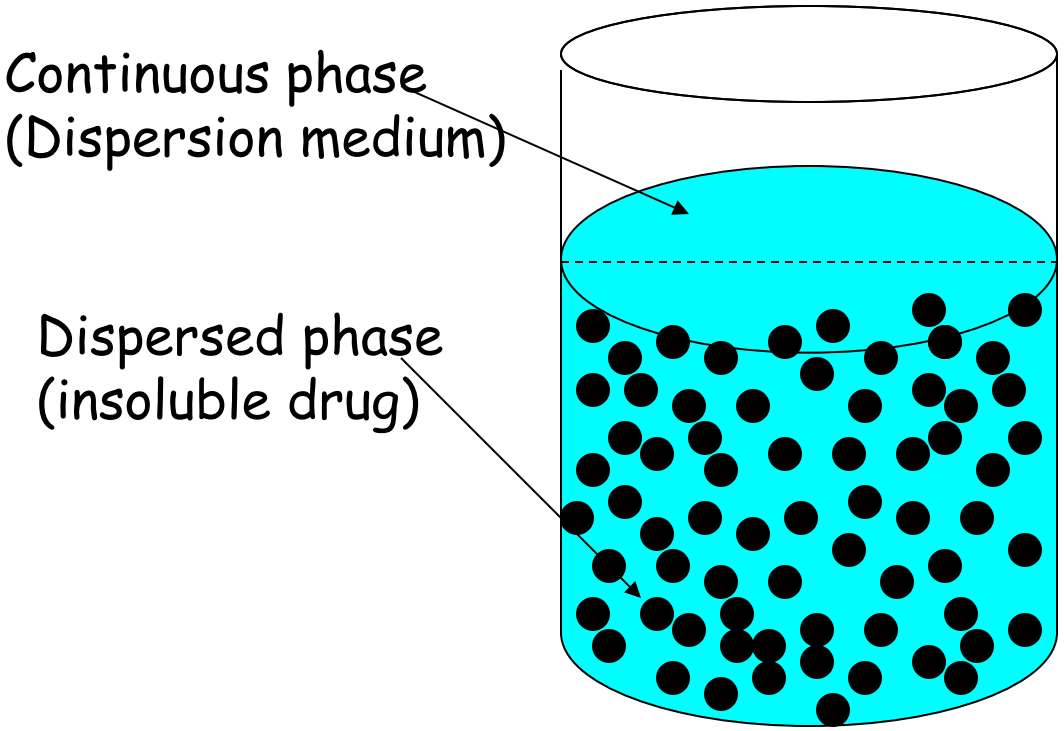
Pharmaceutics- (Suspensions)

Suspensions-Diffinition

- **Suspension:** is a two-phase system consisting of a finely divided solid particles dispersed in liquid (solid drug in liquid vehicle).



- The insoluble solid drugs is uniformly suspended throughout the suspending vehicle (dispersion medium) by the aid of a single of a combination of suspending agents.

- The suspending vehicle is
- generally aqueous, and in some instances, may be an organic or oily liquid for non oral use.

Suspensions-Classification

- **Based on the of adminsitration**
  - Oral
  - Ocular
  - Otic
  - Rectal
  - Parenteral
  - Topical

- **Based on the size of solid particles dispersed**
  - Coarse suspension (>1 micron)
  - Nanosuspension (< 1 micron)

Suspensions-Advantages

- Pharmaceutical suspensions are useful for drugs having low solubility, **e.g., prednisolone**. Although low-solubility drugs may be solubilized and administered as a solution, the volume of the solvent required to perform this may be large. Besides, formulations in which the drug is solubilized using a co-solvent may exhibit precipitation upon storage.
- Suspension can improve chemical stability of certain drug like antibiotics (**e.g., Procaine penicillin G, oxytetracycline**).
- Suspensions can be formulated to provide controlled drug release, e.g., IM injections.

Suspensions-Advantages

- Drug in suspension exhibits higher rate of bioavailability than other dosage forms. bioavailability is in following order:
  Solution > Suspension > Capsule > Compressed Tablet > Coated tablet.

- Suspension can mask the unpleasant/ bitter taste of drug. e.g., Chloramphenicol palmitate.

- Suspensions may be beneficial for patients having difficulty to swallow solid dosage forms.

Suspensions-Disadvantages

- Physical stability, sedimentation and compaction (caking) can causes problems .
- It is bulky sufficient care must be taken during handling and transport.
- It is difficult to formulate
- Uniform and accurate dose can not be achieved unless suspensions are packed in unit dosage form.

Suspensions

Features desired in pharmaceutical suspensions:

- Slow settling and readily dispersed when shaken
- Acceptable odor and color.
- Gets easily into syringe or flows easily through a needle (parenteral).
- It should be physically, chemically and microbiologically stable during its shelf life.
- Parenteral/ophthalmic suspension should be sterilizable.
- Spreads over surface but doesn't run off, providing a film containing the drug (for lotion application).

Applications

- Suspensions can be prepared:
  - For oral internal use
    - For nasogastric tube administration
    - For infants, children, and geriatric patients
  - For topical use
  - For ophthalmic, otic, and nasal use
- Another application of the suspension dosage form is to enhance the stability of a drug that is poorly stable in solution. Using an insoluble form of the drug places more of the drug in the suspended form, not in solution, and not available for solution degradation.

Suspensions

Properties of suspensions:

1. Sedimentation behavior

2. Electrokinetic properties

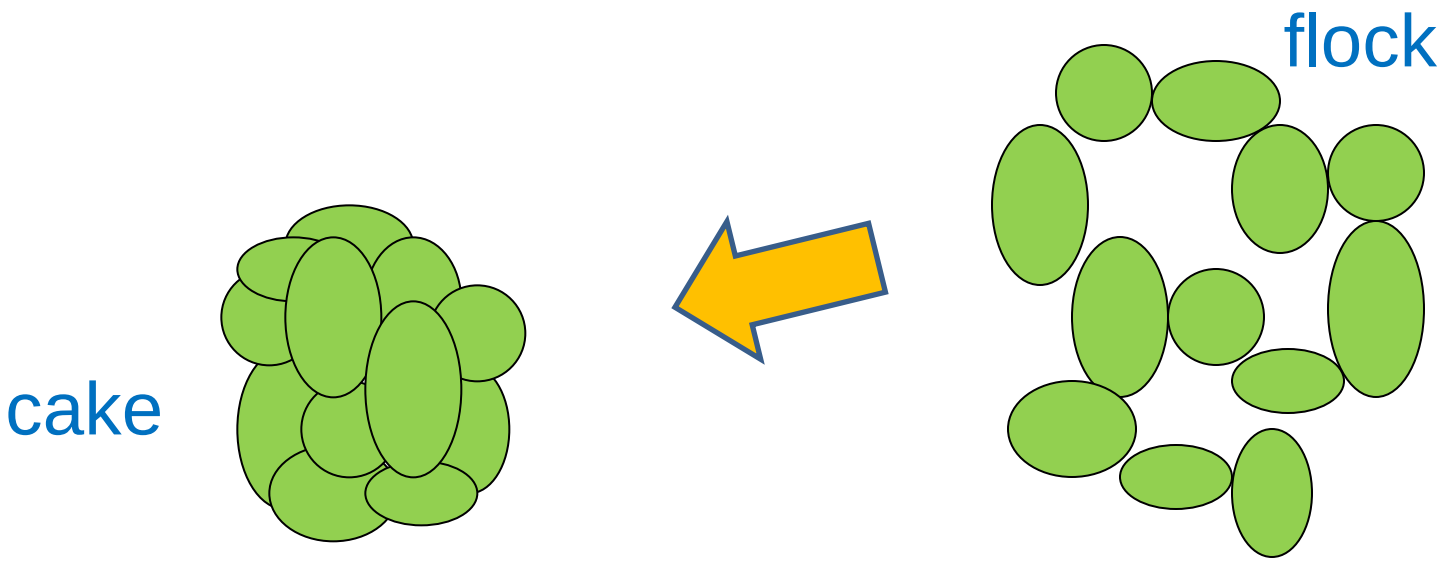
Factors affecting suspension stability

- particle size
- movement of particles / viscosity / sedimentation
- Electrical charge of particles
- Concentration of suspensoid
- Use of surfactants/wetting agents

Suspensions- properties

1. Sedimentaion & aggregation:

✓ Settling of particles or floccules occur under the gravitational force in a liquid dosage form.



Suspensions- properties

1. Sedimentation & aggregation:

- Settling and aggregation may result in formation of cakes (e.g., in suspension) that is difficult to resuspend or phase separation (e.g., in emulsion)

So, suspensions are physically unstable due to particle-particle interactions and ultimately caking (compaction)

Possible interactions:

1- van der waals attaction .
2. Electrostatic repulsion

Suspensions- properties

1. Sedimentation & aggregation:

- **Velocity of sedimentation (V) expressed by Stoke's equation**

$$v = \frac{d^2(\rho_s - \rho_o)g}{18\eta_o}$$

- Where, v = sedimentation velocity in cm / sec
- d = Diameter of particle
- ρ_s = density of disperse phase
- ρ_o = density of disperse media
- g = acceleration due to gravity
- η = viscosity of disperse medium (Pa s)

Suspensions- properties

❑ Sedimentaion-Factors affecting sedimentation

- ***Particle size diameter***

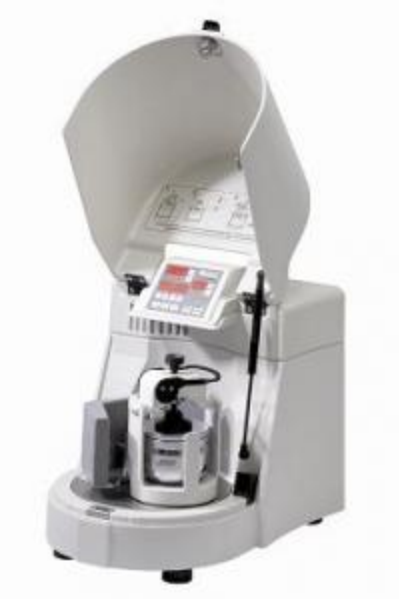
- According to Stoke's equation, sedimentation velocity (V) is directly proportional to the square of diameter of particle.
- Particle size of any suspension is critical; too large and too small particles should be avoided.

Large particles will:

- Settle faster at the bottom of the container.
- Particles > 5 microns impart a gritty texture to the product and cause irritation if instilled into the eye.
- Particles > 25 microns may block the needle.
- Too fine particles will easily form a hard cake at the bottom of the suspension

Particle Size Reduction

- Comminution



- Levigation

- Obtain uniform, small particles of the drug through particle size reduction.

Particle Size Reduction

Comminution
The reduction of the particle size of a solid substance to a finer state
it is used to facilitate drug extraction, increase dissolution rates of a drug and aid in the formulation of acceptable dosage forms and enhance absorption

- grinding a solid

Levigation
commonly used in small scale preparations of ointments and suspensions to reduce the particle size and grittiness of the added powders
- a paste is formed by combining the powder and a small amount of liquid (the levigating agent) in which the powder is insoluble

Other techniques of size reduction include jet milling which results in fine drug paeticles

Suspensions- properties

❑ Sedimentaion-Factors affecting sedimentation

- ***Density difference between dispersed phase and dispersion medium***

-Generally, particle density is greater than dispersion medium but, in certain cases particle density is less than dispersed phase, so suspended particle floats & is difficult to distribute uniformly in the vehicle.

- If density of the dispersed phase and dispersion medium are equal, the rate of settling becomes zero.

Suspensions- properties

❑ Sedimentaion-Factors affecting sedimentation

- ***Viscosity of dispersion medium***

- Sedimentation velocity is inversely proportional to viscosity of dispersion medium.
- So, increase in viscosity of medium, decreases settling, so the particles remain dispersed for longer time yielding higher stability to the suspension, but greater increase in viscosity gives rise to problems like pourability, syringeability and re-dispersibility of suspension.

So, viscosity of suspension should be maintained within optimum range to yield stable and easily pourable suspensions.

Suspensions- properties

❑ Sedimentaion-Factors affecting sedimentation

- ***Viscosity of dispersion 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.
- Problems in syringeability and pourability. Inconvenience to patients upon dosing.

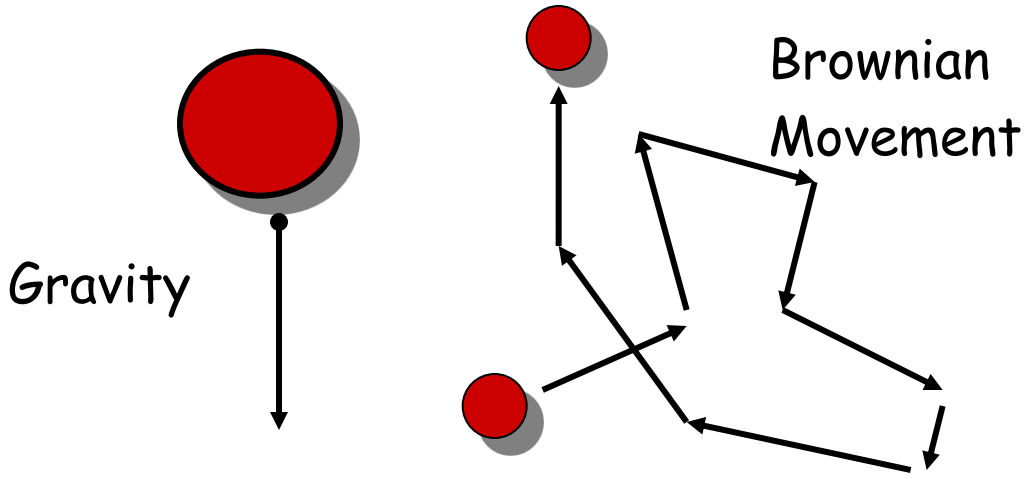
Suspensions- properties

❑ Sedimentaion-Factors affecting sedimentation

- ***Brownian motion***

- Can be observed if the particle size is 2-5 microns.
- Brownian movement of particle prevents sedimentation by keeping the dispersed material in random motion.
- depends on the density of dispersed phase and the density and viscosity of the disperse medium.

Sedimentation equilibrium: Gravity is neutralized by Brownian movement



Suspensions

- **Sedimentaion behavior of flocculated and deflocculated suspensions.**

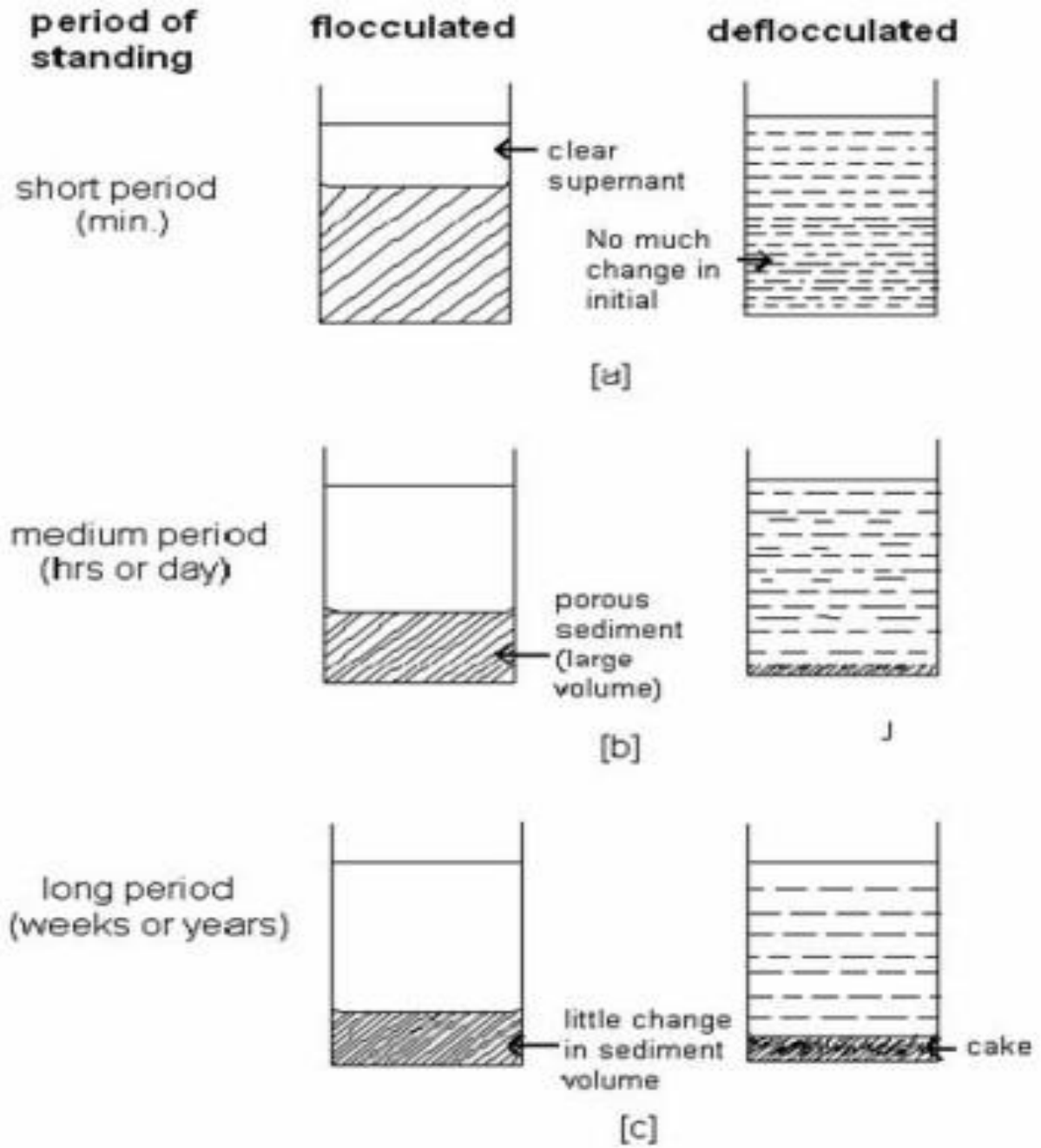
✓ **Flocculated suspensions:**

- Flocs (loose aggregates) are first formed, increasing the sedimentation rate due to increase in size of sedimenting particles. Hence, flocculated suspensions sediment more rapidly. Sedimentation depends not only on the size of the flocs but also on the porosity of flocs (liquid entrapped).

✓ **Deflocculated suspensions:**

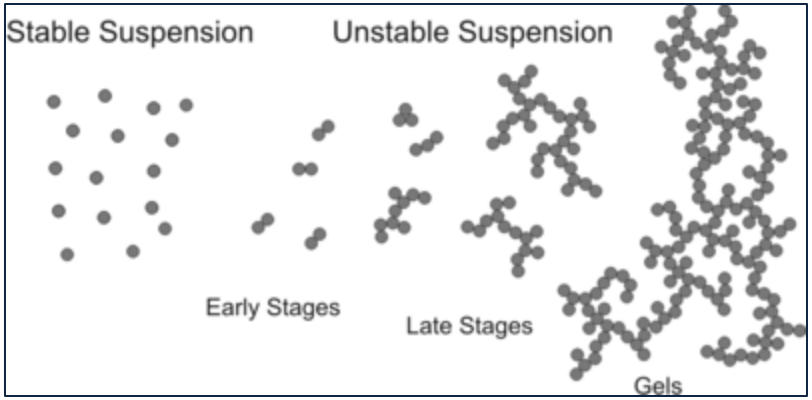
- Individual particles are settling, so rate of sedimentation is slow which prevents entrapping of liquid medium which makes it difficult to re-disperse by agitation. This phenomenon also called 'cracking' or 'claying'

Deflocculated	Flocculated
Particles exist in suspension as **separate entities**.	Particles form **loose aggregates**.
Rate of sedimentation is **slow**, since each particle settles separately and particle size is minimal.	Rate of sedimentation is **high**, since particles settle as a floc, which is a collection of particles.
A sediment is formed **slowly**.	A sediment is formed **rapidly**.
The sediment eventually becomes very **closely packed**, due to weight of upper layers of sedimenting material. Repulsive forces between particles are overcome and a hard cake is formed which is **difficult, if not impossible, to redisperse**.	The sediment is **loosely packed** and possesses a scaffold-like structure (**large volume of final sediment**). Particles do not bond tightly to each other and a hard, dense cake does not form. The sediment is **easy to redisperse**, so as to reform the original suspension.
The suspension has a **pleasing appearance**, since the suspended material remains suspended for a relatively long time. The supernatant also remains cloudy, even when settling is apparent.	The suspension is somewhat **unslightly**, due to rapid sedimentation and the presence of an obvious, clear supernatant region. This can be minimized if the volume of sediment is made large. Ideally, volume of sediment should encompass the volume of the suspension.



Sedimentation behaviour of flocculated and deflocculated suspensions


Flocculation

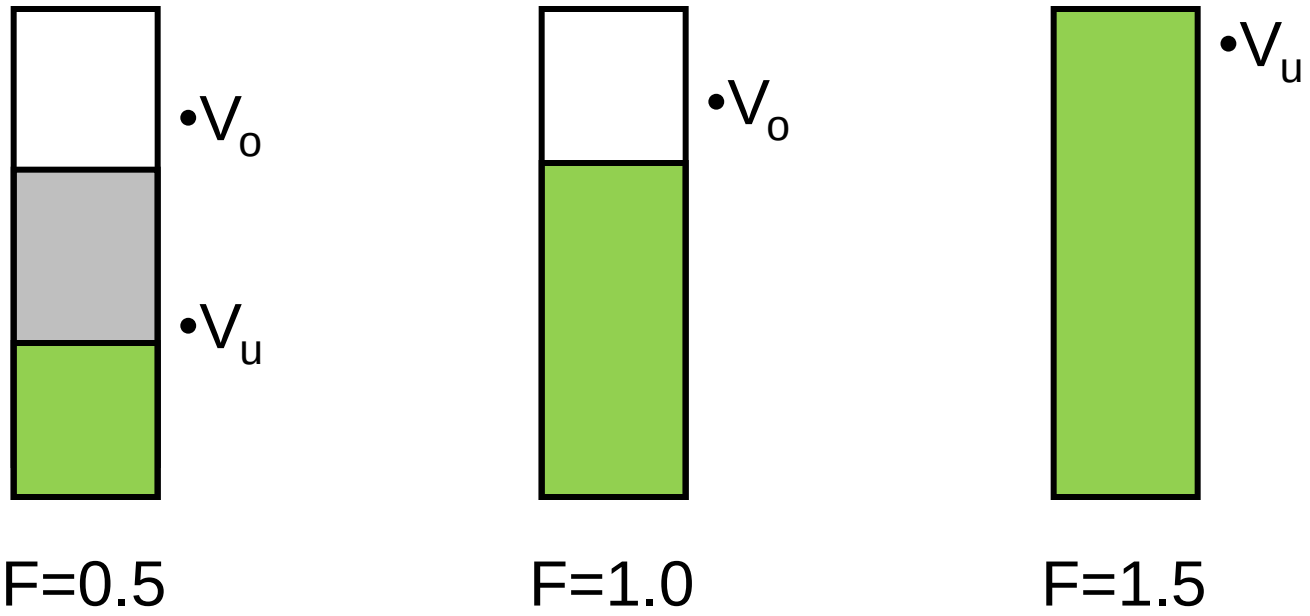

Stable Suspension
Unstable Suspension
Early Stages
Late Stages
Gels


Time = 0
SS-BUD
SS-FFD
BUD-FFD
SpringerImages
Time = 24 hrs
SS-BUD
SS-FFD
BUD-FFD

Suspensions

- **Important parameters of sedimentaion-Volume of sediment**

F={volume of sediment V_u}/{original volume V_o}



Sedimentation volume: is the ratio of the ultimate volume of sediment (Vo) to the original volume of suspension before settling (Vu). The sedimentation volume gives only a qualitative account of flocculation

Suspensions

- Important parameters of sedimentaion-Degree of flocculation

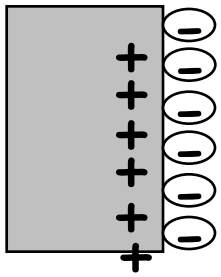
- ✓ The ratio of sedimentaion volume of flocculated suspension to that of the deflocculated suspension

Suspensions- porperties

1. Electrokinetic properties-Zeta potential:

Particles may become charged by

- adsorption of ionic species present in solution or preferential adsorption of OH^-
- ionization of -COOH or $-NH_2$ group



hydroxyl ion (HO^-)

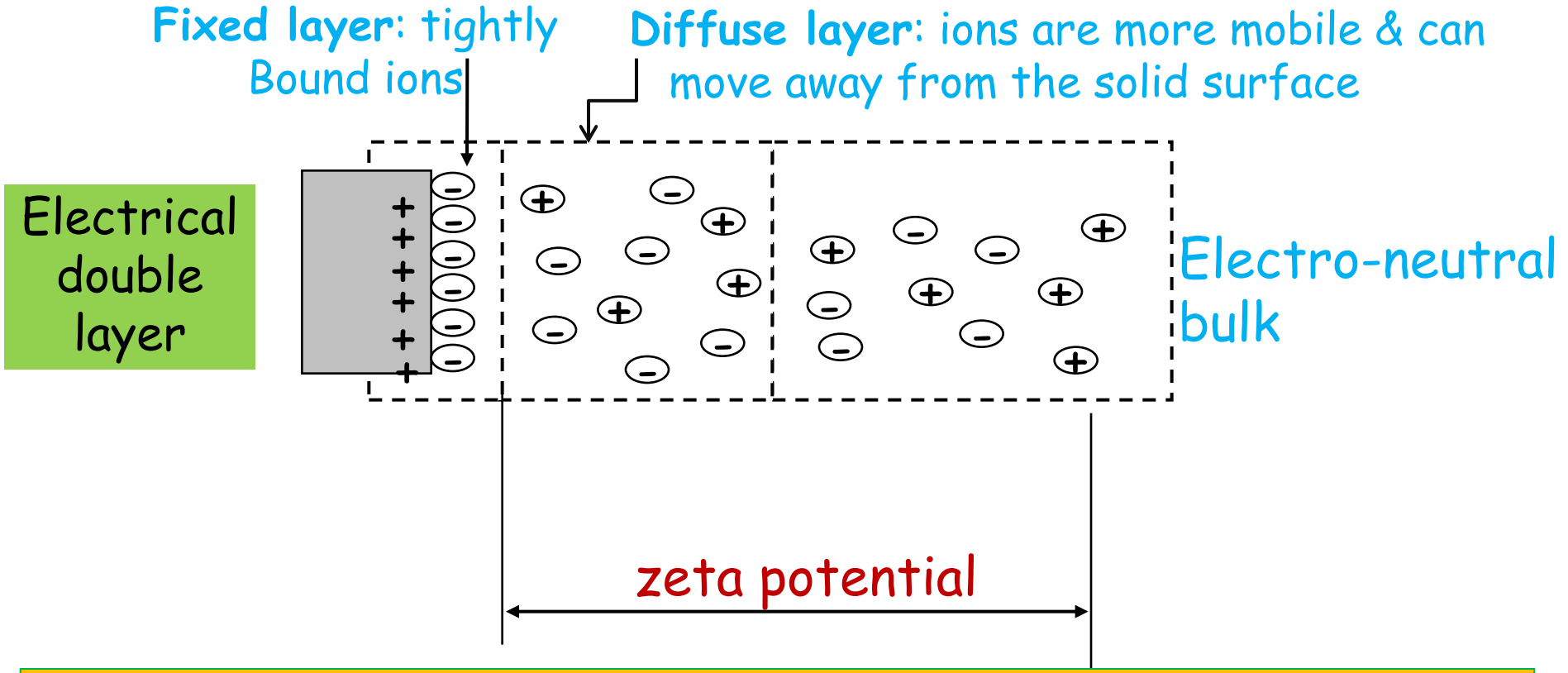
Solid

Particle in aqueous medium

$$H_2O \longleftrightarrow H^+ + HO^-$$

Suspensions- properties

1. Electrokinetic properties-Zeta potential:

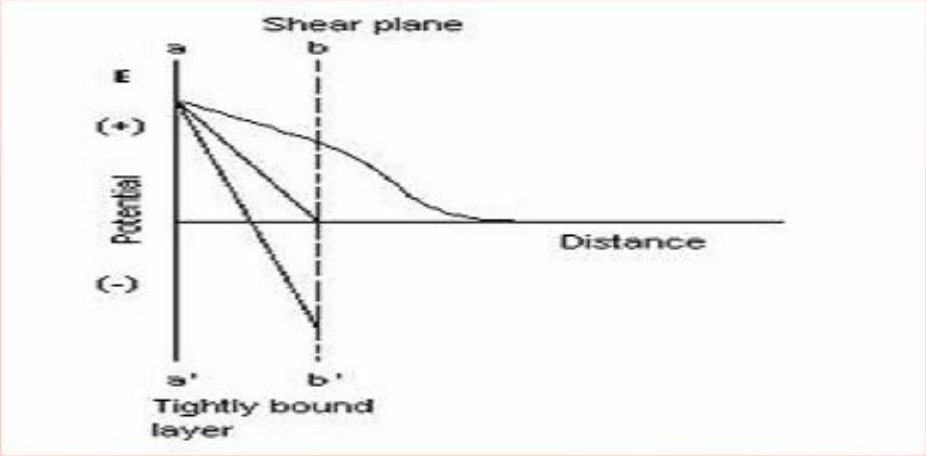


Zeta potential

- potential difference between the tightly bound layer and the bulk (electro-neutral region of solution)
- governs electrostatic force of repulsion between adjacent, similarly dispersed particles

Suspensions- properties

1. Electrokinetic properties-Zeta potential:



- As the potential drops off rapidly at first, followed more gradual decrease as the distance from the surface increases.

- This is because the counter ions close to the surface acts as a screen that reduce the electrostatic attraction between the charged surface and those counter ions further away from the surface.

Suspensions- porperties

1. Electrokinetic properties-Zeta potential:

- If the zeta potential is reduced below a certain value (which depends on the particular system being used), the attractive forces exceed the repulsive forces, and the particles come together. This phenomenon is known as flocculation.

So, zeta potential determines the ability of a liquid to carry a solid material in a suspension. Besides, the phenomenon of flocculation and deflocculation depends on zeta potential carried by particles.

Zeta potential has practical application in stability of systems containing dispersed particles .

flocculation versus caking (claying)

They are determined by forces of attraction (van der Waals) versus forces of electrostatic repulsion.

Deflocculated:

- repulsion > attraction
- affected by [electrolytes]

Flocculated:

- attraction > repulsion

- **Flocculating Agents**
- *Examples of flocculating agents are:*

Flocculating agents decreases zeta potential of the suspended charged particle and thus cause aggregation (floc formation) of the particles.

1. **Electrolytes such as KCl, NaCl**: Electrolytes decrease electrical barrier between the particles and bring them together to form floccules. They reduce zeta potential near to zero value that results in formation of bridge between adjacent particles, which lines them together in a loosely arranged structure.
2. **Sulfate, citrates, phosphates salts**
3. **pH change** : alters the electrical barrier between the particles of the suspenoid and forming a bridge to link them together

Flocculation may also occur when polymer solubility is decreased in the dispersion medium.The part of the long chain is adsorbed on the surface of the particles and remaining part projecting out into the dispersed medium. Bridging between these later portions, also leads to the formation of flocs.

Composition of a pharmaceutical suspension

Components	Function
API	Active drug substances
Wetting agents	They are added to disperse solids in continuous liquid phase.
Flocculating agents	They are added to floc the drug particles
Thickeners/viscosity or density modifiers/suspending agents	They are added to increase the viscosity of suspension.
Buffers 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.
Colorants, flavorants, sweeteners	They are added to impart desired color, color & taste to suspension and improve elegance.
Preservatives	They are added to prevent microbial growth.
External liquid vehicle	They are added to construct structure of the final suspension.

Composition of a pharmaceutical suspension

Types of preservatives that might be used in suspensions

- Alcohol 5-10%
- Benzoates 0.1-0.3%
- Parabens 0.02-0.2%
- Phenols 0.2-0.5%
- Quats 1:10,000- 1:50,000
- Sorbic Acid and Salts 0.05-0.2%

- **Wetting Agents**

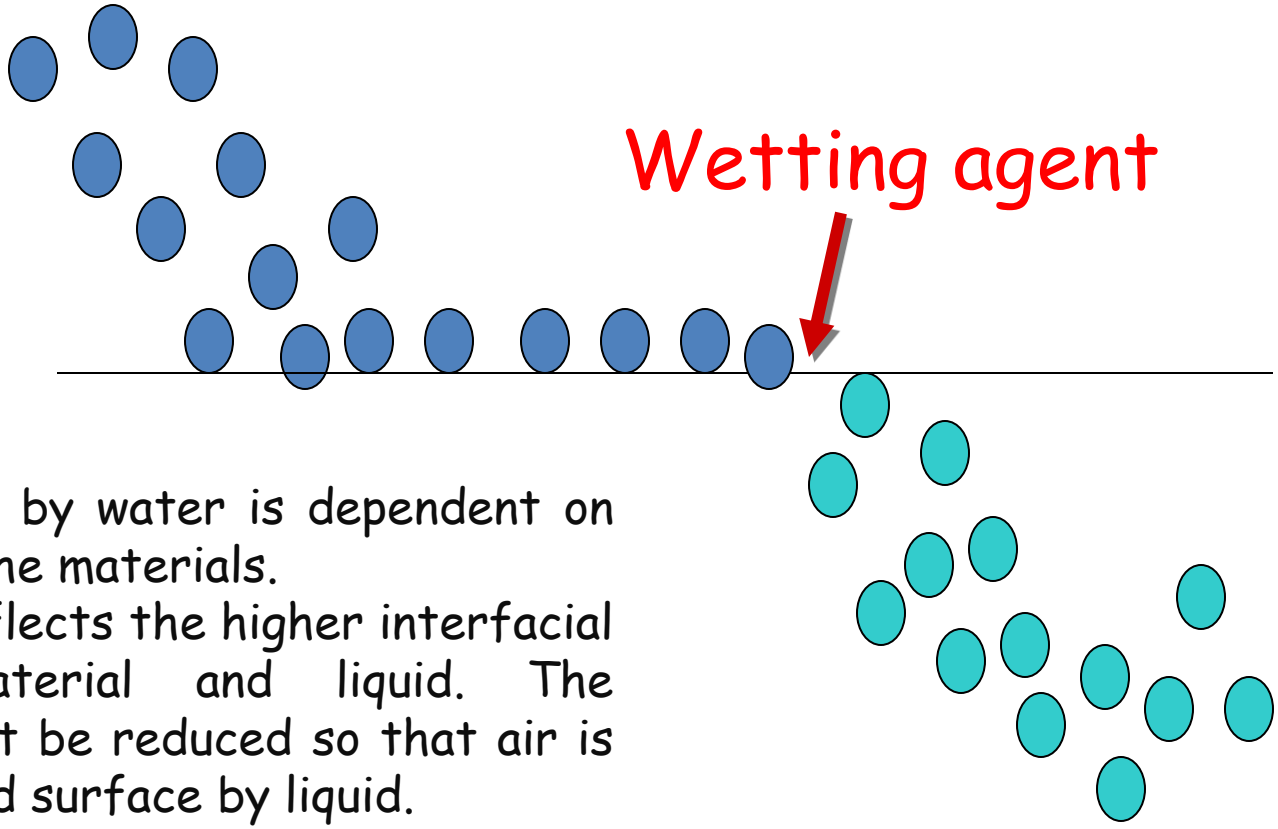
- It is important that solid particles are homogeneously distributed in the suspension to ensure accurate and reproducible dosing.
- However, solid particles of suspension are not easily wetted by water due to their hydrophobic nature, and this phenomenon is referred to as surface tension (inhomogenous, inelegant and irreproducible product).

Rduction of surface tension

Promoting movement of solvent across particles throghout the medium and thus good dispersal of particles thoughout the medium

Increased wettability

Wetting



- ✓ The extent of wetting by water is dependent on the hydrophillicity of the materials.
- ✓ Inability of wetting reflects the higher interfacial tension between material and liquid. The interfacial tension must be reduced so that air is displaced from the solid surface by liquid.

- ✓ Some wetting agents do this by reducing the interfacial tension between the solid particle and the liquid medium. Tese are called are surfactants below their cmc.

- ✓ Other wetting agents act by spreading onto solid surface, then breaking cohesive forces between liquid molecules to create new surface area.

Hydrophobic solids

↓

Show high surface tension

↓

Low wettability with water

•Wetting Agents

I. surfactants

Surface tension is the elastic tendency of liquids which makes them acquire the least surface area possible.

- ✓ The cohesive forces between liquid molecules are responsible for the phenomenon known as surface tension. The molecules at the surface do not have other like molecules on all sides of them and consequently they cohere more strongly to those directly associated with them on the surface. This forms a surface "film" which makes it more difficult to move an object through the surface than to move it when it is completely submersed.

- ✓ Surface tension is typically measured in dynes/cm, the force in dynes required to break a film of length 1 cm.

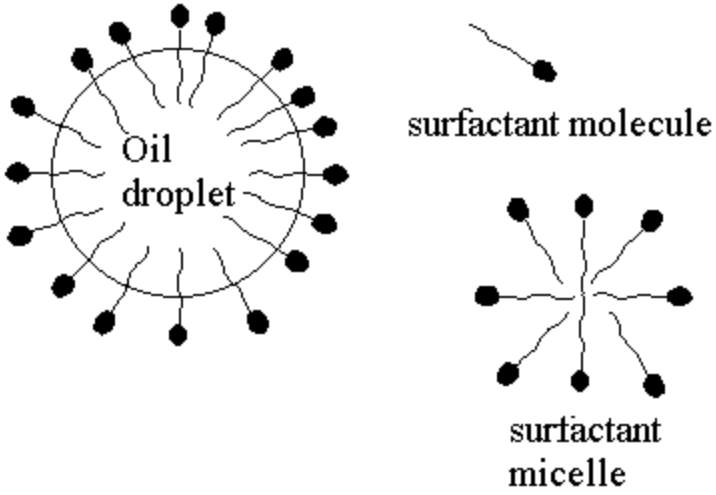
- ✓ So, a surfactant is a material that adsorbs strongly at the interface and has the effect of substantially lowering surface tension when added in small amounts

surfactant

Sodium Lauryl Sulphate

Sorbitan esters

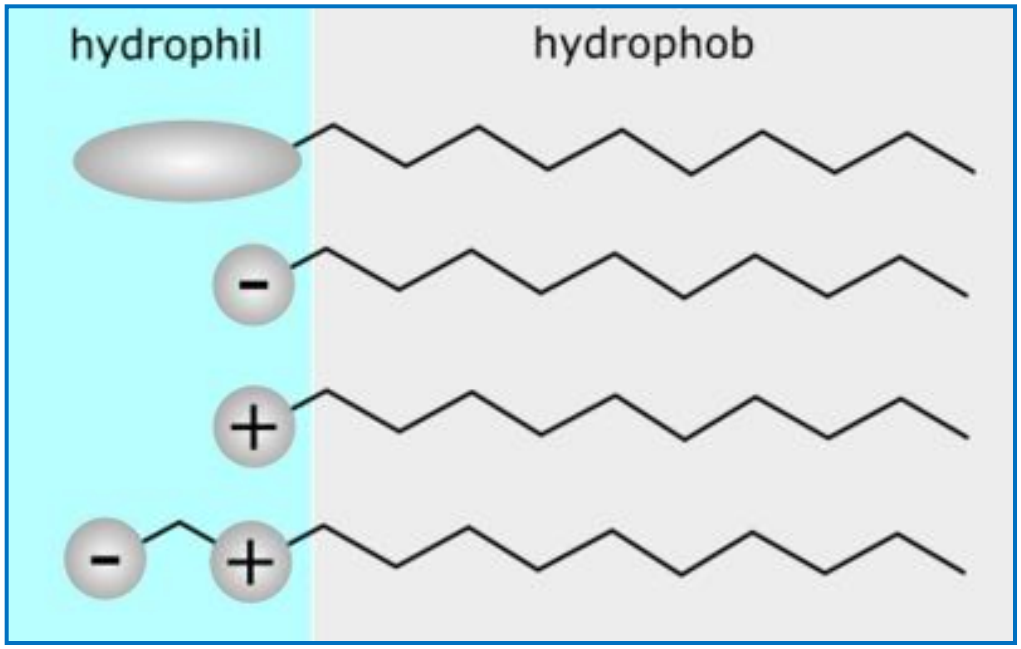
Polysorbates (tween)



•Both ionic and non-ionic surfactants can be used to bring about flocculation of suspended particles.

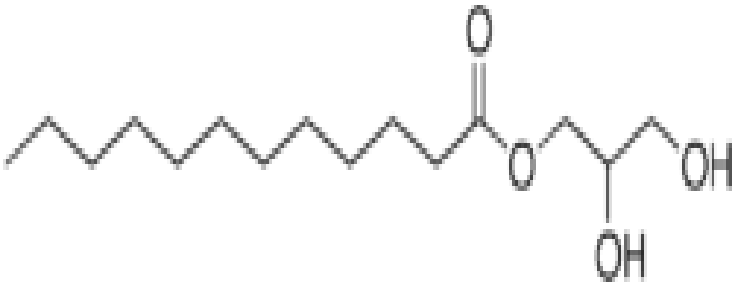
• Optimum concentration is necessary because these compounds also act as wetting agents to achieve dispersion.

• Optimum concentrations of surfactants bring down the surface free energy by reducing the surface tension between liquid medium and solid particles. This tends to form closely packed agglomerates.

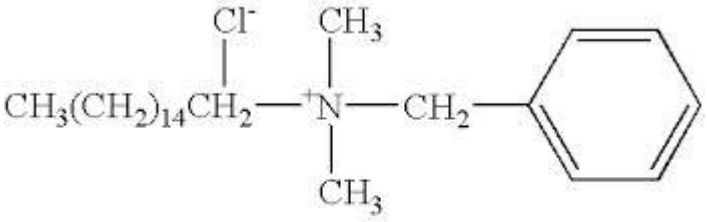


Types of surfactants

Sodium lauryl sulphate



glyceryl laurate



Benzalkonium Chloride

Surfactants

Polymeric surfactants

They polyxamers (also known as **pluronics®** are a series of neutral synthetic polyoxyethylene-polyoxypropylene block co-polymers. E.g., poloxamer 188 (Pluronic ® F68).

Ionic surfactants are rritant & toxic to the mucous membranes

- Anionic surfactants
- cationic surfactants

They also have antimicrobial properties & are the most toxic and irritant, as compard with other surfactants e.g., cetrimide (cetyltrimethyl ammonium bromide, benzalkonium chloride)

Least toxic surfactants

- Non-ionic surfactants

e.g, Tweens, Spans (polysorbates), macrogols

Amphoteric surfactants

E.g., phospholipids, Glyceryl monostearat, glyceryl monooleate

- **Wetting Agents**

Non-ionic surfactants are most commonly used as wetting agents in pharmaceutical suspension. The concentration used is less than 0.5 %.

- Polysorbate 80 (Span 80) is the most widely used for parenteral and oral preparations for the following reasons:

1. It is non-ionic, so no change in pH of medium
2. No toxicity.
3. Safe for internal use.
4. Less foaming tendencies, however it should be used at concentration less than 0.5%.
5. Compatible with most of components.
6. It assists re-dispersion of sedimented particles in suspension
   ⟹ flocculating effect.

Ionic surfactants are used to a lesser degree because they are not compatible with many components and cause change in pH.

- **Wetting Agents**

- ✓ Surfactants, in general, may have disadvantages in that they have foaming tendencies and bitter in taste (except pluronics).
- Some surfactants such as polysorbate 80 interact with preservatives such as methyl paraben and reduce antimicrobial activity.

- **WettingAgents**

II. Hydrocolloids

- Hydrophilic colloids coat hydrophobic drug particles in one or more than one layer. This will provide hydrophillicity to drug particles and facilitate wetting.
- They cause deflocculation of suspension because force of attraction is declined.
- Examples:

- Polymers: [gums likes acacia (arabic gum), tragacanth, xanthan gum, guar gum, polysaccharides like pectin, alginates , Cellulose derivatives]
- Proteins: egg yolk, gelatin
- Inorganic hyrocolloids: betonite, hectorite, Veegum, attapulgite, colloidal silicon dioxide.

- **WettingAgents**

II. Solvents

The most commonly used solvents used are alcohol, glycerin, polyethylene glycol and polypropylene glycol. The mechanism by which they provide wetting is that they are miscible with water and reduce liquid air interfacial tension. Liquid penetrates in individual particle and facilitates wetting.

- **Wetting Agents**

Wetting of the particles

- Hydrophilic materials (talc, ZnO, Mg2CO3) are easily wetted by water, while hydrophobic materials (sulphur, charcoal) are not due to the layer of adsorbed air on the surface.
- Thus, the particles, even high density, float on the surface of the liquid until the layer of air is displaced completely.
- The use of wetting agent allows removing this air from the surface and to easy penetration of the vehicle into the pores.
- However hydrophobic materials are easily wetted by non-polar liquids & surfactants.

- **Viscosity enhancers, thickeners, suspending agents.**

1. Some natural gums (acacia, tragacanth), cellulose derivatives (sodium CMC, methyl cellulose), clays (bentonite, veegum), carbomers, colloidal silicon dioxide (Aerosil), and sugars (glucose, fructose) are used to enhance the viscosity of the dispersion medium. They are known as suspending agents.

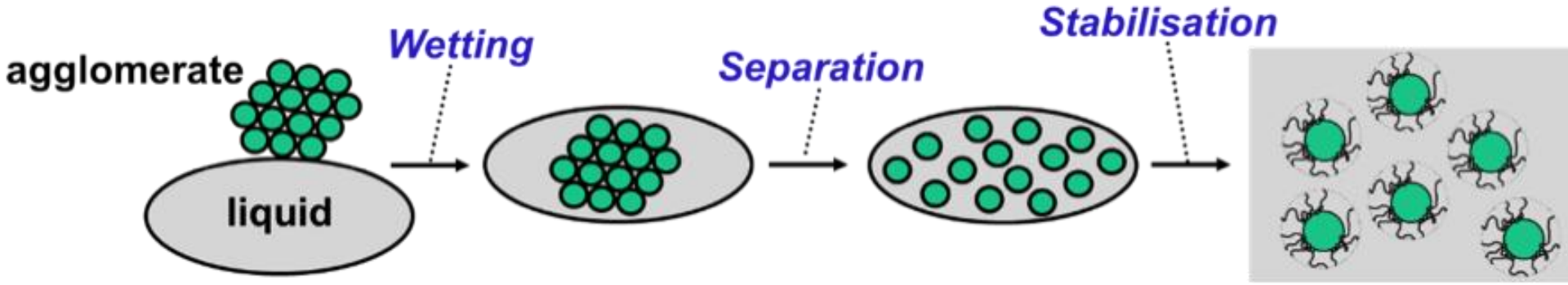
- Most suspending agents perform two functions i.e. besides acting as a suspending agent they also imparts viscosity to the solution. Suspending agents form film around particle and decrease interparticulate attraction.
- At rest the solution is sufficient viscous to prevent sedimentation and thus aggregation or caking of the particles. When agitation is applied the viscosity is reduced and provide good flow characteristic from the mouth of bottle.

- **List of Suspending Agents**
- Alginates
- Methylcellulose
- Hydroxy methylcellulose
- Carboxy methylcellulose (CMC).
- Hydroxypropyl methyl cellulose
- Hydroxypropyl methylcellulose
- Microcrystalline cellulose
- Hydroxy ethylcellulose
- Acacia, Tragacanth, Xanthan gum
- Bentonite
- Carbomer
- Powdered cellulose
- Carrageen
- Gelatin

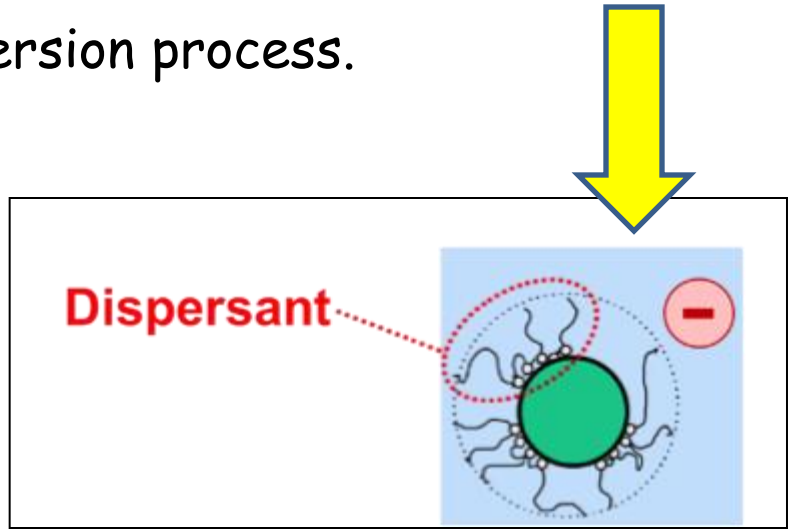
2. Co-solvents

- Some solvents which themselves have high viscosity are used as co-solvents to enhance the viscosity of dispersion medium:

  Glycerol, propylene glycol, sorbitol.



The three steps in the dispersion process.



viscosity (the measure of a fluid's ability to resist gradual deformation by shear or tensile stresses) .

Rheology: is the study of the flow of matter, primarily in a liquid state, but also as 'soft solids' or solids under conditions in which they respond with plastic flow rather than deforming elastically in response to an applied force

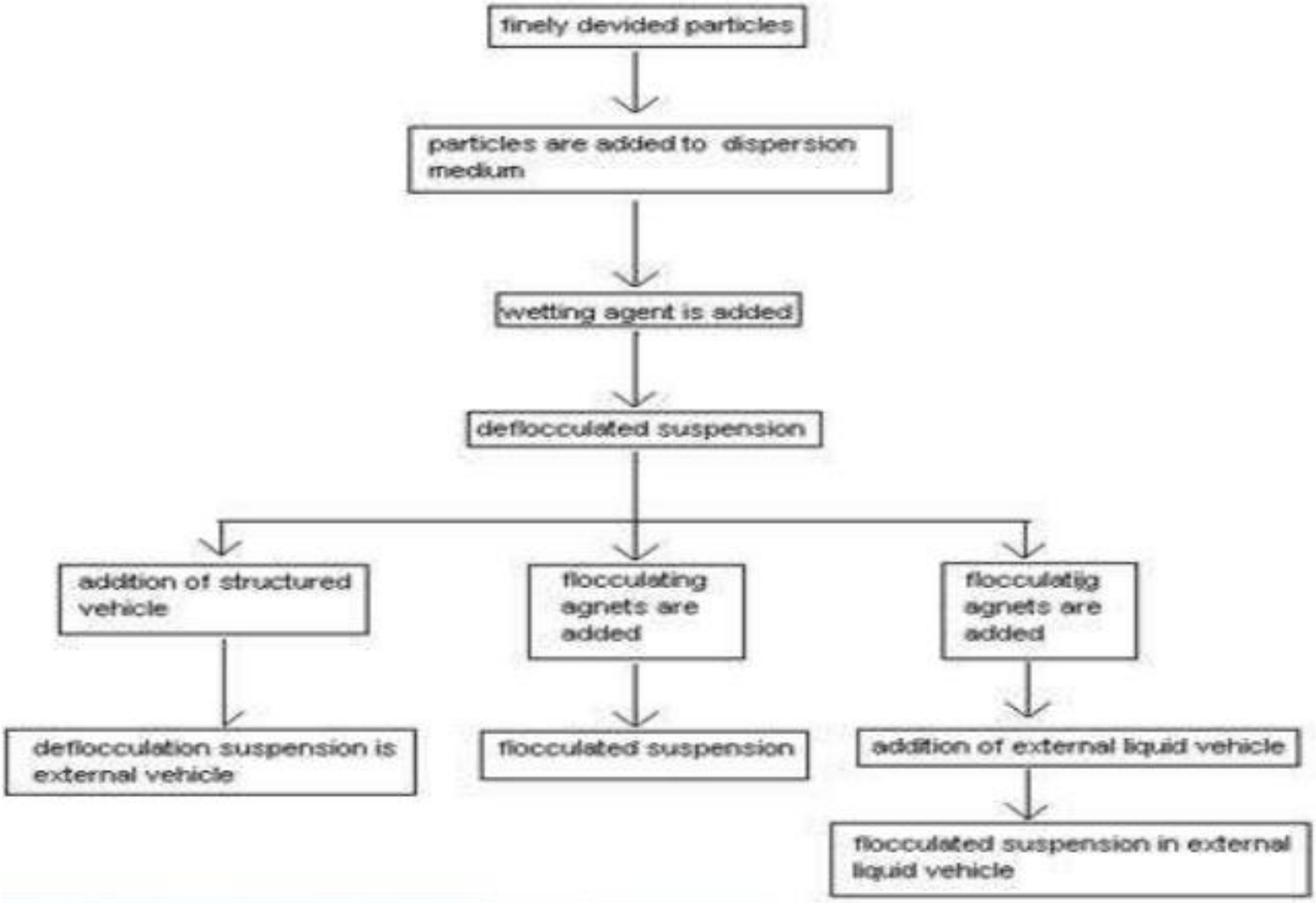
✓ Thixotropic suspensions

- Non-newtonian: refers to time-dependent (non-newtonian) shear thining property of materials.
- Certain gels or fluids that are thick (viscous) under static conditions will flow (become thin, less viscous) over time when shaken, agitated, or otherwise stressed
- Thixotropic suspensions subject to gel-sol-gel transformation, wherre under static consitions the suspensions builds up a network that stabilizes it and prevent sedimentation, while under shaking it becomes fluid or less viscous for proper dispensing and then it regains its viscosity.
- Anti-thixotropic: shear stress for a time causes an increase in viscosity or even solidification. Constant shear stress can be applied by shaking or mixing. Fluids which exhibit this property are usually called rheopectic.

✓ Thixotropic suspensions

- For stability select a non-Newtonian flow property of suspension Use a suspending agent that produces a pseudoplastic (shear-thinning) or thixotropic (time- dependent thinning upon shear) flow

Flow chart of formulation of suspension



Suspensions-

TYPES OF PHARMACEUTICAL SUSPENSIONS

1. Antacid oral suspensions
2. Antibacterial oral suspension
3. Dry powders for oral suspension (antibiotic)
4. Analgesic oral suspension
5. Anthelmentic oral suspension
6. Anticonvulsant oral suspension
7. Antifungal oral suspension

Suspensions-

Specific Quality Control

- Weight / volume
- Extent of settling
- Ease of redispersibility
- Appearance
- Odor
- Pourability
- pH
- Viscosity
- Active drug content

Suspensions-

- Suspensions should not be frozen.

- If available as freeze-dried powders, they are reconstituted upon use and should be keept in the fridge.

- Must be shaken before use.