PHARMACEUTICAL SUSPENSIONS -2

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Classification of suspensions

- Based on the proportion of solids, suspensions are empirically classified as dilute or concentrated systems.

i) **Dilute suspensions** : Solid content 2 - 10 % e.g. Cortisone acetate and prednisolone acetate suspension.

ii) **Concentrated suspensions**: Solid content 10 - 50 % e.g. Zinc oxide suspension for external use, Procaine penicillin G injection, Antacid suspension etc.

CLASSIFICATION OF SUSPENSIONS

- Depending on the nature and behavior of solids, suspensions are classified as ***flocculated*** and ***deflocculated***.

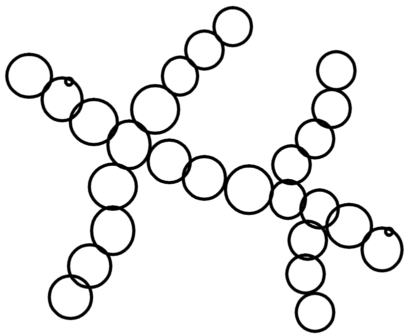


Fig. floccule

Fig. Coagule

CLASSIFICATION OF SUSPENSIONS

1. **DEFLOCCULATED SUSPENSION**

- In this system, solids are present as individual particles.

CLASSIFICATION OF SUSPENSIONS

2. **FLOCCULATED SUSPENSION**

- In this system, particles aggregate themselves by physical bridging. These flocs are light, fluffy conglomerate which are held together by weak van der Waal's forces of attraction.
- If the aggregate is an open network it is called floccule. They are fibrous, fluffy, open network of particles. It is loosely packed after sedimentation.
- If the aggregate is a closed one - it is called coagule. They are tightly packed, produced by surface film bonding.

CLASSIFICATION OF SUSPENSIONS

TABLE: Comparison between Deflocculated and Flocculated System

Deflocculated System	Flocculated System
i) Pleasant appearance, because of uniform dispersion of particles.	i) Somewhat unsightly sediment.
ii) Supernatant remains cloudy.	ii) Supernatant is clear
iii) Particles exist as separate entities	iii) Particles form loose aggregates.
iv) Rate of sedimentation is slow, as the size of particles are small.	iv) Rate is high, as flocs are the collection of smaller particles having a larger size.
v) Particles settle independently and separately	v) Particles settle as flocs.
vi) The sedimentation is closely packed and form a hard cake.	vi) Sediment is a loosely packed network and hard cake cannot form.
vii) The hard cake cannot be redispersed.	vii) The sediment is easy to redisperse.
viii) Bioavailability is higher due to large specific surface area.	viii) Bioavailability is comparatively less due to small specific surface area.

FACTORS AFFECTING THE STABILITY OF A SUSPENSION

- **SETTLING IN SUSPENSIONS**

Brownian movement

- Brownian movement of particles prevents sedimentation. In general, particles are not in a state of Brownian motion in pharmaceutical suspensions, due to

i) larger particle size (Brownian movement is seen in particles having diameter of about 2 to 5 μm (depending on the density of the particles and the viscosity and the density of the suspending medium.

ii) and higher viscosity of the medium.

FACTORS AFFECTING THE STABILITY OF A SUSPENSION

Sedimentation

- The rate of sedimentation of particles can be expressed by the Stoke's law, using the following formula:

$$Sedimentation\ rate = \frac{d^2(\rho_s - \rho_l)g}{18\eta}$$

Where

	d	is the particle diameter
	ρ_s, ρ_l	are densities of a particle and liquid respectively.
	g	is the acceleration of gravity.
	η	is the viscosity of the medium.

FACTORS AFFECTING THE STABILITY OF A SUSPENSION

- Stock's law is applicable if:

i) particles are spherical; but particles in the suspension are largely irregular.

ii) Particles settle freely and independently.

FACTORS AFFECTING THE STABILITY OF A SUSPENSION

- In suspensions containing 0.5 - 2 % (w/v) solid, the particles do not interfere with each other during sedimentation - hence free settling occurs.
- Most pharmaceutical suspensions contain 5 - 10 % or higher percentages of solid. in this cases particles interfere with one another as they fall - hence hindered settling occurs and Stoke's law no longer applies.

FACTORS AFFECTING THE STABILITY OF A SUSPENSION

- Stoke's law is applicable to deflocculated systems, because particles settle independently. However, this law is useful in a qualitative manner in fixing factors which can be utilized in formulation of suspensions.

STOKE'S LAW INTERPRETATION

1. <u>Particle size</u>

Rate of sedimentation $\propto$ *(diameter of particle)*^{2}

- So smaller the particle size more stable the suspension. The particle-particle interaction results in the formation of floccules or coagules where the sedimentation rate increases. The particles are made fine either by **dry milling** prior to suspension or **wet-milling** of the final suspension in a colloid mill or a homogenizer.

STOKE'S LAW INTERPRETATION

2. <u>Viscosity of the medium</u>

According to Stoke's law:

Rate of sedimentation ∞ 1 / (viscosity of the medium)

- The viscosity of suspension should be optimum. Viscosity can be increased by adding suspending agents or thickening agents. selection of high viscosity have both advantages and disadvantages.

STOKE’S LAW INTERPRETATION

- <u>Advantages</u>

i) Sedimentation rate is retarded, hence enhances the physical stability of the suspension.

ii) Inhibits crystal growth, because movement of particles is diminished.

iii) Prevents the transformation of metastable crystals to stable crystals.

STOKE'S LAW INTERPRETATION

- Disadvantages

i) Redispersibility of the suspension on shaking is difficult.

ii) Pouring out of the suspension from the container may be difficult.

iii) Creates problems in the handling of materials during manufacture.

iv) May retard absorption of drugs from the suspension.

STOKE'S LAW INTERPRETATION

- **3. <u>Density</u>**

Rate of sedimentation ∞ (density of solid – density of liquid medium)

- Lesser the difference between the densities of solid particles and liquid medium slower is the rate of sedimentation. Since it is very difficult to change the absolute density of the solid particles so the density of the liquid medium can be manipulated by changing the composition of the medium.

- The addition of nonionic substances such as sorbitol, polyvinylpyrrolidone (PVP), glycerin, sugar, or one of the polyethyleneglycols or combination of these may be helpful in the manipulation.

STOKE'S LAW INTERPRETATION

- If the density of the particles is greater than the continuous medium the particles will settle downwards, the phenomenon is known as sedimentation.
- If the density of particle is lesser than that of the liquid medium then the particles will move upward - the phenomenon is known as creaming.

Formulation of suspensions

General Requirements

The product must:

1) Flow readily from the container
2) Possesses a uniform distribution of particles in each dose.

FORMULATION OF SUSPENSIONS

- **Two approaches are commonly employed to secure the two requirements:**

(i) The use of **structured vehicle** to maintain deflocculated particles in suspension. Structured vehicles are pseudoplastic and plastic in nature;

- It is frequently desirable that thixotropy be associated with these two type of flow.
- Structured vehicles act by entrapping the particles so that, ideally no settling occurs.
- In reality some degree of sedimentation will usually take place. The *shear thinning* property of these vehicle does however facilitate the redispersion when shear is applied.

FORMULATION OF SUSPENSIONS

ii. The application of the principles of flocculation to produce flocs that, although, they settle rapidly are easily redispersed with a minimum of agitation.

FORMULATION OF SUSPENSIONS

WETTING OF PARTICLES

- The initial dispersion of an insoluble powder in a vehicle is an important step in the manufacturing process. Powders sometimes are added to the vehicle, particularly in large scale operations, by dusting on the surface of the liquid. It is frequently difficult to disperse the powder owing to an adsorbed layer of air, minute quantity of grease and other contaminants.

FORMULATION OF SUSPENSIONS

- Powders those are not easily wetted by water and accordingly show a large contact angle, such as sulfur, charcoal and magnesium stearate are said to be ***hydrophobic***.
- Powders those are readily wetted by water when free of adsorbed contaminants are called ***hydrophilic***. e.g. zinc oxide, talc, magnesium carbonate etc. belong to this category.

Formulation of Suspensions

- When a strong affinity exists between a liquid and a solid, the liquid easily forms a film over the surface of the solid.
- When this affinity is non-existent or weak, the liquid faces difficulty in displacing the air or other substances surrounding the solid.

FORMULATION OF SUSPENSIONS

- Hydrophilic solids usually can be incorporated into suspensions without the use of a wetting agent, but hydrophobic materials are extremely difficult to disperse and frequently float on the surface of the fluid owing to poor wetting of the particles or the presence of tiny air pockets on the surface of the solid particles.
- To reduce the **contact angle** between solid and liquid (i.e. increase the wettability) the following agents can be used:

FORMULATION OF SUSPENSIONS

1. **Surfactants** Solid-liquid interfacial tension is reduced by incorporating a surfactant with a HLB value between 7 to 9. These are employed to allow the displacement of air from hydrophobic material and permit the liquid, to surround the particles and provide a proper dispersion.

- The surfactant is mixed with the solid particles if required by shearing.
- The hydrocarbon chain is preferentially adsorbed to the hydrophobic surface, with the polar part of the surfactant being directed towards the aqueous phase.

FORMULATION OF SUSPENSIONS

2. **Hydrophilic polymers** such as sodium carboxymethyl cellulose, certain water-insoluble hydrophilic material such as bentonite, aluminum-magnesium silicates, and colloidal silica, either alone or in combination can be incorporated in desired concentration. These materials are also used as suspending agents and may produce a deflocculated system particularly if used at low concentration.

FORMULATION OF SUSPENSIONS

3. **Solvents** such as alcohol, glycerol and glycols which are water miscible will reduce the liquid / air interfacial tension. The solvent will penetrate the loose agglomerates of powder displacing the air from the pores of the individual particles thus enabling wetting by dispersion medium.

Method of selection of a suitable wetting agent

- In order to select a suitable wetting agent Heistand has used a narrow trough, several inches long and made of a hydrophobic material, such as Teflon, or coated with paraffin wax.
- At one end of the trough is placed the powder and the other end the solution of the wetting agent.
- The rate of penetration of the wetting agent solution into the powder can then be observed directly.
- Greater the rate of penetration of the solution into the powder better is the wetting property of the solution.

RHEOLOGIC CONSIDERATIONS

- **Rheologic consideration are important in:**

(i) the viscosity of a suspension as it affects the settling of particles. As viscosity increases rate of sedimentation of the particles reduces.

(ii) the change in flow properties of the suspension when the container is shaken and when the product is poured out off the bottle.

(iii) the spreading quality of the lotion when applied to the affected area.

(iv) during the manufacture of the suspensions.

Importance of suspending agents

- The particles in a suspensions are experiencing bombardment constantly with each other owing to the Brownian movement.
- During this type of inter-particular interaction the particles may circumvent the repulsive force between them and form larger particles which will then settle rapidly.
- Suspending agents reduce this movement of the particles by increasing the viscosity of the medium.

Importance of suspending agents

- According to Stoke's law rate of sedimentation is inversely proportional to the viscosity of medium. So the settling of the particles , either in flocculated or deflocculated system, can be slowed down by increasing the drag force on the moving particles by increasing the viscosity of the medium.
- Hydrophilic polymers such as sodium carboxymethyl cellulose, certain water-insoluble hydrophilic material such as bentonite, aluminum-magnesium silicates, and colloidal silica, either alone or in combination can be incorporated in low concentration as **wetting agent.**

Importance of suspending agents

- Hydrophilic polymers also acts as **protective colloids** and particles coated in this manner are less prone to cake than are uncoated particles.
- **Cellulose polymers** e.g. sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose.
- **Proteins** e.g. gelatin.
- **Synthetic polymer** e.g. Polyacrylic acid (Carbopol)
- **Clays** essentially hydrated aluminum and/or magnesium silicates are also useful in suspension formulation.

Characteristics of ideal suspending agent

(i) An ideal suspending agent should have a high viscosity at negligible shear; i.e. during shelf storage; and it should have a low viscosity at high shear rates, i.e. it should be free flowing during agitation, pouring and spreading on the skin.

(ii) Suspending agents should coat the particles which will be less prone to caking than the uncoated particles.

Characteristics of ideal suspending agent

- Pseudoplastic substances e.g. tragacanth, sodium alginate and sodium carboxymethylcellulose show these desirable qualities. It is a shear thinning system, i.e. when this type of system is shaken or agitated the viscosity diminishes.
- A suspending agent that is thixotropic as well as pseudoplastic should prove to be useful since it forms gel on standing and becomes fluid when disturbed. e.g. Bentonite - Carboxymethylcellulose has both pseudoplastic and thixotropic behavior.

Characteristics of ideal suspending agent

Suspending agent	Concentration in which generally used
Sodiumcarbxymethylcellulose	0.5 – 2.5 %
Tragacanth	1.25 %
Guargum	0.5 %
Carbopol 934	0.3 %

CONTROLLED FLOCCULATION

- Assuming that the powder is properly wetted and dispersed, attention may now be given to the various means by which controlled flocculation may be produced so as to *prevent compact sediment which is difficult to redisperse*. Controlled flocculation can be described in terms of the materials used to produce flocculation suspensions, namely, (i) electrolytes, (ii) surfactants, and (iii) polymers.

CONTROLLED FLOCCULATION

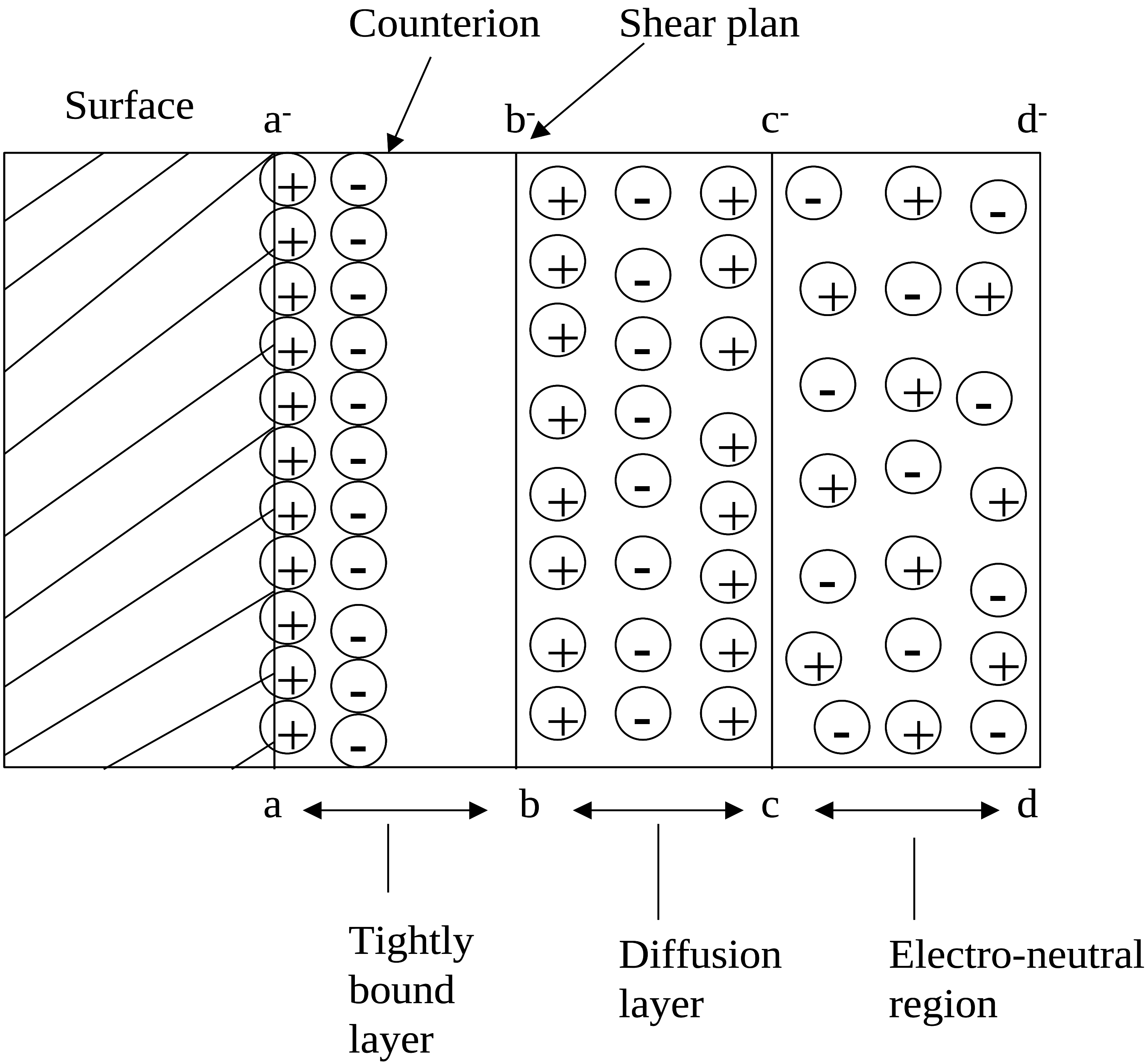
(i) Electrolytes act as flocculating agents by reducing the electric barrier between the particles, as evidenced by a decrease in the zeta-potential and formation of a bridge between adjacent particles so as to link them together in a loosely arranged structure.

CONTROLLED FLOCCULATION

- *<u>Example</u>*: When bismuth subnitrate is suspended in water it has been found (by electrophoretic studies) that they possess a large positive charge, or zeta potential.
- Because of the strong forces of repulsion between adjacent particles, the system remains in deflocculated state.
- The addition of monobasic potassium phosphate (KH_2PO_4) to the suspension causes the positive **<u>zeta-potential</u>** to decrease owing to the adsorption of the negatively charged phosphate anion. The particles then can come closer to form aggregates.

Zeta Potential

- The zeta potential is defined as the difference in potential between the surface of the tightly bound layer (shear plane) and electro-neutral region of the solution.


Counterion
Shear plan
Surface
a-
b-
c-
d-
a
b
c
d
Tightly bound layer
Diffusion layer
Electro-neutral region

CONTROLLED FLOCCULATION

(ii) Surfactants both ionic and nonionic, have been used to bring about flocculation of suspended particles. The concentration necessary to achieve this effect would appear to be critical since these compounds may also act as wetting agents to achieve dispersion.

CONTROLLED FLOCCULATION

(iii) Polymers 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 into the dispersion medium. Bridging between these latter portions leads to the formation of flocs.

- hydrophilic polymers also acts as protective colloids and particles coated in this manner are less prone to cake than are uncoated particles.

FLOCCULATION IN STRUCTURED VEHICLE

- Although the controlled flocculation approach is capable of fulfilling the desired physical chemical requisites of a pharmaceutical suspension, the product can look unsightly if F, the sedimentation volume, is not close to or equal to 1. So a suspending agent is added to retard sedimentation of the flocs. Such agents as carboxymethylcellulose (CMC), Carbopol 934, Veegum, tragacanth or bentonite have been employed, either alone or in combination.

FLOCCULATION IN STRUCTURED VEHICLE

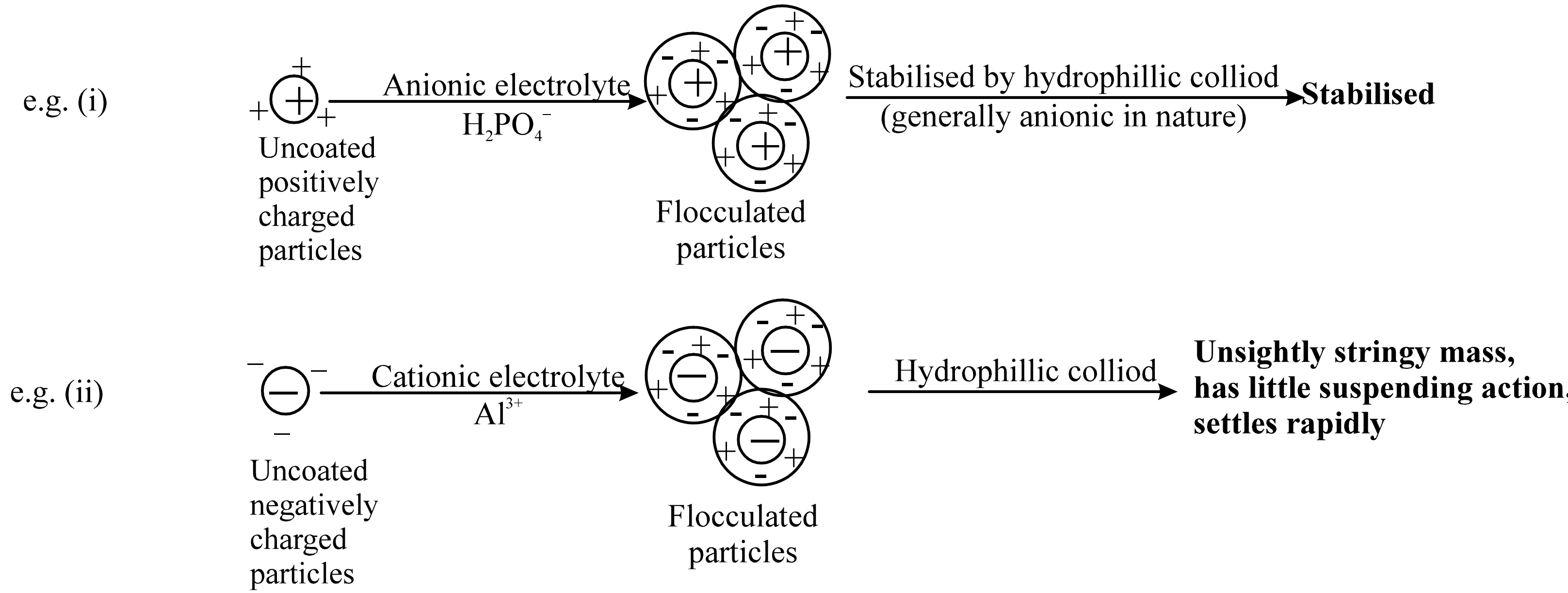
- These may lead to incompatibilities, depending on

(i) the initial particle charge

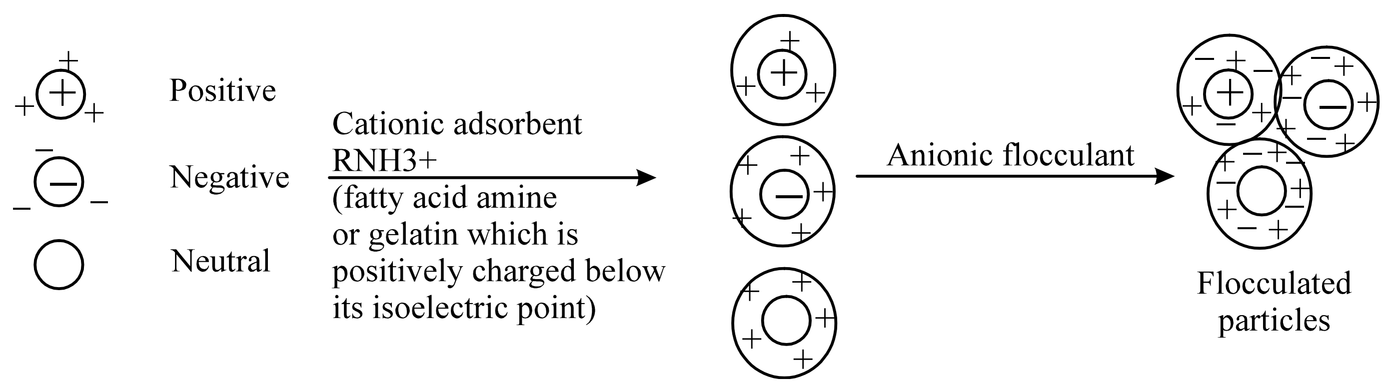
(ii) the charge carried by flocculating agent and

(iii) the charge carried by suspending agent.

FLOCCULATION IN STRUCTURED VEHICLE



To overcome this incompatibility the following method is applied



To be Continued