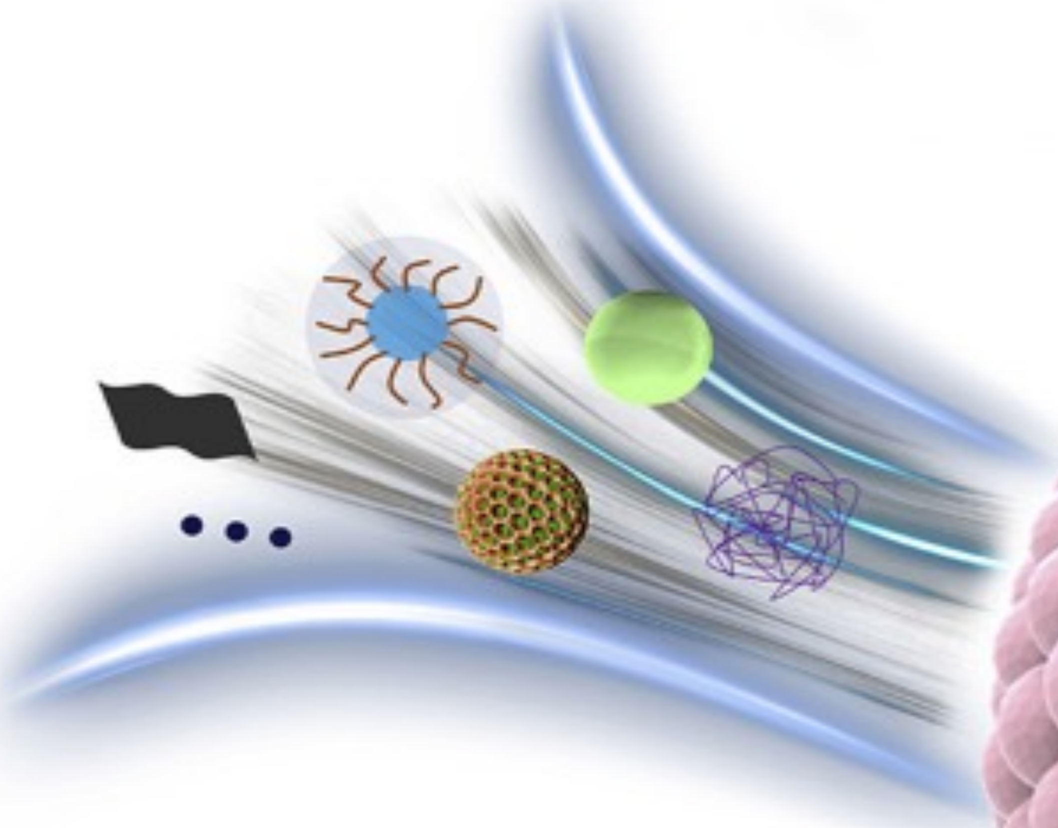
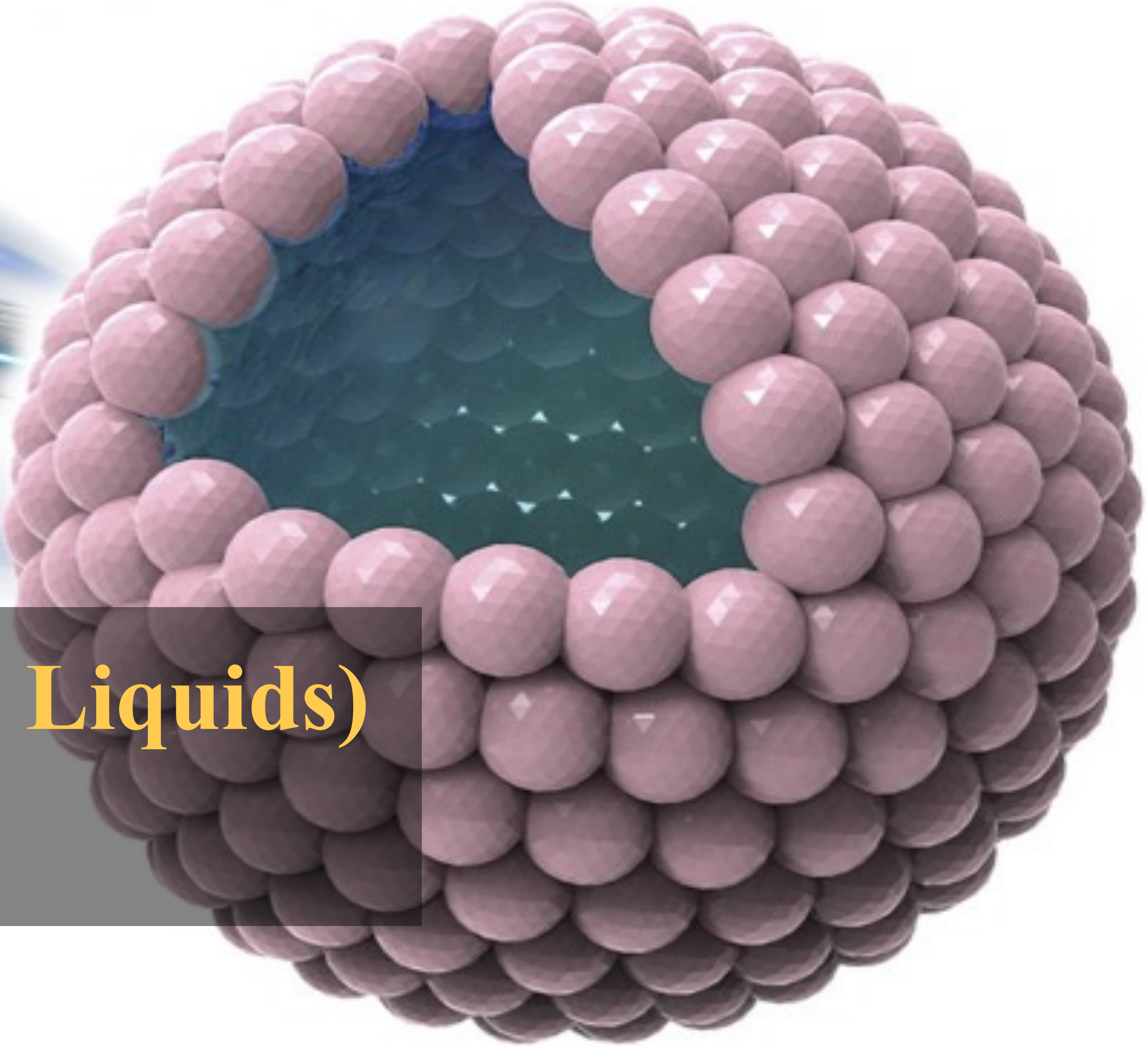


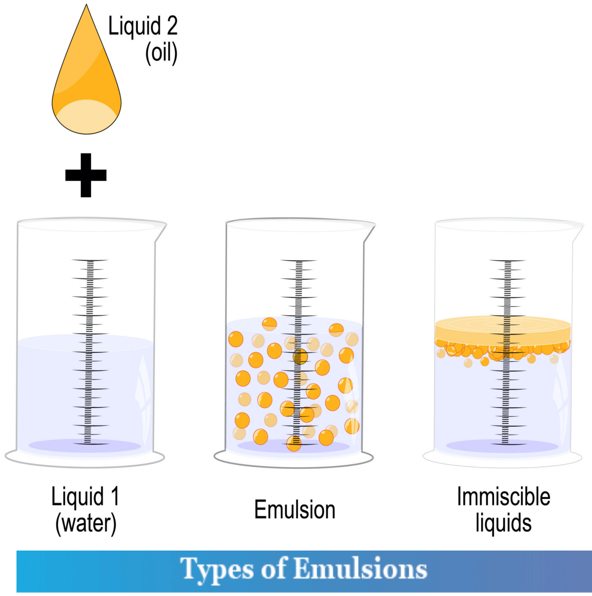


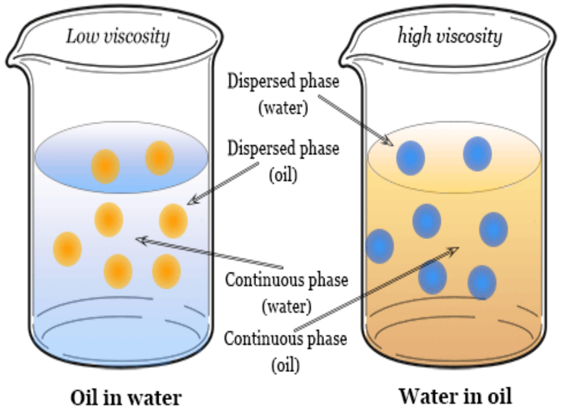
Emulsions (Biphasic Liquids)

Mohammed Albarki, BSPharm, PhD.

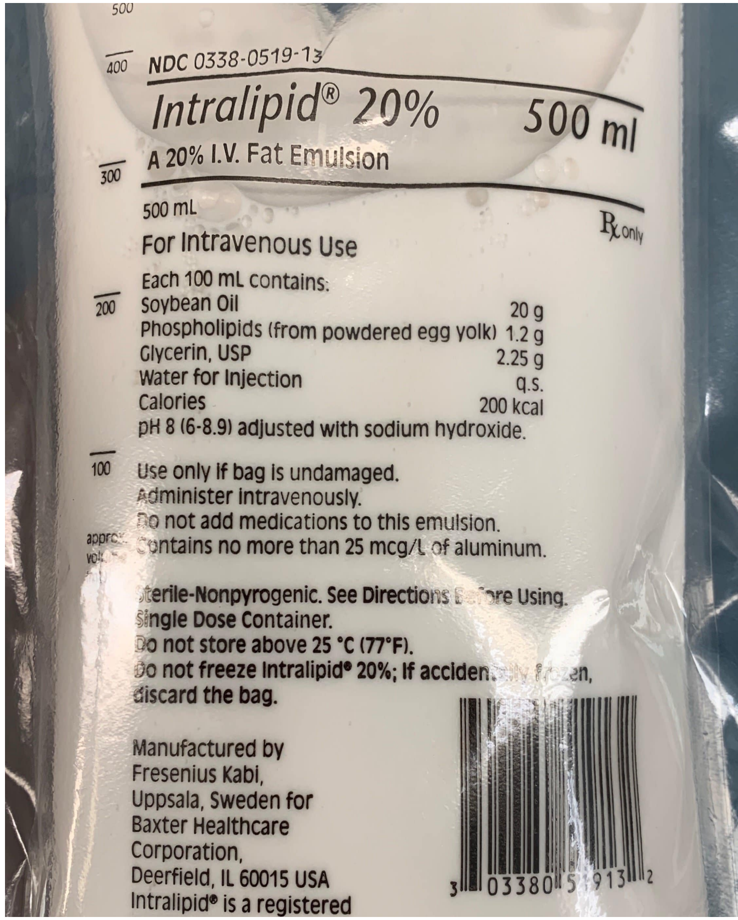
Introduction

- Emulsions are water, oil, and emulsifying agents.
- An emulsion is a (**thermodynamically unstable**) mixture of **two immiscible liquids**, one of which is finely subdivided and uniformly distributed as droplets (the **dispersed** phase) throughout the other (the **continuous** phase), stabilized by an emulsifier.
- In emulsion terminology, the **dispersed phase** is the **internal phase**, and the **dispersion medium** is the **external** or continuous phase.
- The viscosity of emulsions can vary greatly and they may be prepared as liquids or semisolids (cream).
- Liquid emulsions may be employed orally, topically, or parenterally while semisolid emulsions employed topically.





- **Oil-in-water (o/w)**
- Suitable for oral, parenteral, and topical routes of delivery
- Propofol emulsion (Diprivan®) –intravenous anesthetic
- Intralipid® -Lipid Emulsion for parenteral nutrition
- Miscible with water and aqueous diluents as water is the continuous phase



- **Water-in-oil (w/o)**
- Exclusively for external application
- For example: Cold Cream
- Not miscible with aqueous diluents as **oil** is the continuous phase

How to Identify Type of Emulsion

- Emulsion type will depend mainly on:
  1. The **volume ratio** of the oil and aqueous phases and
  2. The **types of emulsion stabilizers** (emulsifiers) present
- The phase that is present in greater concentration generally tends to be the external phase
- However, an emulsifier that favors a particular type of emulsion (o/w or w/o) can overcome an unfavorable ratio of oily and aqueous phases

- **Bancroft's Rule** –"The phase in which an emulsifier is more soluble constitutes the continuous (external) phase"

Emulsions as a Pharmaceutical Dosage Forms

Advantages

1. Allows for the preparation of a relatively stable mixture of two immiscible liquids. This facilitates the **delivery of oily or oil-soluble drugs**
2. **Taste-masking**(if the drug is oil-soluble)
3. Dispersion of the drug-containing phase into **microscopic** globules may aid in **improved bioavailability**
4. Enables intravenous administration of an oil (e.g., parenteral nutrition or propofol)
5. External applications such as creams, lotions, etc.

Pharmaceutical Emulsions: Examples

Emulsion	Therapeutic category	Route of administration
Lidocaine and Prilocaine Cream (EMLA®)	TopicalAnesthetic	**Topical**
Restasis(Cyclosporin ophthalmic emulsion)	For chronic dry eye (increases tear production)	**Ophthalmic**
Propofol injectable emulsion USP (Diprivan®)	Anesthetic	**Intravenous**
Mineral Oil emulsion USP	Laxative	**Oral**
Diazepam intravenous emulsion (Diazemuls®)	Sedative Anti-anxiety	**Intravenous**

Not for save

Critical Emulsion Attributes

Desirable product properties

1. The droplet size of the dispersed phase (oil or water) should **remain fairly constant** during undisturbed standing for long periods (minimal coalescence of droplets)
2. **Consistency** should be appropriate for the intended use (pourable/syringeable/ spreadable etc.)
3. If liquid emulsions exhibit some 'creaming' on storage, the oil phase should be readily and uniformly re-dispersed upon shaking (**re-dispersible**).

Formulation of Emulsions

Stokes Law

- Defines the rate of **upward** movement of oil droplets dispersed in an aqueous medium or **downward** movement of water droplets dispersed in an oil phase
- Note: Stokes law is strictly valid only for **uniform, spherical droplets in a dilute emulsion.**

$$\frac{dx}{dt} = \frac{D^2(\rho_{(internal\ phase)} - \rho_{(continous\ phase)}) * g}{18\eta}$$

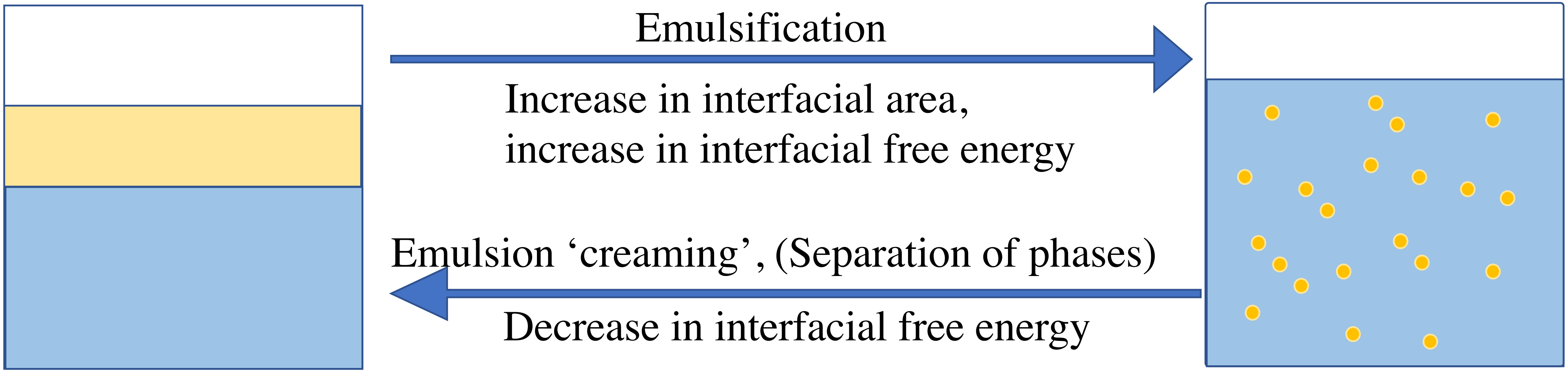
- Where:
- $\frac{dx}{dt}$= sedimentation rate in (cm/s) ; D= particle diameter (cm)
- ρ = density in g/ml ; g= gravity constant (980.7 cm. s^{-2})
- η= medium viscosity in g. cm^{-1} . s^{-1} or (poise)
- When $\boldsymbol{\rho}_{ip} < \boldsymbol{\rho}_{cp}$: o/w emulsion; $(\boldsymbol{\rho}_{ip} - \boldsymbol{\rho}_{cp})$ = -ve, droplets rise
- When $\boldsymbol{\rho}_{ip} > \boldsymbol{\rho}_{cp}$: w/o emulsion; $(\boldsymbol{\rho}_{ip} - \boldsymbol{\rho}_{cp})$ = +ve, droplets settle

Formulation of Emulsions

Creaming of an Emulsion

- The **smaller** the globules of the disperse phase, the **slower** will be the rate of creaming in an emulsion. The size of these globules can also affect the viscosity of the product, i.e., the smaller the globules, the higher viscosity.
- However the smaller the droplet the higher the thermodynamic instability.

$$\Delta G = \gamma \Delta A$$



Formulation of Emulsions

- In many cases simple blending of the oil and water phases with a suitable emulgent system.
- The initial blending may be accomplished on a small scale by the use of a **pestle and mortar** or by using a mixer fitted with an impeller type of agitator, the size and type of which will depend primarily on the **volume and viscosity** of the product.
- **Colloid mills** are also suitable for the preparation of emulsions. The extensive shearing of the product produces emulsions of very small globule size.

Formulation of Emulsions

- Fat or oil drugs for **oral** administration are formulated as o/w emulsions.
  - In this form, the presence of a flavor in the aqueous phase **will mask** any unpleasant taste.
- Emulsions for **intravenous** administration **must** also be of the o/w type, although intramuscular injections can also be formulated as w/o products if a water-soluble drug is required for depot therapy (S.R).
- Emulsions are most widely used for **external applications**. Semisolid emulsions are **termed creams** and more fluid-containing preparations are called either lotions or liniments (liniments are intended for skin massage).

Emulsifying Agents

- Can be divided into **three** categories: surface active, hydrophilic colloids, and finely-divided solids.
- Only the surface active agent is considered as a **main** emulsifying agent. The other two are considered auxiliary emulsifiers.

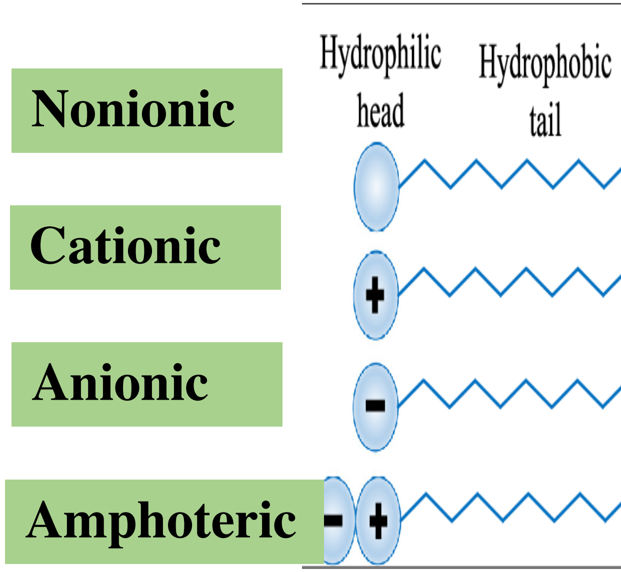
1. They **reduce interfacial** tension (thermodynamic stabilization) and/or
2. Act as **barriers** to prevent/reduce droplet coalescence since they adsorb at the interface (interfacial film formation).
3. They can also act by **electrical repulsion** or electrical barriers for agents that possess a surface charge such as cationic surfactants.

Emulsifying Agents

Surface Active Agents or "Surfactants"

- Based on their structure, emulsifiers may be described as molecules comprising **both** hydrophilic and hydrophobic portions
- Adsorbed at the Oil-water interface and formed monomolecular films. They act by:

1. They **reduce** the interfacial tension between two liquids. (**this action is for surfactants only**)
2. They may also prevent the coalescence of droplets by **forming a coherent** monolayer at the interface of the droplets. (**this action is similar to the other two and it is more important in surfactant action**)
3. If the emulsifier is **ionized**, it confers a surface charge to the droplet and might prevent coalescence due to repulsive forces between droplets (**not all surfactants have this action**)



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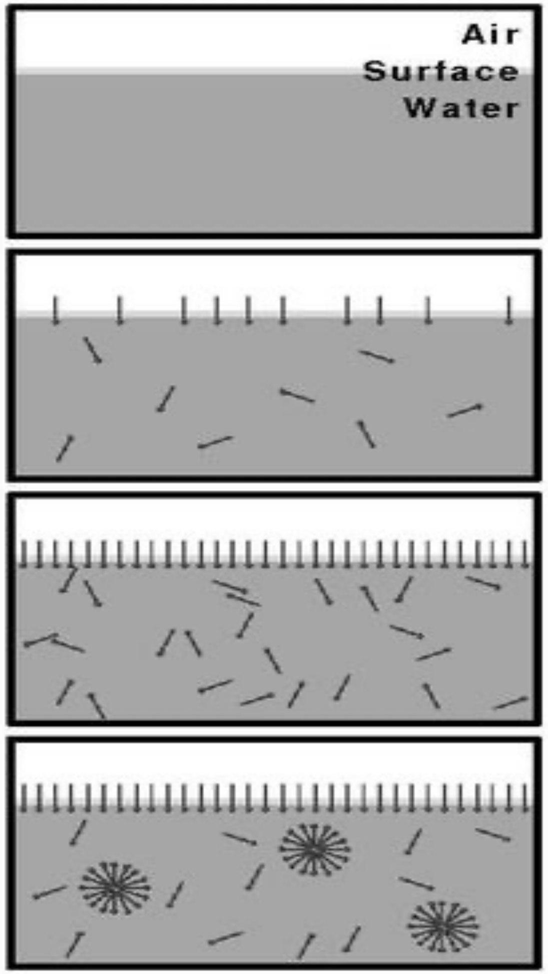
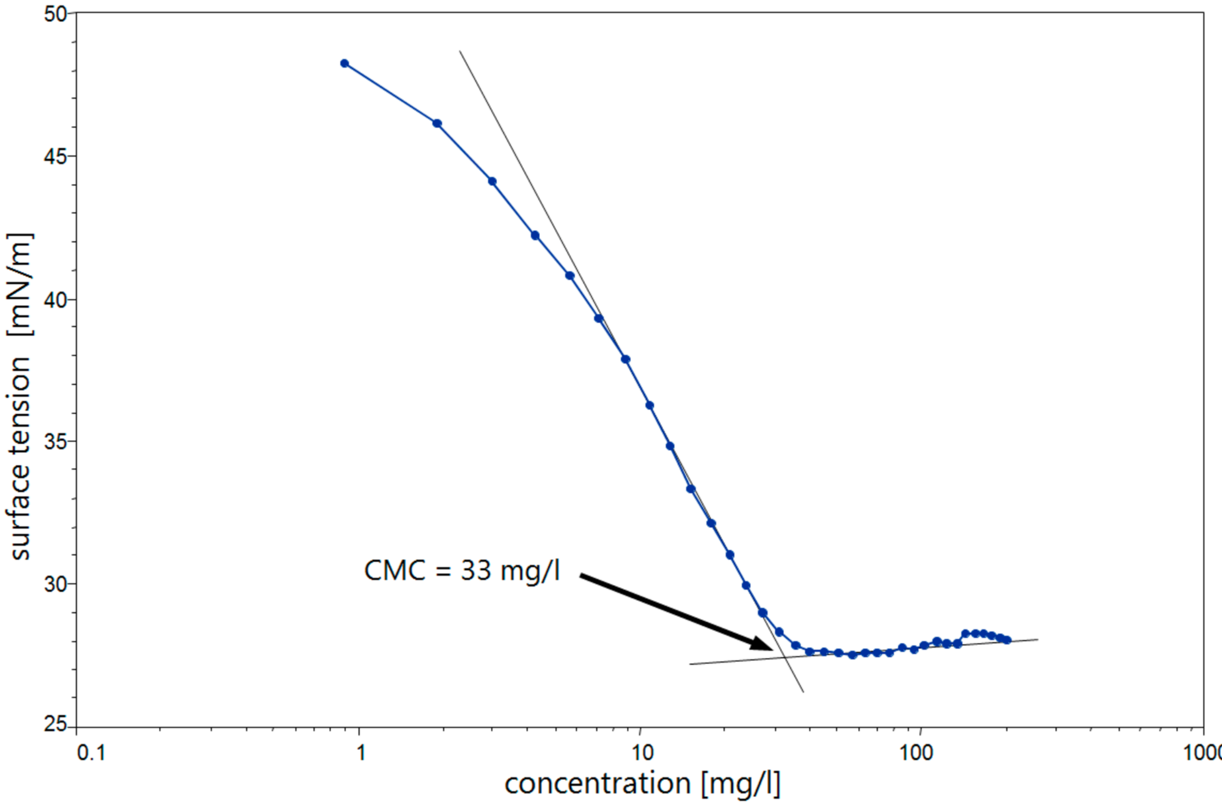
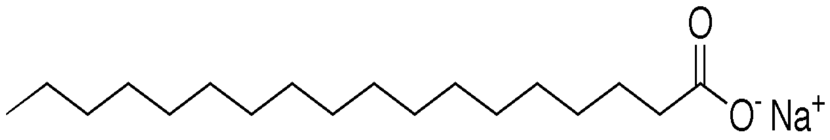

Air
Surface
Water


50
45
40
35
30
25
surface tension [mN/m]
0.1
1
10
100
1000
concentration [mg/l]
CMC = 33 mg/l

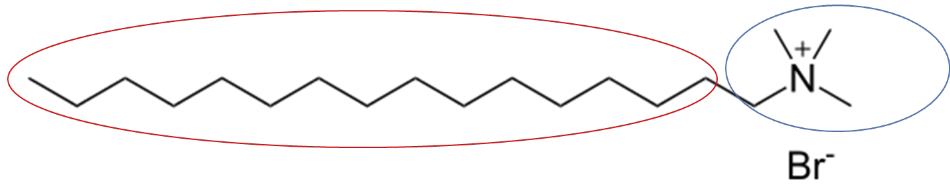
Emulsifying Agents

- **Surface Active Agents or Surfactants**
- Surfactants are classified into four types based on the charge carried by the **hydrophilic** part of the surfactant



Sodium Stearate

1. **Anionic Surfactants**: bear a negative charge. Example: potassium laurate, sodium stearate.
   - Good emulsifiers **but** cause gastrointestinal irritation (**limits oral use**).



Cetrimide

2. **Cationic Surfactant**: bears a positive charge (eg. Cetrimide, benzalkonium chloride).
   - **These are Weak** emulsifiers. Very hydrophilic and highly soluble in water. Formulated with auxiliary emulsifiers.

Emulsifying Agents

3. **Amphoteric surfactants:** this type possesses both positively and negatively charged groups, depending on the pH of the system. An example is lecithin.
4. **Non-ionic surfactants:** No charge, Not susceptible to pH changes and presence of electrolytes Examples:
    - Span® -Sorbitan esters of fatty acids
    - Tween® -Polysorbates, Polyoxyethylene derivatives of Span®
        - Forms **interfacial films** decrease **interfacial tension** and stabilize the interface
        - Provide **steric stabilization** against coalescence (additional advantage).

HLB Value

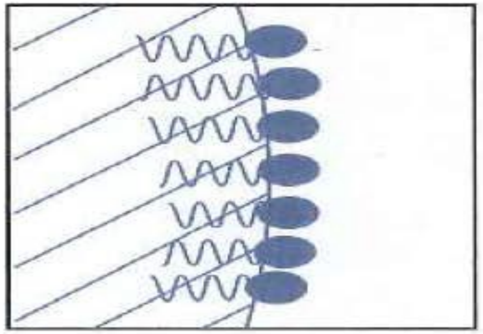
- HLB value defines relative affinity for the water and oil phases. This value is **only** for **nonionic surfactants**.
- **Lipophilic**: HLB values < 10 (more soluble in oil ➔used for w/o emulsions)
- **Hydrophilic**: HLB values > 10 (more soluble in water ➔ used for o/w emulsions)
- **Note**: HLB **does not** provide information on the amount of surfactant required.
- Surfactant levels required need to be **experimentally** determined.
- Mixtures of emulsifying agents can also be used to obtain the desired '**effective HLB**' values required for the oil phase in question.

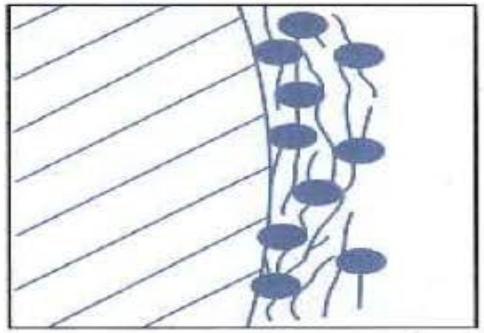
Not for save

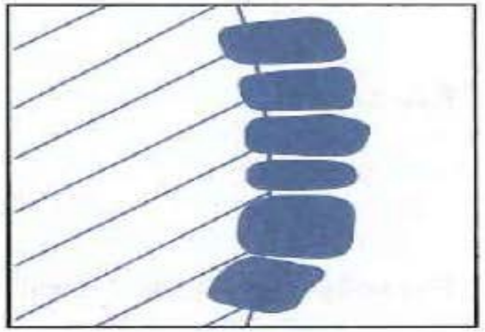
HLB range	Use of Surfactant
4-6	Water in oil emulsifying agents
7-9	Wetting agents
8-18	Oil in water emulsifying agents
13-15	Detergents
10-18	Solubilizing agents

Auxiliary Emulsifiers

- Normally these agents are **incapable** of forming emulsions by themselves at low concentrations
- Function by:
  1. Increasing viscosity (**thickening agents**) **or**
  2. By forming a gel-like structure that provides a barrier to the coalescence of droplets.

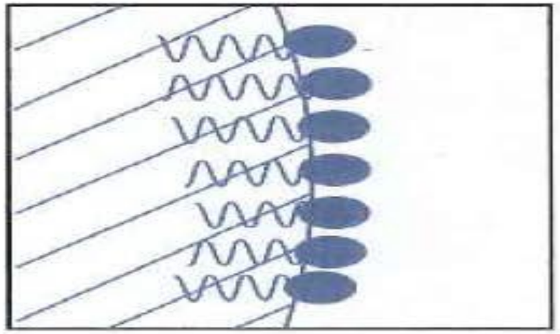


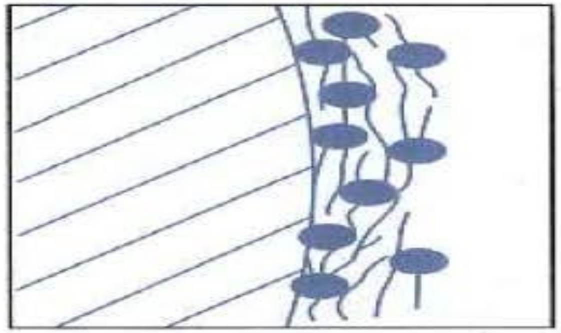


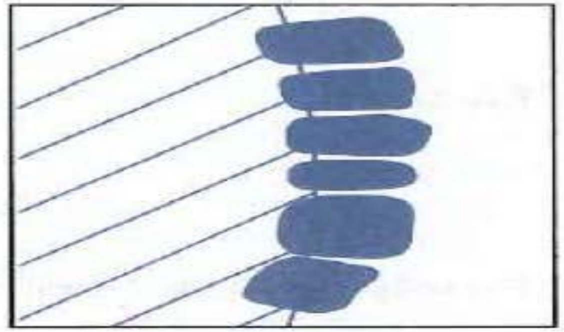


1. **Hydrophilic colloids**: polymers that are water sensitive which are **swellable** or soluble and form multi-molecular films around the droplets. It also increases the viscosity of the medium.
   - It can be from natural sources for example bentonite clay. Or completely Synthetic agents such as Carbopol®.

2. Finely divided solids:







- Adsorbed on the interface. **Wetted** to some degree by both the liquid phases (a requirement for localization at the interface).
- Their particle size is much smaller than the droplet
  - Examples are polar inorganic heavy metal oxide, barium sulfate

Symptom of Instability

- **Creaming:**
- Under the effect of gravity, the suspended particle tends to rise or sediment depending on the differences in specific gravity between the phases.
- A simple example is the creaming of milk when fat globules slowly rise to the top of the product.
- If creaming takes place **without aggregation**, the emulsion can be reconstituted by shaking or mixing, and creaming is just a simple problem
  - Otherwise, it is a serious stability problem. In this case, droplets will coalesce with each other and may lead to emulsion cracking (separation).

Symptom of Instability

- **Coalescence**
- It is a growth process during which the emulsified particles join to form larger particles.
- The major factor that **prevents** coalescence in flocculated and un-flocculated emulsion is the mechanical strength of the interfacial barrier
- Coalescence results in the separation of the two phases and emulsion failure (**irreversible case**).
- Coalescence is usually attributed to the **failure of the emulsifying agent** to do its job.