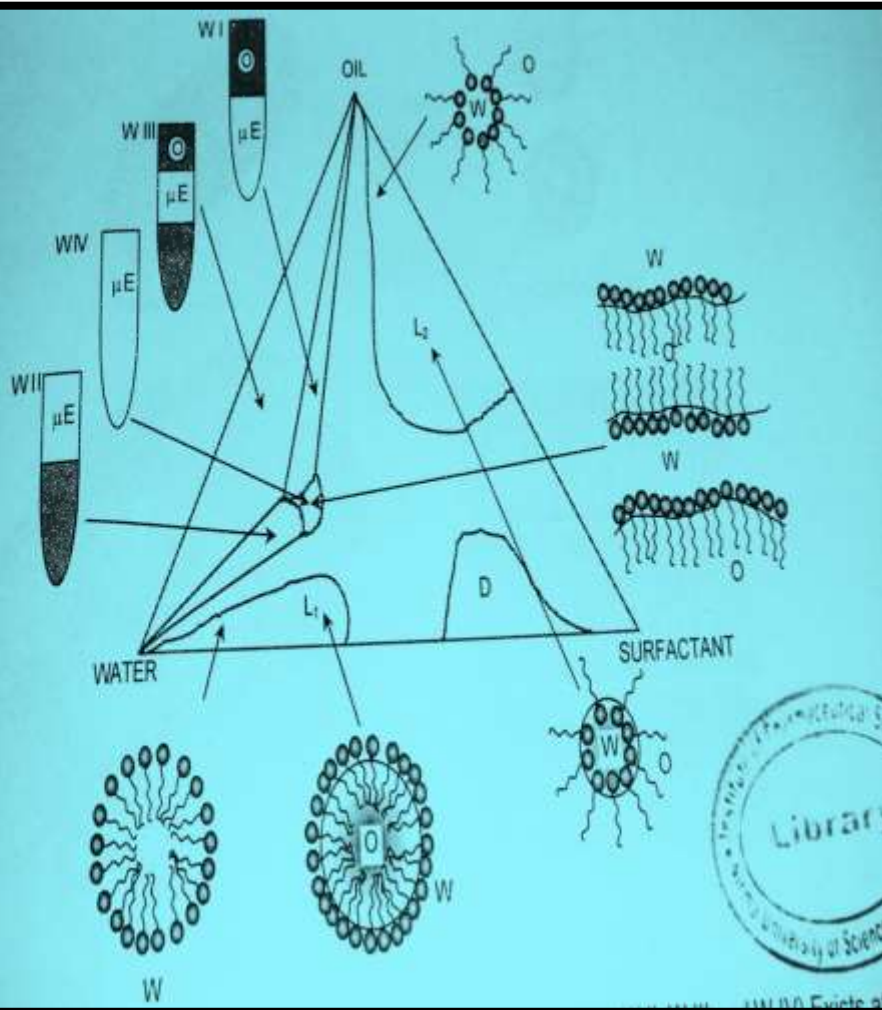
Micro Emulsion in Our Life



PHASE BEHAVIOR STUDY

Ternary phase diagram

The phase behavior of simple microemulsion system composing oil, water and surfactant can be studied with the **Ternary phase diagram**.



➤ **WINSOR PHASE** :- W_I , W_{II} , W_{III} , W_{IV}

➤ **O** :- Oil **W** :- Water

➤ **L_1** :- A single phase region of normal micelles or oil in water micro emulsion.

➤ **L_2** :- A reverse micelles or water in oil micro emulsion.

➤ **D** :- Anisotropic lamellar liquid crystalline phase

➤ **μE** :- Microemulsion.

Figure 3: Ternary phase diagram

- In this **diagram a corner will represent the binary mixture** of two components such as surfactant/co-surfactant, water/drug or oil/drug.
- At **low concentration of surfactant there are certain phases exists in equilibrium.** These phases are referred to as **WINSOR PHASES.**

- ✓ **WINSOR-1** :- With **two phases**, the **lower (o/w) microemulsion phase in equilibrium with excess oil.**
- ✓ **WINSOR-2** :- With **two phases**, **upper (w/o) microemulsion phase in equilibrium with excess water.**
- ✓ **WINSOR-3** :- With **three phases**, **middle microemulsion phase (o/w plus w/o, called bio-continuous) in equilibrium with upper excess oil and lower excess water.**
- ✓ **WINSOR-4** :- In **single phase**, with oil, water, and surfactant homogenously mixed.

Pseudo Ternary Phase Diagram

These diagrams were constructed with oil, surfactant/co-surfactant and water using Phase Titration method. The procedure consisted of preparing solutions containing oil and the different ratio of surfactant to co-surfactant by weight such as: 1:1, 2:1, 3:1 etc, these solutions then vortexed for 5 min and isotropic mixture was obtained. observed for their appearance (turbid or clear). Turbidity of the samples would indicate formation of a coarse emulsion, whereas a clear isotropic solution would indicate the formation of a microemulsion. Percentage of oil, smix and water. the values were used to prepare Pseudo ternary phase diagram.

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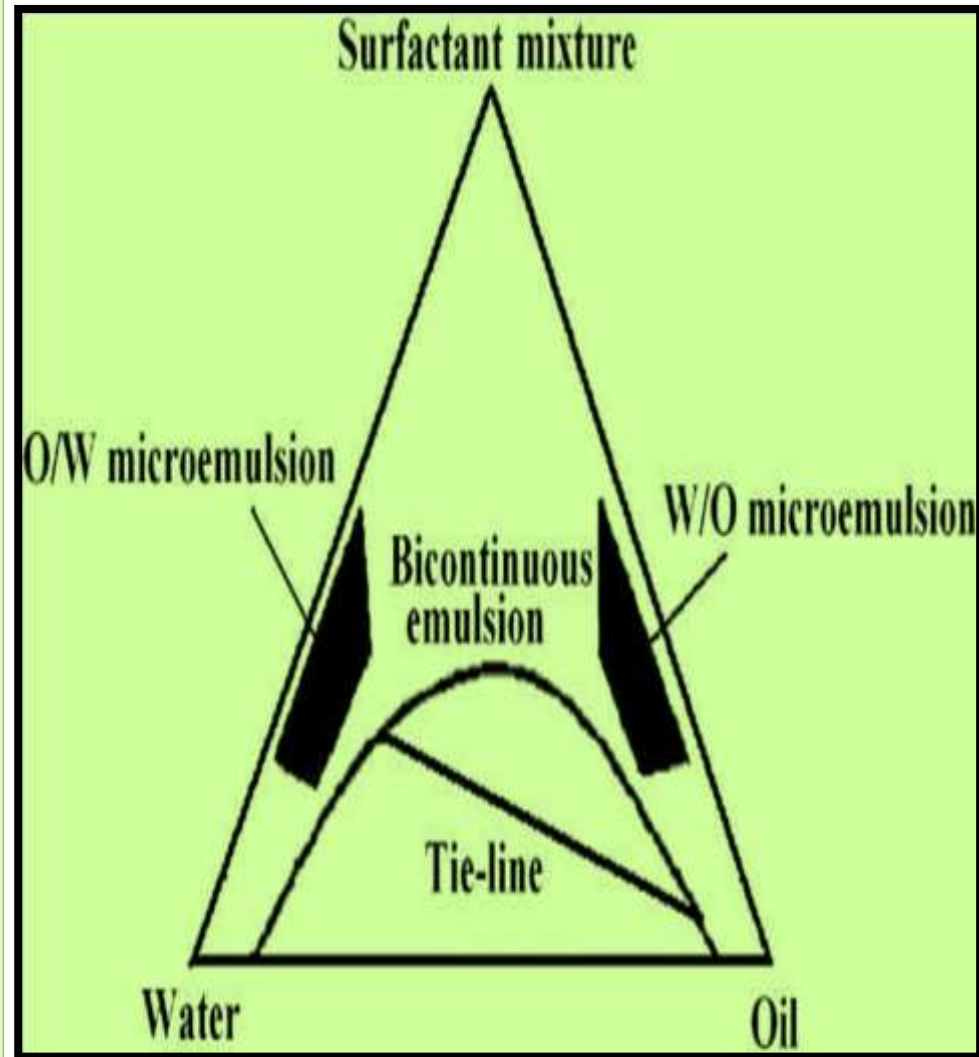


Figure 4: Pseudo Ternary Phase Diagram

Evaluations of Microemulsion

- ❖ **Scattering Technique**
- ❖ **Fourier transform-infrared spectroscopy (FT-IR)**
- ❖ **Transmittance (U.V.)**
- ❖ **Viscosity Determination**
- ❖ **Electro Conductivity Study**
- ❖ **Macroscopic evaluation**
- ❖ **Differential scanning Calorimetry (DSC)**
- ❖ **Droplet Size Analysis and Particle Size Measurements**
- ❖ **Stability Testing Evaluation**

Scattering Technique

- ❖ In this technique **Small Angle X-ray Scattering (SAXS)**, **Small Angle Neutron Scattering(SANS)** and static as well as **dynamic light** scattering are widely applied technique in the study of microemulsion.
- ❖ **Small Angle X-ray Scattering technique** and **Static Light Scattering** techniques both are **used to determine the microemulsion droplet size and shape.**
- ❖ **Dynamic Light Scattering** is used to **analyze the fluctuation** in the intensity of scattering by droplets due to **Brownian motion.**

Fourier Transform-infrared Spectroscopy

1. Microemulsion can be determined using FT-IR. **Liquid sample or Solid Sample** should be placed in the **sample holder** and result can be recorded.
2. Any type of **chemical interaction** should be determined using FT-IR.

Transmittance Test

1. **Stability of optimized microemulsion** formulation with respect to dilution was checked by **measuring Transmittance through U. V. Spectrophotometer (UV-1700 SHIMADZU)**.
2. Transmittance of **samples was measured at 650 nm**.

Viscosity Determination

The rheological properties of the micro emulsion are evaluated by Brookfield viscometer. This viscosities determination conform whether the system is w/o or o/w. If system has **low viscosity then it is o/w type** of the system and **if high viscosities then it are w/o type** of the system.

Electro Conductivity Study

- ✓ The Microemulsion system **contains ionic or non-ionic surfactant, oil, and water.**
- ✓ This test is performed for **measurement of the electro conductive nature of system.**
- ✓ The electro conductivity of resultant system **is measured by electro conductometer.**

Macroscopic Evaluation

- ✓ Macroscopic analysis was carried out in order to observe the **homogeneity of microemulsion formulations.**
- ✓ Any **change in color and transparency or phase separation** was observed in microemulsion formulation.

Differential Scanning Calorimeter

- ✓ Differential scanning calorimetry was determined Microemulsion.
- ✓ **Liquid sample and Solid sample** should be **placed in the aluminium pan** and result can be recorded.
- ✓ Any type of **chemical interaction** should be determined using DSC.

Droplet Size Determination

- ✓ it is a precise method for **evaluation of stability**.
- ✓ Size of droplet is measured by **photon-correlation spectroscopy (PCS)** with Zetasizer.
- ✓ All measurements are carried out at **scattering angle of 90° and 25°C temperatures**.
microemulsion is **diluted in two-steps**.
- ✓ first step it is **diluted with equal amount of water**.
- ✓ second step **the mixture is further diluted to appropriate concentration for the measurement**. That depends on droplet size (Usually diluted 100-200 times).

ZETA POTENTIAL MEASUREMENT

Zeta potential for microemulsion was determined using **Zetasizer HSA 3000** (Malvern Instrument Ltd., UK).

Samples were placed in clear disposable zeta cells and results were recorded.

Stability Studies

- 1.The physical stability of the microemulsion must be determined under different storage conditions (4, 25 and 40 °C) during 12 months.**
- 2.Dependent on different regulatory agency requirement it'll vary according to them.**
- 3.Effect of surfactant and their concentration on size of droplet is also be studied.**

Applications of Microemulsion

- ❖ **Oral bioavailability enhancement poorly water soluble drugs**
- ❖ **Protection against Biodegradation**
- ❖ **Solid State formulation**
- ❖ **Supersaturable Microemulsion System**
- ❖ **Ocular Drug delivery System**
- ❖ **Parenteral Drug Delivery System**
- ❖ **Topical Drug Delivery System**
- ❖ **Mucosal Drug Delivery System**
- ❖ **Transdermal Drug Delivery System**

Marketed Preparations

Brand	Drug	Dosage form	Dose(mg)	Indication
Neoral®	Cyclosporine	Soft gelatin capsules	25, 100	Immunosuppressant
Norvir®	Ritonavir	Soft gelatin capsules	100	HIV antiviral
Lipire®	Fenofibrate	Hard gelatin capsules	200	Antihypertensive
Convule®	Valproic acid	Soft gelatin capsules	100, 200	Antiepileptic

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Thank you