SUSPENSIONS

Institute of Pharmaceutical Technology and Biopharmacy

Content of lecture

- Definition of suspensions
  (dosage form, chemical system)
- Physico-chemical properties of suspensions
- Examinations of suspensions
- Preparation of suspensions

Suspensions

Definition

Suspension – as a dosage form– is **externally or internally** used **liquid** pharmaceutical preparation, in which the **solid internal phase is permanently dispersed** in the continuous (external) phase, and after sedimentation it is **resuspendable.**

Pharmaceutical suspensions are **dispersions of solid drug particles** in a **vehicle** in which the drug has **low solubility.**

Particle size of the drugs may vary from one formulation to the other depending on the physicochemical characteristics of the drug and the rheological properties of the formulation.

Suspensions

- According to material structure aspect; suspensions are categorized into **heterogeneous S/L systems**, having liquid state of matter.
- **Multicomponent systems** (dispersed particles/dispersion medium)
- When size of dispersed particles is around **colloidal range**, then it is called **colloidal suspension**.

Suspensions

Particle size

Most of the pharmaceutical suspensions are **rough/coarse suspension**.

Some of the approved suspension preparation are available as **dry powders** that must be reconstituted before administration but occasionally some products in the market are **ready-to-use**.

In the cases of these medications, products are not so stable once reconstituted; **must be used within 7 to 10 days.**

Suspensions

Types of preparations

- „ready to use” (prepared suspension)
- dry powders (dispersed with water before use)

Suspensions

When should it be prepared?

- If the API has a **low solubility** (or insolubility) in the particular medium (the bioavailability in liquid form is better than in other pharmaceutical dosage form) (e.g. prednisolone suspension).
- If the **stability** in this form is **better** than in other forms.
- The **release** of the drug can be **controlled**
  (e.g. Insulin zinc suspension)
- If the **taste** of the API is **unpleasant** (e.g. chloramphenicol).

Suspensions

Advantages

- API content is **not limited** by the solubility of API, compared to solutions.
- **Chemical stability** is higher than in the case of solutions (e.g. procaine, oxytetracyclin, penicillin G).
- Effect may be **prolonged** (crystal injection).
- **Bioavailability** can be increased.
- **Taste** of API can be **masked** (e.g. bitter taste).

Suspensions

Disadvantages

- The **physical stability is lower** than in case of solutions (settles).
- High risk of **microbiological contamination.**
- **Particle size can be changed** during storage therefore precision of dosage consequently changes.

Suspensions

Pharmaceutical requirements

- **Homogeneous** distribution at least during the dosing (after shaking).
- Settled particles should be **redispersed** easily.
- Size of particles should **not change**.
- **Viscosity** preferably inhibits sedimentation, but has to allow free pouring of suspension.
- To have appropriate **microbiological stability**.

Suspensions

Main properties

- Particle size: **0.1-100 μm**
- Concentration of the solid phase: **0.5-40%**.
- The continuous (external) phase is usually: **water**, sometimes **oil**
- It is usually contains **polymers** like **mucilage** or other viscosity enhancers.
- Dispersion medium can be **diluted polymer solution** (water + mucilage), **water and polyols** (glycerol), but can contain other dissolved components (saccharose in case of syrups).

Theoretical background of suspensions

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Theoretical background of suspensions

Classification of suspensions based on particle size:

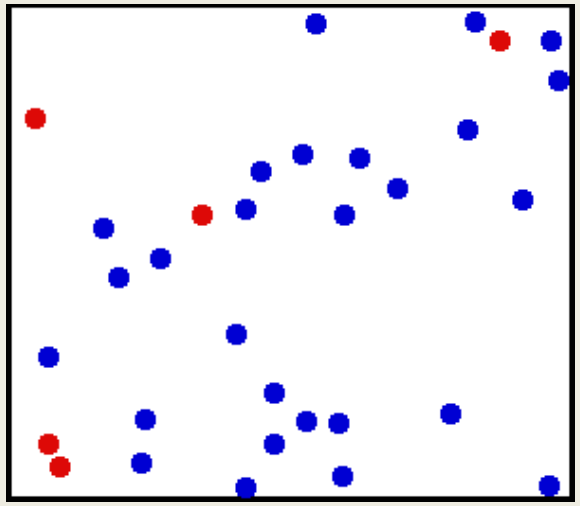
- ***Colloidal suspensions***
  particle size between 1-500 nm.

- ***Rough suspensions***
  size of particles is larger than 1 µm.

Theoretical background of suspensions

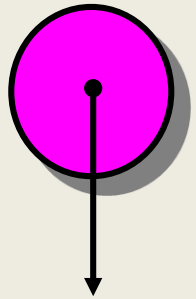
Force acting on particles
Motion forms

Solution
Brown motion



Constant motion

Suspension
gravity



Sedimentation and then stopping of motion

Theoretical background of suspensions

Sedimentation

1. **In low concentrated disperse systems**, the particles are so far from each other that does not inhibit their sedimentation
   (1-20% solid material).

2. **In higher concentrated disperse systems** – particles get close to each other, collide to each other and affect the motion of each other.
   a) In a definite distance attractive forces are dominant.
      If these forces are strong enough, then particles **bind to each other**.
   b) Larger particles settle faster than smaller ones.

3. **Adhesion forces** along the wall of container slow the sedimentation process.

Theoretical background of suspensions

The stability of the suspension depends on the interaction between the particles and between the particle and the medium.

The three most important properties:

- ***wetting*** *of the solid phase,*
- ***electrokinetic potencial*** *between the particles*
- *the* ***absorption of the polymers on the surface*** *of the particles*

These interactions can influence the preparation process and the stability, too.

Theoretical background of suspensions

Wetting

The ***liquids*** should wet the surface of the particles and should ***enter into the spaces, pores and channels*** which are between the aggregated particles.

The medium eliminating the air, gets into the inside of particles.

It is important to create a ***liquid-solid interface***.

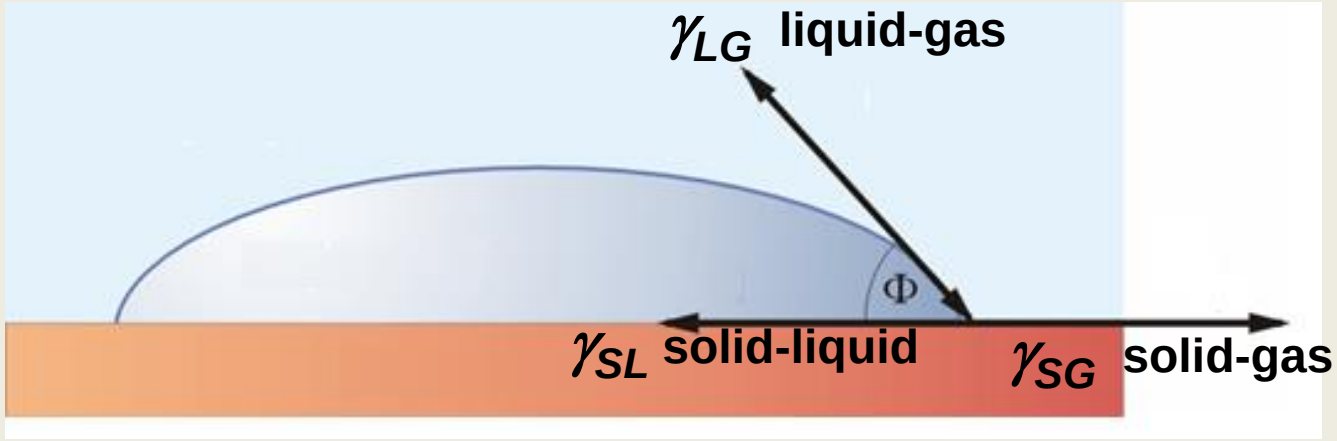
Wetting can be facilitated by ***surfactants***.

Theoretical background of suspensions

Young equation: Wetting process can be described by the contact angle, which is formed on the solid surface.

Contact angle (Φ): Contact angle decreases if the surface tension of the liquid decreases.

$$\gamma_{SG} = \gamma_{SL} + \gamma_{LG} \cos\Theta$$



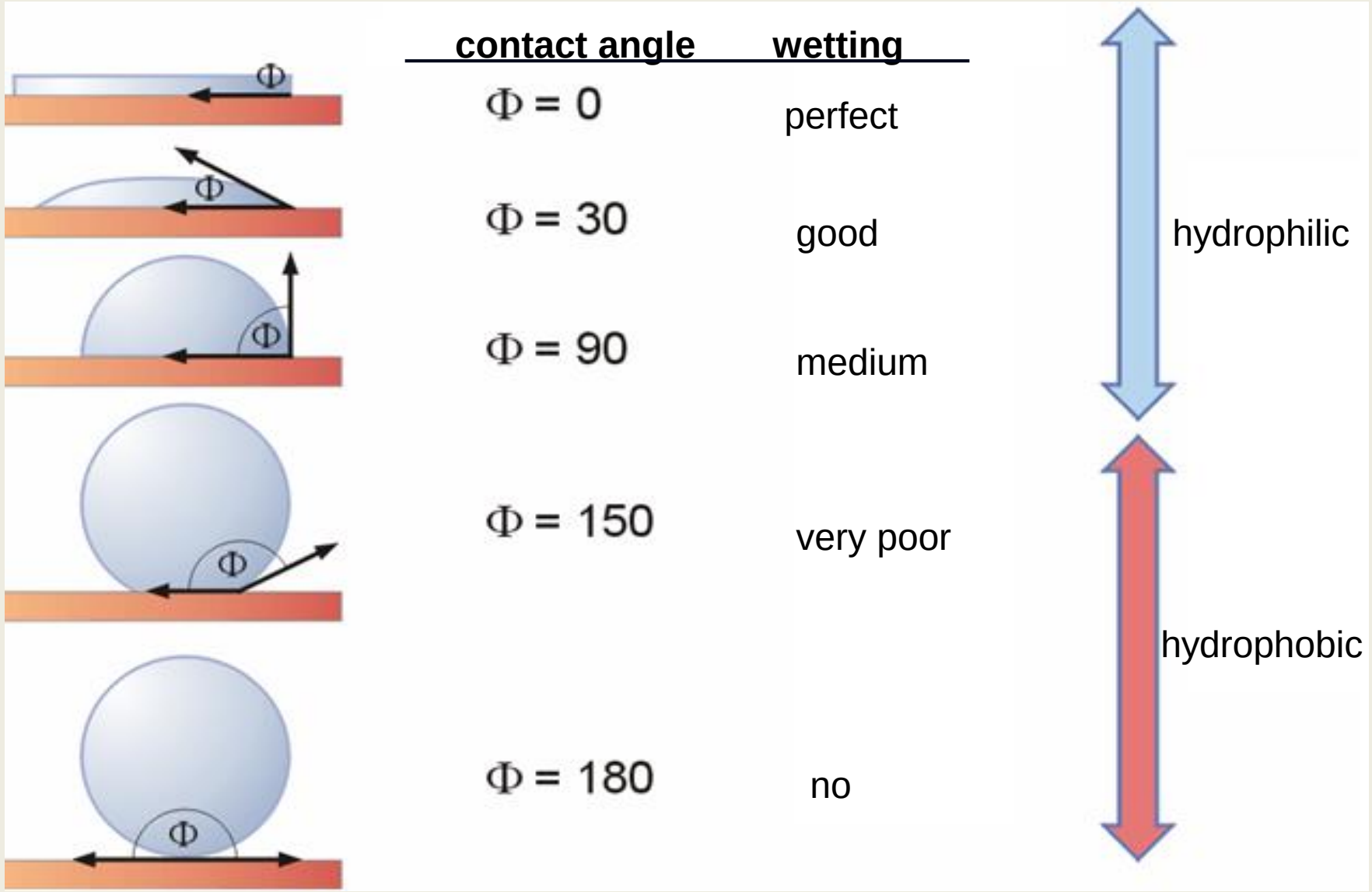
A contact angle of a liquid sample

Theoretical background of suspensions

Contact angle (Φ): Contact angle decreases if the surface tension of the liquid decreases.

Theoretical background of suspensions

Wetting contact angle



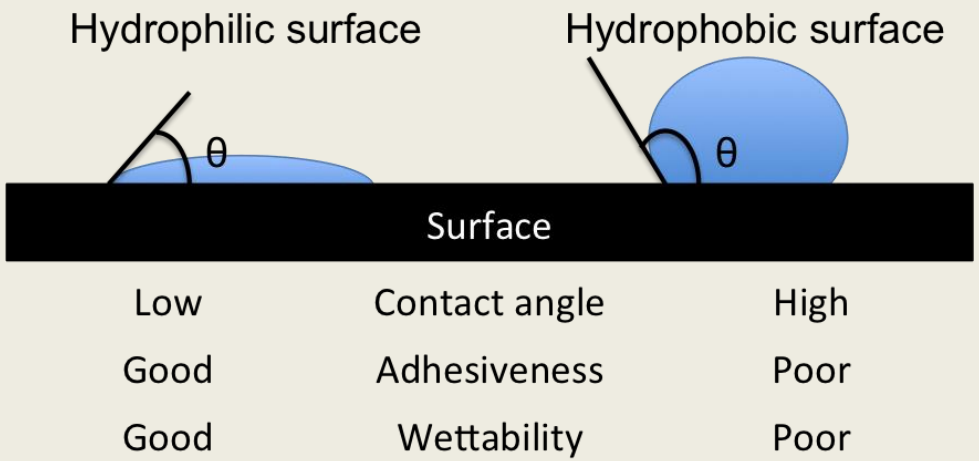
Theoretical background of suspensions

Wetting contact angle

The wetting is better if the contact angle is low.

In the case of perfect wetting, the value of the contact angle is 0.

If the contact angle is 180°, the surface is not wetted



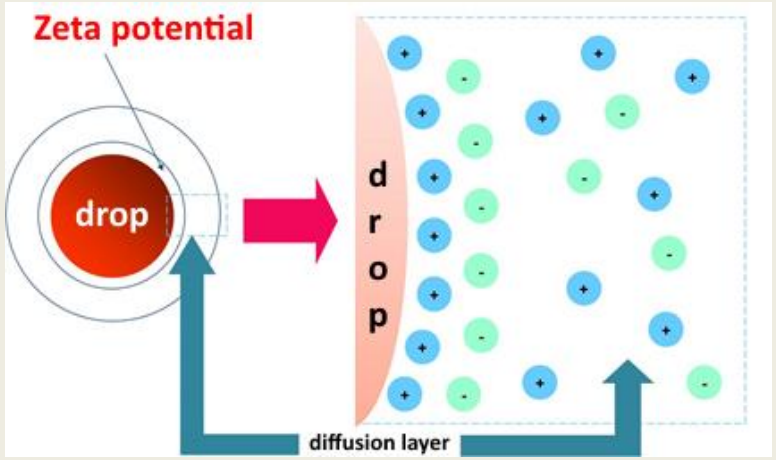
Theoretical background of suspensions

Electrokinetic potential (Zeta potential)

The **surface charges** can influence the particle-particle interactions and so the stability of the system.

Main causes of the formation of the **double layer**:

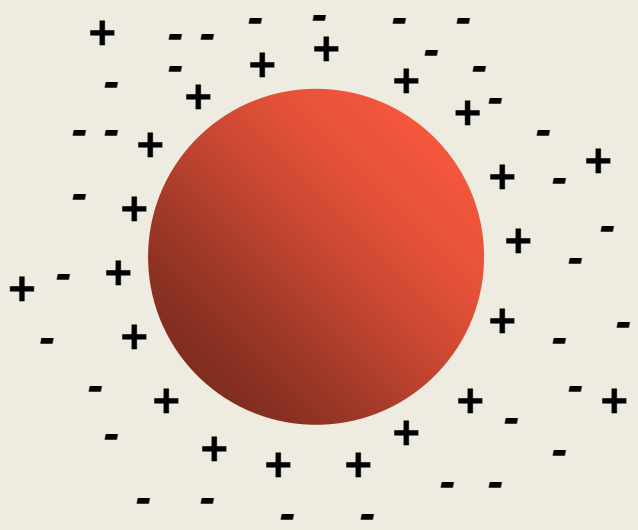
- the solid particles have a **permanent charge,**
- **polar molecules** are on the surface,
- **ions adsorb on the surface** of the particles,
- **chemical dissociation** happens on the surface.



Theoretical background of suspensions

Electric double-layer (EDL, also called as double layer, DL)

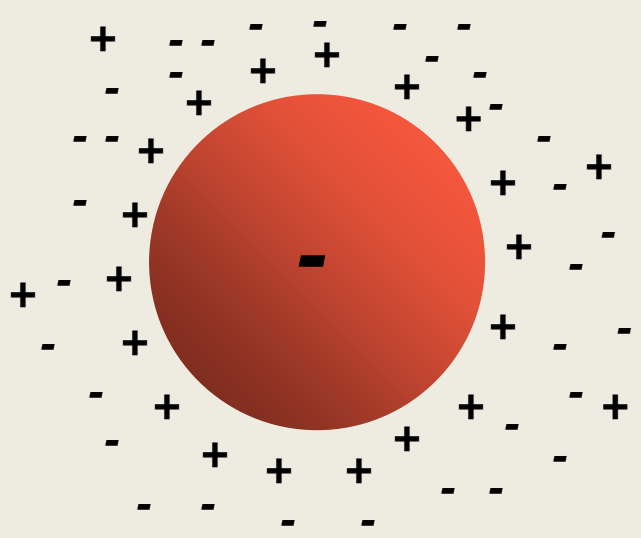
Charges **accumulate on the surface** of the particle.
These charges (ions) have **opposite charges** than the charge of the surface.
These structure can **influence the stability** of the emulsion(drop)/suspension system.
This double layer is **sensible to pH and ions**.



Theoretical background of suspensions

Electric double-layer (EDL, also called as double layer, DL)

The first layer contains ions adsorbed directly to the surface (called as Stern layer).
The second layer is composed of ions attracted to the surface charge via the coulomb force, electrically screening the first layer.
This second layer is **loosely associated** with the surface of particles, because it is made of free ions which move in the fluid under the influence of electric attraction and thermal motion rather than being firmly anchored. Thus it is called the diffuse layer.

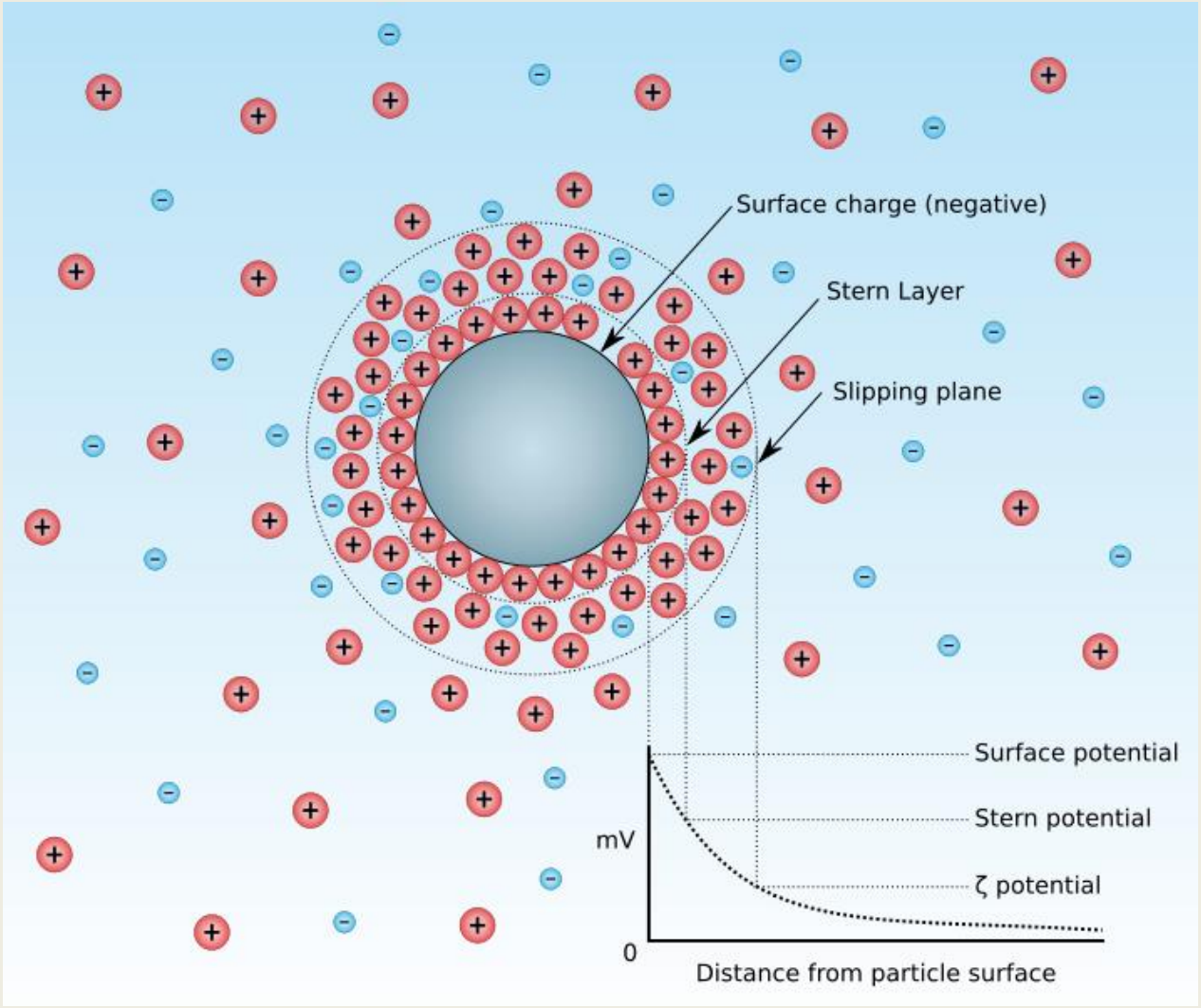


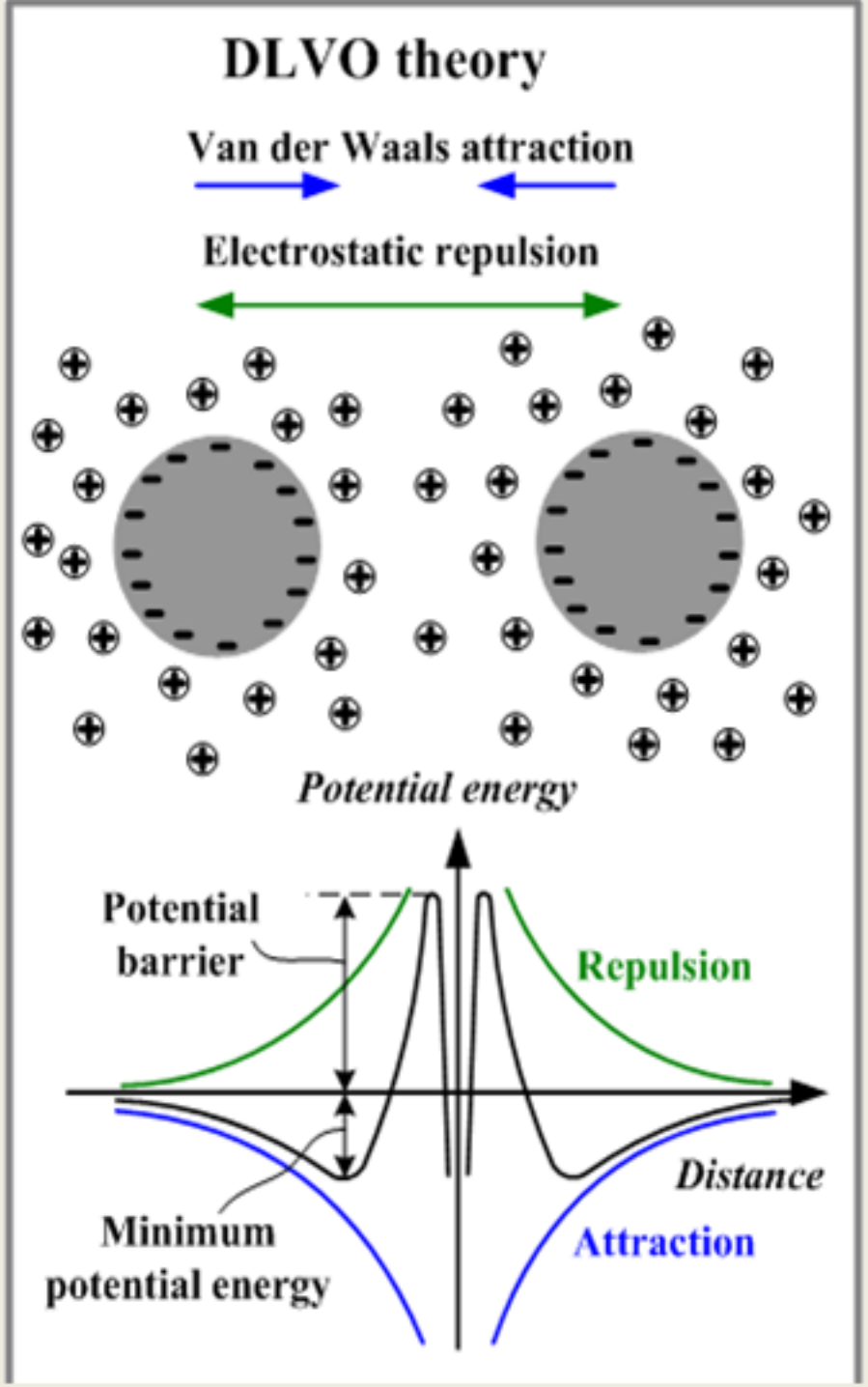
Theoretical background of suspensions

Zeta potential

The electrical double layer also explains the ***repulsive effect*** occurring between the particles.

Every factor that **decreases the thickness of the double layer** also decreases the repulsive forces acting between particles.





DLVO - theory

The theory developed by Derjagin, Landau, Verwey and Overbeek (DLVO- theory) interprets the **aggregate stability of disperse systems** as the resultant of **attractive and repulsive forces** between particles, saying that:

- **attractive** forces **increase** with distance according to the power function,
- **repulsive** force **decreases** exponentially.

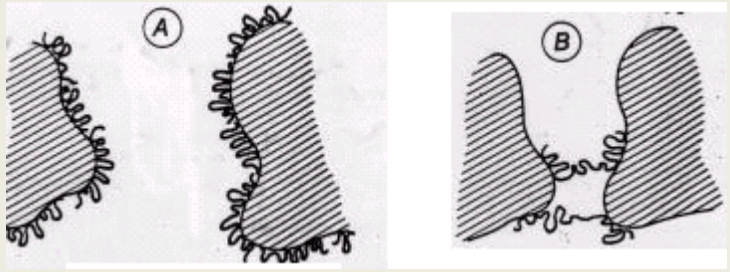
Theoretical background of suspensions

Absorption of polymers

Viscosity enhancer materials have two different types of effect to the particles:

A) anti-aggregative affect (protective)

the macromolecules fit to the surface and **no connection** between the covered particles



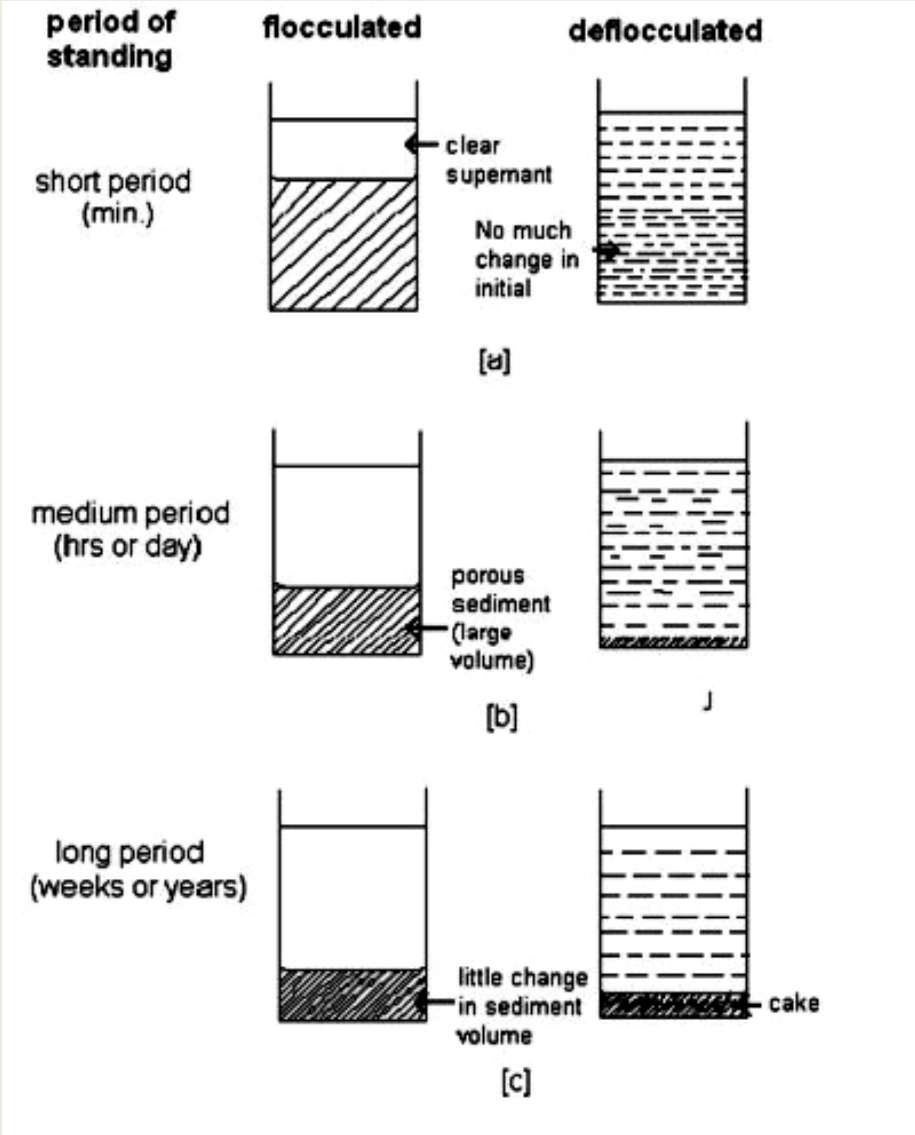
B) aggregative effect

there are **bridges** between the adsorbed macromolecules

The effect depends on: **concentration of the polymers** (the appropriate concentration is needed to the perfect covering, if there are ‘holes’ then the particles can aggregate).

Theoretical background of suspensions

Flocculation and deflocculation



Theoretical background of suspensions

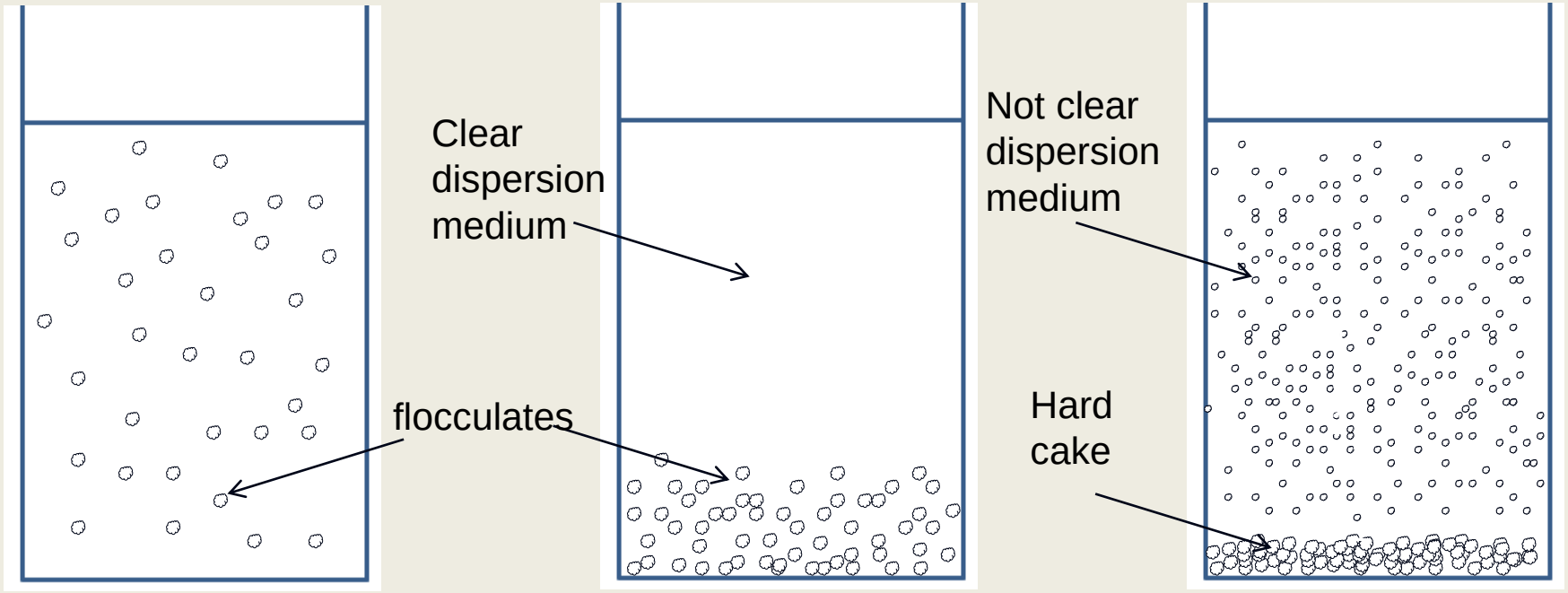
Flocculated and deflocculated particles

Flocculated	Deflocculated
1. Particles forms **loose aggregates** and form a network like structure	1. Particles exist as **separate entities**
2. Rate of sedimentation is **high**	2. Rate of sedimentation is **slow**
3. Sediment is **rapidly formed**	3. Sediment is **slowly formed**
4. Sediment is **loosely packed** and doesn't form a hard cake	4. Sediment is very **closely packed** and a hard cake is formed
5. Sediment is **easy to redisperse**	5. Sediment is **difficult to redisperse**
6. Suspension is **not pleasing in appearance**	6. Suspension is **pleasing in appearance**
7. The floccules **stick to the sides of the bottle**	7. They **don't stick** to the sides of the bottle

Theoretical background of suspensions

Flocculation and deflocculation

This is a controlled aggregation process, where the proper amount of polymer is applied. These aggregates have loose structure, **easily resuspendable and separable.**
The deflocculated sediment has a compact structure, which is **not resuspendable perfectly**.



Theoretical background of suspensions

A **flocculated sediment** can be prepared by:

- **Increasing attractive forces** until getting loose clusters
  (electrolytes can decrease the double layer)
- **Covering of the particles** surface with polymers
- **Change the charge** of the medium
  (other liquid is added)
- **Surfactants**
  - *The **ionic** surfactants can decrease the **zeta potential** like the ions*
  - *The **non-ionic** surfactants can decrease the **double layer**, and can interact with each other like the polymers*

Theoretical background of suspensions

Advantages and disadvantages due to **viscosity** of **medium**

Advantages

- High viscosity inhibits the crystal growth.
- High viscosity prevents the transformation of metastable crystal to stable crystal.
- High viscosity enhances the physical stability.

Disadvantages

- High viscosity hinders the re-dispersibility of the sediments.
- High viscosity retards the absorption of the drug.
- High viscosity creates problems in handling of the material during manufacturing.

Theoretical background of suspensions

Stokes-law: not concentrated suspension

where the particles **do not inhibit** the sedimentation of other particles.

$$V = \frac{h}{t} = \frac{2r^2(\rho_S - \rho_L)g}{9\eta}$$

v = speed of sedimentation
t = time, what is needed to the ‘h’ distance
g = gravity
ρ_S = density of solid phase
ρ_L = density of liquid phase
η = viscosity of the dispersion medium
r = particle radius

Theoretical background of suspensions

Kozeny-Carman-equation for concentrated suspensions

where the particles **inhibit** the sedimentation of other particles.

$$v = \frac{1}{\kappa \eta A_f^2} \frac{\varepsilon}{\left(1-\varepsilon^2\right)}$$

v = speed of sedimentation
ε = porosity
κ = Kozeny-constant
η = viscosity
A_F = surface area

Theoretical background of suspensions

Summation of the Stokes and Kozeny-Carman-equation:

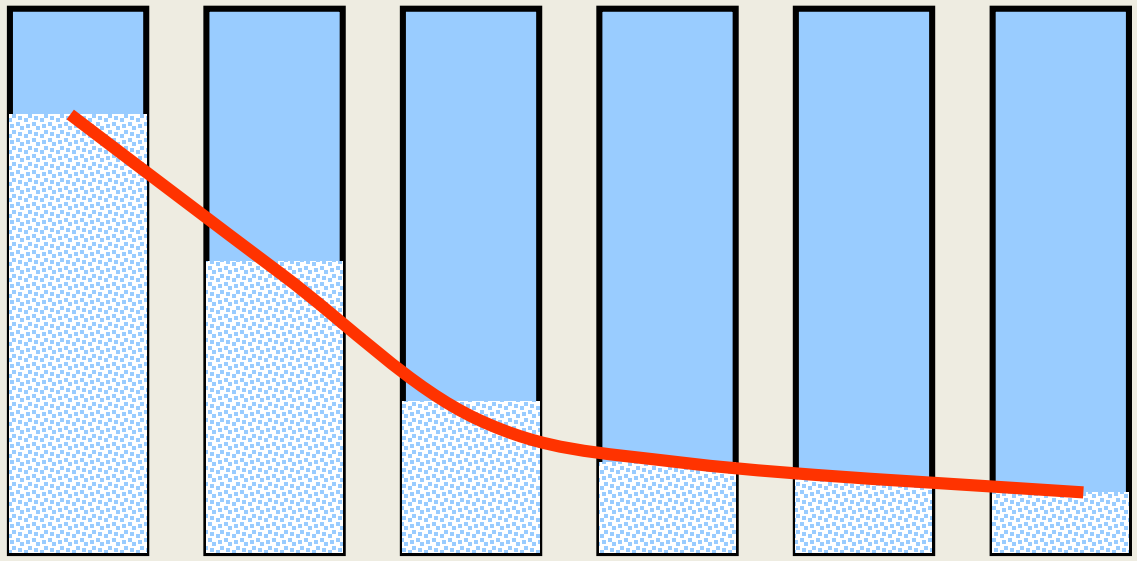
$$v = \frac{(\rho_S - \rho_L)g}{\kappa \eta A_F{}^2} \frac{\varepsilon}{(1-\varepsilon^2)}$$

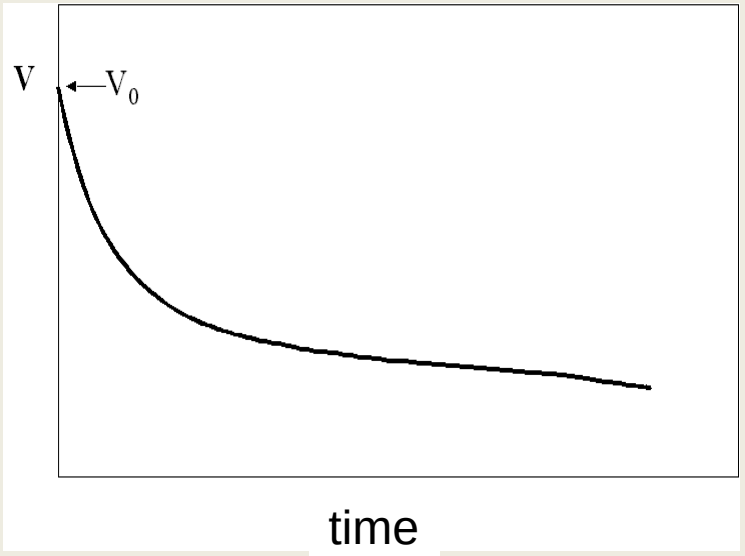
v	= speed of sedimentation
g	= gravity
ρ_S	= density of solid phase
ρ_L	= density of liquid phase
η	= viscosity of the dispersion medium
ε	= porosity
κ	= Kozeny-constant
A_F	= surface area

Theoretical background of suspensions

Sedimentation process

The sedimentation process can be characterized by the front of the sedimenting phase and this can be plotted against the time.





Theoretical background of suspensions

Sedimentation volume (*F*) or height (*H*) for flocculated suspensions

Sedimentation volume is a **ratio** of the **final** or ultimate volume of sediment (V_u) to the **original** volume of sediment (V_O) before settling.

$$F = \frac{V_u}{V_o} = \frac{H_u}{H_o}$$

V_u = final or ultimate volume of sediment

V_O = original volume of suspension before settling.

Preparation of suspensions

I. ***condensation (precipitation) in homogeneous systems***

II. ***dispersing***

Preparation of suspensions

Various excipients, which are used in suspension formulation

Components	Function
API……	Active drug substances
Wetting agents……	They are added to disperse solids in continuous liquid phase.
Flocculating agents ……	They are added to flocculate particles
Viscosity enhacers……	They are added to increase the viscosity of suspension.
Buffers and pH adjusting agents……	They are added to stabilize the suspension to a desired pH range.
Osmotic agents……	They are added to adjust osmotic pressure comparable to biological fluid.
Coloring agents……	They are added to impart desired color to suspension and improve elegance.
Preservatives……	They are added to prevent microbial growth.
Liquid vehicle……	They are added to construct structure of the final suspension.

Preparation of suspensions

Suspending agents

Suspending agents	Concentration range
Sodium alginate	1– 5 %
Methylcellulose	1– 2 %
Hydroxyethylcellulose	1-2%
Hydroxypropylcellulose	1-2%
Hydroxypropylmethylcellulose	1-2%
CMC	1-2%
Na-CMC	0.1-5%
Microcrystalline cellulose	0.6– 1.5 %
Tragacanth	1-5%
Xanthangum	0.05-0.5%
Bentonite	0.5– 5.0 %
Carageenan	0.5– 1 %
Guargum	1-5%
Colloidalsilicon dioxide	2– 4 %

Preparation of suspensions

Preservatives

Name of preservatives	Concentration range
Propylene glycol	5-10%
Disodium edentate	0.1%
Benzalkonium chloride	0.01-0.02%
Benzoic acid	0.1%
Butyl paraben	0.006-0.05% oral suspension 0.02-0.4% topical formulation
Cetrimide	0.005%
Chlorobutanol	0.5%
Potassium sorbate	0.1-0.2%
Sodium benzoate	0.02-0.5%
Sorbic acid	0.05-0.2%
Methyl paraben	0.015-0.2%

Preparation of suspensions

Flavoring agents

Acacia
Ginger
Sarsaparilla syrup
Anise oil
Glucose
Spearmint oil
Benzaldehyde
Glycerin
Thyme oil
Caraway oil
Glycerrhiza
Tolu balsam
Cardamom (oil, tincture, spirit)
Honey
Vanilla
Cherry syrup
Lavender oil
Vanilla tincture
Cinnamon (oil, water)
Lemon oil
Tolu balsam syrup
Citric acid syrup
Mannitol
Wild cherry syrup
Citric acid
Nutmeg oil
Clove oil
Methyl salicylate
Cocoa
Orange oil
Cocoa syrup
Orange flower water
Coriander oil
Peppermint (oil, spirit, water)
Dextrose
Raspberry
Ethyl acetate
Rose (oil, water)
Ethyl vanillin
Rosemary oil
Fennel oil
Saccharin sodium

Preparation of suspensions

Condensation

One of the properties of the solution is changed.
If the new conditions is not suitable to the API than it will be **precipitating**.

- exchange of solvent,
- pH changes,
- changing the ionic strength,
- insoluble complex formation.

Preparation of suspensions

Dispersing

Dispersing is a **wet disintegration and crushing** at the same time.

The **wet** grinding is **more effective** than the dry crushing.

- This effect can be forced by the application of surfactants too. Due to wetting introduction of channels is better, holes, spaces of the aggregated particles is filled more with vehicle.

- The liquids are incompressible, so the pressure energy is not able to spread and absorbing into a compressible medium.
  The forced energy will break down the solid bridges of the aggregates.

Preparation of suspensions

Excipients

- Wetting agent
- Viscosity enhancers

  (mucilage, cellulose derivatives, alginate, carragen, polyacrilates)
- Protective colloids

  (silica colloidales anhydrica)
- Zeta-potency influencing agents

  (electrolytes, surfactants, polymers)
- Microbiological preservatives
- Taste and smell enhancers

Preparation of suspensions

In pharmacy

- Particle size of dispersed phase (solid) should be **not bigger** than 160 µm (sieve with No. 6).
- The wetting process should be done by the application of the proper amount of surfactant (wetting agent).
- The water based suspensions, which contain mucilage as well, must be **preserved** by the proper amount of substance or stock solution.

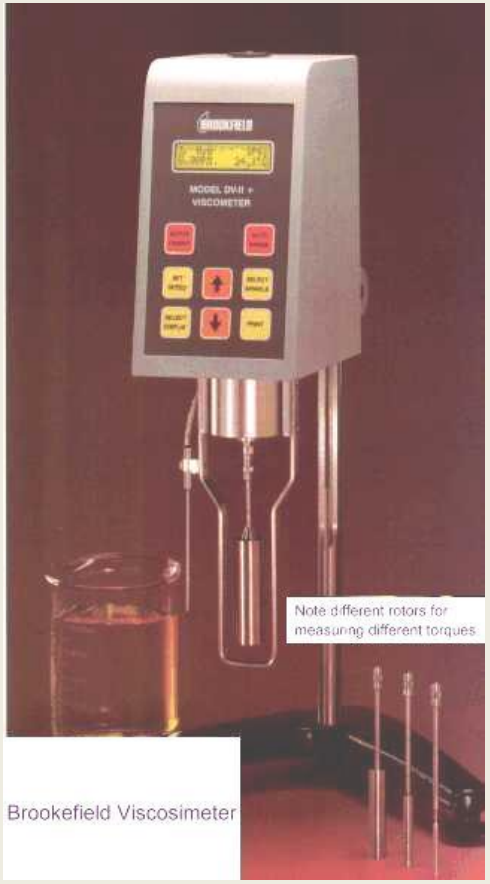
Preparation of suspensions

Main steps of preparation

1. Taking the solid ingredient into the mortar
2. Addition of the wetting agent
3. Producing a concentrated suspension with a small amount of outer phase in the mortar (diluting the suspension)
4. Washing this concentrated suspension using the outer phase into the bottle
5. Measurement the microbiological preservative directly into the bottle
6. Completion the suspension with the outer phase to the prescribed weight.

Preparation of suspensions
In pharmacy

Examination of suspensions



Rotational viscosimeter

Particle size and distribution

1. Sedimentation technique

a. sedimentation with gravity
(Andreasen-cylinder, Wiegner-tube, Sartorius scale)
b. sedimentation with centrifugation

2. Optical methods

- microscopic methods with digital imagine,
- light scattering methods

3. Impulse method with conductivity

(Coulter-counter)

Particle size and distribution

Sedimentation technique

(Andreasen cylinder)

- Size distribution is determined by allowing a homogeneous suspension to settle in a cylinder and taking samples from the settling suspension at a fixed horizontal level at intervals of time.
- Each sample will contain a representative sample of the suspension, with the exception of particles greater than a critical size, all of which will have settled below the level of the sampling point.
- The concentration of solid in a sample taken at time ‚t' is determined by centrifugation of the sample followed by drying and weighing or simply by drying and weighing.
- This concentration expressed as a percentage of the initial concentration gives the percentage (w/w) of particles whose falling velocities are equal to or less than x/t. Substitution in the equation above gives the corresponding Stokes' diameter.

Particle size and distribution

Sedimentation technique

(Andreasen cylinder)

$$v = \frac{h}{t} = \frac{2r^2(\rho_1 - \rho_2)g}{9\eta}$$

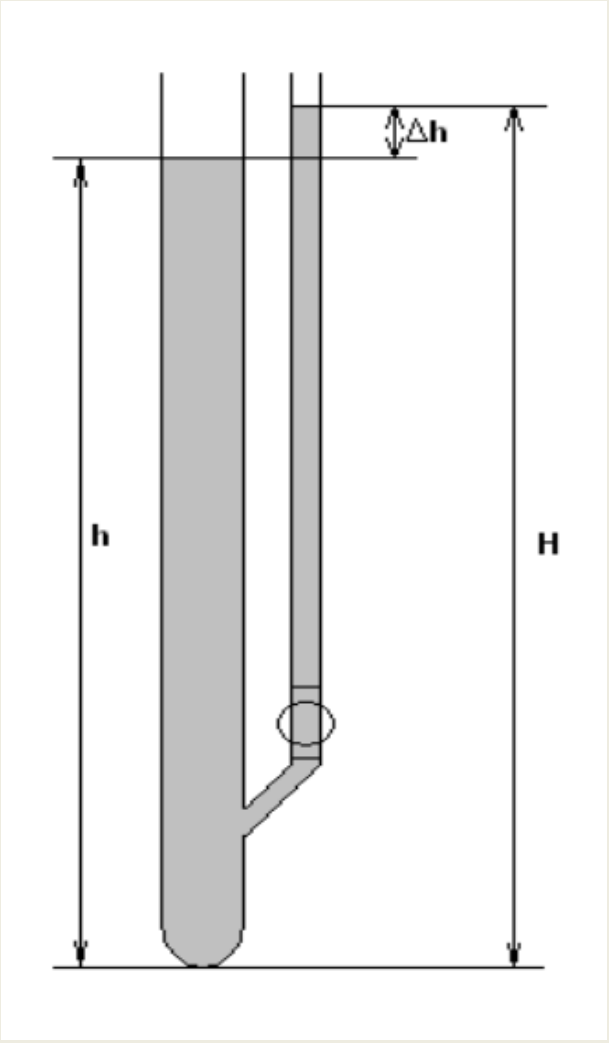
$$t = \frac{9\eta}{2(\rho_1 - \rho_2)g}\frac{h}{r^2} = k\frac{h}{r^2}$$

If we know the ***k*** value, then we can calculate the sedimented particles' size at the given ***t*** time.

Particle size and distribution

Sedimentation technique

(Wiegner tube)



$$\frac{H}{h} = \frac{\rho_{sz}}{\rho_f}$$

$$\Delta h = \frac{h}{\rho_f}(\rho_{sz} - \rho_f)$$

$$P = \frac{A}{\frac{1}{\rho_f} - \frac{1}{\rho_{sz}}} \Delta h$$

H = height of the liquid level in the measuring tube [m]
h = height of the liquid level in the settling tube [m]
ρ_{sz}= density of suspension [kg/m3]
ρ_f= density of dispersion medium [kg/m3]

ρ_{sz} and ρ_f the density of the solid or liquid

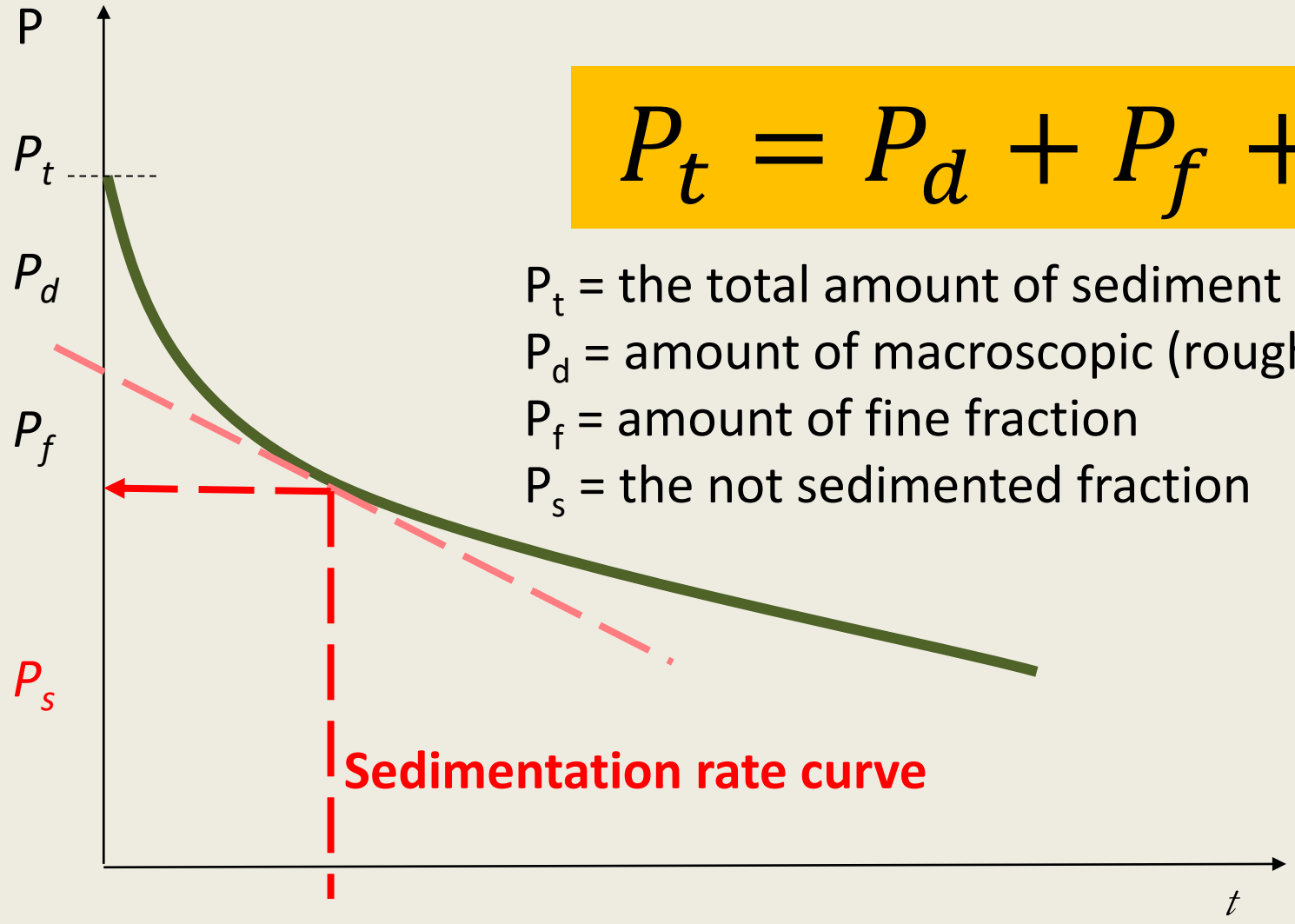
P the amount of particles that are at h (height)

A the surface of the sedimentation tube

Particle size and distribution

Sedimentation technique

(Wiegner tube)



$$P_t = P_d + P_f + P_s$$

P_t = the total amount of sediment

P_d = amount of macroscopic (rough) fraction

P_f = amount of fine fraction

P_s = the not sedimented fraction

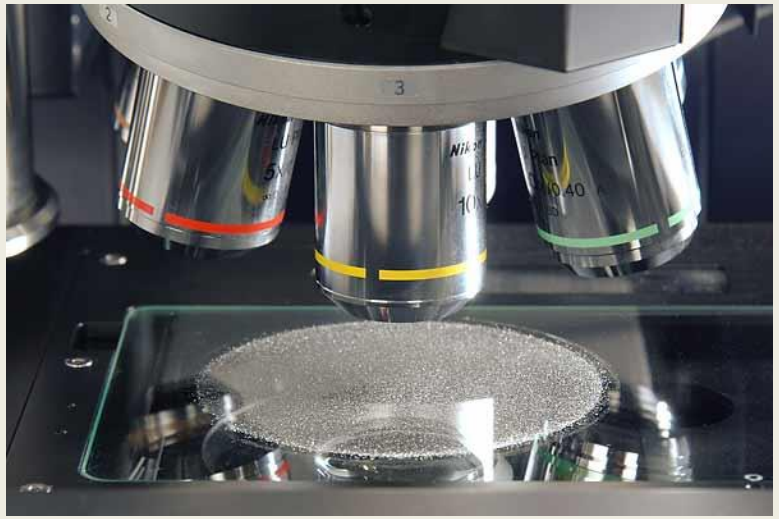
Particle size and distribution

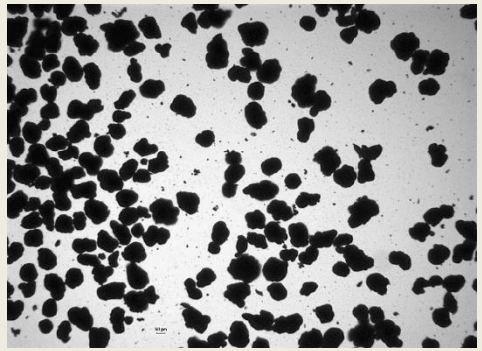
Optical methods

a. microscopic methods with digital imagine,

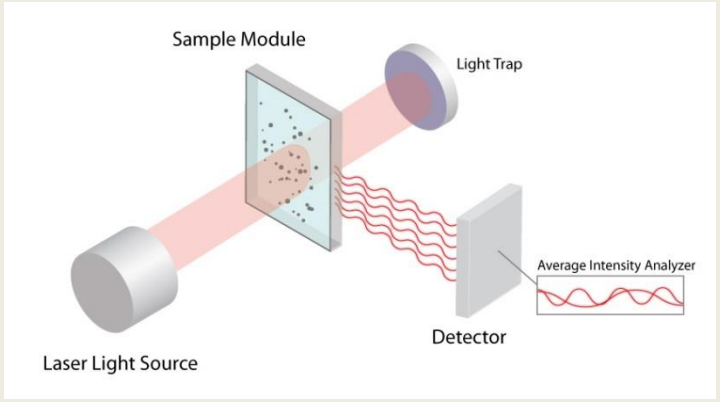
b. light scattering methods

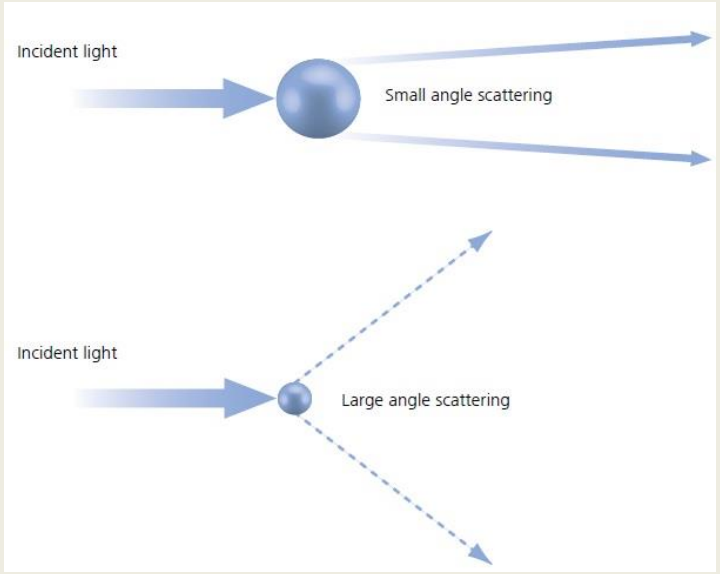
a.





b.





Particle size and distribution

Impulse method with conductivity
(Coulter-counter)

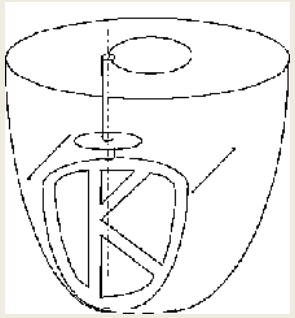
- Particles suspended in a conductive electrolyte solution are drawn through a small aperture.
- A DC current is applied, creating a „sensing zone”.
- As each particle passes through the aperture, it displaces an amount of saline equivalent to its size, creating impedance resulting in a voltage pulse proportional to the particle volume.

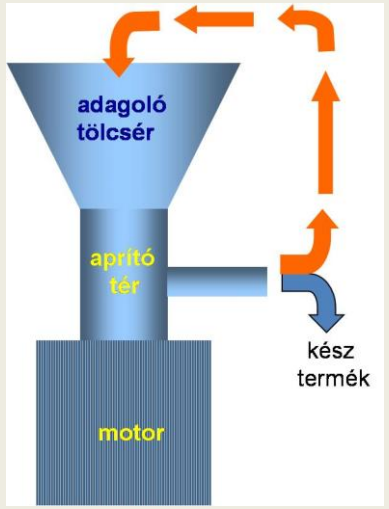
Equipment for producing suspensions

Institute of Pharmaceutical Technology and Biopharmacy

Equipments for making suspensions

Different types of mixers, crushers, homogenizers (see in lecture of emulsions).





Application of suspensions

Application of suspensions

- oral (eg. brushing)
- per oral (eg. adsorbents, acid binders, anti-bacterial)
- dry powders to prepare suspensions
- dermal (eg. drying ointment, antibiotic, antifungal)
- ear (eg. antibiotics)
- vaginal (eg. flushing, medication)
- nasal (eg. mucosal treatment)
- parenteral (injection-crystalline)
- ocular (irritation due to rare)
- rectal (eg. enemas).

Application of suspensions

Examples of Pharmaceutical Suspensions:

- Antacid oral suspensions
- Antibacterial oral suspension
- Dry powders for oral suspension (antibiotic)
- Analgesic oral suspension
- Anthelmentic oral suspension
- Anticonvulsant oral suspension
- Antifungal oral suspension

Important suspensions

Suspensio anaesthetica

For anesthesia of the mouth, throat, esophagus, mucous membranes.
Shake before use. Keep in a cool place.
Expiry 1 month.
Localanaestheticum. Antiemeticum.

SUSPENSIO ANAESTHETICA
(Susp. anaesth.)

I. Benzocainum	**3,0**	**g**	
II. Mucilago hydroxyaethylcellulosi . .	**40,0**	**g**	
III. Diluendum menthae FoNo VII	**5,0**	**g**	
IV. Solutio conservans	**1,0**	**g**	
V. Sirupus sorbiti FoNo VII	**ad 100,0**	**g**	**(51,0 g)**

Készítés: Az I-t a II. kis részleteivel eldörzsöljük. A szuszpenziót az V-kel, a III-kal és a IV-kel üvegbe mossuk és összerázzuk.

Important suspensions

Suspensio antiseptica

Slight disinfectant shaking blend for surface abrasion, acne, non-dermatitis skin inflammation.
External use. Shake before use. Keep in a cool place
Expiry 1 month.
Dermatologicum.
Application not suggested under age 14!

SUSPENSIO ANTISEPTICA

(Susp. antisept.)

Cliochinolum . .	**3,0**	**g**	
Talcum	**40,0**	**g**	
Oleum helianthi	**ad 100,0**	**g**	**(57,0 g)**

Important suspensions

Suspensio siccans

Drying suspension.
External use. Shake before use. Keep in a cool place
Dermatologicum

SUSPENSIO SICCANS

(Susp. sicc.)

Szárító szuszpenzió

Acidum boricum	**6,0 g**
Aqua destillata	**212,0 g**
Polysorbatum 20	**2,0 g**
Aluminium aceticum tartaricum solutum	**30,0 g**
Glycerinum	**150,0 g**
Mucilago methylcellulosi	**300,0 g**
Zincum oxydatum	**150,0 g**
Talcum	**150,0 g**

Készítés: A bórsavat desztillált vízben melegítéssel oldjuk. A lehűtött oldathoz elegyítjük a többi alkotórészt, amellyel végül a cink-oxid és talkum keverékét eldörzsöljük.

Important suspensions

Suspensio zinci aquosa

Acute, non-dermatologic dermatitis, urticaria, pruritus of senile cooling, to reduce itchiness.
External use. Shake before use. Keep in a cool place.
Dermatologicum.

SUSPENSIO ZINCI AQUOSA

(Susp. zinc. aquos.)

1. Zincum oxydatum	20,0	g
1. Talcum	20,0	g
II. Glycerinum	10,0	g
II. Alcoholum dilutum 70%	10,0	g
II. Aetheroleum menthae piperitae . .	X	gtt
III. Solutio acidi borici 2% FoNo VII. . .	40,0	g

Készítés: Az I. alatti alkotórészek homogén keverékét a II. folyadékeleggyel eldörzsöljük, a III-kal üvegbe mossuk és összerázzuk.

Important suspensions

Suspensio zinci oleosa

Acute, non-dermatologic dermatitis, urticaria, pruritus of senile cooling, to reduce itchiness.
External use. Shake before use. Keep in a cool place.
Dermatologicum. Adstringens.

SUSPENSIO ZINCI OLEOSA
(Susp. zinc. oleos.)

Zincum oxydatum	**40,0**	**g**
Oleum helianthi	**60,0**	**g**

Application of suspensions

Ophthalmic Suspensions

The bioavailability of ophthalmic suspension is influenced by:

- the ***viscosity*** of the vehicle
- the ***particle size*** of the suspended drug particles

Polymers are used (polyvinyl alcohol, polyvinyl pyrolidone, cellulose derivatives) for adjust the adequate viscosity and adequate particle settling.

The particle size must be ***below 10 micron*** to delay the absorption from cornea.
The particle size is related with dissolution rate as well as retention within the conjuctival sac.

Application of suspensions

Parenteral suspensions

In case of parenteral suspension the dissolution characteristic of drugs influences which drug will be absorbed into the systemic circulation at the site of administration and therefore dissolution characteristic of drugs will determine the bioavailability.

Further suspensions

Nano-Crystals

For low-soluble or permeable active molecules, the molecular **nano-crystalline** form is used to demonstrate higher dissolution rates due to their higher surface / volume ratio.
This helps improve bioavailability, including permeation.

These submicroscopic nanoparticles are equally preferred as conventional nanoparticles having a particle size of **less than 100 nm**, but scalable and suitable for any manufacturing process.
This allows optimization of nano-crystals and surface efficiency to optimize migration and targeted drug effect.

THANK YOU FOR ATTENTION!