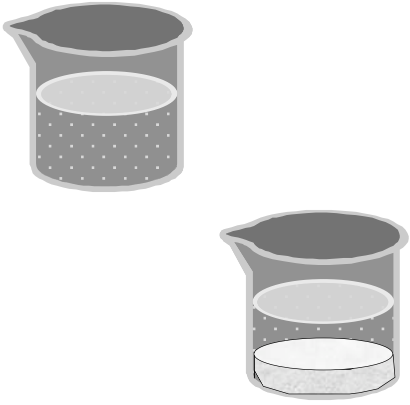
Suspensions and Emulsions
Surfactants

5,6,27

Suspensions and Emulsions



- **Dispersion of solid particles or of oil in solution**
- **Used for**
  - **Oral delivery of non soluble substances when the use of tablets leads to low patience compliance**
  - **Topical administration**
  - **Parenteral use for substances of low solubility or for controlled delivery**

Dispersions

Important dispersions

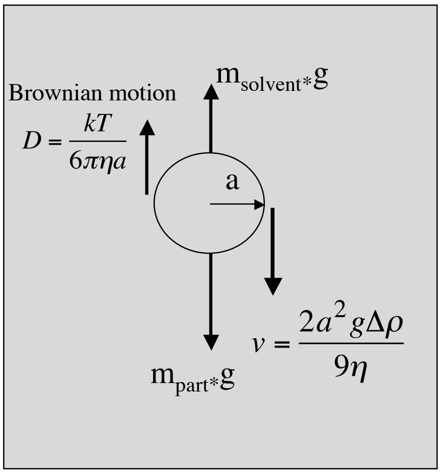
Internal Phase	*External Phase*	*Type*
Gas	Liquid	Foam
Gas	Solid	Solid foam
Liquid	Gas	Aerosol
Liquid	Liquid	Emulsion
Solid	Gas	Solid aerosol
Solid	Liquid	Suspension
Solid	Solid	Solid suspension

Definition

A system in which one component is dispersed as particles in another one

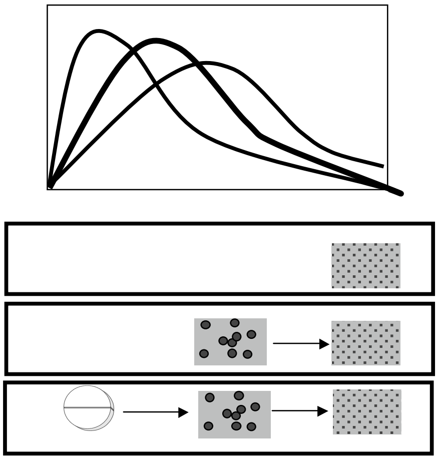
- **Coarse dispersions**
- **Colloidal: 1nm-1μm**
- **Association colloids: surfactants**
- **Lyophobic: thermodynamically unstable**
- **Lyophillic: thermodynamically stable for colloids**

Forces acting on a dispersion: sedimentation



- **For small particles <0.5μm Brownian motions counteract gravitationall forces and the system will be stable**
- **Stability can be increased by**
  - **Use of small particle size**
  - **Use of high viscosity of the solution**
  - **Using low difference in gravity between the particle and the solution**
- **If Δρ<0 creaming occurs**

Pharmacodynamics considerations



- Factors affecting release
  - Size and size distribution of particle
  - Particle porosity
  - Particle erosion
  - State of the active substance in the particles (dispersed, continuous, at the surface, etc.)
  - Rheology of the medium
  - Solubility of the solid material
  - Partition coefficient between oil and water

Formulation demands

- **Ideal formulation**
  - Homogeneous during dosing
  - Easy to resuspend or stable dispersion
  - Proper viscosity
  - Particles that are (small and) uniform in size
- **In reality**
  - The stability of dispersion is a critical problem
  - The large surface area is a risk for chemical stability
  - The solution creates a risk of microbiological growth

Formulation of suspension and emulsions

- Solid or oil (containing the active substance)
- Solvent (normally water)
- Surface active agent (always in emulsions)
- Other excipients
  - Viscosity modifiers and density modifiers to improve the stability
  - Buffers to control the pH
  - Antioxidants
  - Flavours colours perfumes, and sweating agents
  - Bactericides

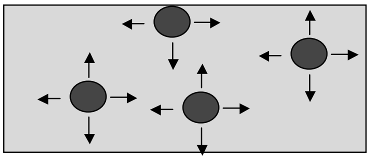
Emulsion

- **Types of emulsions**
  - **Macroscopic emulsions**
    - **O/W oil in water**
    - **W/O water in oil**
    - **Thermodynamically instable**
  - **Microemulsions**
    - **Chemically stable**

- **Formulation issues**
  - **Choice of surfactants**
  - **Self emulsified systems or “long-term stable emulsions”**
  - **Solubility of the active substance in oil and in the water phase**
  - **Toxicity**

Forces acting at a surface

Definition of surface energy
The amount of work needed to increase the surface area by one unit.



How will this affect emulsions and dispersions?

How can we change the surface tension??

Stabilisation of emulsions

- An emulsion is more stable if a surface-active compound is adsorbed to the interface
- The stabilisation effect depends on
  - Surface tension
  - Surface viscosity of the film
  - Polymers, surfactants or small particles are used to stabiles emulsion

HLB values can be used as a rule of thumb for choice of surfactant

$$HLB = 7 + \sum hphil - \sum hphob$$

HLB	Use
15-18	Solubilisation
13-15	Detergency
8-16	O/W emulsion
3-6	W/O emulsion
7-9	Wetting agent

Excipients

- Wetting agents
  - There to
    - Reduce particle size (emulsions)
    - Increase wetting
    - Effect flocculation
    - Stabilize dispersion
  - Excipients, block polymers or surfactants (Tween, Polysorbates)
  - High concentrations of surfactants may cause foaming
- Density modifiers
  - Decreases sedimentation
  - Density modification is only possible within a narrow temperature range
  - Typical excipients sucrose, glycerol and propylene glycol
- Rheological modifiers
  - Excipients polymers; CMC, poly acrylic acid, PEG
  - should not affect the handling of the drug such as the force needed to inject the formulation

Quality of dispersions and emulsions

- **Particle size**
  - **Affects stability**
  - **Affects the dissolution**
  - **>5μm: gritty texture**
  - **>25μm: risk for blocking of hypodermic needles**
- **Degree of flocculation**
  - **Affects sedimentation**
  - **Affects resuspension**
- **Sedimentation rate**
- **Rheology**
- **Content of preservatives and anti oxidants**

Particle size change: crystal growth

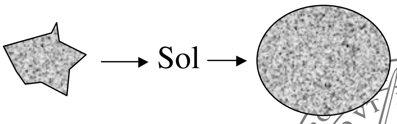
- **Crystal growth occurs when the drug is slightly soluble in the suspension medium and may be accelerated by**
  - **Fluctuation in temperature for example due to sterilisation or to freeze-thaw conditions**
  - **The presence of different polymorphic forms as change in the polymorphic forms may trigger crystal growth and**
  - **Oswald ripening**
- **Problems can be minimised by**
  - **The use of a narrow particle range**
  - **Use of the most stabile crystal form**
  - **Avoiding harsh process conditions**
    - **High temperatures**
    - **High energy milling**
  - **Use of protective colloids or surfactants**
  - **Increase in viscosity so as to decrease the solubility**

Particle size change: Oswald ripening

The pressure is greater on the concave side than at the convex of a curved surface. This leads to an increase in solubility of the material with an increasing curvature of the particle.

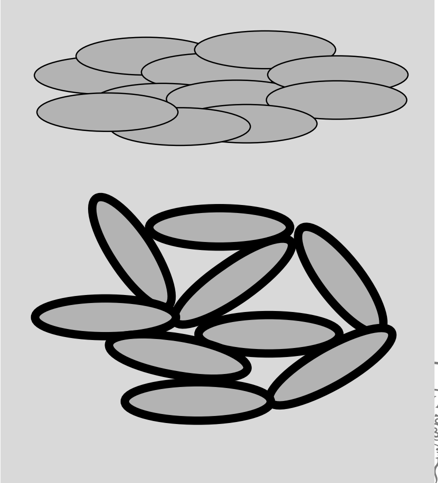
- Small particles tend to be dissolved and large particles to grow
- Particles become increasingly rounded
- Affects solids, emulsions and <u>foams</u>

$$RT\ln\frac{S_r}{S_f}=\frac{2\gamma M}{\rho r}$$



Particle size change: Aggregation

- Caused by attractive interaction between particles in solution
- Can be divided into
  - Coagulation: The particles are difficult to redisperse Particle contact are at the primary minimum in the DLVO theory
  - Flocculation: The particles are easier to redisperse. Particle contact are at the secondary minimum in the DLVO theory or are bridged by polymers



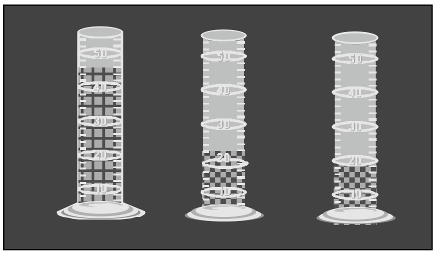
Flocculated or deflocculated systems

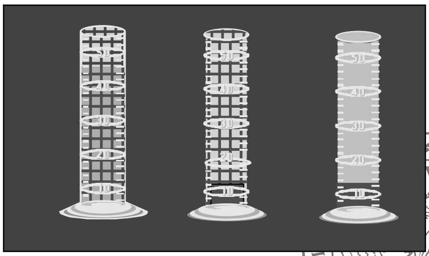
Flocculated systems

- The particles are aggregated
- Sedimentation occurs rapidly
- “Fluffy” sediments
- Large sedimentation volume

Deflocculated systems

- The particles remain as discrete units
- Sedimentation are slower
- Compact sediment
- Small sedimentation volume





Degree of flocculation

- Under flocculation
  - Compact sediment
  - The particles are difficult to resuspend.
- Over flocculation
  - May be irreversible
  - Leads to high viscosity
  - The product looks unattractive
  - Rapid sedimentation
- Deflocculation
  - Can be caused by the addition of surfactants
- How to achieve controlled flocculation
  - Appropriate particle size
  - Use of electrolytes to control the zeta potential
  - Addition of flocculating agents

Zeta potential

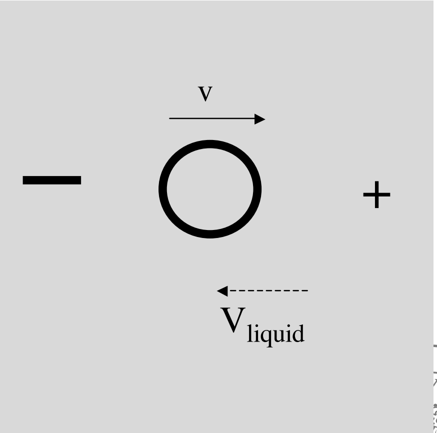
Definition

The zeta-potential represents the net charge at the surface and the potential across the diffuse layer to the surface of share

Techniques for measure z-potential

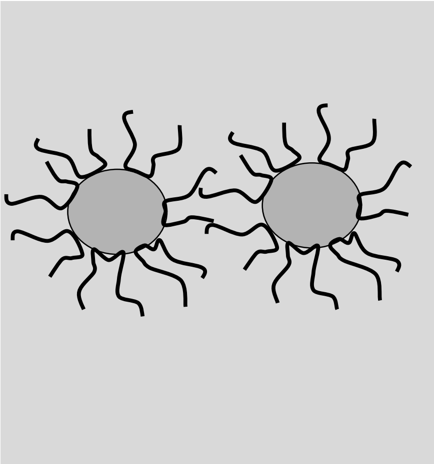
Movement in a electric field

- **Microscope**
- **Light-scattering on the basis of the Doppler effect**



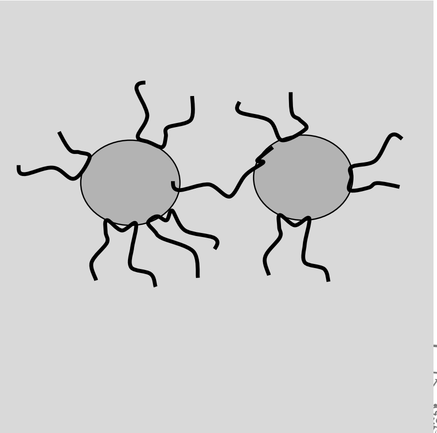
Stabilising dispersions

- **Adsorption of charged species**
  - **Surfactant**
  - **Polymers: risk of bridging**
- **Steric stabilisation**
  - **Non charged polymers**
    - **Gums**
    - **Methyl cellulose**



Flocculating agents

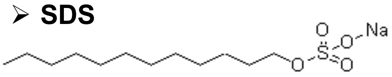
- Flocculating agents
  - Electrolytes
    - Change in the zeta potential
    - Use of divalent or three-valent ions is best
    - Try to avoid charge reversal
  - Surfactants
    - Ionic: zeta potential
    - Non-ionic: bridging
  - Polymers
    - Bridging
    - Also increase in the viscosity



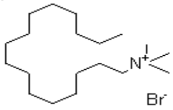
Surfactants

- Characteristic for a surfactant is that it contains both a hydrophilic and a hydrophobic part
- The hydrophilic part can be cationic, anionic, non-ionic or switter-ionic.
- Surfactants can be both soluble and non-soluble.
- Since surfactants can be toxic, only a limiting number of them are accepted for use in drug products.

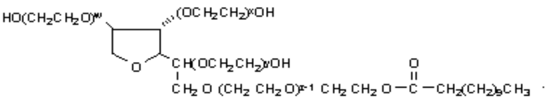
- Typical surfactants
  - SDS



  - CTAB



  - Polysorbate n- Tween



Sum of w + x + y + z = 20

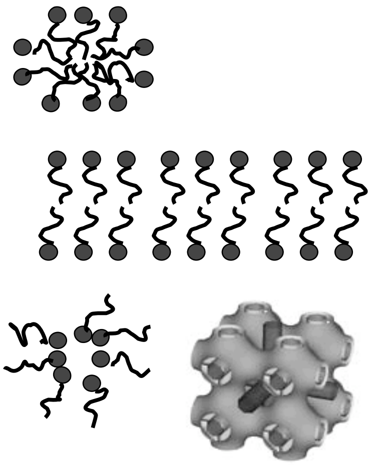
What is typical of surfactants

- They form associated structures above a critical concentration
- They adsorb to interfaces
- They have a tendency to bind to proteins and some polymers

- Use of surfactants
  - As detergents
  - In stabilisation of emulsions and dispersions
  - For wetting of powders
  - For solubilization of hydrophobic substances
  - To stop adsorption of other molecules
  - For controlled release formulations and formulations containing low-soluble substances

Associated structures

- The structures are dependent on
  - The solubility of the surfactant
  - Its concentration
  - Structural factor
- Type of structures formed
  - Micelles
  - Cubic phases
  - Lamellar structures
  - Microemulsions
  - Reversed micelles



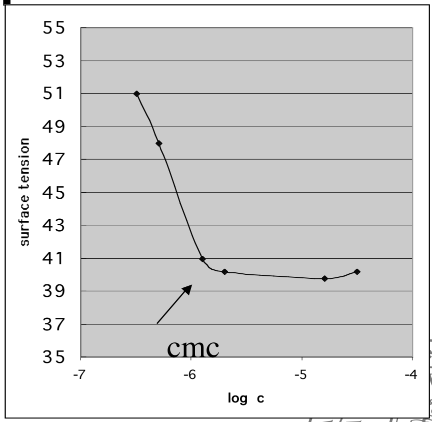
The surface tension of surfactants is related to adsorption

- Gibbs equation

$$\Gamma = -\frac{1}{RT}\frac{\partial \gamma}{\partial \ln c}$$

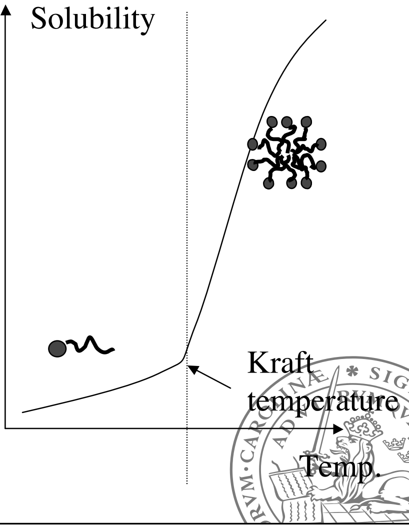
- Area per molecule

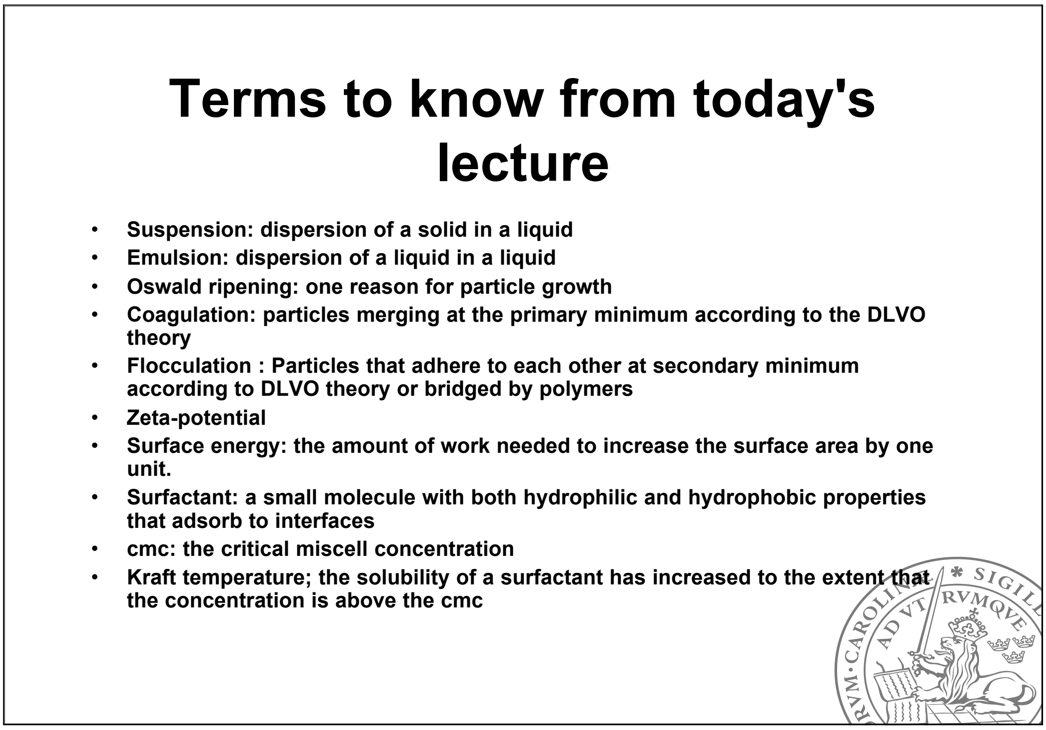
$$A = \frac{1}{\Gamma * N_a}$$



Kraft temperature

The Kraft temperature is the temperature at which the solubility of a surfactant has increased to the extent that the concentration is above the cmc of the surfactant.





Terms to know from today's lecture

- **Suspension: dispersion of a solid in a liquid**
- **Emulsion: dispersion of a liquid in a liquid**
- **Oswald ripening: one reason for particle growth**
- **Coagulation: particles merging at the primary minimum according to the DLVO theory**
- **Flocculation : Particles that adhere to each other at secondary minimum according to DLVO theory or bridged by polymers**
- **Zeta-potential**
- **Surface energy: the amount of work needed to increase the surface area by one unit.**
- **Surfactant: a small molecule with both hydrophilic and hydrophobic properties that adsorb to interfaces**
- **cmc: the critical miscell concentration**
- **Kraft temperature; the solubility of a surfactant has increased to the extent that the concentration is above the cmc**