

NRI INSTITUTE OF PHARMACEUTICAL SCIENCES, BHOPAL



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Subject: Physical Pharmaceutics-II (BP-403T)

Unit: III

Topic: Coarse dispersion (Pharmaceutical Emulsion)

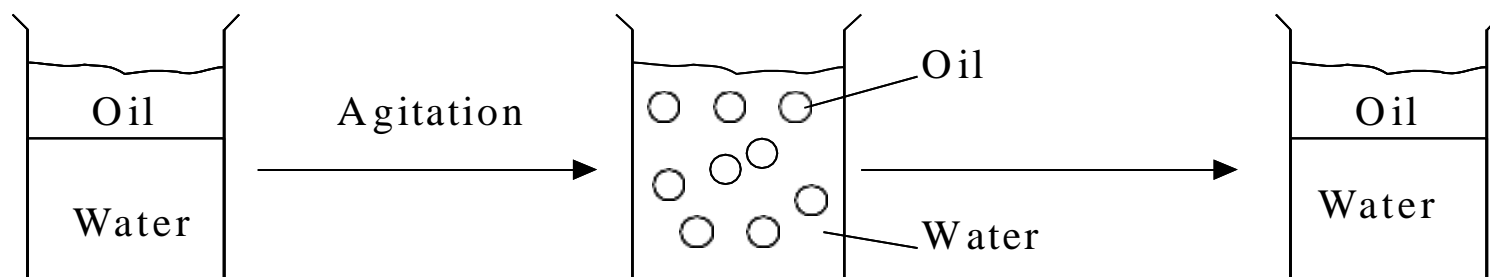
PHARMACEUTICAL EMULSION

DEFINITION:

An emulsion is a thermodynamically unstable system containing **mixture of two or more immiscible liquids** which is **stabilized** by *adding emulsifying agent*.

PHASES IN EMULSIONS

- One liquid is present as droplets distributed throughout the other liquid
- The dispersed liquid is known as the **Internal or Discontinuous phase**.
- Whereas the dispersion medium is known as the **External or Continuous phase**



Separate rapidly into two clear defined layers

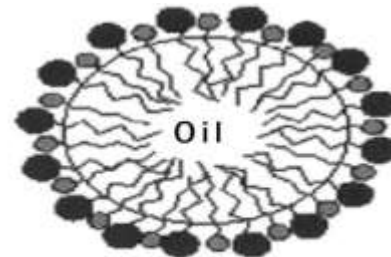
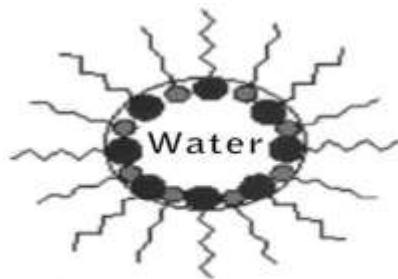
TYPES OF EMULSIONS

Based on dispersed phase:

- Oil in Water (**O/W**): Oil droplets dispersed in water.
- Water in Oil (**W/O**): Water droplets dispersed in oil.
- Water in Oil in water (**W/O/W**): Water in Oil emulsion dispersed in water – **multiple emulsion**.

Based on size of liquid droplets:

- 0.2 – 50 mm Macroemulsions
- 0.01 – 0.2 mm Microemulsions



Emulsion W/O Emulsion O/W

APPLICATIONS OF EMULSION

- Oral administration of water insoluble liquids (Fat soluble vitamins).
- Intravenous administration of API as an emulsion (e.g. taxol)
- Emulsions for external use (e.g. lotions, liniments)
- Emulsions in aerosol can be used to produce foam.

MECHANISM OF ACTION OF EMULSIFYING AGENTS

- When one liquid is broken in large no. of small globules then **interfacial area increases**.
- **Interfacial energy** associated with interface also increases.
- To reduce interfacial energy, globules of dispersed phase **tends to coalesce (merge)**.
- To prevent coalescence and to keep system stable in disperse state it is necessary to add **emulsifying agent**.

MECHANISM OF ACTION OF EMULSIFYING AGENTS

- Reduction of **interfacial tension**-
Thermodynamic stabilization.
- Formation of **interfacial film** barrier (stearic stabilization)
Mechanical barrier to coalescence.
- Formation of **electric double layer**- **Electrical barrier** to approach of globules.

THERMODYNAMIC STABILIZATION OF EMULSION

➤ Interfacial free energy (ΔG) in emulsion

$$\Delta G = \gamma_{LL} \Delta A$$

- ✓ γ_{LL} is interfacial tension
- ✓ Approaches for stable emulsion
- ✓ Reduce γ_{LL} by adding surface active agent

EMULSIFYING AGENTS

- Emulsifying agent prevent coalescence of globules of disperse by forming film around globules.
- An emulsifying agent is any material that enhances the stability of an emulsion
- Emulsifying agents can be divided into 3 groups-
 1. Surfactants (Surface active agents)
 2. Hydrocolloids
 3. Finely divided solids

EMULSIFYING AGENTS (THEORIES OF EMULSIFICATION)

1) **Surfactant (Monomolecular adsorption)**: To reduce the interfacial tension Oil droplets are surrounded by a coherent monolayer of the **surfactant** which prevents coalescence. If the emulsifier is **ionized**, the presence of strong charge may lead to repulsion in droplets and hence **increasing stability**.

2) **Hydrophillic Colloids (Multimolecular adsorption)**

3) **Finely divided solid particles (solid particles adsorption)**: They are adsorbed at the interface between two immiscible liquid phases to form Particulate film.

EMULSIFYING AGENTS (MECHANISM OF ACTION)

- Surface active agents (monomolecular film)
- Hydrophilic colloids (multimolecular film)
- Finely divided solid particles (Particulate film)

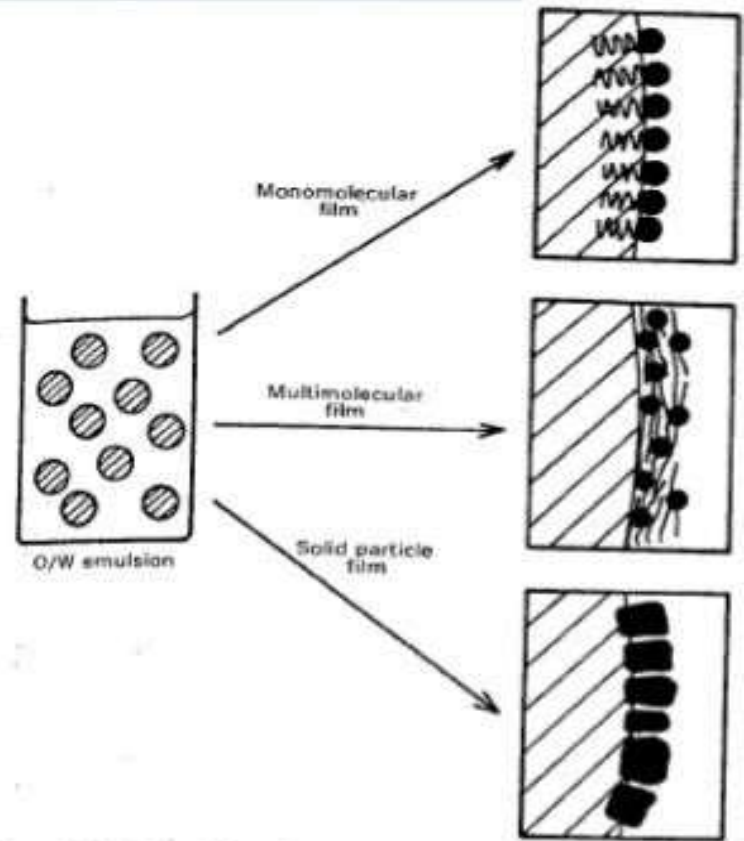
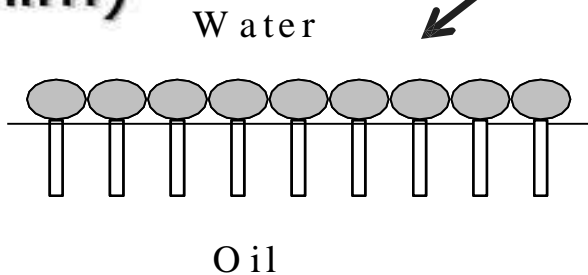


Figure 22-6. Types of films formed by emulsifying agents at the oil-water interface. Orientations are shown for O/W emulsions. \blacksquare : oil. \square : water.

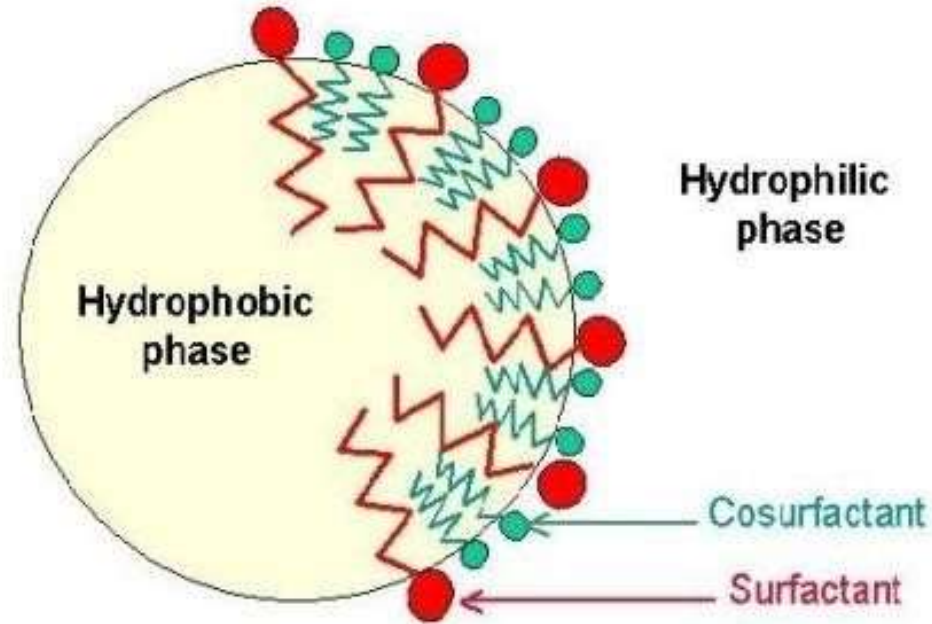
1) MONOMOLECULAR ADSORPTION

- Amphiphiles (surfactants) reduce interfacial tension (to 1 dyne/cm) because of adsorption at interface o/w
- Droplets are surrounded by coherent monolayer that help prevent coalescence (merging) between two droplets.
- Surface Charge cause repulsion between globules.

MONOMOLECULAR ADSORPTION (COMBINATION OF SURFACTANTS)

- Combination of surfactants is generally used as it is more effective.
- Combination of *Sodium cetyl sulphate* and *cholesterol* leads to complex film that produce excellent emulsion.
- Hydrophilic tween can be combined with lipophilic span, varying proportions produce desired emulsion:- w/o or o/w.

SURFACTANT / CO-SURFACTANT

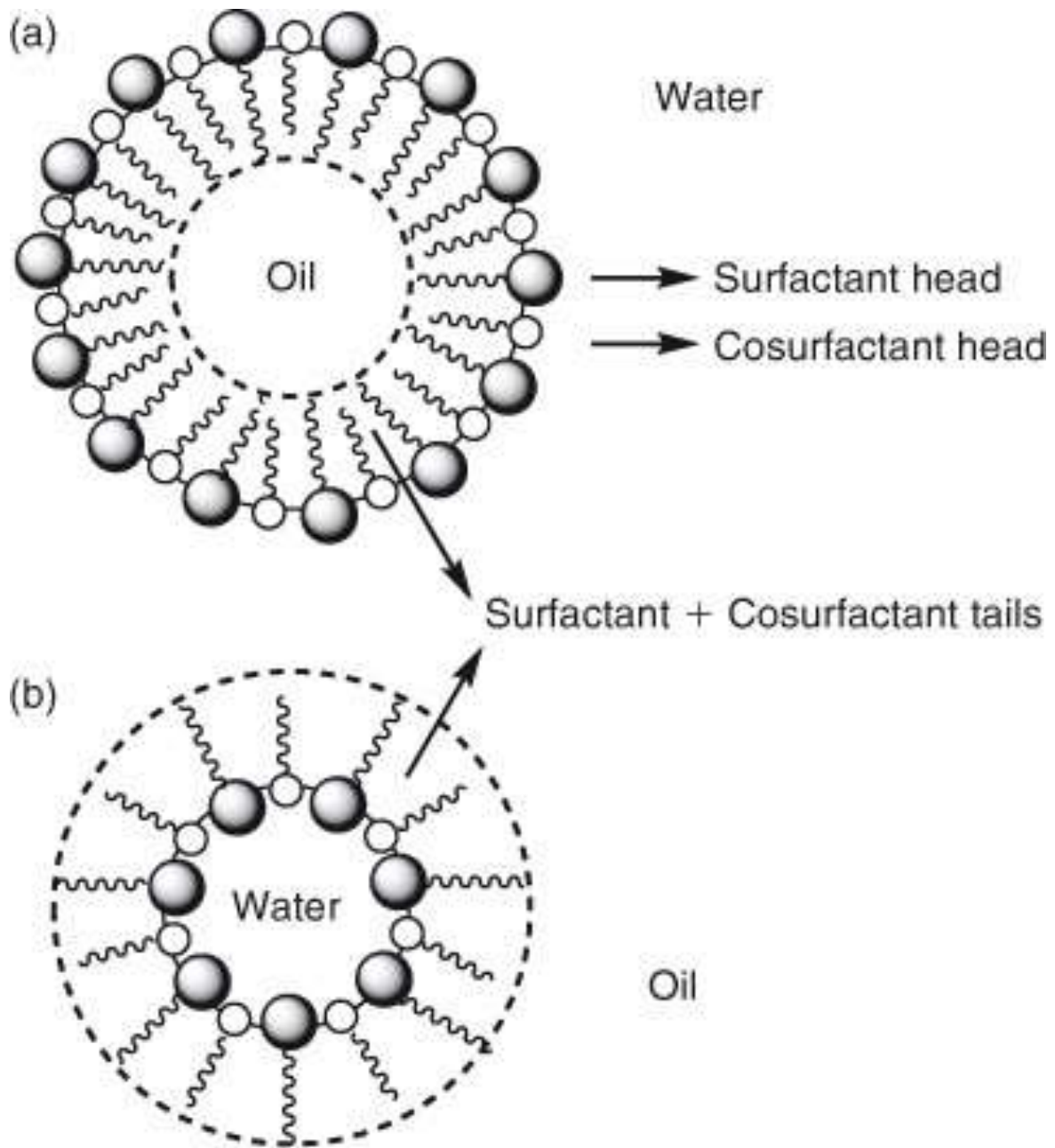


- Surfactant:** Forms the interfacial film
- CoSurfactant:** Ensures flexibility of interfacial layer
=> reduces the interfacial tension

MONOMOLECULAR ADSORPTION

(HLB)

- Type of emulsion produce depend on property of emulsifying agents HLB value.
- Type of emulsion is a function of relative solubility of the surfactant.
- *Rule of Bancroft*: The phase (oil/water) in which surfactant is relatively more soluble will become continuous phase.
- High HLB Surfactant prefer formation o/w emulsion and vice versa.



Emulsifying agents

Surfactants

HLB

- A system was developed to assist in making systemic decisions about the amounts and types of surfactants needed in stable products.
- The system is called the **HLB (hydrophile-lipophile balance) system** and has an arbitrary scale of 1 - 18.
- HLB numbers are experimentally determined for the different emulsifiers.

EMULSIFYING AGENTS SURFACTANTS

HLB

<u>HLB value</u>	<u>Application</u>
1 - 3	Anti-foaming agent.
3 - 6	W/O emulsifying agents.
7 - 9	Wetting agents.
8 - 18	O/W emulsifying agents.
13 - 15	Detergents.
15 - 18	Solubilizing Agents.

EMULSIFYING AGENTS (SURFACTANTS EXAMPLES)

Anionic surfactants:

- These are organic salts which, in water, have a surface-active anion.
E.g.
 - ✓ Alkali metal and ammonium soaps (salts of long chain fatty acids) such as **sodium stearate** and potassium oleate (o/w).
 - ✓ Soaps of divalent and trivalent metals such as **calcium oleate** (w/o).
 - ✓ Amine and ammonium soaps such as **triethanolamine oleate** (o/w).
 - ✓ Alkyl sulphates such as sodium lauryl sulphate (SLS) (o/w).

Disadvantages:

- They are irritant internally so widely used in **external** preparations as o/w emulsifying agents.
- anionic surfactants are generally stable at more alkaline pH

EMULSIFYING AGENTS (SURFACTANTS EXAMPLES)

Cationic surfactants:

- These are usually quaternary ammonium compounds which have a surface-active cation.
- Examples include **cetrimide** and benzalkonium chloride.
- They are used in the preparation of o/w emulsions for external use and must be in their ionized form to be effective.
- The cationic surfactants also have antimicrobial activity.

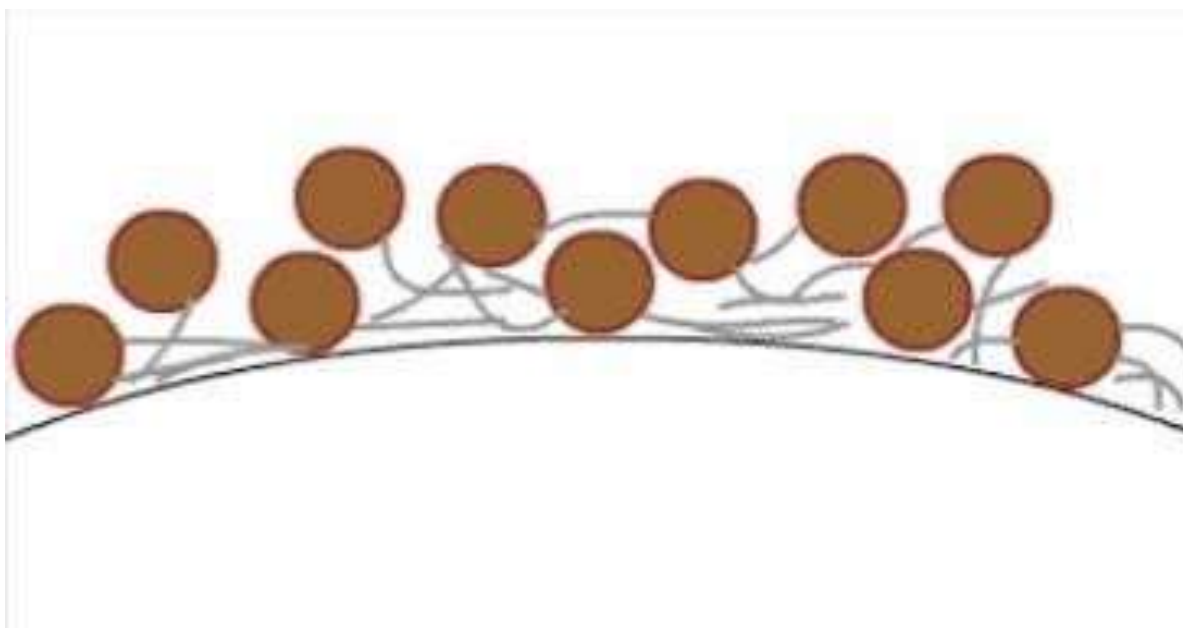
Disadvantages:

- They are sensitive to anionic surfactants and drugs.
- Emulsions formed by a cationic surfactant are generally stable at acidic pH.
- They are more toxic than other surfactants.

2) MULTIMOLECULAR ADSORPTION (HYDROCOLLOIDS)

- Hydrophilic colloids (mucilage of gum acacia) are different in action from surfactants.
- They do not cause lowering of interfacial tension.
- They form multimolecular layer at o/w interface
- They increase viscosity of dispersion medium

MULTIMOLECULAR FILM



EMULSIFYING AGENTS (HYDROCOLLOIDS EXAMPLES)

Natural Polysaccharides: The main problem with these agents is their natural variability between batches and microbial contamination.

- These materials should not be used externally as they leave a sticky feel on the skin.
- **Acacia** is the best emulsifying agent for extemporaneously prepared oral emulsions as it forms a thick film at the oil- water interface to act as a barrier to coalescence. It is too sticky for external use.
- **Tragacanth** is used to increase the viscosity of an emulsion and prevent creaming.
- Other polysaccharides, such as **starch**, pectin and carrageenan, are used to stabilize an emulsion.

EMULSIFYING AGENTS (HYDROCOLLOIDS EXAMPLES)

Semi-synthetic polysaccharides:

- These are derived from the naturally occurring polysaccharide **cellulose** and generally form o/w emulsions.
- Examples include low-viscosity grades of
 - ✓ Methylcellulose (MC)
 - ✓ Carboxymethylcellulose (CMC)
 - ✓ Hydroxypropylmethylcellulose (HPMC)

Synthetic hydrocolloids:

- ✓ Carbopol
- ✓ Polyvinyl alcohol (PVA).
- ✓ Polyvinyl pyrrolidone (PVP)

3) SOLID PARTICLES ADSORPTION

- Solid particles that can be wetted by oil as well as water can act as emulsifying agent
- Their concentration is higher at interface
- They **form particulate film** around dispersed droplets to prevent coalescence
- Example of agents: **Bentonite** ($\text{Al}_2\text{O}_3 \cdot 4\text{SiO}_2 \cdot \text{H}_2\text{O}$), **Veegum** (Magnesium Aluminum Silicate)

EMULSIFYING AGENTS (FINELY DIVIDED SOLID EXAMPLE)

➤ These agents form a particulate layer around dispersed particles.

➤ These agents **swell in the dispersion medium to increase viscosity** and reduce the interaction between dispersed droplets.

➤ Most commonly they support the formation of o/w emulsions:-

✓ Bentonite

✓ Veegum,

✓ Hectorite,

✓ Magnesium Hydroxide,

✓ Aluminum Hydroxide

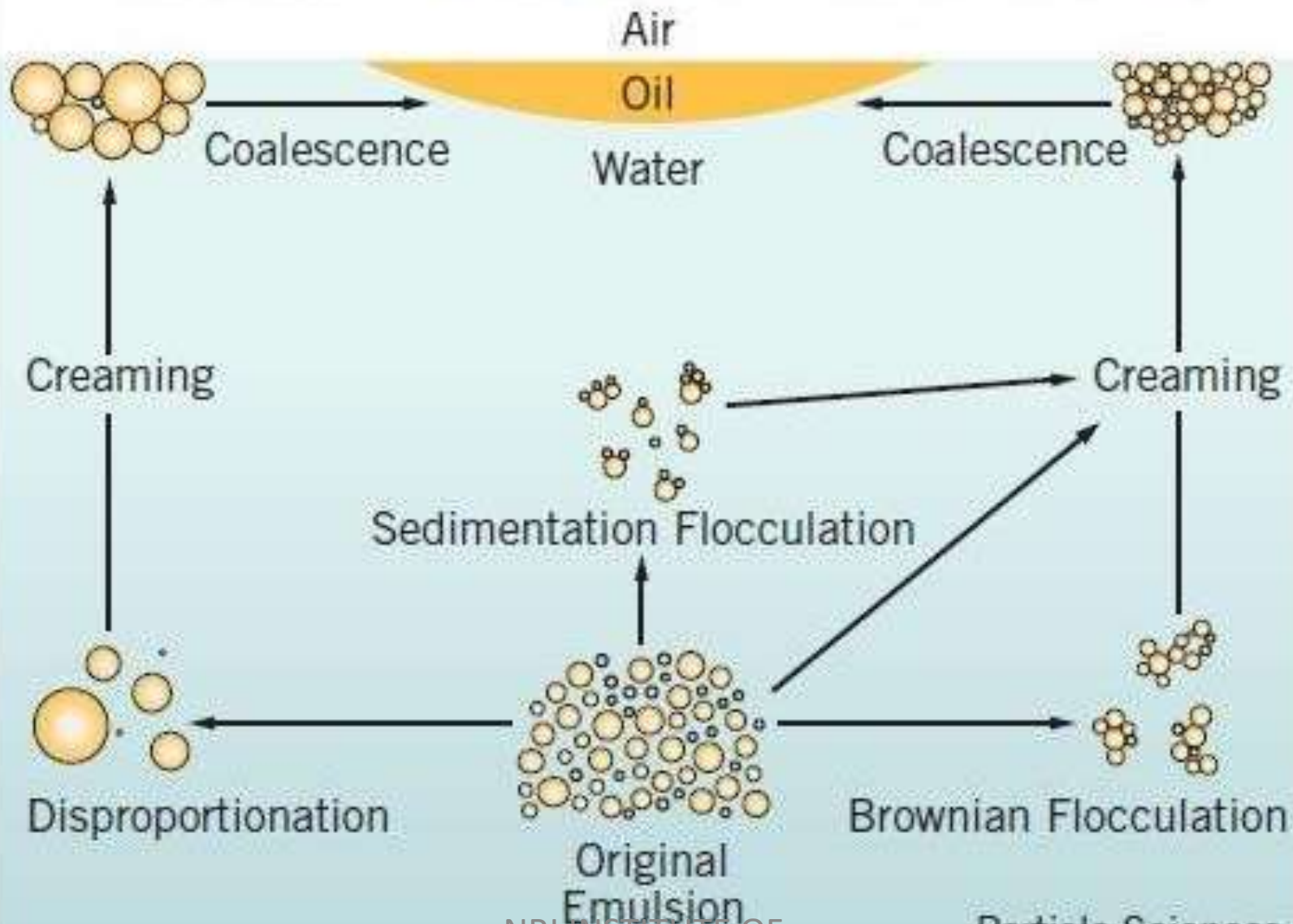
✓ Magnesium Tri silicate.

STABILITY OF EMULSION

STABILITY PROBLEMS

1. Sedimentation and creaming.
2. Thermodynamic instability (coalescence or cracking).
3. Phase inversion.

SCHEMATIC OF MECHANISMS LEADING TO COALESCENCE OF AN OIL-IN-WATER EMULSION



STABILITY OF EMULSIONS

Creaming and sedimentation:

- As the dispersed droplets are subjected to gravity force, they tend to move upward (creaming) or downward (sedimentation) but not both.
- Creaming usually happens in o/w emulsions.
- Sedimentation usually happens in w/o emulsion.
- The rate of sedimentation or creaming is described by Stoke's law.

$$v = \frac{2r^2(\sigma - \rho)g}{9\eta}$$

Where v = velocity of sedimentation or creaming of a dispersed particle of radius r , and density σ , in a liquid of density ρ , and viscosity η , and where g is the acceleration due to gravity.

STABILITY OF EMULSIONS

Creaming and sedimentation:

- The process is **reversible** and gentle shaking redistributes the droplets throughout the continuous phase.
- However, creaming is undesirable because
 - ✓ it is inelegant and **inaccurate dosing** is possible if shaking is not thorough.
 - ✓ Additionally, creaming increases the likelihood of **coalescence of globules** and therefore break down of the emulsion due to cracking.

STABILITY OF EMULSIONS

Cracking or coalescence:

- Emulsions are thermodynamically unstable systems; there is interfacial free energy (IFE) (ΔG) between the two phases.
- $\Delta G = \gamma_{LL} \Delta A$
Where γ_{LL} is interfacial tension
- To enhance their stability, the dispersed droplets come closer to each other and fuse in an attempt to decrease the exposed surface area.
- Coalescence is the fusion of two or more droplets of the disperse phase forming one droplet.
- This ends up to the separation of the disperse phase as a separate layer (phase separation).
- Coalescence is an **irreversible** process and redispersion cannot be achieved by shaking.

STABILITY OF EMULSIONS

How to enhance stability (to prevent creaming and cracking)?

➤ **Globule size:**

- ✓ Smaller particles have slower creaming or sedimentation than larger particles (Stoke's law).
- ✓ Stable emulsions require a maximal number of small sized (1-3 μm) globules and as few as possible larger (>15 μm) diameter globules.
- ✓ A homogenizer will efficiently reduce droplet size by forcing the emulsion through a small aperture to reduce the size of the globules.
- ✓ Additionally, reducing droplet size may additionally increase the viscosity if more than 30% of disperse phase is present.

STABILITY OF EMULSIONS

How to enhance stability (to prevent creaming and cracking)?

➤ **Viscosity of the continuous phase:**

✓ Increasing the viscosity of the continuous phase will reduce the potential for globule creaming and hence coalescence as this reduces the movement of globules.

➤ How to increase viscosity?

✓ Viscosity enhancing agents, which increase the viscosity of the continuous phase, may be used in o/w emulsions. e.g tragacanth, sodium alginate and methylcellulose.

✓ Higher percentages of oil phase (o/w).

✓ Decreasing the globule size of the internal phase.

✓ Higher amounts of solid fats in the oily phase (i.e. high ratios of solid fat to liquid fats).

STABILITY OF EMULSIONS

How to enhance stability (to prevent creaming and cracking)?

- **Using emulsifying agents (hydrocolloids, surfactants and other) :**
- ✓ Forming interfacial film mechanical barrier which decreases the potential for coalescence (more important).
- ✓ Surfactants may reduce the interfacial tension between the two phases (less important).
- ✓ Hydrocolloids enhance the viscosity of the medium.

Note: Care should be taken for any effects that could affect the interfacial film (chemical, physical or biological effects).

STABILITY OF EMULSIONS

How to enhance stability (to prevent creaming and cracking)?

➤ *Storage temperature:*

- ✓ Extremes of temperature can lead to an emulsion cracking.
- ✓ When water freezes it expands, so undue pressure is exerted on dispersed globules and the emulsifying agent film, which may lead to cracking.
- ✓ Conversely, an increased temperature decreases the viscosity of the continuous phase and disrupts the integrity of the interfacial film. An increasing number of collisions between droplets will also occur, leading to increased creaming and cracking.

STABILITY OF EMULSIONS

Phase inversion

- Emulsion type is determined by:
 - ✓ The oil to water ratio (amounts).
 - ✓ The solubility of the emulsifying agent.
- Phase inversion is the process in which an emulsion changes from one type to another, say o/w to w/o.
- The most stable range of disperse phase concentration is 30-60%. If the amount of disperse phase approaches or exceeds a theoretical maximum of 74% of the total volume, then phase inversion may occur.
- Addition of substances which alter the solubility of an emulsifying agent may also cause phase inversion.
- The process is **irreversible**.

METHODS FOR EVALUATION OF STABILITY OF EMULSION

- Size frequency analysis over the time by microscopic observation.
- Velocity of creaming (as it is proportional to droplet diameter).
- Globule size analysis using coulter-counting, ultra centrifugal.
- Turbidimetric analysis.
- Thaw freeze cycle and centrifugation analysis.
- Conductivity test during heating-cooling- heating cycles.