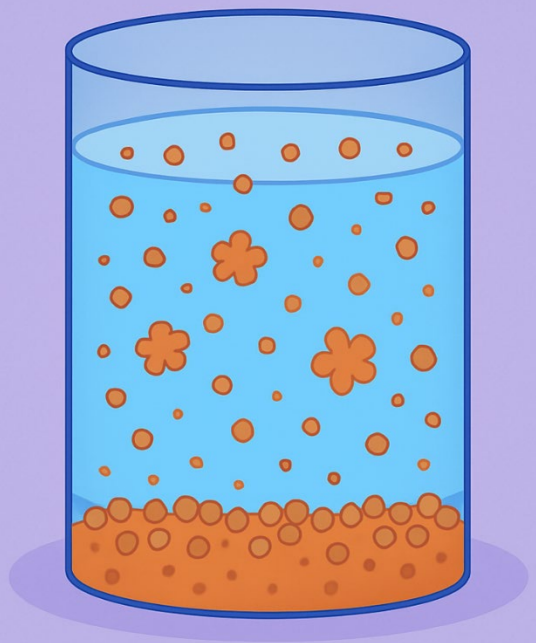
VNIVERSITAT DE VALÈNCIA
Facultat de Farmàcia i Ciències de l'Alimentació

UNIT 11. SUSPENSIONS



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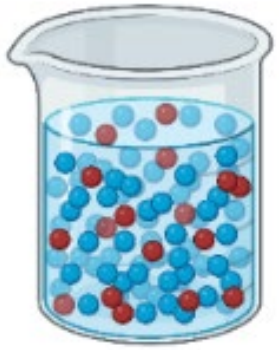
Pharmaceutical Technology I
Academic year 2025-2026



What are the disperse systems?

Disperse systems are physical mixtures composed of at least two substances of different chemical nature that are intimately combined, with one phase dispersed within another.

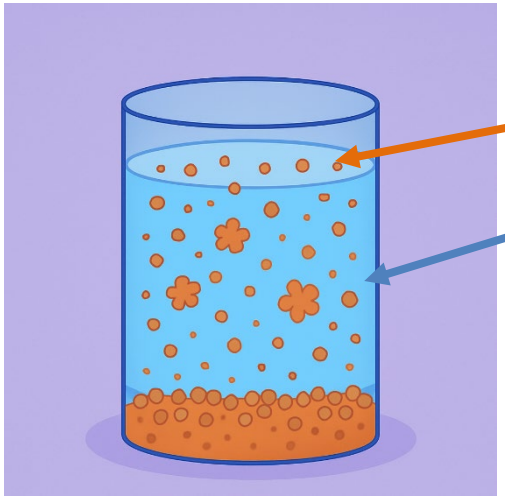
What is the disperse or internal phase?

It is the substance that is distributed as **particles** within the continuous medium.

What is the continuous or external dispersion medium?

It is the **medium** in which the dispersed particles are distributed.

1. State of matter of the continuous and disperse phase:



Dispersion medium	Disperse phase	Name
Liquid	Solid	Solution // **Suspension**

2. Degree of **homogeneity** in the distribution of physical and chemical characteristics:

System	Definition
HETEROGENEOUS	A system composed of regions with different physical and/or chemical properties (e.g. suspensions, emulsions)

3. Particle **size** of the internal phase:

System	Particle size
COARSE	> 1µm

What are the suspensions?

Suspensions are **coarse heterogeneous dispersions** in which insoluble solid particles, > 1 µm in diameter, are dispersed in a liquid medium, usually aqueous.

What are the components?

External or continuous phase or dispersion medium:

- **LIQUID** (usually aqueous) or
- **SEMISOLID**

Internal or disperse phase:

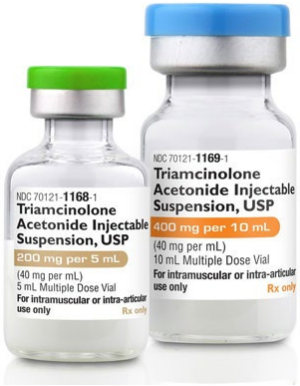
- insoluble **SOLID** particles> 1 µm

Which are the pharmaceutical applications and advantages of oral suspensions?

- Suitable for **patients who have difficulty swallowing solid dosage forms** (e.g., children, elderly).
- Useful for **drugs that are insoluble or poorly soluble in water**.
- Allow **improved stability** compared to solutions for certain active ingredients.
- **Fine suspensions** increase the **gastrointestinal surface area**, enhancing **toxin adsorption** and **pH neutralisation**.
- Can be **flavoured or sweetened to mask unpleasant tastes** (e.g., chloramphenicol, paracetamol).
- Enable **modification of drug release**, including **controlled or sustained release formulations.**

Suspensions

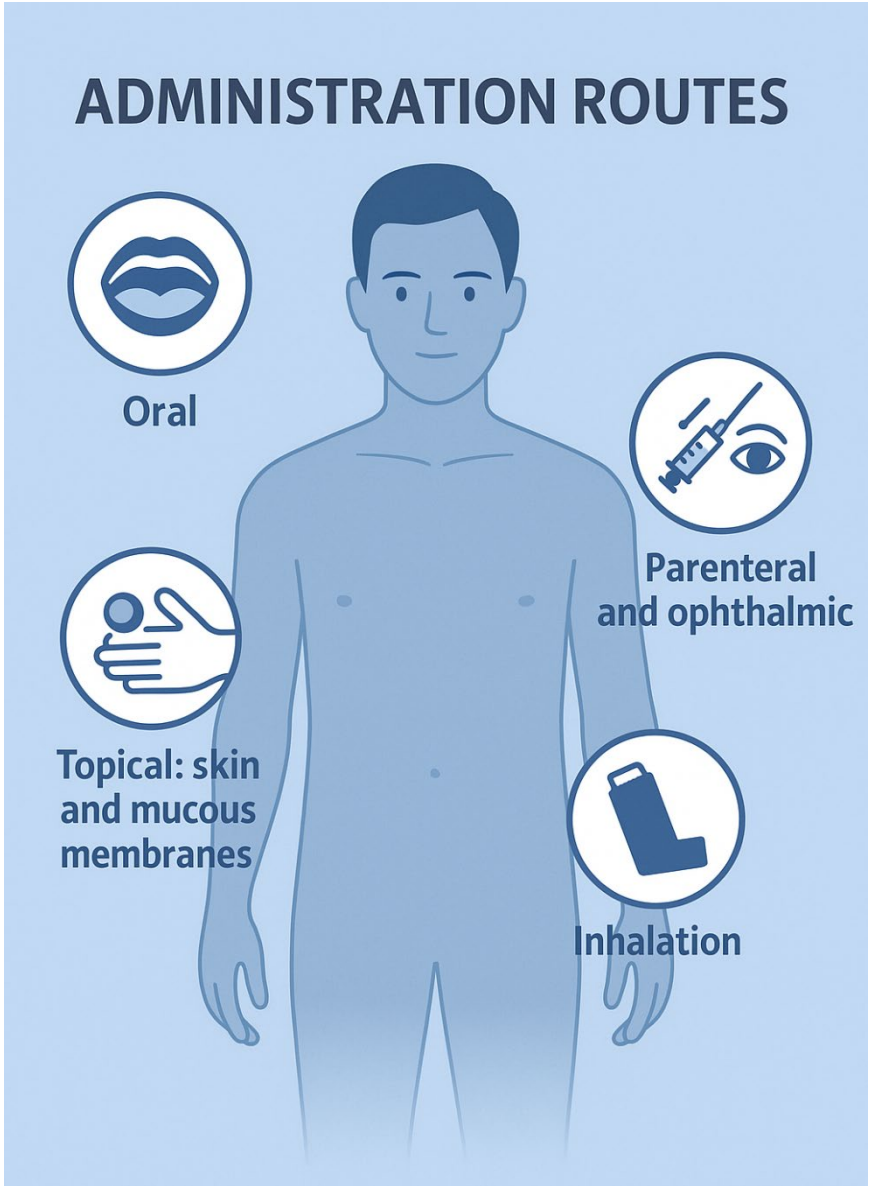
Administration for inhalation



Administration for parenteral route

Administration for ocular application

For oral administration



Suspensions are **thermodynamically unstable systems** ($\Delta G = \gamma \cdot \Delta A$), where several **physical phenomena** can compromise stability:

- Humectation
- Sedimentation
- Caking (formation of a non-redispersible sediment)
- Crystalline growth (Ostwald ripening)

Definition of stability

A suspension is stable when particles remain evenly dispersed (uniformly distributed) without aggregation.

Key Quality Criteria for Pharmaceutical Suspensions

- The suspension must remain **homogeneous** between shaking and dosing to ensure **dose uniformity**.
- **Sedimentation** should occur **slowly**, and any sediment formed during storage should be **easily redispersed** upon shaking.
- The **viscosity** should be properly balanced:
    - High enough to **reduce sedimentation**.
    - Low enough to **allow easy withdrawal and administration**.
- **Particle size** should be **small and uniform**, providing a **smooth texture** and stable appearance.

Internal Phase

- **Active ingredient:** solid (insoluble)

External Phase

- **Vehicle:** liquid (water or another solvent)
- **Wetting agents:** facilitate dispersion of the solid
- **Viscosity enhancers:** improve stability by slowing sedimentation
- **Flocculating agents:** promote redispersible sediment
- **Other excipients (depending on route):**
    - Oral: organoleptic correctors
    - Topical: particle size < 35 µm
    - Ophthalmic: sterile, isotonic, physiological pH
    - Parenteral (SC/IM): sterile, physiological pH, pyrogen-free, isotonic, particle size < 5 µm

Flavours, Sweeteners, Colours

- Improve palatability (especially for paediatric oral use).
- Common sweeteners: saccharin, acesulfame K, aspartame *(phenylketonuria caution)*.
- Must consider their effect on particle charge (DLVO interactions).

Antimicrobial Preservatives

- Prevent contamination in aqueous suspensions.
- Examples: parabens, benzoic acid, sorbic acid, benzalkonium chloride.
- Must assess their ionic effect on flocculation and stability.

Buffers

- Maintain pH within desired range.
- Affect ionization and flocculation behaviour.

Chemical Stabilizers

• Increase drug stability (e.g. antioxidants like ascorbic acid, EDTA as chelator).

Viscosity & Density Modifiers (Suspending Agents)

• Control sedimentation and redispersion balance.

• Examples: cellulose derivatives (HPMC, CMC), alginates, gums, clays.

Wetting Agents & Flocculation Modifiers

• Improve particle wetting and control aggregation behaviour.

• Surfactants (e.g. sodium lauryl sulfate) modify surface charge.

• Flocculation modifiers (e.g. NaCl, $CaCl_2$) adjust ionic strength to tune flocculation.

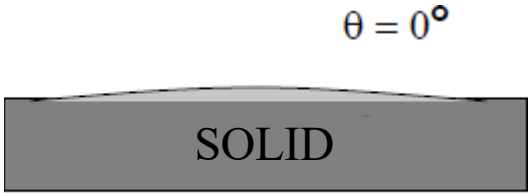
5.1. Humectation

Solid-liquid interface

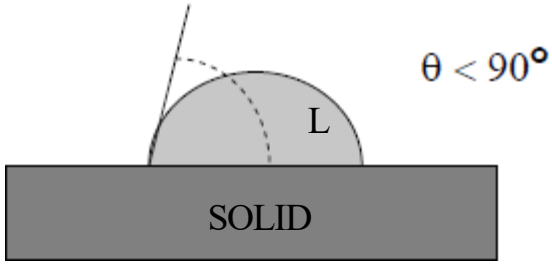
In suspension formulation, ensuring that the liquid phase wets the solid particles is essential. The extent of wetting, or *wettability*, is quantified by the contact angle formed between the solid surface and the liquid.

5.1. Humectation

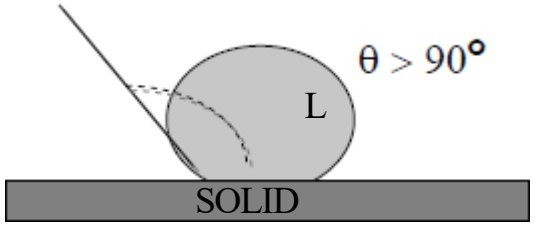
Solid-liquid interface



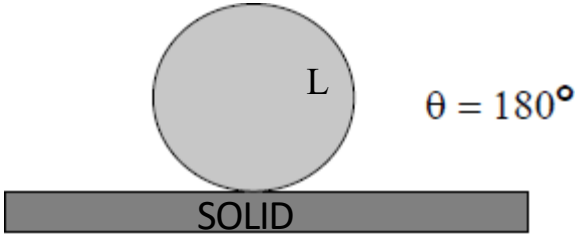
The liquid fully spreads across the solid surface, indicating complete wetting.



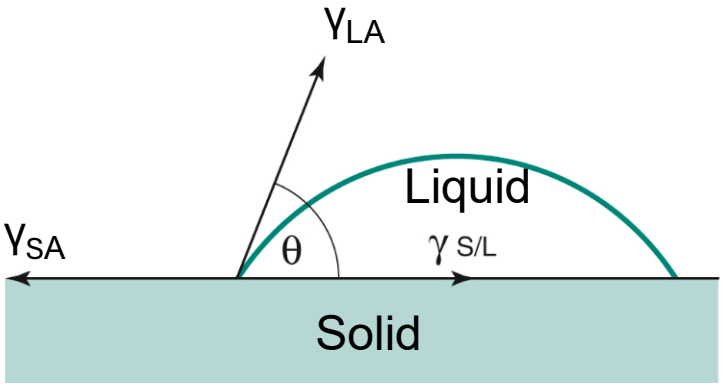
Good wetting occurs on hydrophilic solid surfaces.



Poor wetting occurs on hydrophobic solids where the liquid does not spread easily.



No wetting — The liquid drop does not spread on the solid surface.



$$\gamma_{SA} = \gamma_{SL} + \gamma_{LA} \cdot \cos\theta$$

Balance between the different forces of wetting:

γ_{SA} = Solid surface tension

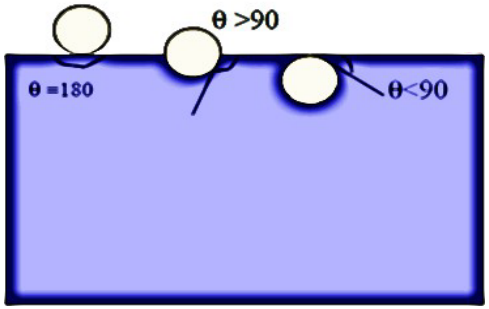
γ_{LA} = Liquid surface tension

γ_{SL} = Solid-liquid interfacial tension

θ = contact angle

Young equation

$$\cos\theta = \frac{\gamma_{SA} - \gamma_{SL}}{\gamma_{LA}}$$



Cos 180º = -1

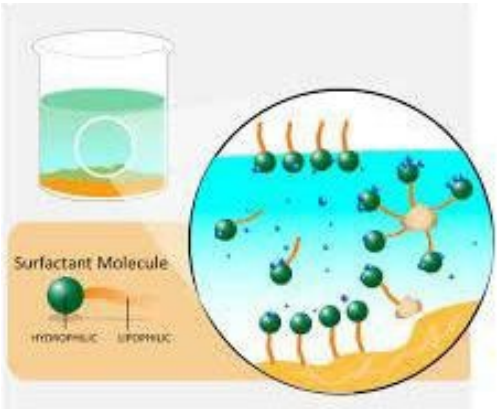
Cos 90º = 0

Cos 0º = 1

Wetting condition	Contact angle (θ)	Surface tension relationship	cos θ value	Behaviour / System type
Non-wetting	90° < θ ≤ 180°	γSA < γSL	cos θ < 0	Particles float; poor wetting and dispersion
Partial wetting	θ ≈ 90°	γSA = γSL	cos θ = 0	Limited contact; deflocculated system
Good wetting	0° < θ < 90°	γSA > γSL	cos θ > 0	Liquid spreads easily; flocculated system

Wetting Agents in Pharmaceutical Suspensions

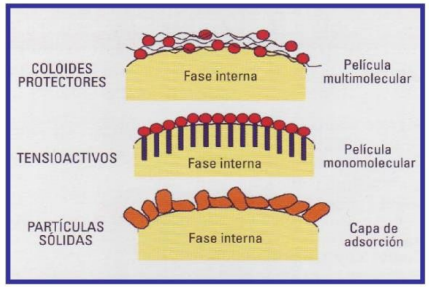
Surfactants (γSL and γLA)



- HLB range: 7–9 (max concentration 0.1%).
- Improve wetting by reducing surface and interfacial tension.
- Excess may produce foaming or deflocculation.

◆ Examples:
- Oral: Tween® and Span®
- Topical: Sodium lauryl sulphate, dioctyl sulfosuccinate
- Parenteral: Polysorbates, polyoxyethylene/polyoxypropylene copolymers, lecithins

Hydrophilic Colloids (= η)



- Increase viscosity and improve suspension stability.
- Excess leads to gelation; deficiency causes deflocculation.

◆ Examples:
- Polymers: Sodium carboxymethylcellulose, acacia gum, alginates, tragacanth gum
- Other hydrophilic materials: Bentonite, silicates, colloidal silica

Water-Miscible Solvents (γLA)

◆ Examples: alcohol, glycerol, glycols — enhance wetting and dispersion.

Sedimentation Process and Stokes' Law

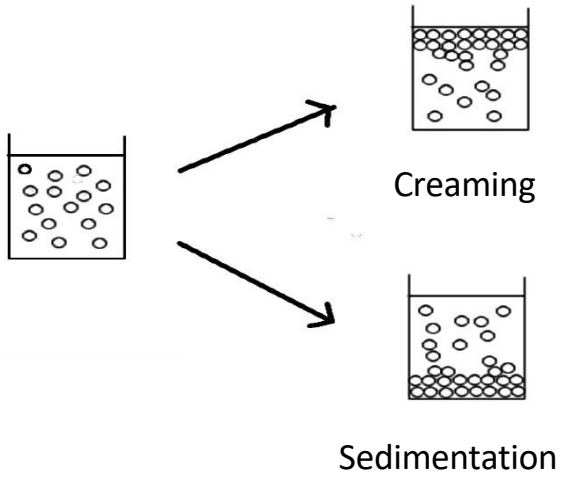
📘 Stokes' Equation:

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

v = sedimentation rate
r = particle radius (disperse phase)
ρ_1 = particle density (disperse phase)
ρ_2 = continuous phase density
g = acceleration due to gravity
η = viscosity of the continuous phase

⚙️ Factors Affecting Sedimentation:

- Particle size (larger particles settle faster).
- Density difference between the solid and the medium.
- Viscosity of the medium (higher viscosity slows sedimentation).



⏳ How to Slow Down Sedimentation:

- Reducing particle size to decrease settling rate.
- Adjusting the density difference between phases (rarely practical).
- Increasing viscosity using hydrophilic colloids or non-ionic emulsifiers.

🎯 **Sedimentation can be minimized through formulation strategies that balance particle size, density, and viscosity.**

Sedimentation Parameters

🧪 Sedimentation Volume (R)

$$R = Vs / Vt = h_\infty / h0$$

Vs = volume of the sediment layer
Vt = total volume of the suspension
h_∞ = height of the sediment layer
h0 = initial height of the suspension

💡 The higher the R value, the better the redispersibility of the suspension (larger floccules).
Acceptable range: R = 0.3 – 0.6

⚗️ Degree of Flocculation (β)

$$\beta = R / R_\infty$$

R = sedimentation volume of the flocculated suspension
R_∞ = sedimentation volume of the deflocculated suspension

β = 1 → No flocculation (deflocculated system)
β > 1 → Flocculated system (presence of aggregates)

🎯 **Controlled flocculation provides a stable suspension with a moderate sedimentation volume and easy redispersion.**

Relative Properties of Flocculated and Deflocculated Suspensions

Property	Deflocculated System	Flocculated System
Particle state	Particles exist as individual, separate entities.	Particles form loose aggregates (floccules).
Sedimentation rate	Slow — each small particle sediments independently.	Fast — floccules settle together due to larger size.
Sediment formation	Sediment forms slowly and gradually.	Sediment forms quickly but loosely.
Sediment characteristics	Forms a compact, dense sediment, often difficult or impossible to redisperse.	Forms a loose, porous sediment, easily redispersed with gentle shaking.
Appearance of suspension	Appears uniform for longer, but the supernatant remains cloudy.	Appears less uniform (clear supernatant visible), but is easier to redisperse.

Flocculated and Deflocculated Systems (DLVO Theory)

Which type of system is best for pharmaceutical suspensions?

🔵 Deflocculated Systems

• **Advantages:** slow sedimentation and uniform dose distribution.

• **Disadvantages:** compact sediment (caking), very difficult or impossible to redisperse.

🔴 Flocculated Systems

• **Advantages:** easy redispersion; prevents caking.

• **Disadvantages:** faster sedimentation rate, potential risk of dose non-uniformity.

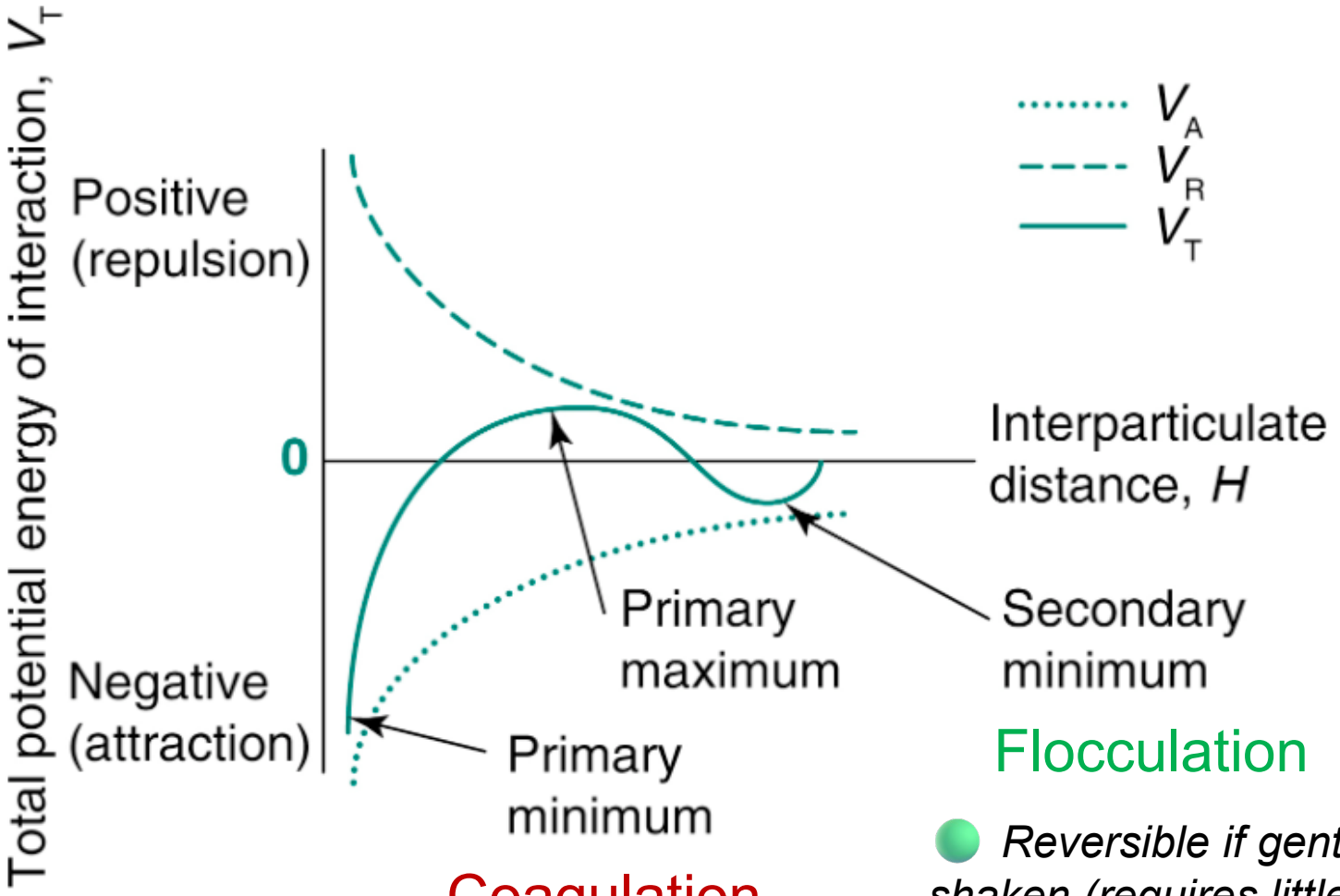
💡 **Best option: Flocculated systems in which the sedimentation rate is reduced by increasing the viscosity of the medium.**

Aggregation and Flocculation (DLVO Concept)

• Particle aggregation may occur at two energy minima:

- Primary minimum → Coagulation (irreversible, strong attraction)
- Secondary minimum → Flocculation (reversible, weak attraction)

✨ Controlled flocculation method: Formulate suspensions so that aggregation occurs at the secondary minimum, producing stable and easily redispersible floccules.



Coagulation

- *Essentially irreversible (e.g. due to coalescence)*

Flocculation

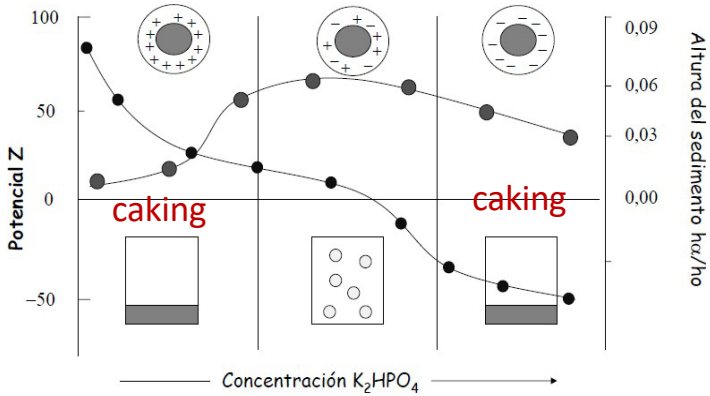
- *Reversible if gently shaken (requires little energy)*

Controlled Flocculation and Flocculating Agents

Stabilization of Electrically Charged Particles

Electrolytes: Reduce the electrical repulsion between particles

- Efficiency increases with ion valence (Schulze–Hardy rule).
- Optimal concentration is key: too low → unstable; too high → caking.
- Hydration and valence affect performance:
  - Monovalent/divalent (acetates, phosphates, citrates): safer.
  - Trivalent: stronger but can precipitate hydrophilic polymers.

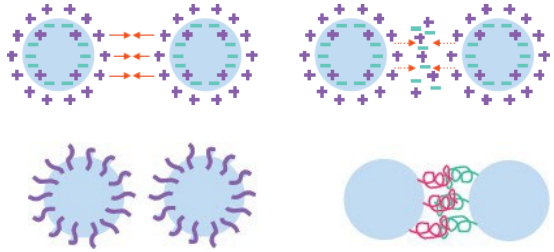


Surfactants: Modify interparticle forces

- Ionic surfactants: neutralize particle charge.
- Non-ionic surfactants: create steric stabilization or bridging between particles.

Hydrophilic Polymers: Provide steric stabilization

- Form a hydrated film around particles, preventing aggregation.
- Increase viscosity and mechanical stability.
- Common examples: starch, alginates, cellulose derivatives, tragacanth gum.



Particle Size and Crystal Growth in Suspensions

Importance of Controlling Particle Size

- Optimal particle size ensures uniform texture, stability, and safety.
- Particles > 5 µm can cause irritation (ocular or parenteral routes).
- Particle size influences drug release rate and bioavailability.
- Smaller particles reduce sedimentation rate and improve homogeneity.

Crystal Growth: Causes and Consequences

Crystal growth involves an increase in the average particle size during storage, leading to instability.
It may occur due to:

- Temperature variations → Solubility changes cause recrystallization on cooling.
- Heterodispersion (Kelvin effect) → Small particles dissolve, large ones grow.
- Polymorphic transitions → Conversion to more stable, less soluble forms.
- pH fluctuations → Alter solubility and favour recrystallization.

Prevention of Crystal Growth

- Use surfactants and polymers that adsorb on particle surfaces, preventing coalescence.
- Maintain stable temperature and pH conditions during storage.
- Optimize particle size distribution to minimize heterodispersion.

- **Dispersion methods:** Finely powdered solid is dispersed directly into the liquid vehicle.

Small-scale production

1.Mix the **active ingredient (A.I.)**, the **wetting agent**, the **viscosity enhancer (polymer)**, and **part of the vehicle**.
2.Add **other soluble components** and the **remaining vehicle**.
3.Adjust the preparation to the **final volume**.

Large-scale production

1.Prepare a **concentrated polymer dispersion** in the vehicle and allow **complete hydration**.
2.Add the **active ingredient** and the **wetting agent**.
3.Incorporate **other soluble components** with another portion of the vehicle.
4.Adjust to the **final volume**.
5. Homogenize to ensure uniformity.

- **Precipitation method**: involves forming a suspension by precipitating the insoluble drug from a solution of its soluble form.

- **Choice of raw materials**
  - Select high-purity active and excipient substances.
  - Control particle size, shape, and density to ensure uniform dispersion.

- **Wettability and dispersion**
  - Proper use of **wetting agents** to ensure complete particle dispersion.
  - Prevent aggregation during mixing.

- **Mixing and homogenization**
  - Adequate mixing speed and time are crucial for a **uniform suspension**.
  - Avoid excessive shear that could cause particle breakage or air entrapment.
  - Use a **stirred hopper** to prevent particle settling during packaging.
  - Evaluate the **shear forces** at the dispensing nozzle, as they can affect suspension stability.

- **Viscosity adjustment**
  - Use **suspending agents** (e.g. cellulose derivatives, gums) to achieve optimal flow and stability.
  - Balance between pourability and sedimentation control.

- **Preservation and stability**
  - Incorporate **antimicrobial preservatives** for multi-dose formulations.
  - Control **pH** and use stabilizers to prevent crystal growth or caking.

- **Sterilization (for parenteral or ophthalmic suspensions)**
  - Apply **aseptic processing** or **terminal sterilization** compatible with product composition.

- **Packaging and storage**
  - Use containers that allow easy redispersion (e.g. bottles with wide necks).
  - Protect from light, temperature changes, and contamination.
  -

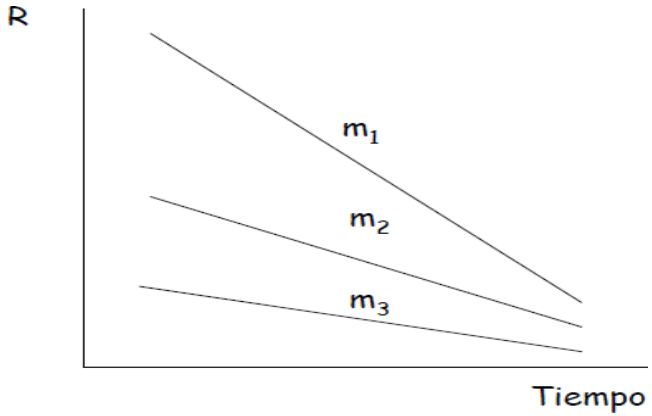
- **Cost**
  - Cost control is important in formulation development.
  - The active drug is often the most expensive component, especially in investigational products.

7. Evaluation and Control of Pharmaceutical Suspensions

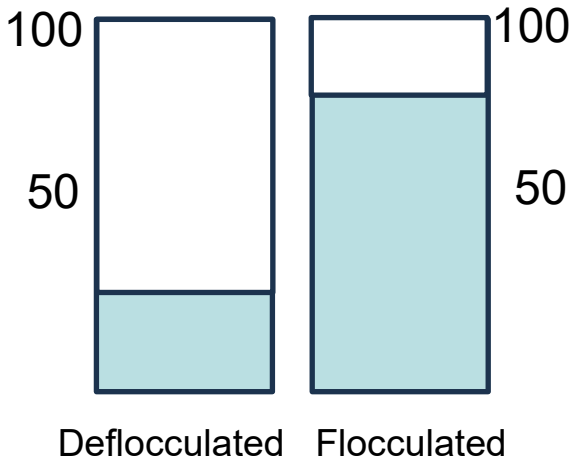
Tests are conducted at initial time (t_0) and after storage to assess stability.

Physical stability:

- **Sediment volume or height (R):** Indicates degree of dispersibility (higher R means better stability, dispersibility).
- **Sedimentation rate:** Determined by plotting *R* vs. Time (slope = sedimentation rate *m*).
  - Centrifugation may be used to accelerate sedimentation.
- **Ease of redispersion:** Evaluated by manual or mechanical agitation; faster redispersion means higher stability (reduce variability).
- **Degree of flocculation:** β =Vsed.f./Vsed.def. = hsed.f./hsed.def



👉 **A lower slope indicates a slower sedimentation rate.**



Sedimentation volume

$R_A = V_{sediment}/V_{total} = 20/100$

$R_B = V_{sediment}/V_{total} = 80/100$

Degree of flocculation

β=0,80/0,20=4

7. Evaluation and Control of Pharmaceutical Suspensions

- **Particle size analysis**
  Determines particle size distribution and changes in crystal habit.
  - Microscopy: Direct observation of particle shape and size distribution.
  - Laser diffraction: Measures particle size based on light scattering patterns.
  - Coulter counter: Determines size and number of particles by electrical resistance changes as they pass through an aperture.
- **Rheological behaviour**
  - **Instrument:** *Viscometers*
  - **Purpose:** To measure viscosity and flow properties of the suspension.
  - **Importance:** These parameters directly influence sedimentation rate and ease of redispersion after storage.
- **Electrokinetic measurements**
  - **Zeta potential (ζ):** Determines the charge at the particle surface.
  - The optimum **ζ** corresponds to maximum physical stability.

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