Department of Pharmaceutics
School of Pharmacy
Ahwaz Jundishapur University of Medical Sciences

Microemulsions and Nanoemulsions

FORMULATIONS AND APPLICATIONS

Moghimipour E., PhD
Professor in Pharmaceutics
Ahvaz Jundishapur University of Medical Sciences

Pharmacy Updates

IPharmS

Headlines

- Definition
- Applications
- Classification
- Preparation and formulation
- Methods of evaluation
- Researches
- Conclusion

Introduction

- Emulsion is a heterogeneous system consisting of at least one immiscible liquid dispersed in another in the form of droplet with the help of surfactant.
- There are two types of emulsions: oil-in-water (O/W) (oil is dispersed phase while water is continuous phase) and water-in-oil (W/O) (water is dispersed phase and oil is continuous phase).
- Depending on the size of the dispersed droplets, emulsions can be classified into: macroemulsion (droplet size- 1.5-100 µm); nanoemulsion (droplet size- 50-500 nm) and microemulsion (droplet size- 3-50 nm)

Table 1: Major differences between microemulsion and conventional emulsion

No.	Property	Microemulsion	Conventional Emulsion
1	Appearance	Transparent	Cloudy
2	Interfacial Tension	Ultra Low	High
3	Optical isotropy	Isotropic	Anisotropic
4	Structure	Dynamic	Static
5	Droplet size	3-50 nm	1.5-100 µm
6	Stability	Thermodynamically Stable, Long shelf life	Thermodynamically unstable, Kinetically Stable
7	Phases	Monophasic	Biphasic
8	Viscosity	Low	High
9	Preparation	Relatively lower cost for commercial production	Require a large input of energy, higher cost

Major differences between microemulsion and conventional emulsion (*Ashish D. et al, 2014*)

History and Definition

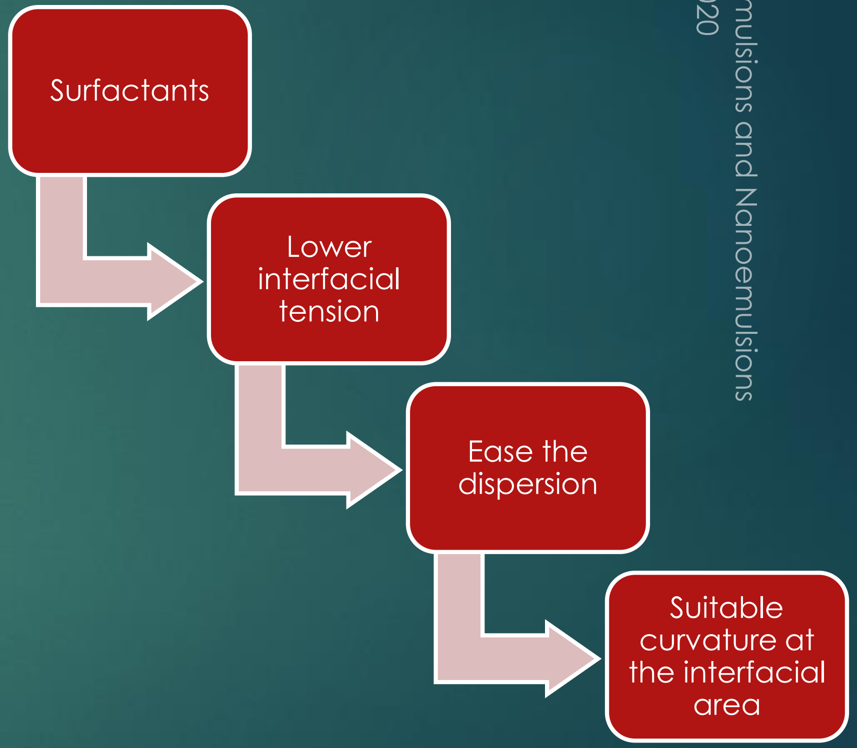
- The word **microemulsion** was originally proposed by Hoar and Schulman in the earliest of the 1940s.
- They were generated a clear single-phase solution by titrating a milky emulsion with hexanol.
- Microemulsions are thermodynamically stable, isotropic clear colloidal dispersion of oil, water and surfactant, frequently in combination with a **cosurfactant** which have high stability, ultra low interfacial tension, large interface area , low viscosity and ease of preparation

Main Constituents

- Microemulsion is a system containing oil, water, surfactant and co-surfactant as major components.
- A large number of oils and surfactants can be used for microemulsion formulation but their toxicity, unclear mechanism of action, limit their use.
- The materials should be biocompatible, nonhazardous and safe while using.
- The emulsifiers should be used in proper proportion that will give amiable and unambiguous microemulsions.
- To summarize, all the components used to make microemulsion should be considered as generally regarded as safe (GRAS).

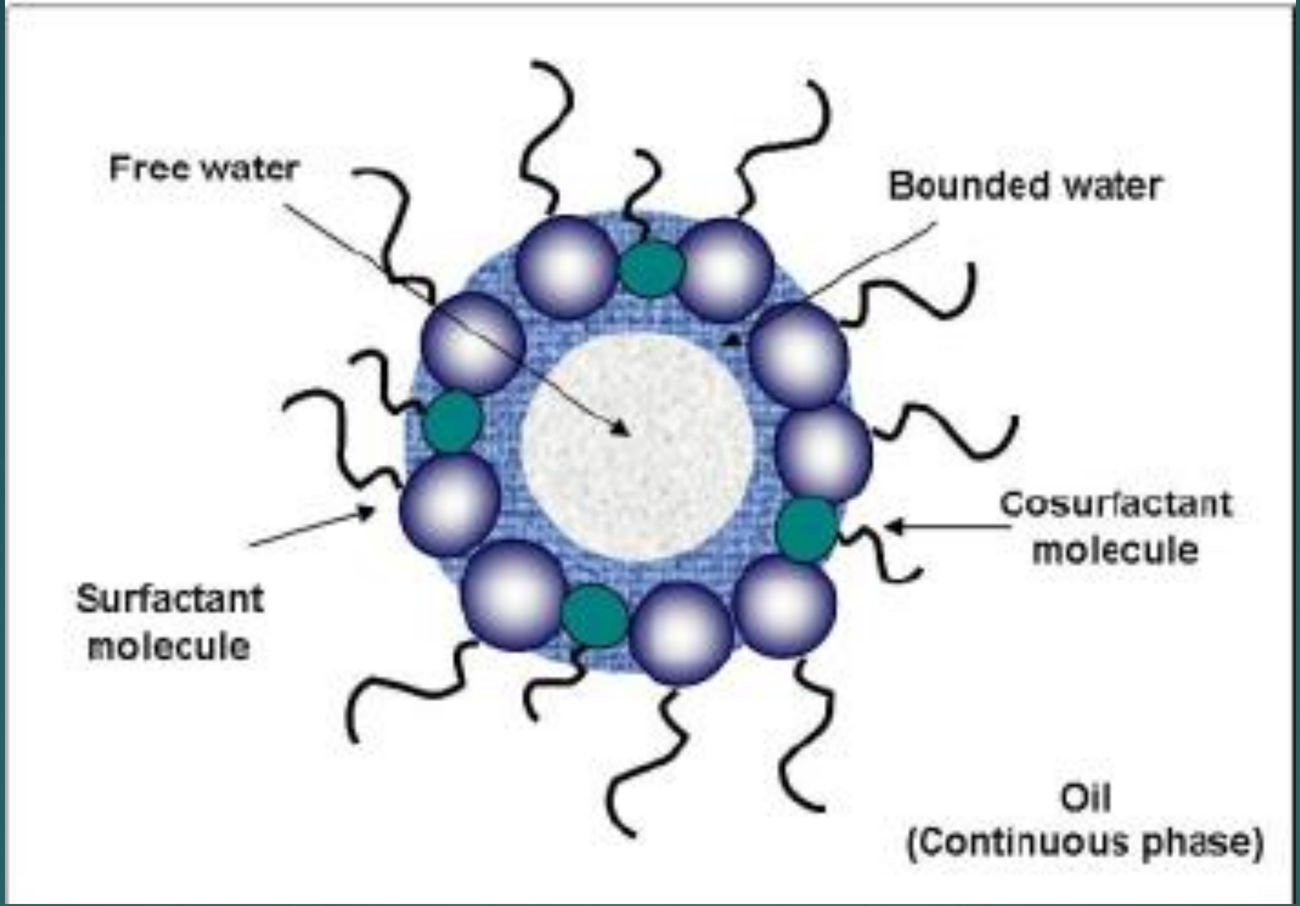
Main Constituents: Surfactants

- Surfactants having low HLB value (HLB<10) is suitable to water-in-oil (W/O) microemulsion whereas those having high HLB value (HLB> 10) is suitable for oil-in-water (O/W) microemulsion.
- Most of the times, surfactants alone are not able to reduce the interfacial tension significantly to enable microemulsion formation.



Main Constituents: Co-Surfactants

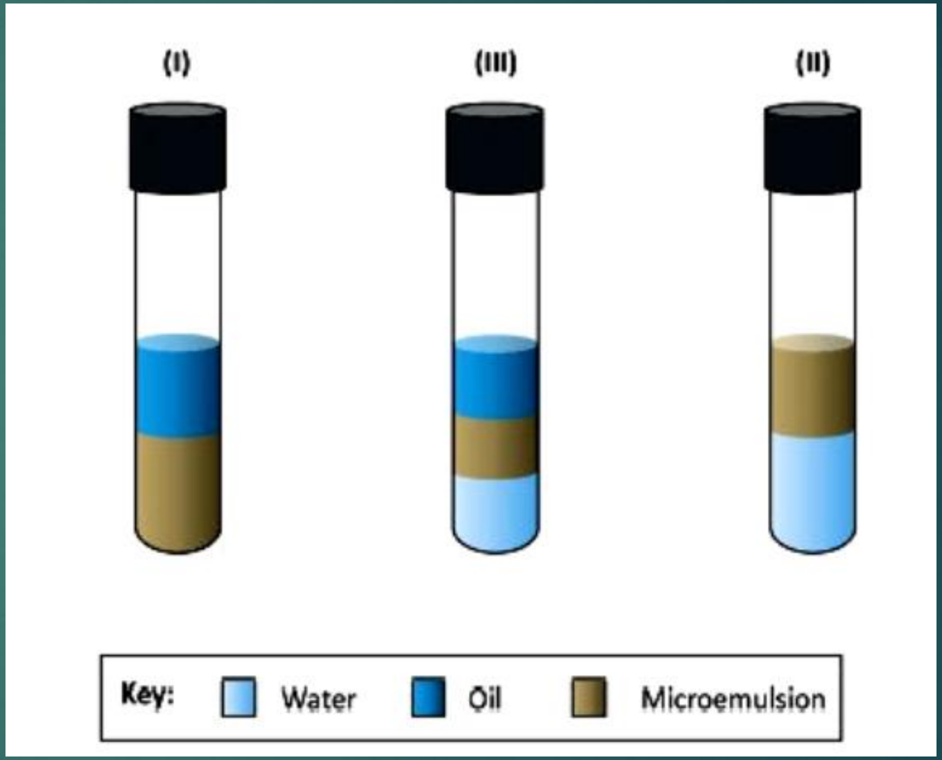
- Co-surfactants play important role by providing significant flexibility to commence various curvatures needed to build These components integrate into interfacial films, but they are not surfactants and **can not form micelles** on their own.
- Classical co-surfactants in colloid science are molecules with **a small polar head group and an alkyl chain** of a suitable length, e.g. n-hexanol, n-pentanol, n-octanol etc.



Schematic representation of W/O microemulsion droplet. (Adapted with permission from Moulik, 1998).

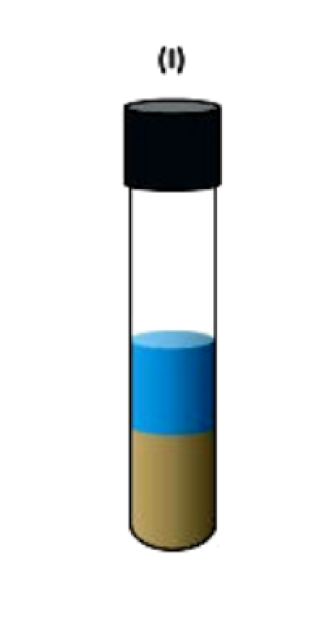
Classification

- Conventional microemulsions can be classified oil- in -water, (o/w), water -in- oil (w/o) and bicontinuous phase microemulsions.
- Winsor identified four general types of phase equilibria.
- On that basis, microemulsion can be classified into four types (Winsor, 1948)



Classification

- Type I ("Winsor I" microemulsion): In this type of microemulsions, oil-in-water (O/W) microemulsion is formed by solubilizing surfactant preferably in water phase.
  - The surfactant-rich water phase accompanies with the oil phase and the surfactant exists as monomer at small concentration.

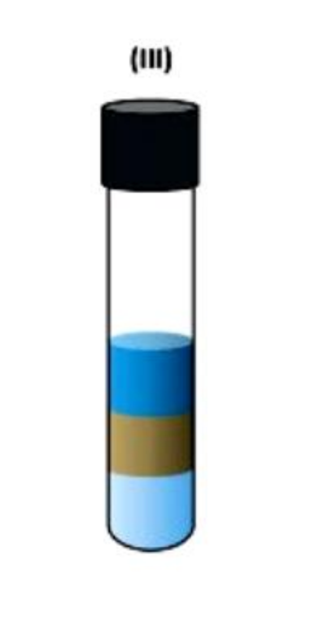


Classification

- Type II ("Winsor II" microemulsion): In this type of microemulsions, water-in-oil (W/O) microemulsion is formed by solubilizing surfactant preferably in oil phase.
  - The surfactant loaded oil phase combines with the surfactant-poor aqueous phase.

Classification

- Type III ("Winsor III" Microemulsion): Surfactant-loaded middle phase combines with both water and oil phases and forms three phase microemulsion.
  - In this microemulsion, both the water and oil are surfactant-deficient phases.



Classification

- Type IV: An isotropic (single micellar) solution is formulated by adding sufficient quantity of surfactant and alcohol (amphiphile) (Winsor IV).
  - A Winsor type IV microemulsion is an extension of a Winsor Type III at higher surfactant concentrations, where the middle phase extends and becomes a single phase.

Applications

- Some advantages offered by microemulsions include
  - improvement in poorly drug solubility,
  - enhancement of bioavailability,
  - protection of the unstable drugs against environmental conditions and
  - a long shelf life.

Phase Diagram Study

Pseudo-ternary phase diagram

- To investigate concentration range of components for the existing boundary of MEs, pseudo-ternary phase diagrams are constructed using different methods including water titration method.
- The pseudo ternary phase diagram (four component system) is constructed to find the different zones including microemulsion zone

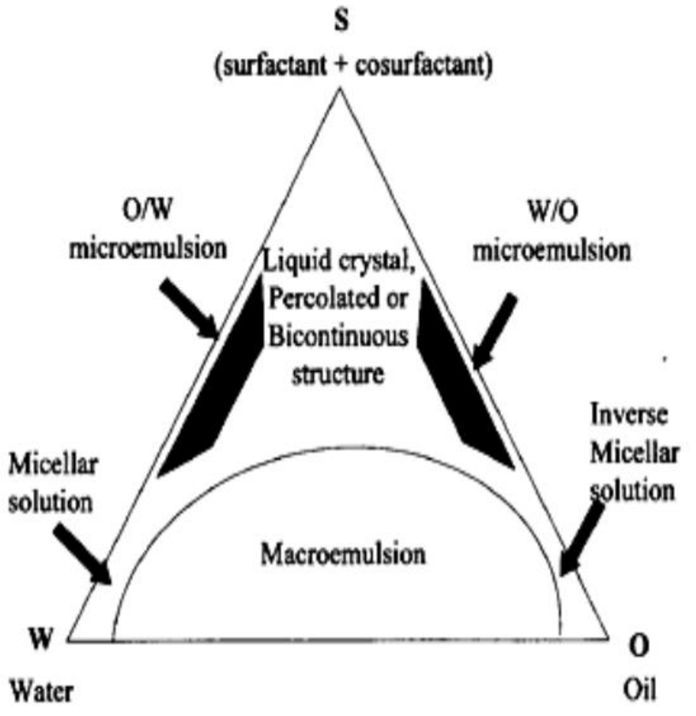
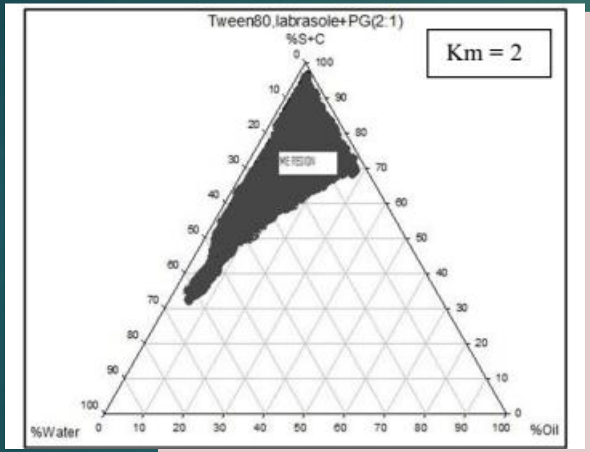
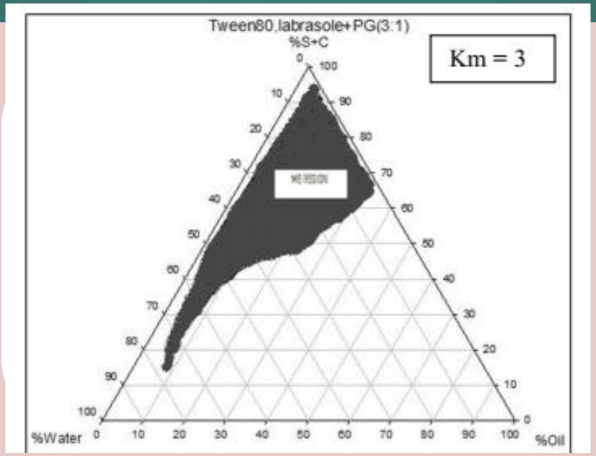


Fig. 5: Schematic presentation of phase diagram of microemulsion. (Patel, 2007)

Pseudo-ternary phase diagram





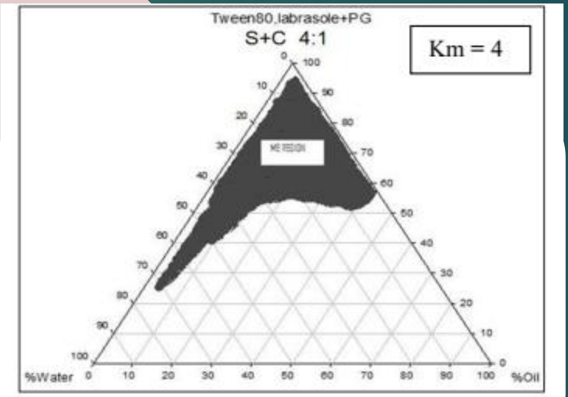
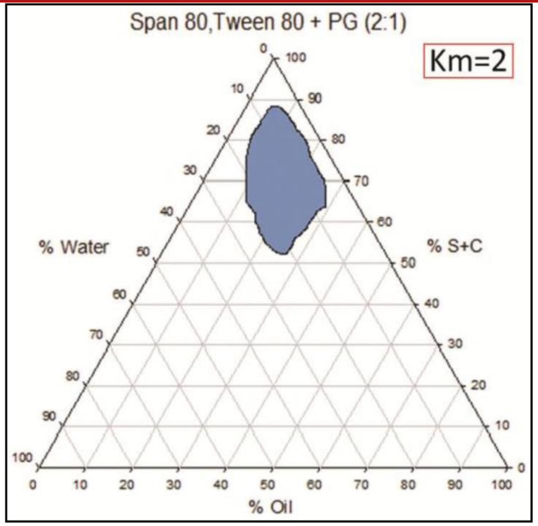
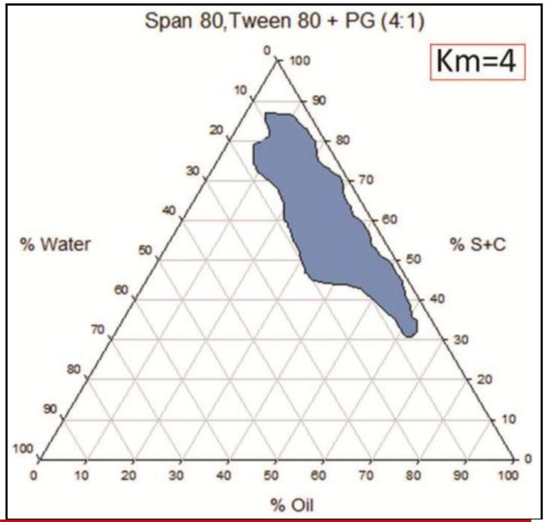
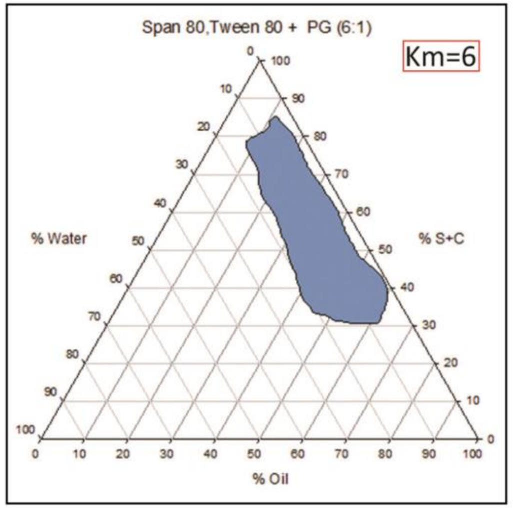


Fig 1. The pseudo-ternary phase diagrams of the oil-surfactant/cosurfactant mixture–water system at the 2:1, 3:1, and 4:1 weight ratio of labrasol /Tween 80/ Propylene glycol at ambient temperature, dark area show microemulsions zone.

Pseudo-ternary phase diagram







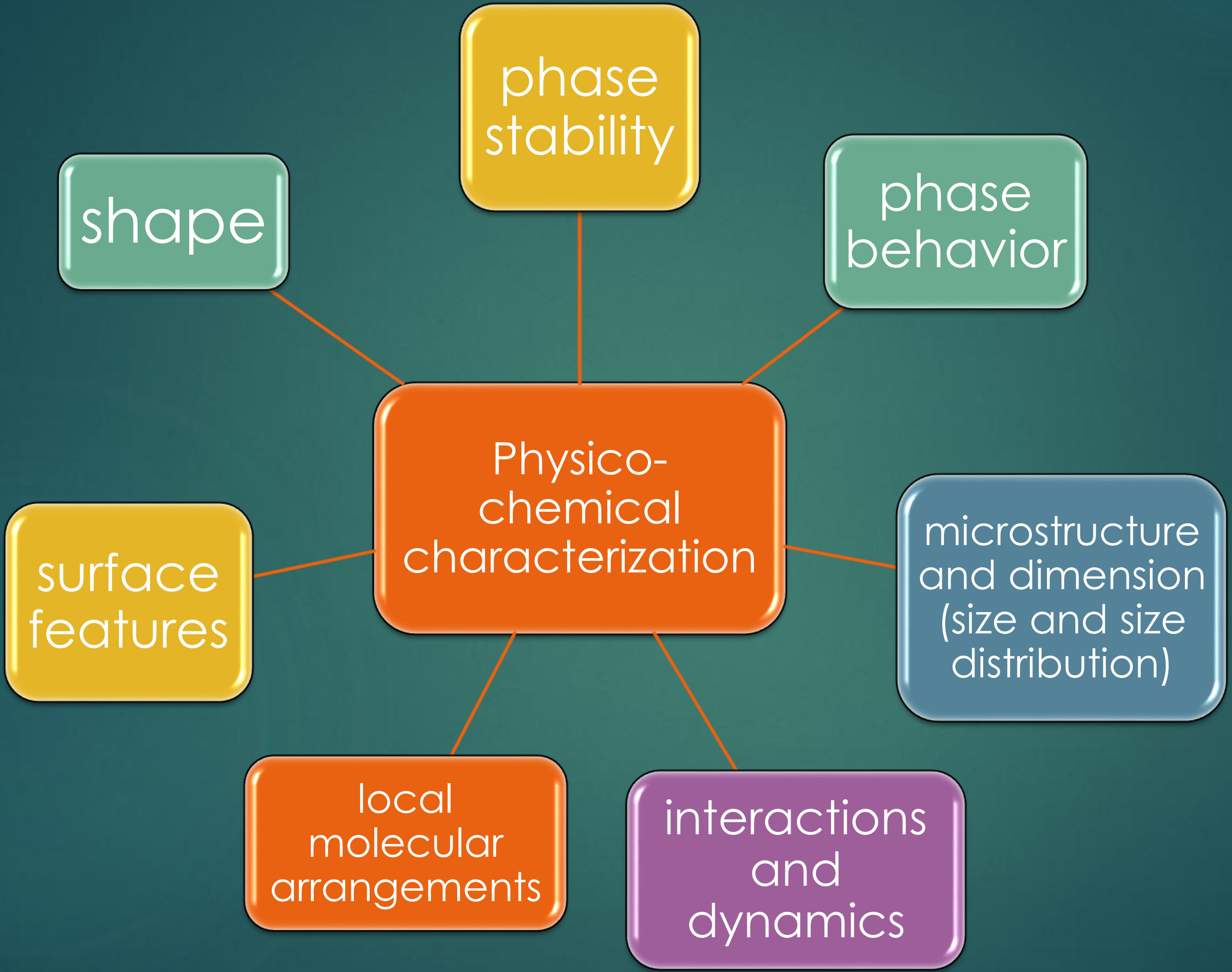
Preparation of Microemulsions

Phase Inversion Method	Phase Titration Method
• Phase Inversion Concentration • Phase Inversion Temperature	• spontaneous emulsification • Construction of the phase diagram

Depending on the chemical composition of each component, microemulsions are formed along with various related structures, like emulsions, micelles, lamellar, cubic, hexagonal and different gels and oily dispersions.

Preparation of Microemulsions

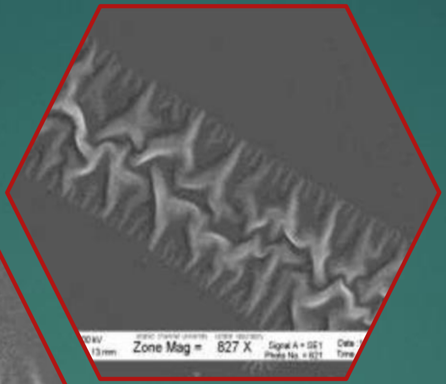
- The phase inversion method makes drastic physical changes in the system such as changes in particle size.
- In phase inversion temperature (PIT) method, the interfacial tension is the key factor.
- On cooling, the interfacial tension get lowered and can be found in the phase inversion region from water-in-oil (W/O) microemulsion to an oil-in-water (O/W) microemulsion.
- In the phase inversion region, this low interfacial tension helps in the spontaneous formation of finely dispersed, blue shining O/W PIT microemulsion.

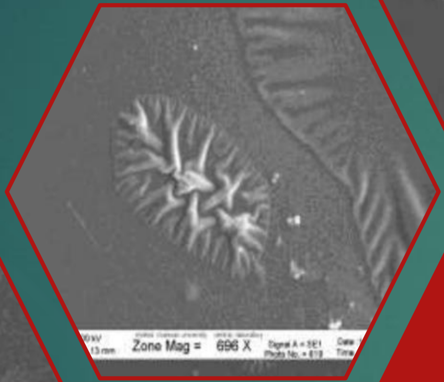

phase stability
shape
phase behavior
Physico-chemical characterization
surface features
microstructure and dimension (size and size distribution)
local molecular arrangements
interactions and dynamics

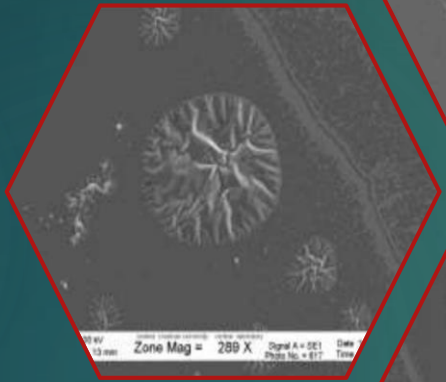
Size and Size Distribution

- The size distribution of microemulsion is very important to understand the mechanism involving stability and penetration into the membrane.
- Methods that are useful to get significant information about size, shape and activity of the components.

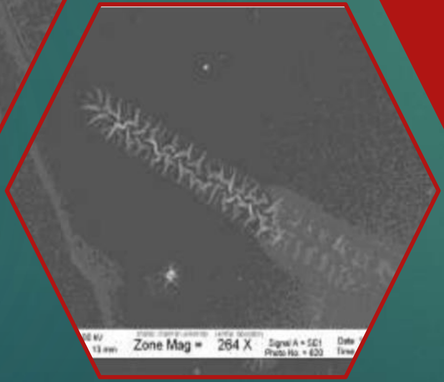
  - *dynamic light scattering (DLS)*
  - *small angle neutron scattering (SANS)*
  - *small angle X-ray scattering (SAXS)*
  - *cryo transmission electron microscopy*
  - *pulsed field gradient spin echo NMR*
  - *scanning electron microscopy (SEM)*

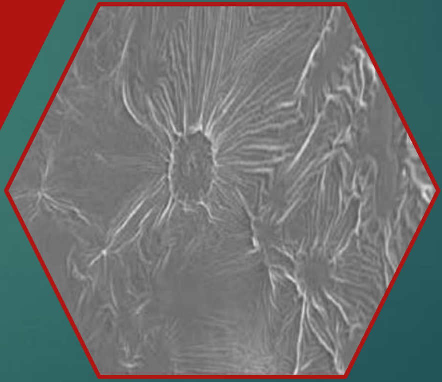






Scanning Electron Microscopy





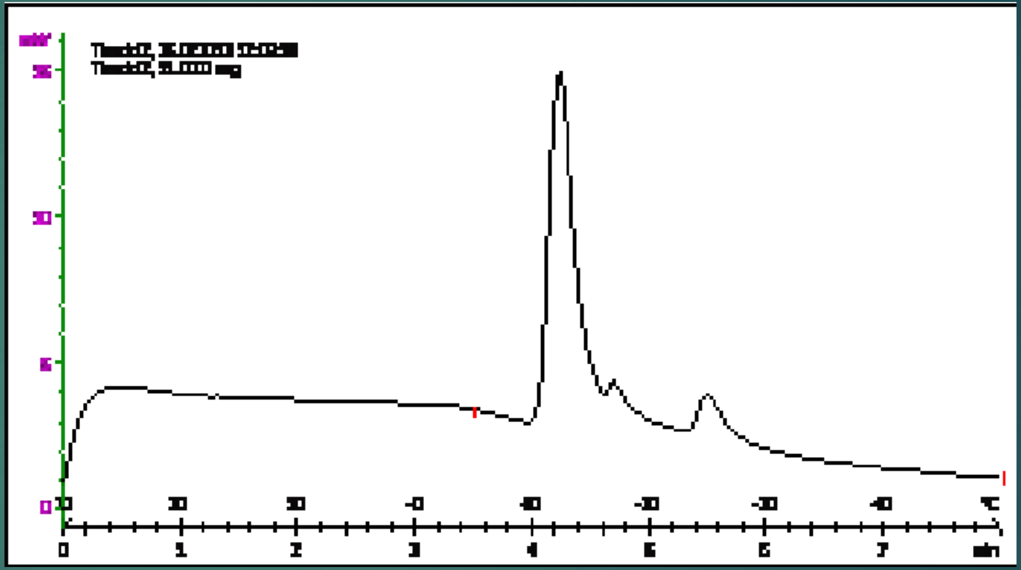
A MICROEMULSION SYSTEM FOR CONTROLLED CORNEAL DELIVERY OF TIMOLOL

Characterization

- Conductivity measurement determines whether a microemulsion is oil-continuous or water-continuous. It also provides a means of monitoring phase inversion phenomena.
- Viscosity measurement signifies the existence of rod-like or worm-like reverse micelles
- Dielectric measurements are used to provide structural and dynamic characteristics of microemulsions.
- The Fourier transform pulsed-gradient spin echo (FT-PGSE) method builds the magnetic gradient on the samples. This facilitates concurrent and rapid determination of the self-diffusion coefficients of many components.

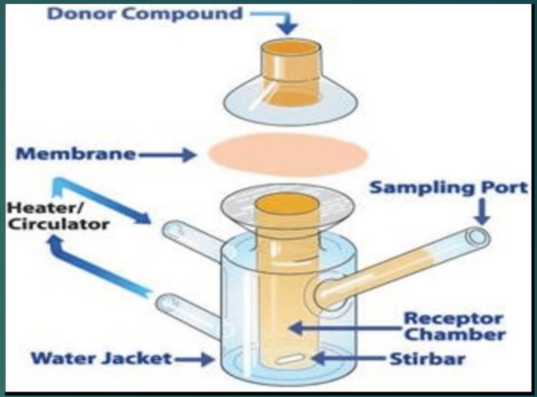
Differential Scanning Calorimetry (DSC)

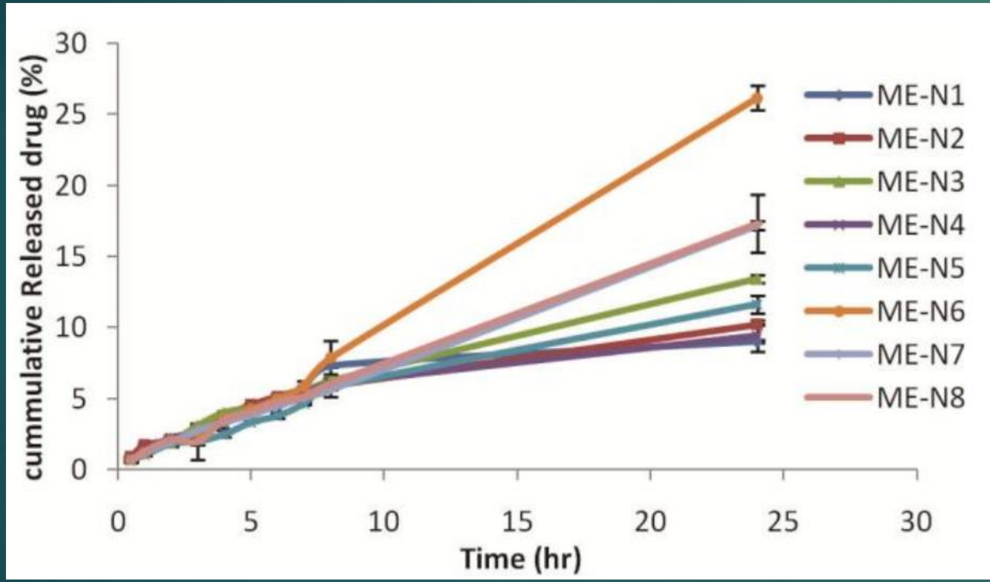
- Changes of Enthalpy quantities (ΔH) are calculated from endothermic and exothermic transitions of thermograms.



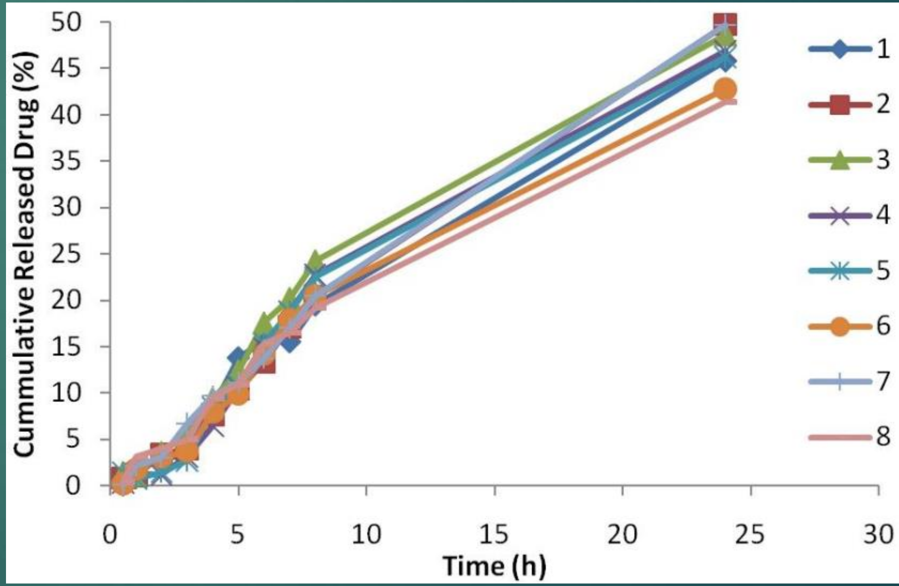
Release Studies

- ✓ *No virtual release expected*
- ✓ *Different Methods of Evaluation*
- ✓ *No release pattern available*





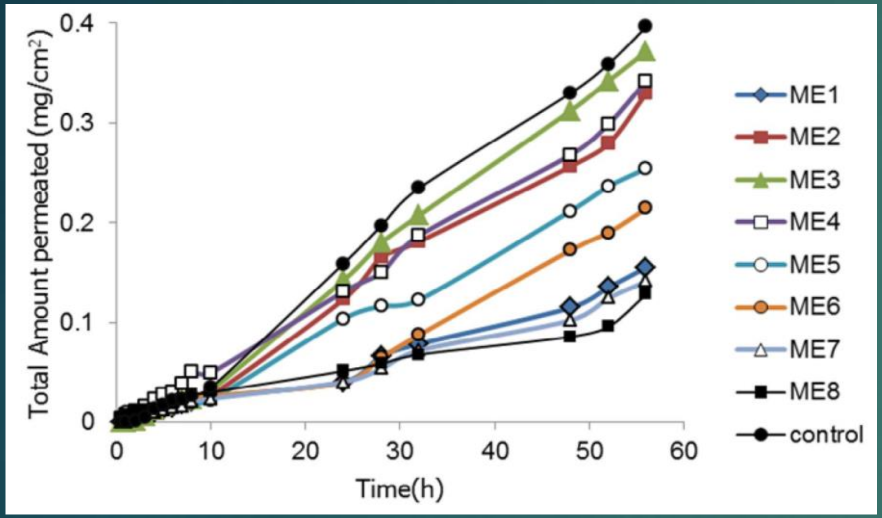
In vitro release profile of MEs formulation of Naproxen



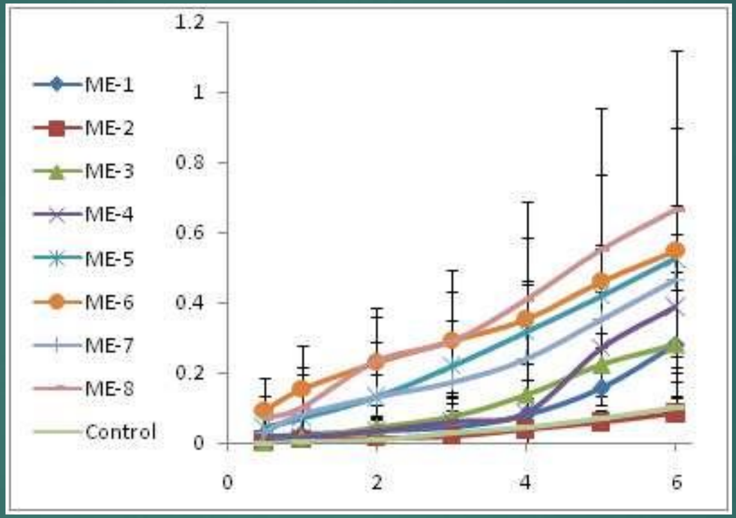
In vitro release profile of MEs formulation of tretinoin

Permeation Studies

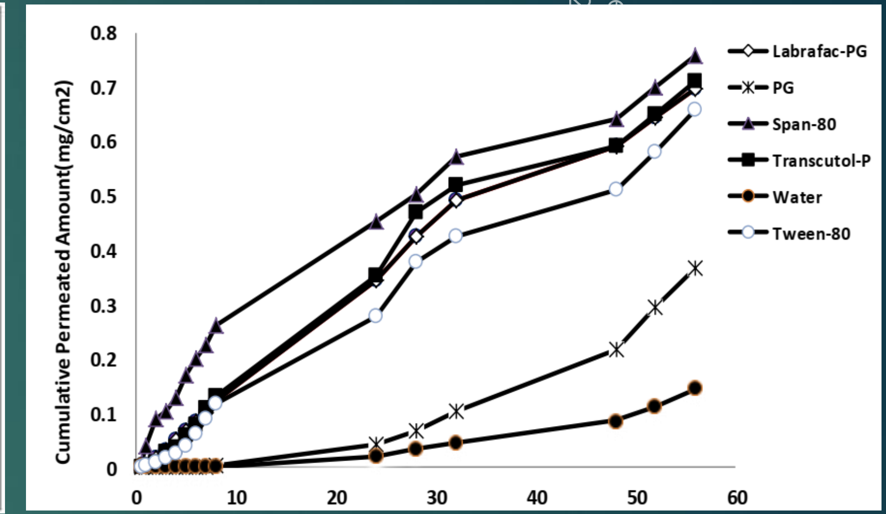
- Different biological membranes



Cumulative amounts of permeated Griseofulvin from different formulations through excised rat skin



Cumulative amounts of permeated Timolol from different formulations through excised rabbit cornea



The amount of naproxen permeated from various vehicles across the rat abdominal skin

Conclusion

- microemulsions provide one of the most promising systems to improve solubility, bioavailability and functionality of hydrophobic compounds.
- Physicochemical properties and in vitro release are dependent upon the contents of S/C, water and, oil percentage in formulations.
- Formulating the drugs as microemulsions may significantly enhance the drug permeation through biomembranes.
- The amount of drug release differ between microemulsion carriers with various internal microstructures.

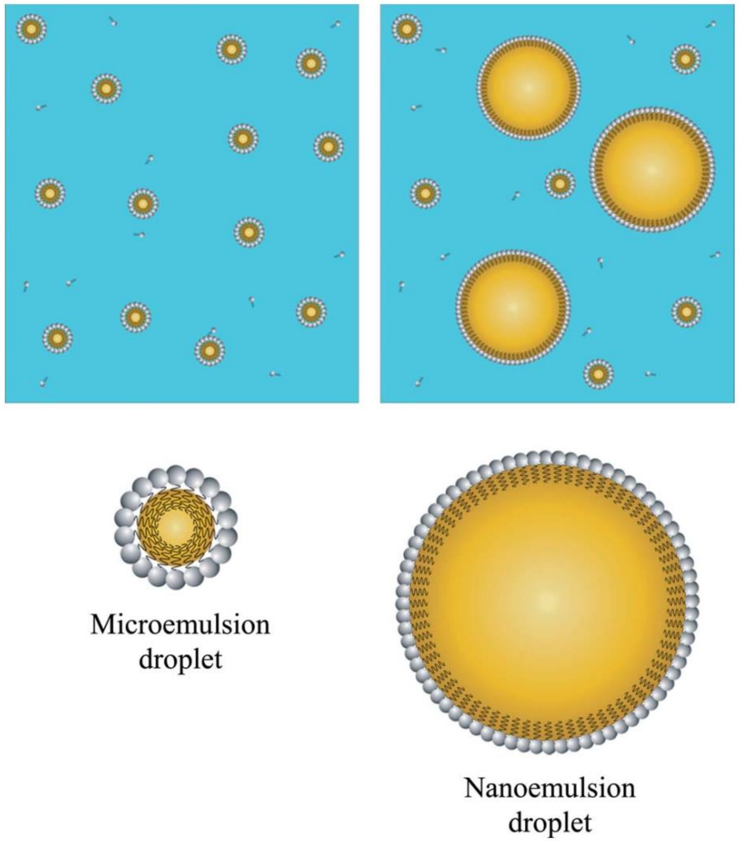


Fig. 1 Schematic diagram of microemulsions and nanoemulsions fabricated from oil, water and surfactant. The structure of the particles in both types of colloidal dispersion is fairly similar—a hydrophobic core of oil and surfactant tails and a hydrophilic shell of surfactant head groups.

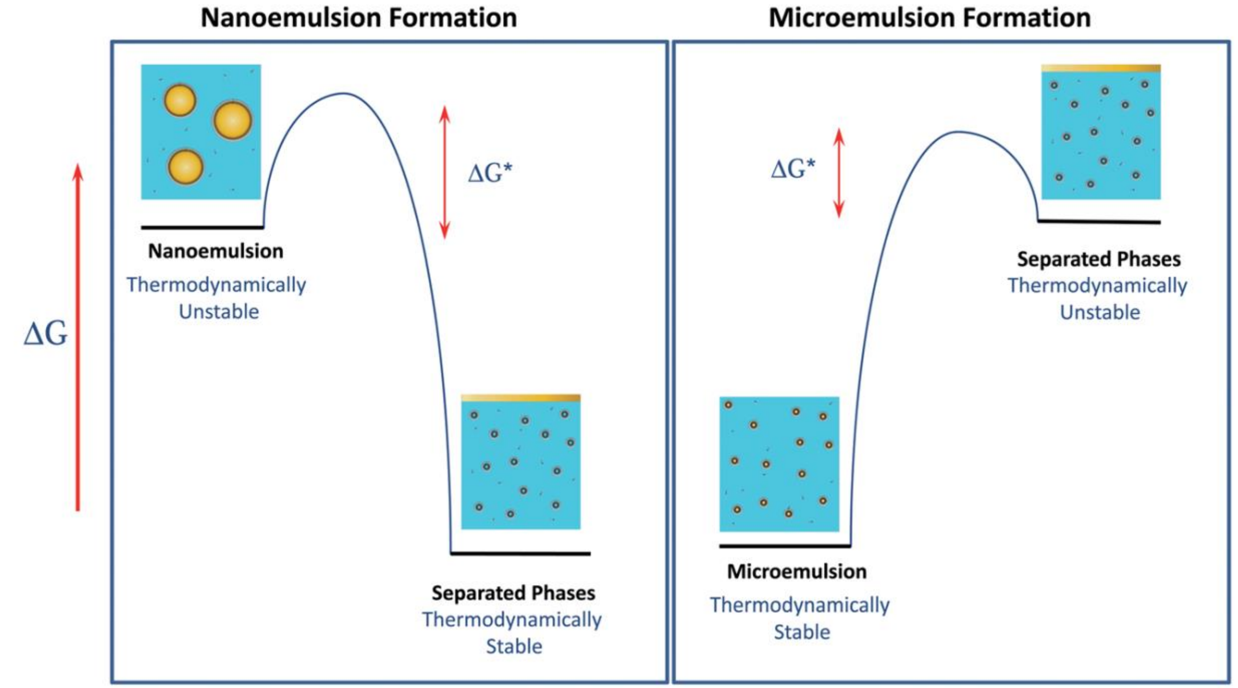


Fig. 3 Schematic diagram of the free energy of microemulsion and nanoemulsion systems compared to the phase separated state. Microemulsions have a lower free energy than the phase separated state, whereas nanoemulsions have a higher free energy. The two states are separated by an activation energy ΔG^*.

Thank You