LEC 5
PHARMACEUTICAL TECHNOLOGY
SUSPENSIONS

3rd stage / 1st course

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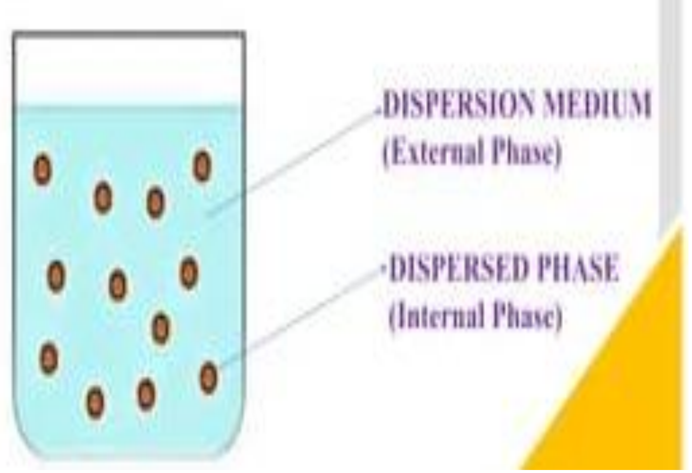
DEFINITION OF SUSPENSION

- Suspensions are dispersion systems consisting of two phases: dispersion (continuous or external) phase and dispersed (internal) phase.
- The external phase is generally a liquid or semisolid phase, mostly aqueous for oral preparations and may be oily or organic for non-oral preparations, and the internal phase is particulate matter (solid).
- The internal phase is insoluble or slightly soluble solid materials but dispersed throughout the external phase.



PARTICLE SIZE

- Particle size of dispersed systems:
- Molecular dispersion: < 1nm.
- Colloidal dispersion: 1 nm – 0.5 µm.
- Fine dispersion: 0.5 µm – 10 µm.
- Coarse dispersion: 10 µm – 50 µm (Suspensions).

- Suspensions can be used orally (metronidazole), parenterally (betamethasone), topically (calamine lotion), rectally (mesalazine), ophthalmically (prednisolone acetate), etc.
- Some suspensions are available in ready to use form (e.g. metronidazole (Flagyl®)) and others are available as dry powders intended for suspension in liquid vehicles, most often purified water (e.g. amoxicillin (Amoxil®)).


2 ml Ampoule
2ml
2mg + 5mg/ml
Diprofos* Injection
BETAMETHASONE SODIUM PHOSPHATE
and BETAMETHASONE DIPROPIONATE
Manufactured by: MEDICAL UNION PHARMACEUTICALS
Abu Sultan - Ismailia - Egypt
Under Authority of
SCHERING-PLOUGH CORPORATION/U.S.A.
Schering-Plough


Flagyl®
(Benzoyl
Metronidazole)
Anti-amoebic and
Anti-infective
120ml
Suspension
Flagyl®
(Benzoyl
Metronidazole)
Anti-amoebic and
Anti-infective
120ml Suspension
SANOFI
Shake well before use.
AA100
APR 2022
MAR 2024
103.51


calamine
lotion
calamine topical
suspension USP
up&up
6 FL OZ (177 mL)

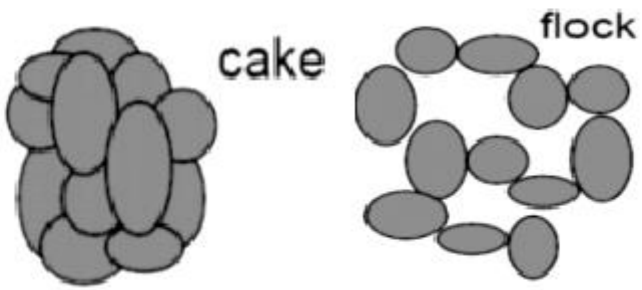

KIT
Mesalamine
Rectal Suspension,
USP Enema
4g/60 mL
Unit-Dose
For Rectal Use Only
SHAKE WELL BEFORE USING
Perrigo


PRED FORTE™
EYE DROPS
SUSPENSION
ALLERGAN
PRED FORTE™
(prednisolone acetate
USP 1%)
EYE DROPS
SUSPENSION
STERILE
5 ml
ALLERGAN
PRED FORTE™
5 ml

PARTICLE SIZE CONTROL:

- ❑ Particle size of any **suspension is critical and must be reduced within the range .**
- ❑ Too large or too small particles should be avoided.

- **For large particles:**
  - Too large particles settle faster at the bottom of the container
  - particles > 5 µm impart a gritty texture to the product and also cause irritation if injected or instilled to the eye
  - particles > 25 µm may block the needle

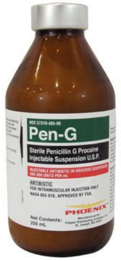


- **For small particles**:
  - Too fine particles will easily form hard cake at the bottom of the container.

THE REASONS TO FORMULATE SUSPENSION

- **When the drug is insoluble in the delivery vehicle, e.g. prednisolone suspension.**

- **To mask the bitter taste of the drug, e.g. chloramphenicol palmitate and metronidazole suspensions.**
- **To increase drug stability, e.g. oxytetracycline suspension.**
- **To achieve controlled/sustained drug release, e.g. penicillin procaine suspension.**



DESIRED PROPERTIES IN THE PHARMACEUTICAL SUSPENSION

- Settle down slowly (remain suspended long enough to withdraw an accurate dose).
- Readily redispersed upon gentle shaking of the container.
- The particle size should remain fairly constant throughout long periods of storage (with no caking).
- Easily pourable from its container (not highly viscous).
- Suitable odour, colour, and taste.
- Stable and not decompose or support growth of moulds.
- Should be free from gritting particles (external, intramuscular, and ophthalmic use)
- Should be pleasant & palatable (orally)

Some Disadvantages of Suspensions

- They must be well shaken prior to measuring a dose.
- The accuracy of the dose is likely to be less than with the equivalent solution.
- Conditions of storage may adversely affect the disperse system which might lead to aggregation and caking.

Storage of suspension

The physical stability of suspension is adversely affected by extreme variation in temperature, suspension should be stored in cool place but not refrigeration. Freezing and very low temperature may cause the suspended particles to reaggregate.

Also should be stored in a wide mouth container that have a space to allow a good agitation before use. Label: "**Shake Before Use**" to ensure uniform distribution of solid particles and thereby uniform and proper dosage.

THEORY OF SEDIMENTATION

The velocity of sedimentation is expressed by *Stoke's law.*

$$V = \frac{d^2 g(\rho_p - \rho_s)}{18\eta}$$

V = sedimentation velocity

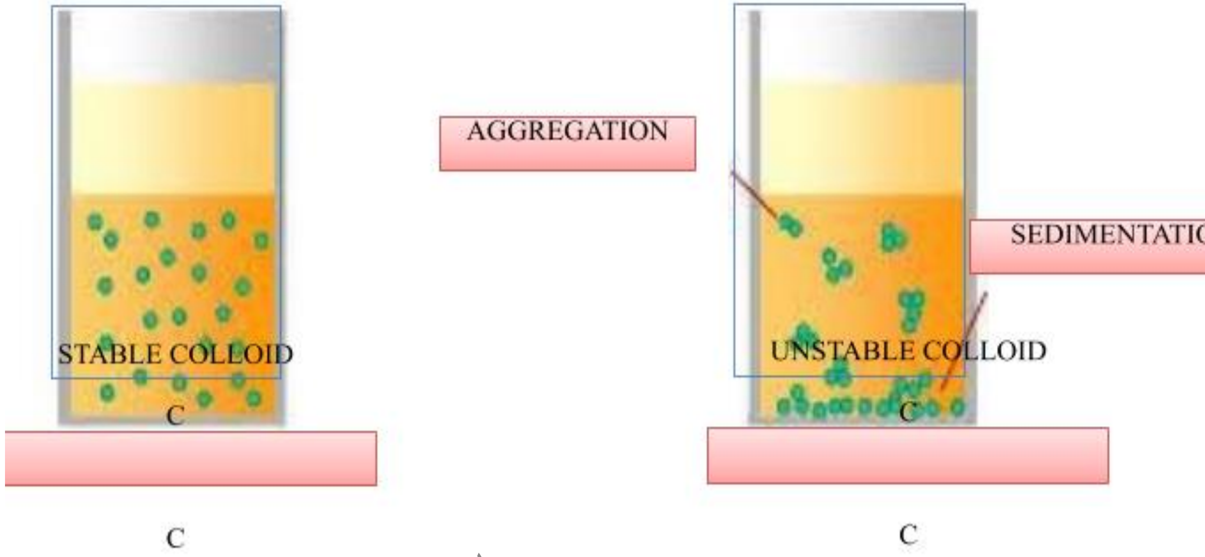
d = diameter of the particle in cm.

ρ_p =density of the dispersed phase (particles).

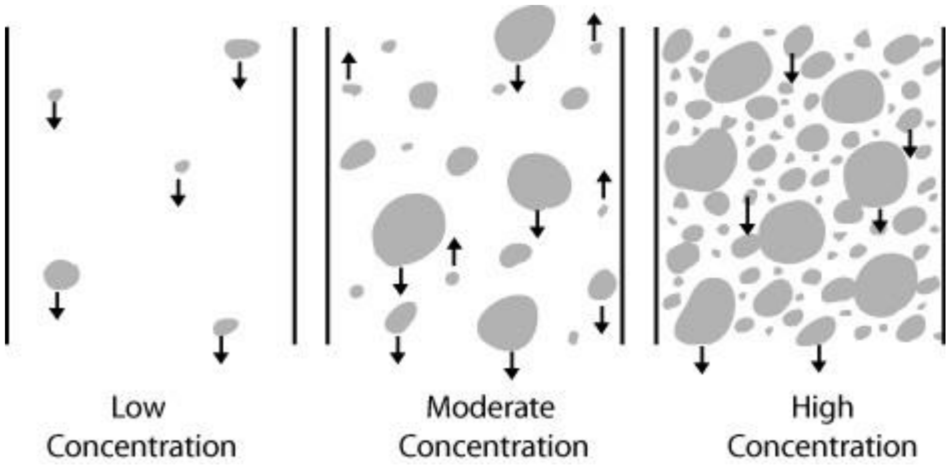
ρ_s =density of the dispersion medium.

g = acceleration due to gravity.

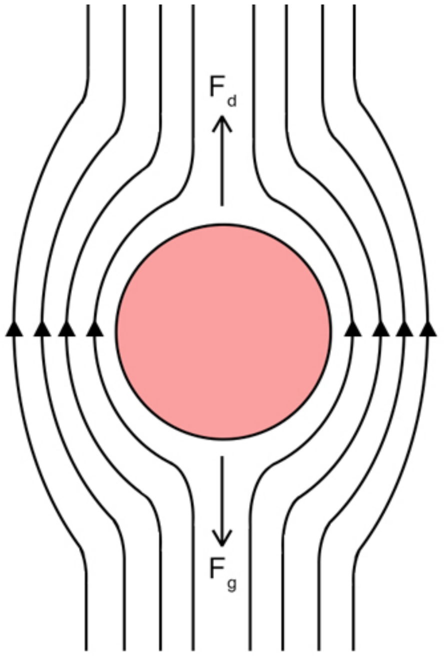
η = viscosity of the dispersion medium in poise.



- **One aspect of physical stability in pharmaceutical suspensions is concerned with keeping the particles uniformly distributed throughout the dispersion.**



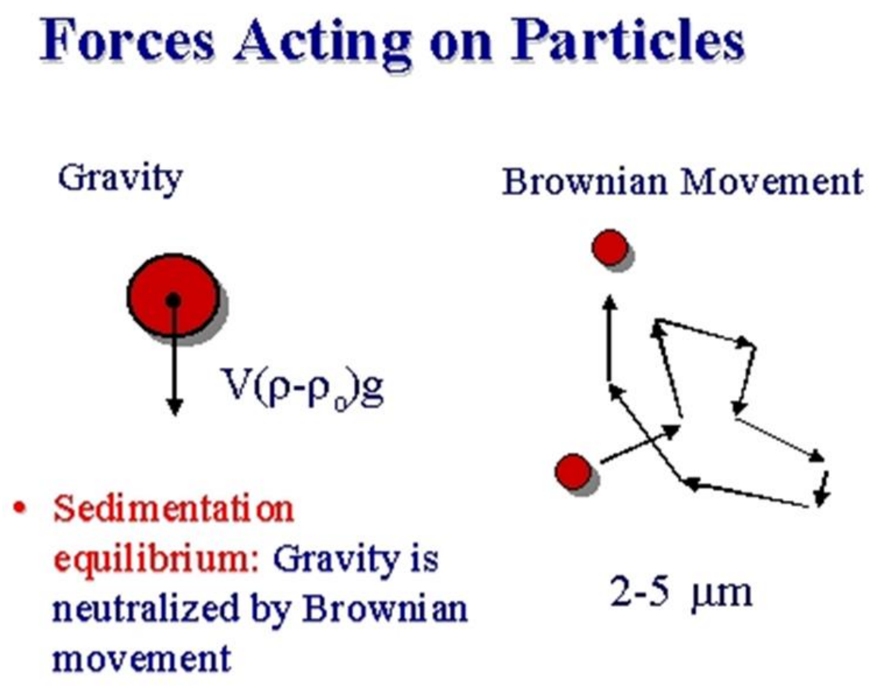
- **While it is seldom possible to prevent settling completely over a prolonged period of time, it is necessary to consider the factors which influence the velocity of sedimentation.**
- **Particle size of any suspension is critical.**
- **Larger particles will settle faster at the bottom of the container.**
- **The particle size can be reduced by using mortar and pestle**
- **But very fine particles will easily form hard cake at the bottom of the container.**

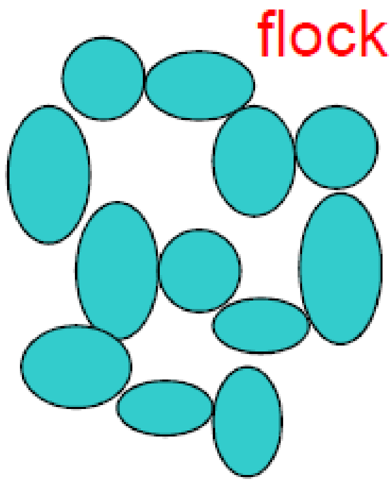


BROWNIAN MOVEMENT

For particles having a diameter of about 2-5 μm, Brownian movement counteracts sedimentation to a measurable extent at room temperature by keeping the dispersed material in random motion.

Brownian movement depends on the particle size, density of dispersed phase and the density and viscosity of the disperse medium.





DEFLOCCULATION AND FLOCCULATION

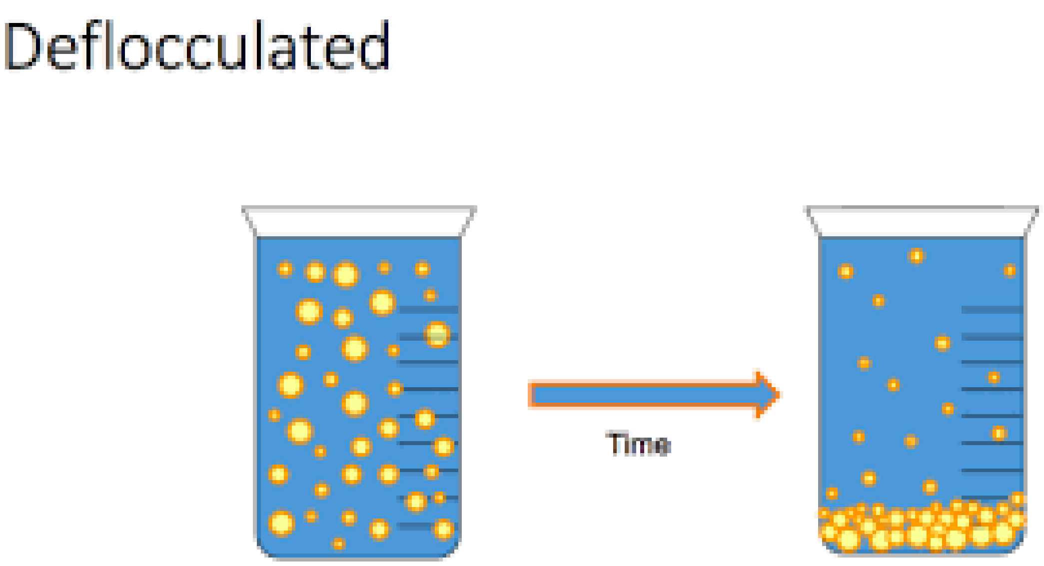
Flocculated Suspensions

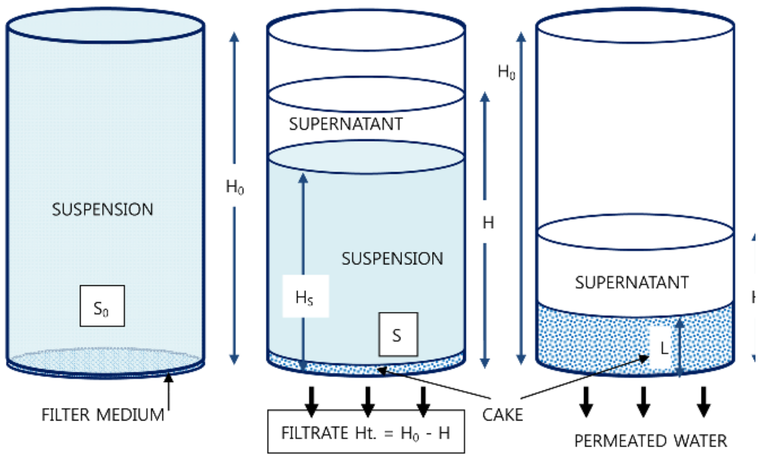
- In flocculated suspension, **formed flocs** (**loose aggregates**) will cause increase in sedimentation rate due to increase in size of sedimenting particles. Hence, flocculated suspensions sediment more rapidly.

- Here, the sedimentation depends **not only on the size** of the flocs but also on the porosity of the flocs.

Deflocculated suspensions

- In deflocculated suspension, individual particles are settling through time.
- Rate of sedimentation is slow, hence the sediment prevents entrapping of liquid medium which makes it difficult to re-disperse by agitation.
- This phenomenon called ‘caking’ or ‘claying’.
- In deflocculated suspension larger particles settle fast and smaller remain in supernatant liquid so supernatant appears cloudy.

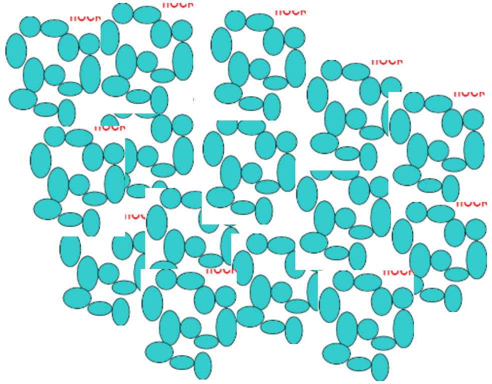




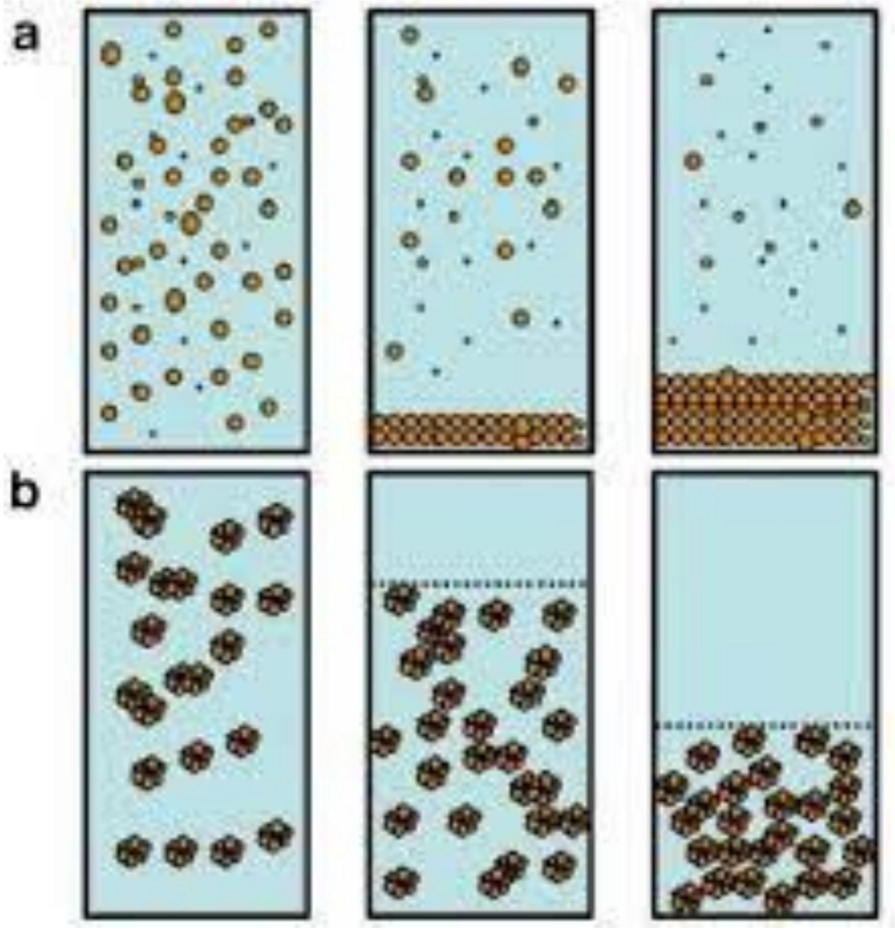
Deflocculated Suspension

flocculated Suspension

Not dense flocks aggregates



Deflocculated



Flocculated

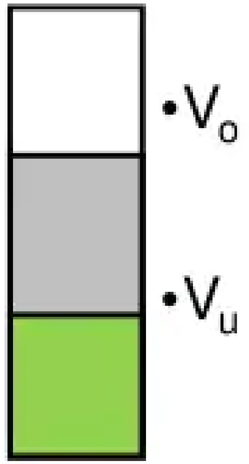
Time

	Flocculated	Deflocculated
Sedimented particle	Forms a network like structure	Separate individual particles
Velocity of sedimentation	fast fall together	slow fall according to size
Boundary	a distinct boundary between sediment and supernatant	no distinct boundary between sediment and supernatant
Supernatant	clear	turbid
Suspension	Not pleasing in appearance	Pleasing in appearance
Viscosity	High	Low
Rheology	plastic & pseudoplastic	Dilatent
Sediment	Loosely packed and doesn't form a cake	Closely packed and form a hard cake
Redispersibility	Easy	Difficult

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

Definition:

Sedimentation volume is the ratio of the ultimate volume of sediment (Vu) to the original volume of sediment (Vo) before settling.



$$F = Vu / VO$$

Where,

Vu = final or ultimate volume of sediment

VO = original volume of suspension before settling

F has values ranging from less than one to greater than one.

I- When $F < 1$ → $Vu < Vo$

II- When $F = 1$ → $Vu = Vo$

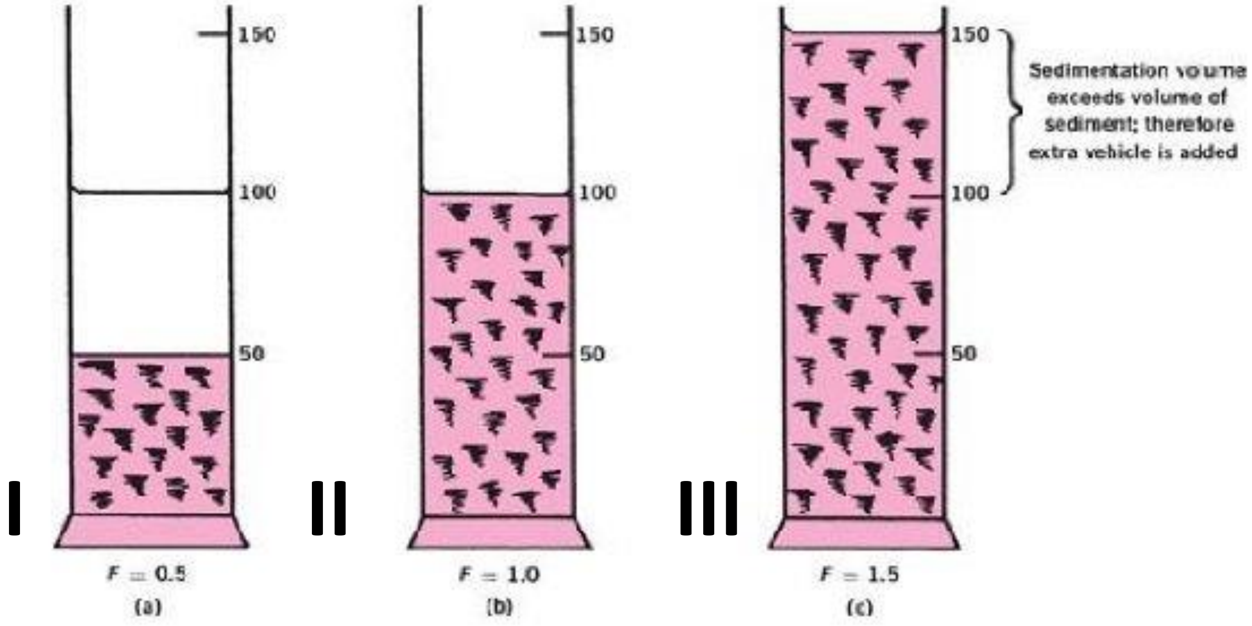
In the second case the system is in flocculated equilibrium and show no clear supernatant on standing.

III- When $F > 1$ → $Vu > Vo$

In this case the sediment volume is greater than the original volume due to the network of flocs formed in the suspension and so loose and fluffy sediment

- It is possible for *F* to have values greater than 1, meaning that the final volume of sediment is greater than the original suspension volume.

- This comes about because the network of flocs formed in the suspension is so loose and fluffy that the volume they are able to encompass is greater than the original volume of suspension.



The sedimentation volume gives only a qualitative account of flocculation.

Degree of flocculation (β)

It is the ratio of the sedimentation volume of the flocculated suspension (F) to the sedimentation volume of the deflocculated suspension (F∞).

$$ß = F / F_\infty$$

$$ß = \frac{(Vu/Vo)\ \text{flocculated}}{(Vu/Vo)\ \text{deflocculated}}$$

- **The maximum value of ß is 1, when flocculated suspension sedimentation volume is equal to the sedimentation volume of deflocculated suspension.**

INGREDIENTS OF SUSPENSION

I - Insoluble drug.

II- Vehicle (suspending medium, continuous phase).

III- Wetting agents.

IV- Compounds allowing control of stability and sedimentation (Flocculating agent, Suspending agent)

V - Additives used to regulate the flow behavior (rheology).

VI- pH regulators

VII- Other additives (flavour, colour, taste preservatives).

1) The Suspending Medium or Vehicle:

1 - Distilled water or deionized water.

2 - Water- alcohol

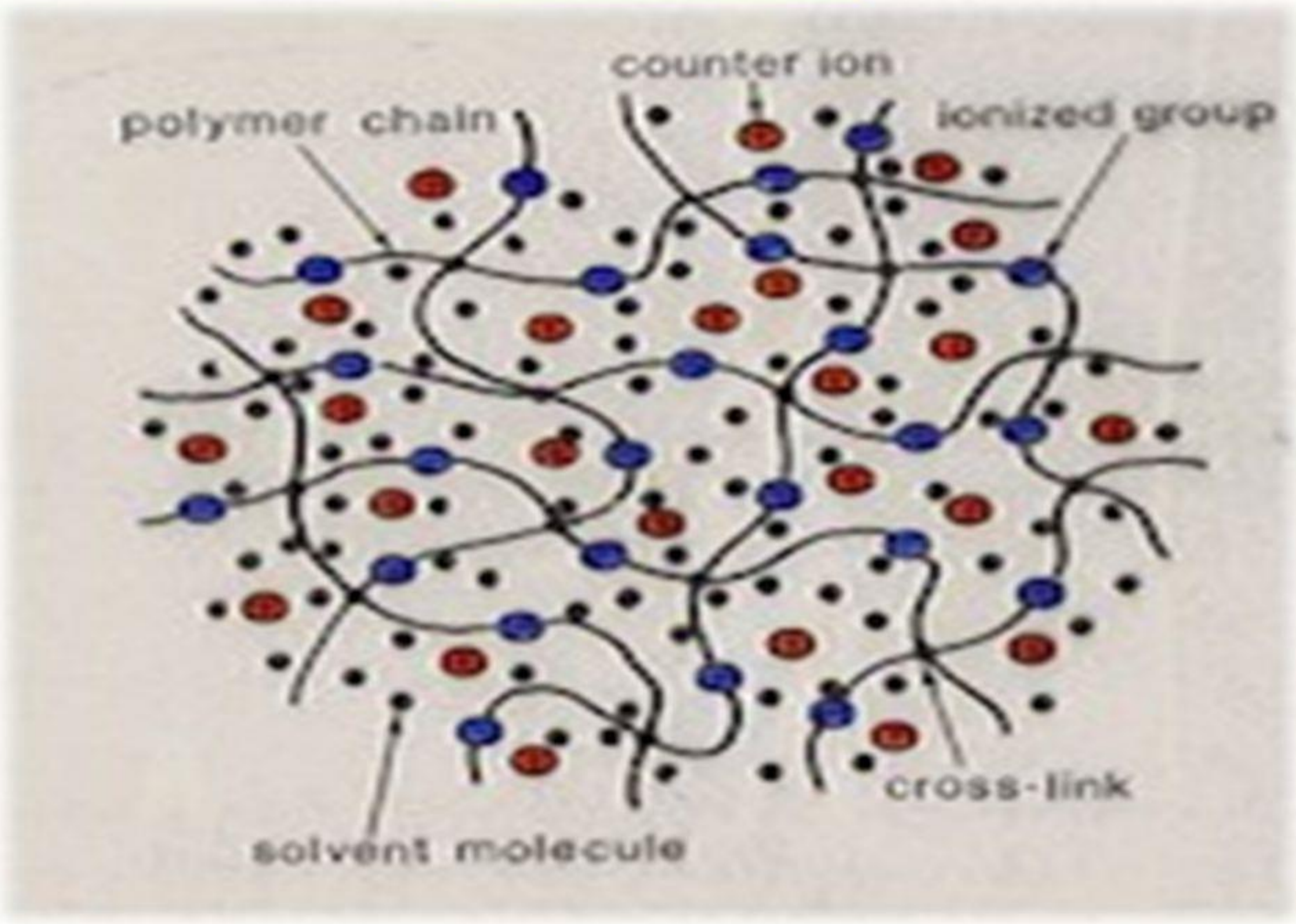
3 - Solution of glycerol.

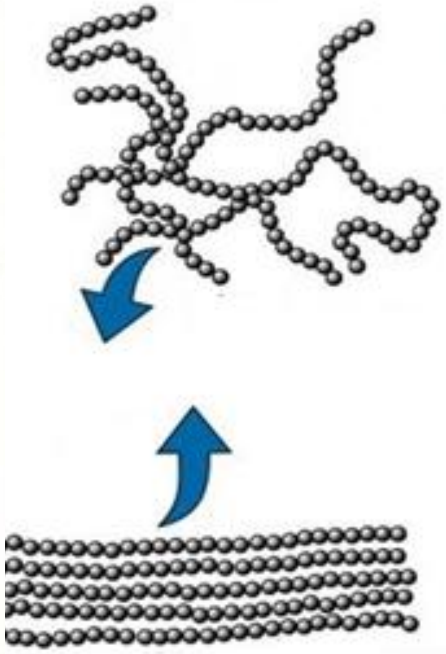
4 – Non-aqueous vehicles (Topical use).

Structured vehicles

- Structured vehicles are vehicles containing thixotropic compounds. Polymers like acacia (suspending agent) which are pseudo-plastic or plastic in nature (like ketchup state).
- Thixotropic compounds/polymers form a three-dimensional gel network structure which entrap the particles; so that, ideally, no settling occurs.
- During shaking the gel network is completely disentangled (pseudoplastic and plastic in nature) so that administration is facilitated.

Structured vehicles



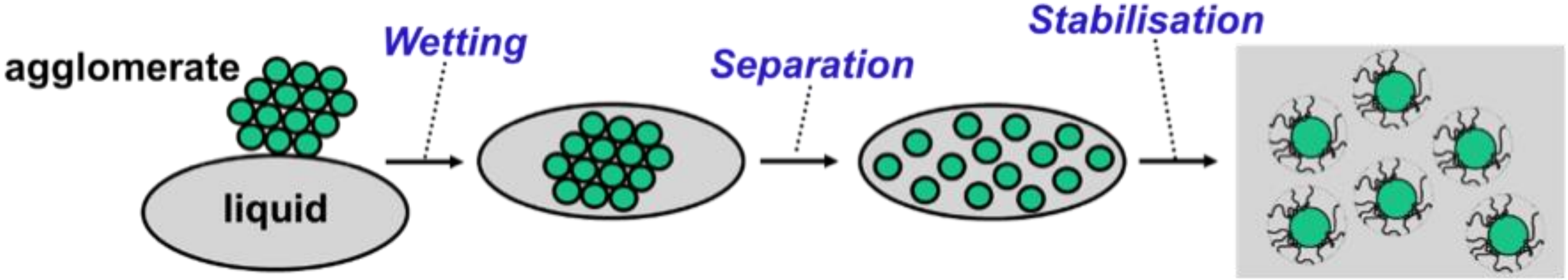


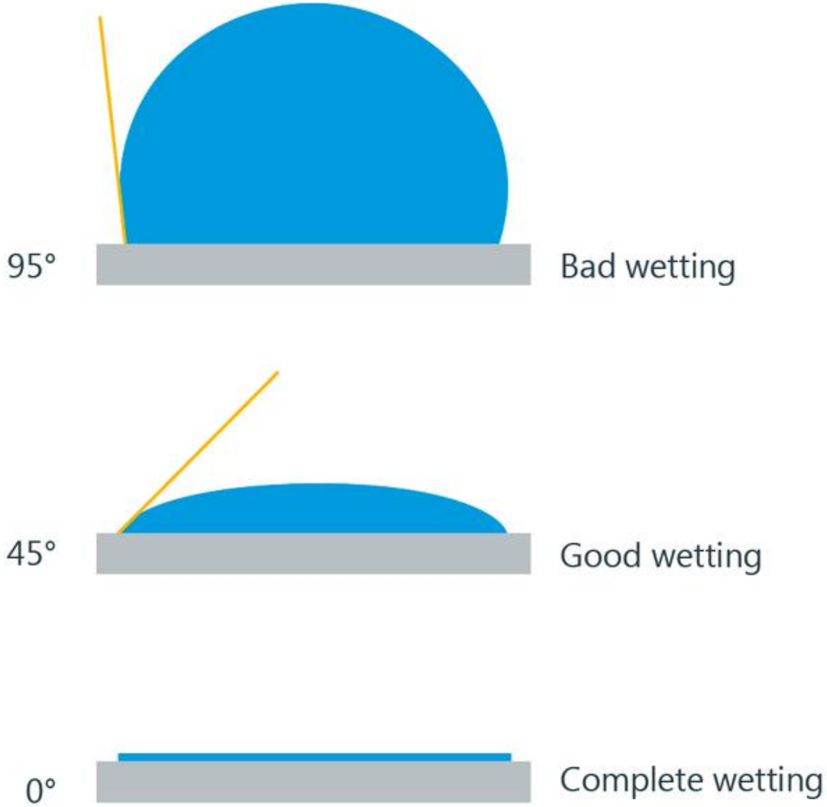
Entangled structure of polymer chain at rest

Disentangled structure of the polymer chain after the application of shear stress.

2) Wetting agents

- It is difficult to disperse solid particles in a liquid vehicle 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.
- Using of wetting agent allows to remove this air from the surface and to easy penetration of the vehicle into the pores.
- Powders, which are not easily wetted by water and accordingly show a large contact angle, such as sulfur, hydrocortisone, charcoal and magnesium stearate.
- The wettability of a powder may be ascertained easily by observing the contact angle and spreading coefficient.


agglomerate
liquid
Wetting
Separation
Stabilisation


95°
Bad wetting
45°
Good wetting
0°
Complete wetting

$Sc = \delta_S - \delta_L - \delta_{SL}$

Sc = Spreading coefficient

δ_S = surface tension of solid

δ_L = surface tension of liquid

δ_{SL} = surface tension of solid - liquid interface.

- So for convenient wetting, the value of spreading coefficient (Sc) should be positive.

- This could be achieved by modification of the values of surface tensions of several surfaces involved until a positive value of the spreading coefficient is reached.

- How modification done??
- By adding Wetting agent (surfactant with HLB value 7-9)
- E.g. Non ionic surfactant polysorbates

Wetting agent types

1 - SURFACTANTS:

- They reduce the interfacial tension between the solid particles and a vehicle (δ_{SL}). As a result of the lowered interfacial tension, the Sc will be positive and the contact angle is lowered, air is displaced from the surface of the particles, and wetting is promoted.

❖ Disadvantages of surfactants are that they have foaming tendencies.

✓ Polysorbate 80 (tween80) is most widely used surfactant both for parenteral and oral suspension formulation.

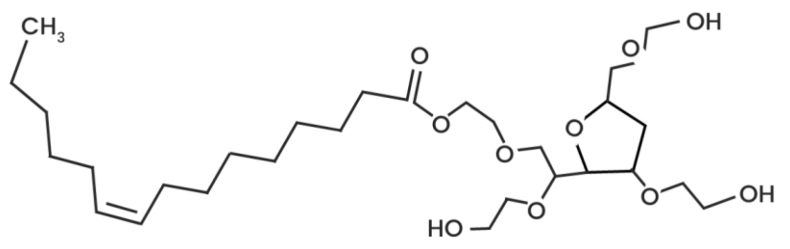
✓ It is non-ionic so no change in pH of medium

✓ Safe for internal use (No toxicity).

✓ Less foaming tendencies.

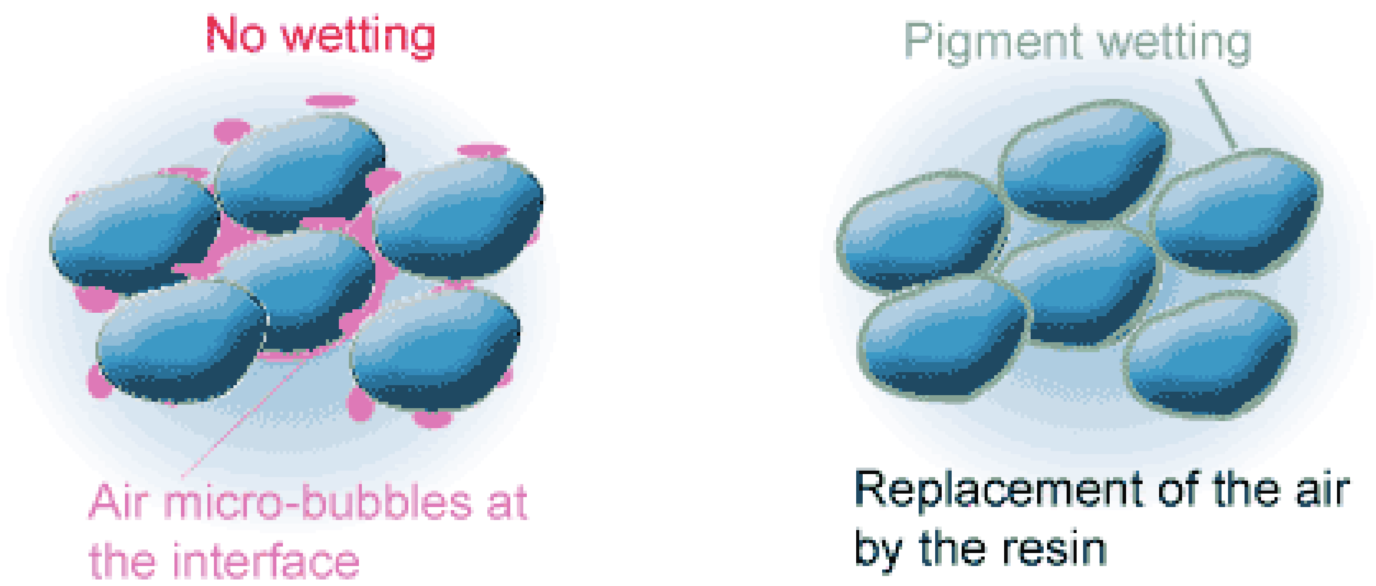
✓ Compatible with most of the adjuvants.

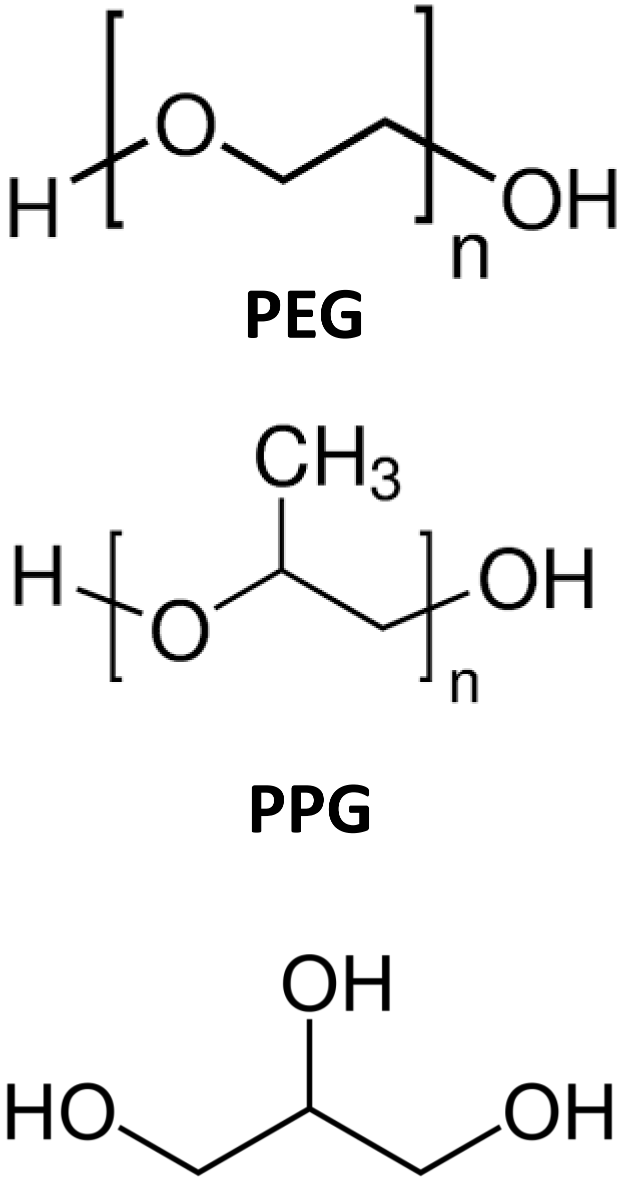
✓ Affect on zeta potential thus stabilizes the suspension (?)



2 - GLYCERIN AND SIMILAR HYGROSCOPIC SUBSTANCES

- **Alcohol, glycerin, polyethylene glycol PEG and polypropylene glycol PPG flows into the voids between the particles to displace the air and reduce liquid air interfacial tension so that water can penetrate and wet the individual particles.**





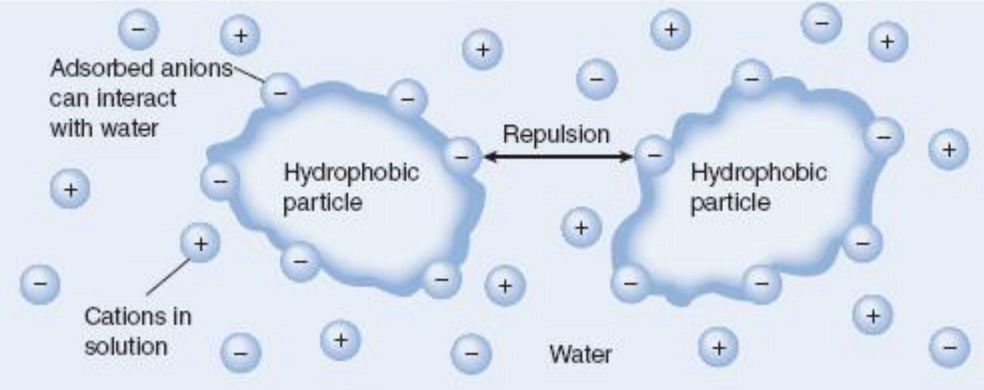
PEG

PPG

glycerin

3- HYDROPHILIC COLLOIDS

- Hydrophilic colloids coat hydrophobic drug particles in one or more than one layer.



- This will provide hydrophilicity to drug particles and facilitate wetting.
- As most of hydrophilic colloids are negatively charged, they cause deflocculation of suspension because force of attraction is declined. e.g. acacia, tragacanth, alginates, guar gum, pectin, gelatin, wool fat, egg yolk, bentonite, Veegum, Methylcellulose etc.

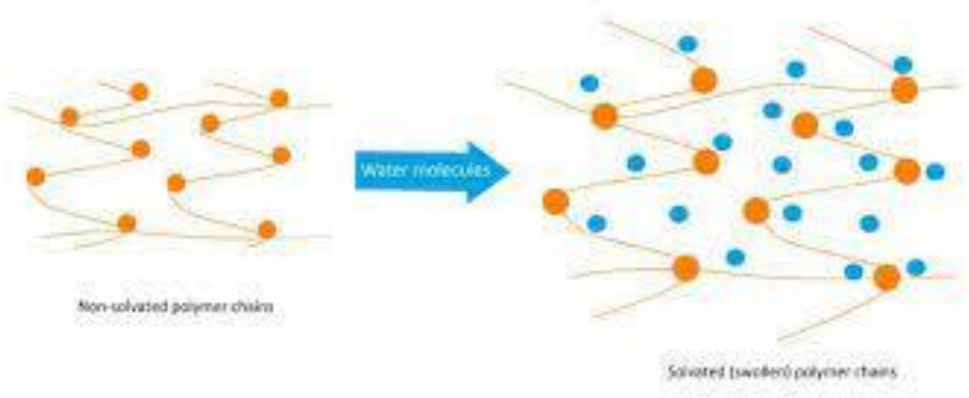
3) Suspending Agents / Viscosity Modifier / Thickener

Compounds Controlling Stability and Sedimentation

- Suspensions have least physical stability amongst all dosage forms due to sedimentation and cake formation.
- Viscosity of suspensions is of great importance for ***stability*** and ***pour ability*** of suspensions.
- When viscosity of the dispersion medium increases, the terminal settling velocity decreases thus the dispersed phase settle at a slower rate and they remain dispersed for longer time yielding higher stability to the suspension.
- On the other hand as the viscosity of the suspension increases, it's pour ability decreases and inconvenience to the patients for dosing increases.
- Therefore viscosity of suspension should be maintained within **optimum range** to yield stable and easily pourable suspensions.

There are different types of suspending agents:

- Natural gums (acacia, tragacanth, Xanthan gum).
- Sugars (glucose, fructose).
- Cellulose derivatives (sodium CMC, methyl cellulose, MCC).
- Alginates & Gelatin .
- Clays (bentonite, vee gum).
- Carbomers (acrylic acid polymers).
- Colloidal silicon dioxide (Aerosil).



Co-solvents

Some solvents which themselves have high viscosity are used as co-solvents to enhance the viscosity of dispersion medium: For example glycerol, propylene glycol.

Acacia

Tragacanth

Xanthan

Gelatin

Bentonite

Veegum

The Ideal Suspending Agent

- Should have a high viscosity at negligible shear, i.e., during storage.
- Should have a low viscosity at high shearing rate, i.e., it should be free flowing during agitation, pouring, and spreading.

✓ Pseudo-plastic substances such as: tragacanth, sodium alginate, and sodium carboxymethyl cellulose show these desirable qualities.

✓ A suspending agent which is **thixotropic** as well as pseudo-plastic are useful since it forms a **gel** on standing and becomes **fluid** when disturbed. (what about dilatant?)

✓ Apart from above, suspending agents should also be inert, non-toxic and compatible with other excipients used in suspensions.

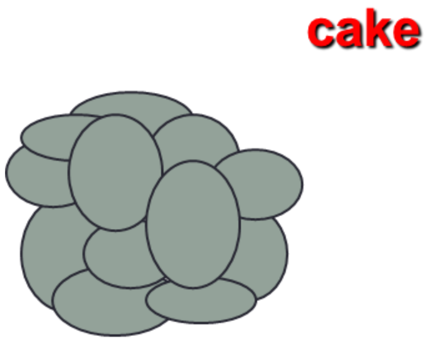
✓ They should be readily dissolved or dispersed in water without need of special technique.

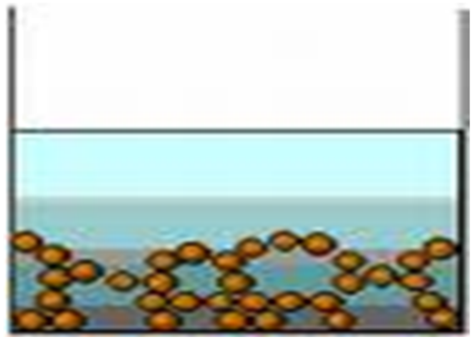
✓ They should not influence the absorption or dissolution rate of the drugs.

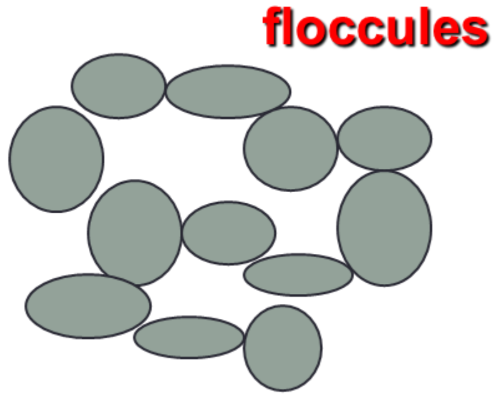
4) FLOCCULATING AGENTS

- Flocculating agents are added to enhance particle re-dispersability.

- Flocculation is the formation of light, fluffy groups of particles held together by weak Van der Waal's forces.







- In contrast to deflocculated particles, flocculated suspensions can always be re-suspended with gentle agitation.

- The best approach is to achieve a controlled flocculation of the particles, where they appear as floccules or like tufts of wool with a loose fibrous structure (flocks).

- Controlled flocculation of particles is obtained by adding flocculating agents, which are (1)-electrolytes (2)- surfactants (3)- polymers

A. Flocculating Agents: Electrolytes

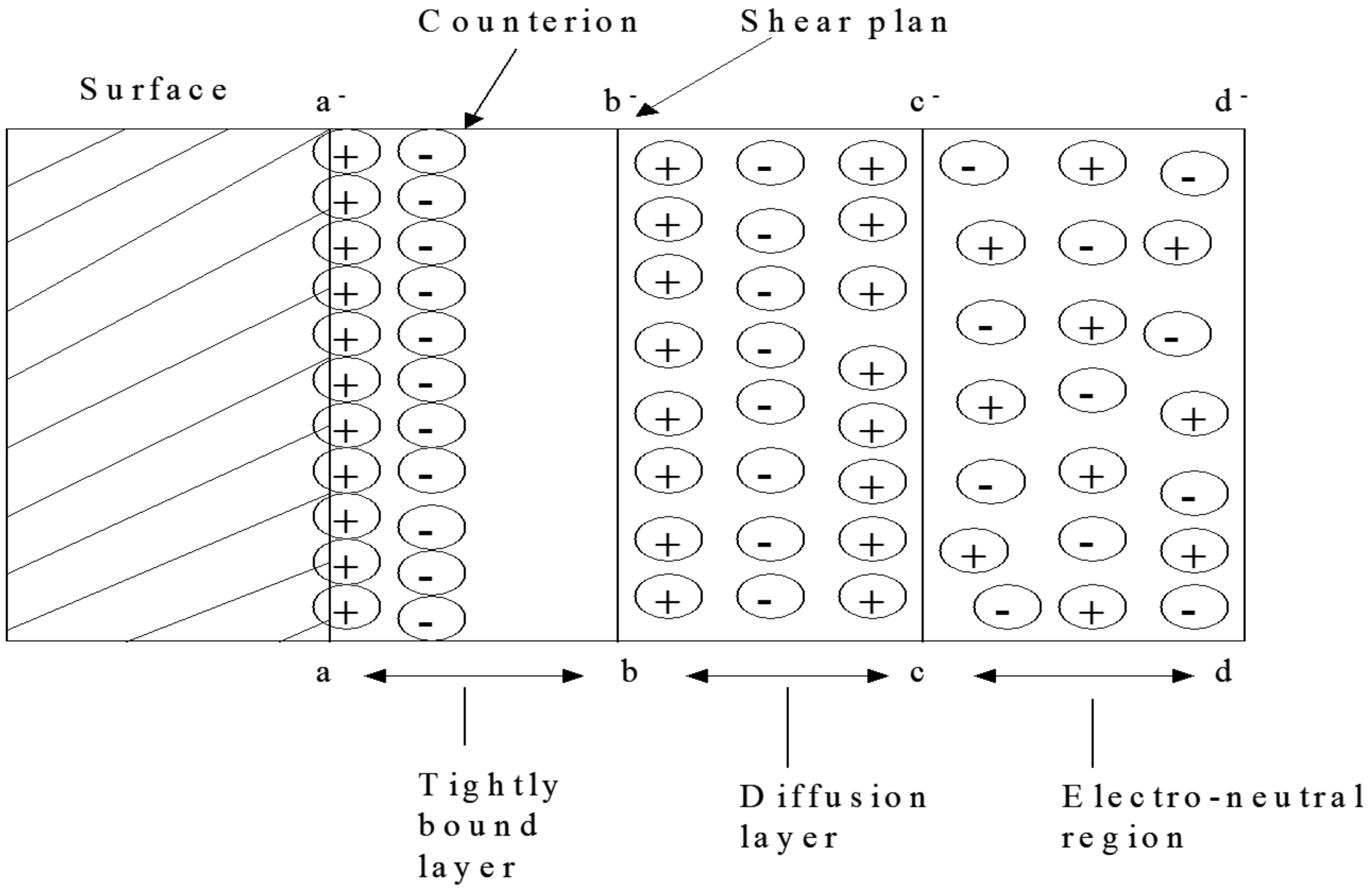
Dispersed solid particles in a suspension may have charge in relation to their surrounding vehicle, because of-

- Ionization of functional group of the particle.
- Selective adsorption of a particular ionic species present in the vehicle.

The ions that gave the particle its charge, are called POTENTIAL-DETERMINING IONS that serve to repel the particles.

Immediately adjacent to the surface of the particle is a layer of tightly bound solvent molecules, together with some ions oppositely charged to the potential-determining ions, called COUNTER IONS. Followed by diffusion layer with its surface potential which determine the repulsion forces.

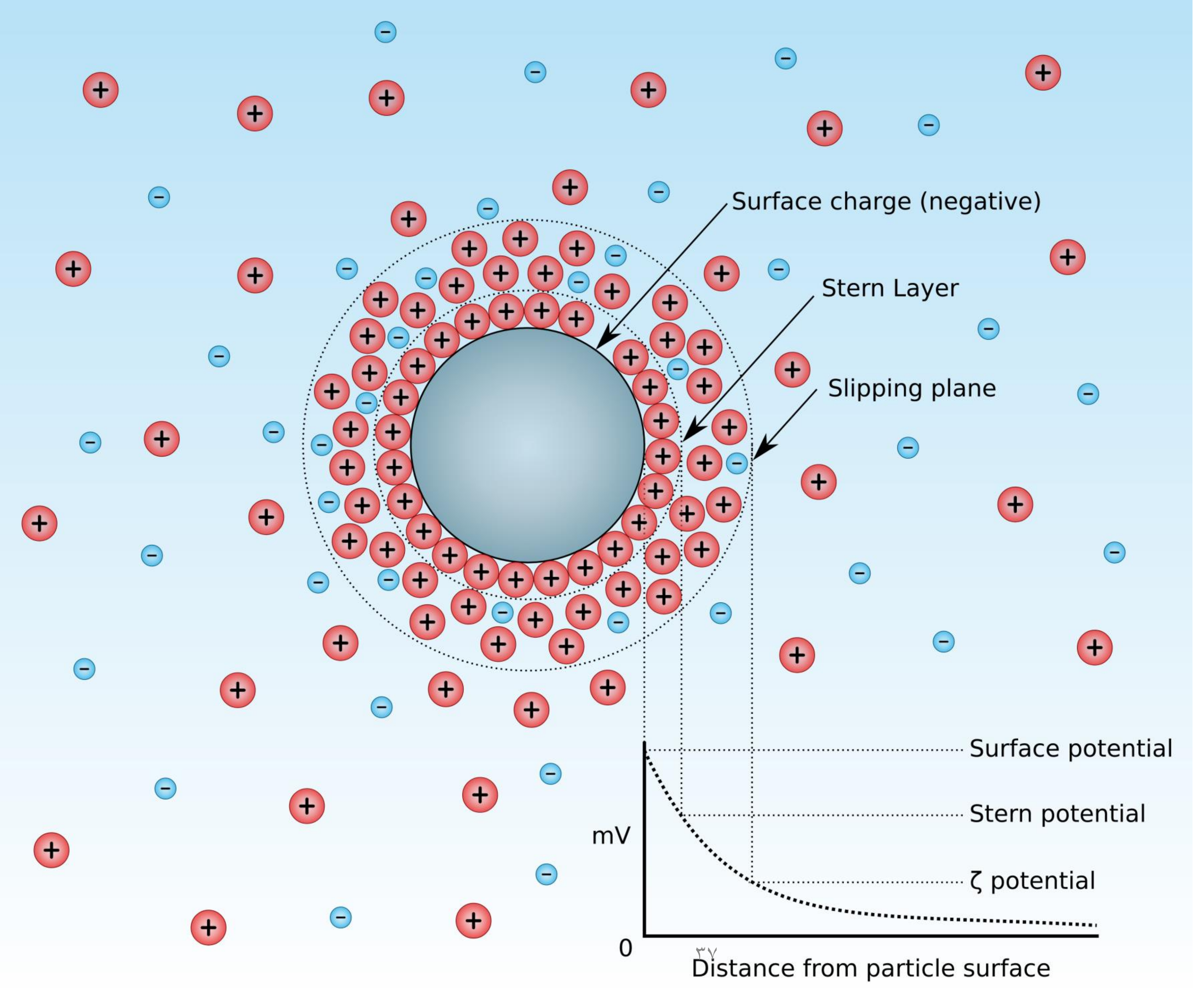
Electrolytes acts as flocculating agents by reducing the electrical barrier between the particles, thus, decrease the *zeta potential*, this leads to decrease in repulsion potential and makes the particle come together to form loosely arranged structure (floccules).

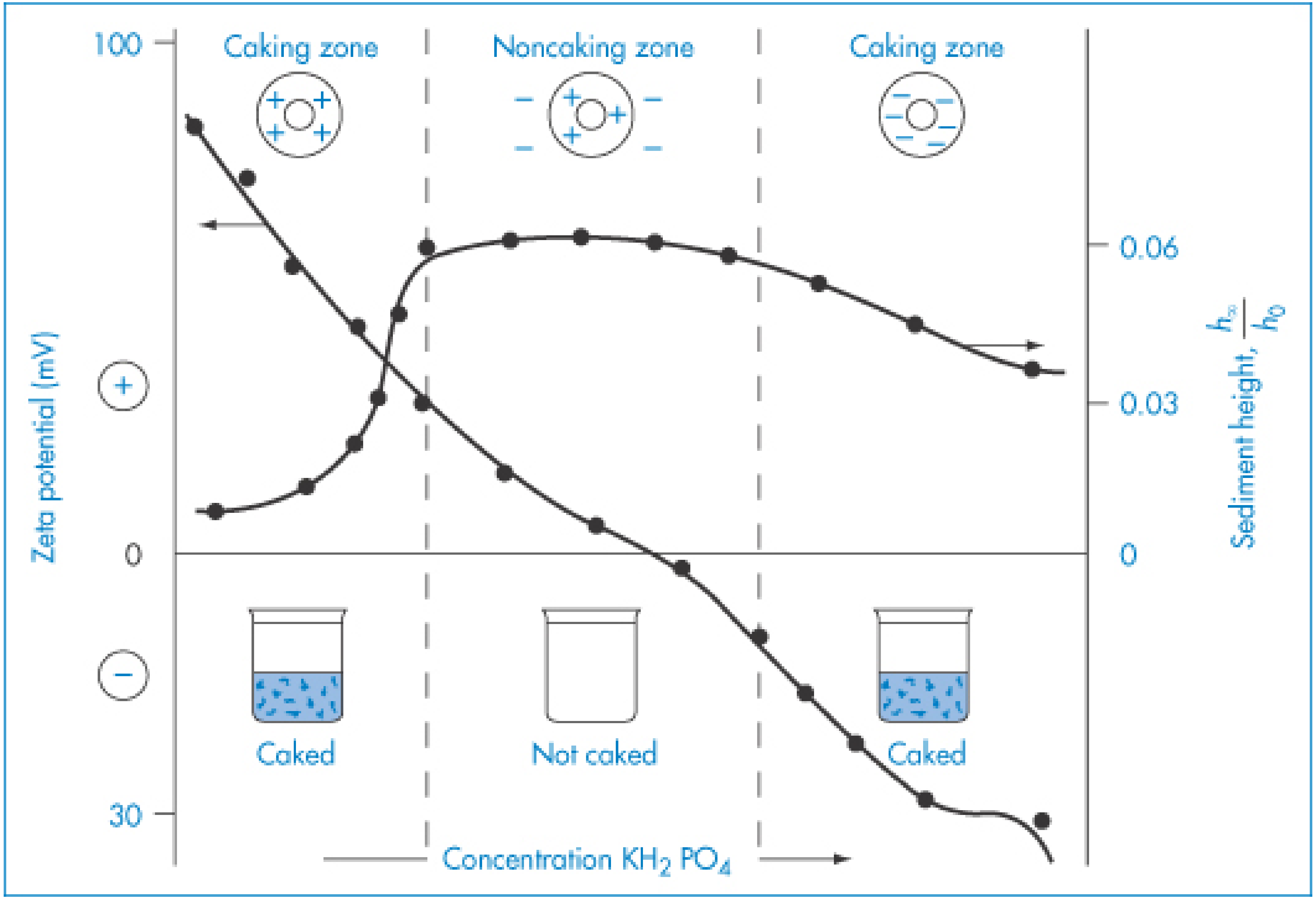


Zeta potential is the *potential difference* between the ions in the tightly bound layer and the electroneutral region.

Zeta potential governs the degree of repulsion between adjacent, similar charged, solid dispersed particles.

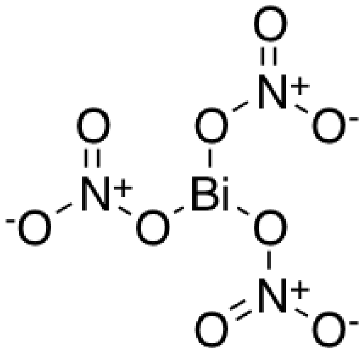
Increasing zeta potential will lead to flocculation or deflocculation?





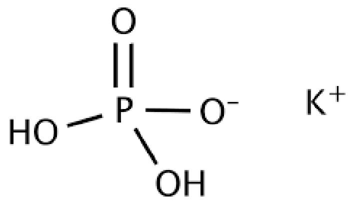
Caking diagram, showing the flocculation of suspension by means of the electrolyte

Electrolyte effect mechanism



- If we disperse particles of bismuth subnitrate in water, we find that, they possess a large positive charge, or zeta potential.

- Because of the strong forces of repulsion between adjacent particles, the system is deflocculated.



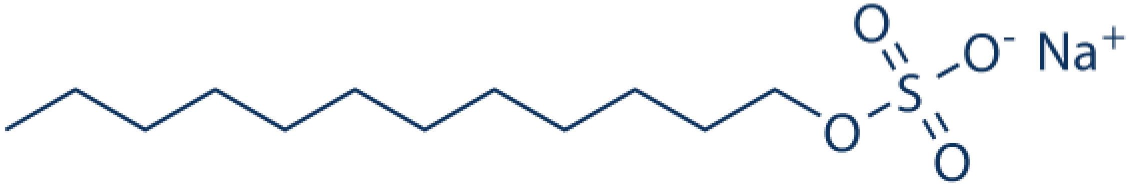
- The addition of monobasic potassium phosphate to the suspended bismuth subnitrate particles causes the positive zeta potential to decrease due to the adsorption of the negatively charged phosphate anion.

- With the continued addition of the electrolyte, the zeta potential falls to zero and then increases in a negative direction.

- The flocculating power increases with the valency of the ions. Calcium ions are more powerful than sodium ions because the valency of calcium is two whereas sodium has valency of one.

B. Flocculating Agents: Surfactants

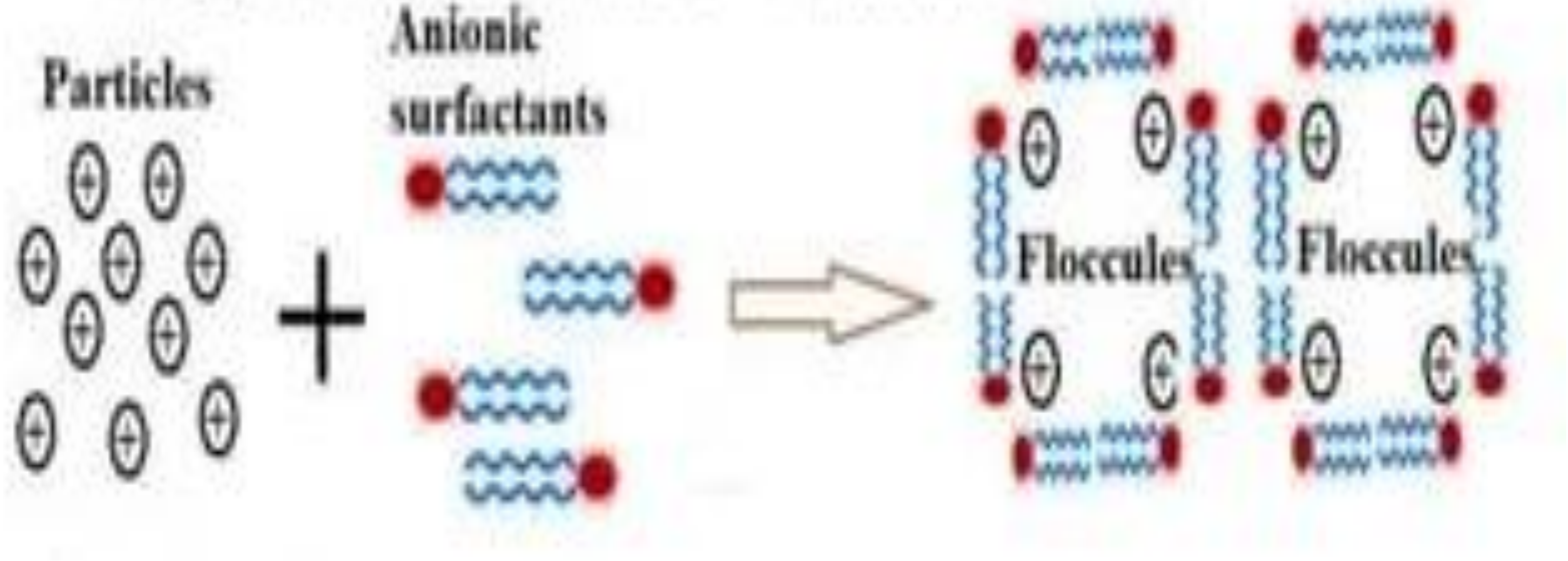
- Both ionic and non ionic surfactants could be used to control flocculation, e.g. Tween 80, Sodium lauryl sulfate.



- The concentration of surfactants necessary to achieve flocculation is critical since these compounds may also act as wetting agents to achieve dispersion.

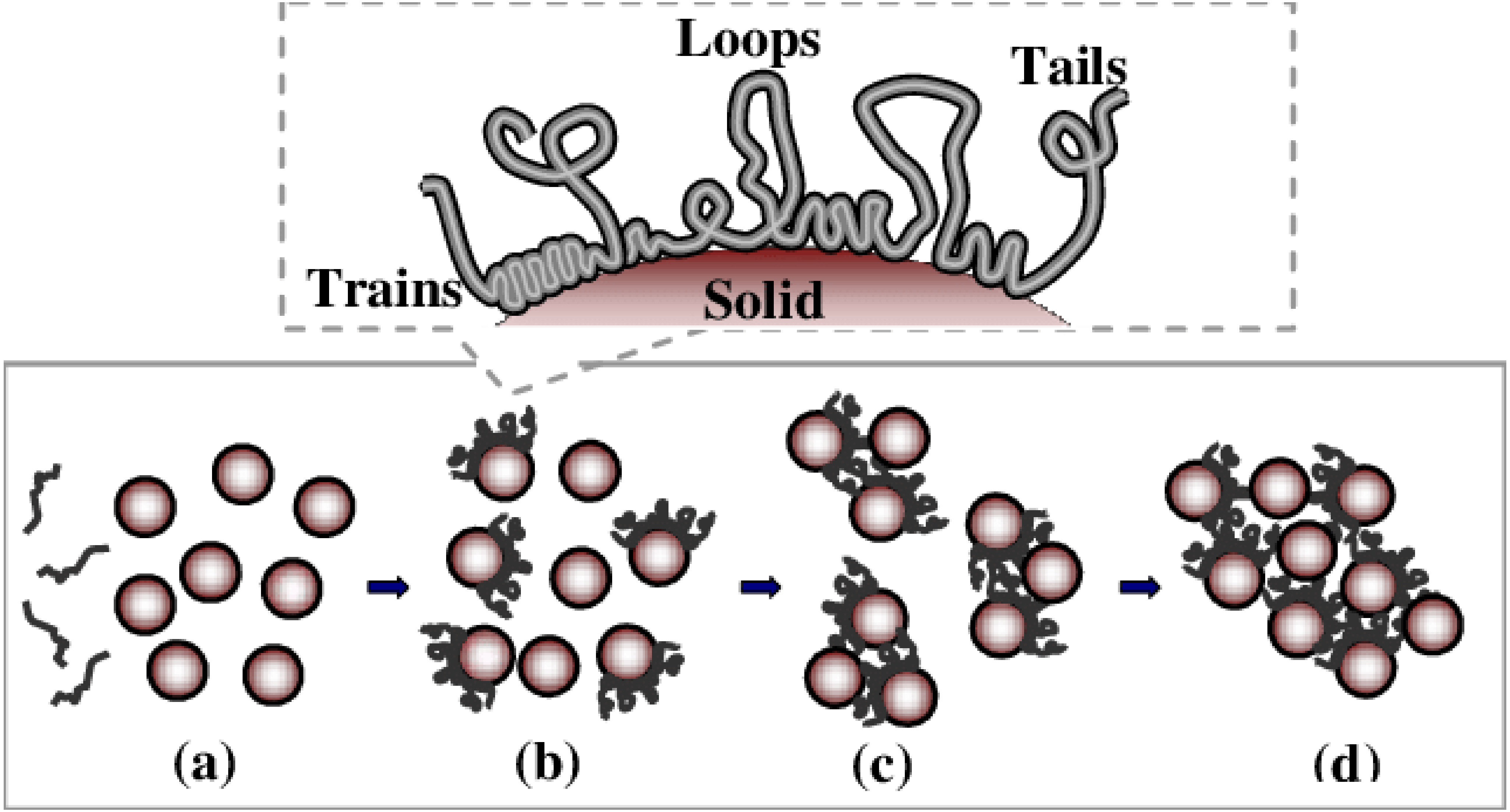
- **Optimum** concentrations of surfactants **bring down the surface free energy** by reducing the surface tension between liquid medium and solid particles. The particles possessing less surface free energy are attracted towards each other by van der-waals forces and forms loose agglomerates (floccules).
- Ionic surfactants cause flocculation by neutralizing the charge on each particle, resulting into a flocculated suspension

bridges between particles ➔ Floccules



C. Flocculating Agents: Polymers

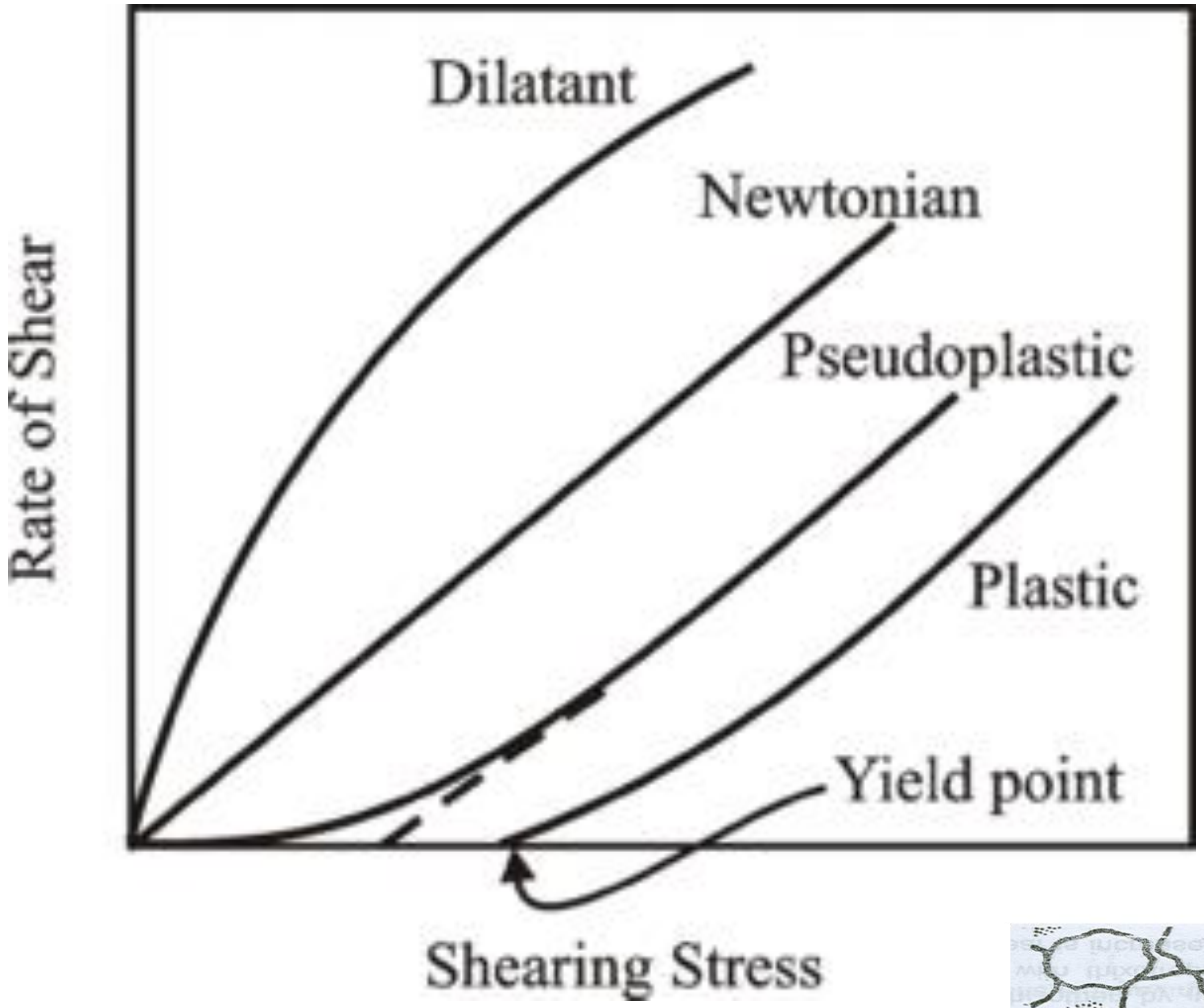
- Polymers like Starch, alginates, cellulose derivatives, carbomers, tragacanth are long chain, **high molecular weight** compounds containing active groups spaced along their length.
- These agents act as flocculating agents because part of the chain is adsorbed on the particle surface with the remaining parts projecting out in the dispersion medium.
- Bridging between these portions leads to the formation of floccules.
- Polymers exhibit pseudo-plastic flow in solution promoting the physical stability of suspension.



Polymers as flocculating agent

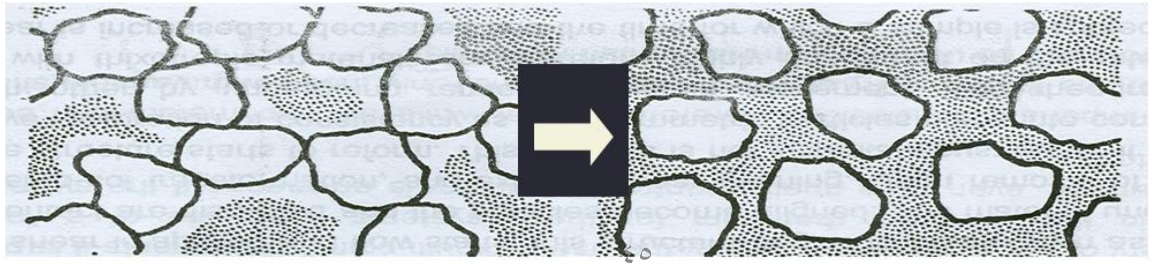
RHEOLOGICAL PROPERTIES OF SUSPENSIONS

- The flow of the acceptable suspension will be either pseudoplastic or plastic & it is desirable that thixotropy be associated with these two types of flow.
- Thixotropy is defined as the isothermal slow reversible conversion of **gel to sol**.
- Thixotropic substances on applying shear stress convert to sol (fluid) and on standing they slowly turn to gel (semisolid).
- 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.



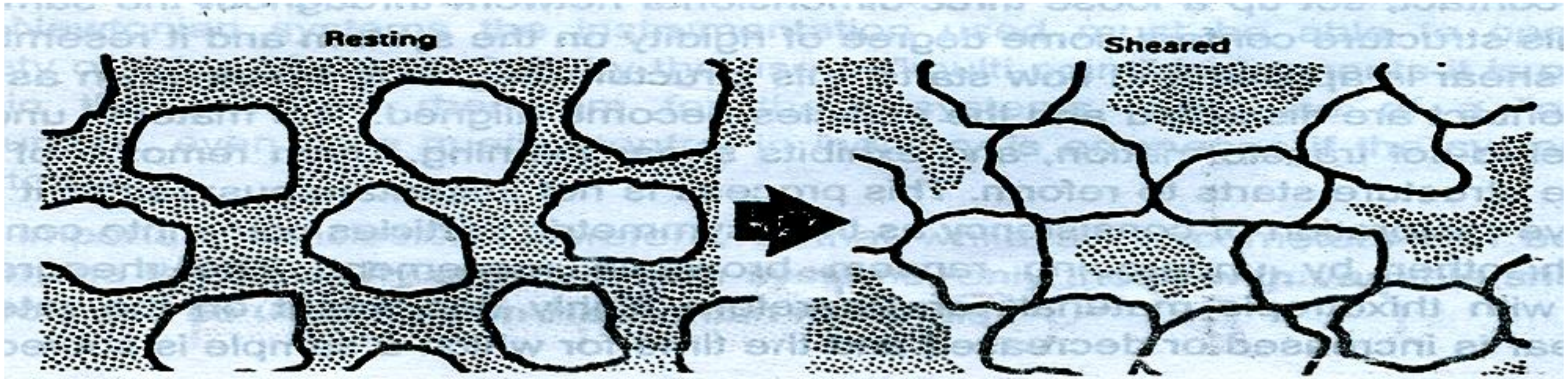
- The yield value is because the van der Waals forces between adjacent particles, which must be broken first before flow can occur.
- The more flocculated the suspension the higher will be the yield value.

Plastic **pseudoplastic**



Deflocculated suspensions exhibit dilatant behavior.

i.e. the viscosity of deflocculated suspensions is low at low shearing stresses and increases as the applied stress increases.



Explanation of dilatant flow behaviour

5) OTHER ADDITIVES

Typical buffering agents, flavors, colorants, and preservative used in suspensions:

Class	Agent
Buffer	Ammonia solution
	Citric acid
	Fumaric acid
	Sodium citrate
Flavor	Cherry
	Grape
	Methyl salicylatte
	Orange
	Peppermint
Colorant	D &C Red No. ٣٣
	FD &C Red No. ٣
	D &C Yellow No. ٣٣
Preservative	Butylparaben
	Methylparaben
	Propylparaben
	Sodium benzoate

THANK YOU