SUSPENSION

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DISPERSE SYSTEM

- The term "Disperse System" refers to a system in which one substance (The Dispersed Phase) is distributed, in discrete units, throughout a second substance (thecontinuous Phase).
- Each phase can exist in solid, liquid, or gaseous state .

- Suspensions are heterogenous system consisting of 2 phases.

DEFINITION

- A Pharmaceutical suspension is a coarse dispersion in which internal phase (**therapeutically active ingredient**)**is dispersed uniformly** throughout the external phase.

- The **internal phase consisting of insoluble solid particles** having a range of size(**0.5 to 5 microns) which is** maintained uniformly through out the suspending vehicle with aid of **single or combination of suspending agent.**
- The external phase (**suspending medium) is generally aqueous in some instance, may be an organic or oily** liquid for non oral use.

The Desirable Features of Suspensions

In addition to therapeutic efficacy and stability, other features apply specifically to the suspensions:

1. A properly prepared suspension should settle slowly and remain homogenous for at least the period between shaking the container and removing the required dose.
2. The sediment produced on storage should be readily redispersed upon gentle shaking of the container.
3. The particle size of the suspended drug should remain constant throughout long periods and do not show crystal growth (i.e., physically stable).
4. The suspension viscosity must not be very high and it should be poured easily from its container.

SOME 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

Classification

Based on General class

- Oral Suspension

e.g. Paracetamol Suspension

- Externally Applied suspension

e.g. Calamine lotion

- Parenteral Suspension

e.g. Insulin zinc suspension

Based on proportion of Solid Particles

- Dilute Suspension (2 to 10% w/v solid)

e.g. cortisone acetate, predinsolone acetate

- Concentrated Suspension (50% w/v solid)

e.g. Zinc oxide suspension

Based on Proportion of Solid Particles

- Dilute suspension (2 to10%w/v solid)

Eg: cortisone acetate, predinisolone acetate

- Concentrated suspension (50%w/v solid)

Eg: zinc oxide suspension

Based on Size of Particle

- **Coarse Suspension:** Suspensions having particle sizes of greater than about 1micron in diameter are called as coarse suspensions.

- **Colloidal Suspension:** Suspensions having particle sizes of suspended solid less than about 1micron in size are called as colloidal suspensions.

- **Nanosuspensions :** Suspensions are the biphasic colloidal dispersions of nanosized(10 nano gram) drug particles stabilized by surfactants. Size of the drug particles is less than 1mm.

Based on electrokinetic nature of Solid particle

- Flocculated Suspension
- Deflocculated Suspension

Deflocculated Suspension	Flocculated Suspension
1. Pleasant appearance as particle are uniformly dispersed.	1. Unpleasant in appearance.
2. Supernatant is clear.	2. Supernatant is cloudy.
3. Particle experience repulsive force.	3. Particle experience attractive force.
4. Rate of sedimentation is slow.	4. Rate of sedimentation is fast.
5. Particle settle independently and separately.	5. Particle settle as flocus.
6. Sediment is closely packed and form hard cake.	6. Sediment are loosely pack net work.
7. The re-dispersion of a sediment formed in a deflocculated suspension is difficult by agitation.	7. The re-dispersion of a sediment formed in a flocculated suspension can easily be done by agitation
8. In potential energy curve it represent primary minimum.	8. In potential energy curve it represent secondary minimum.
9. Bioavailability is relatively high.	9. Bioavailability is comparatively less

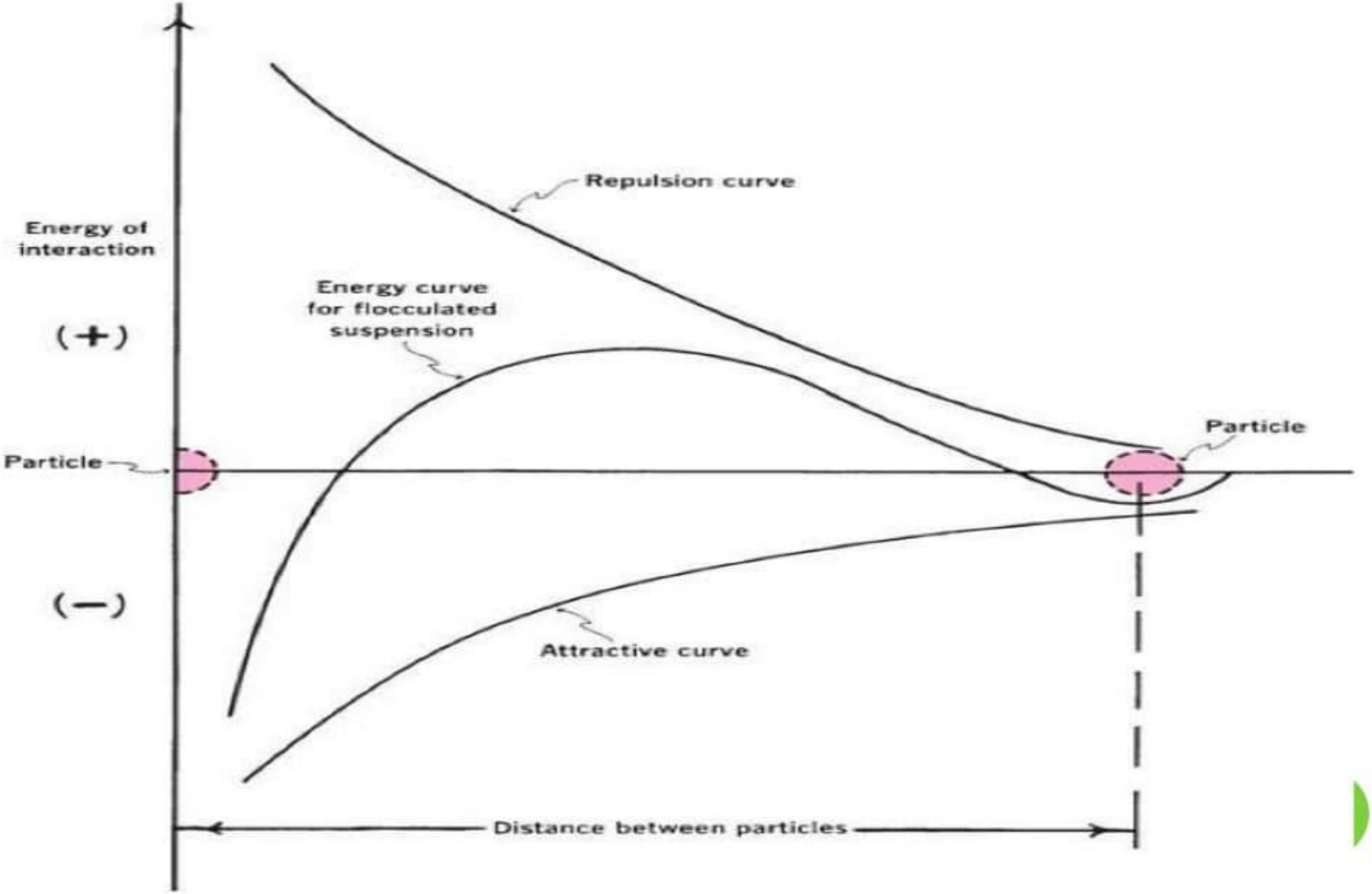
Interfacial Properties of Suspended Particles

- Work must be done to reduce a solid to small particles and disperse them in a continuous medium.
- The large surface area of the particles that results from the comminution is associated with a surface free energy that makes the system *thermodynamically unstable, by which we mean that the particles are* highly energetic and tend to regroup in such a way as to decrease the total area and reduce the surface free energy.
- The particles in a liquid suspension therefore tend to *flocculate, that is, to form light, fluffy* conglomerates that are held together by weak van der Waals forces.
- Under certain conditions—in a compacted cake, for example—the particles may adhere by stronger forces to form what are termed *aggregates*.
- *Caking often occurs by the growth and fusing together of crystals in the precipitates* to produce a solid aggregate.

- The formation of any type of agglomerate, either floccules or aggregates, is taken as a measure of the system's tendency to reach a more thermodynamically stable state.
- An increase in the work, *W, or* surface free energy, ΔG*, brought about by dividing the solid into smaller particles and consequently* increasing the total surface area, ΔA*, is given by*
  - $\Delta G = \gamma_{SL} \cdot \Delta A$
- where γ_{SL} is the interfacial tension between the liquid medium and the solid particles.

- To approach a stable state, the system tends to reduce the surface free energy; equilibrium is reached when $\Delta G = 0$. *This condition can be accomplished, as seen from equation .*
- ***By a reduction of*** interfacial tension, or it can be approached by a decrease of the interfacial area.
- The latter possibility, leading to flocculation or aggregation, can be desirable or undesirable in a pharmaceutical suspension.
- The interfacial tension can be reduced by the addition of a surfactant but cannot ordinarily be made equal to zero.
- A suspension of insoluble particles, then, usually possesses a finite positive interfacial tension, and the particles tend to flocculate.

- The forces at the surface of a particle affect the degree of flocculation and agglomeration in a suspension.
- Forces of attraction are of the London–van der Waals type; the repulsive forces arise from the interaction of the electric double layers surrounding each particle.
- The formation of the electric double layer deals with interfacial phenomena.
- The potential energy of two particles is plotted in Figure as a function of the distance of separation.
- Shown are the curves depicting the energy of attraction, the energy of repulsion, and the net energy, which has a peak and two minima.



Energy of interaction
(+)
(−)
Repulsion curve
Energy curve for flocculated suspension
Particle
Particle
Attractive curve
Distance between particles

- When the repulsion energy is high, the potential barrier is also high, and collision of the particles is opposed.
- The system remains deflocculated.
- When sedimentation is complete, the particles form a close-packed arrangement with the smaller particles filling the voids between the larger ones.
- Those particles lowest in the sediment are gradually pressed together by the weight of the ones above; the energy barrier is thus overcome, allowing the particles to come into close contact with each other.

- To resuspend and redisperse these particles, it is again necessary to overcome the high-energy barrier
- Because this is not easily achieved by agitation, the particles tend to remain strongly attracted to each other and form a hard cake.
- When the particles are flocculated, the energy barrier is still too large to be surmounted, and so the approaching particle resides in the second energy minimum, which is at a distance of separation of perhaps 1000 to 2000 Å.
- This distance is sufficient to form the loosely structural flocs.

- These concepts evolve from (DLVO) theory for the stability of lyophobic sols.
- To summarize, flocculated particles are weakly bonded, settle rapidly, do not form a cake, and are easily resuspended.
- Deflocculated particles settle slowly and eventually form a sediment in which aggregation occurs with the resultant formation of a hard cake that is difficult to resuspend.

Settling in suspensions

- One aspect of physical stability in pharmaceutical suspensions is concerned with keeping the particles uniformly distributed throughout the dispersion.
- It possible to prevent settling completely over a prolonged period of time, it is necessary to consider the factors that influence the velocity of sedimentation.
- ***Theory of Sedimentation***
- ***Particle size***
- ***Effect of Brownian Movement***
- ***Sedimentation of Flocculated Particles***
- ***Sedimentation Parameters***

Theory of Sedimentation

- The velocity of sedimentation is expressed by Stokes's law:

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

- where
- v = terminal velocity in cm/sec,
- d = diameter of the particle in cm,
- ρs and ρo = the densities of the dispersed phase and dispersion medium, respectively,
- g = acceleration due to gravity,
- ηo = viscosity of the dispersion medium in poise.

Stokes law is applicable in following condition

1. The particle should be spherical, but in suspensions particle are largely irregular.

2. The particles do not interfere with one another during sedimentation, and free settling occurs. In most pharmaceutical suspensions that contain dispersed particles in concentrations of 5%, 10%, or higher percentages, the particles exhibit hindered settling. The particles interfere with one another as they fall, and Stokes's law no longer applies.

- The physical stability can be obtained by diluting the suspension so that it contains about 0.5% to 2.0% w/v of dispersed phase.
- This is not always recommended,
- As the addition of a diluent may affect the degree of flocculation (or deflocculation) of the system, thereby effectively changing the particle-size distribution.

Particle size

- Particle size determines the packing arrangement and influence the settling behavior.
- They also effect the re-suspendability and stability.
- Symmetrical particle (barrel shaped particles of calcium carbonate) produces stable suspension without cracking.
- Asymmetrical particle (needle shaped) forms hard cake, which cannot be re-disperesible.

Effect of Brownian Movement

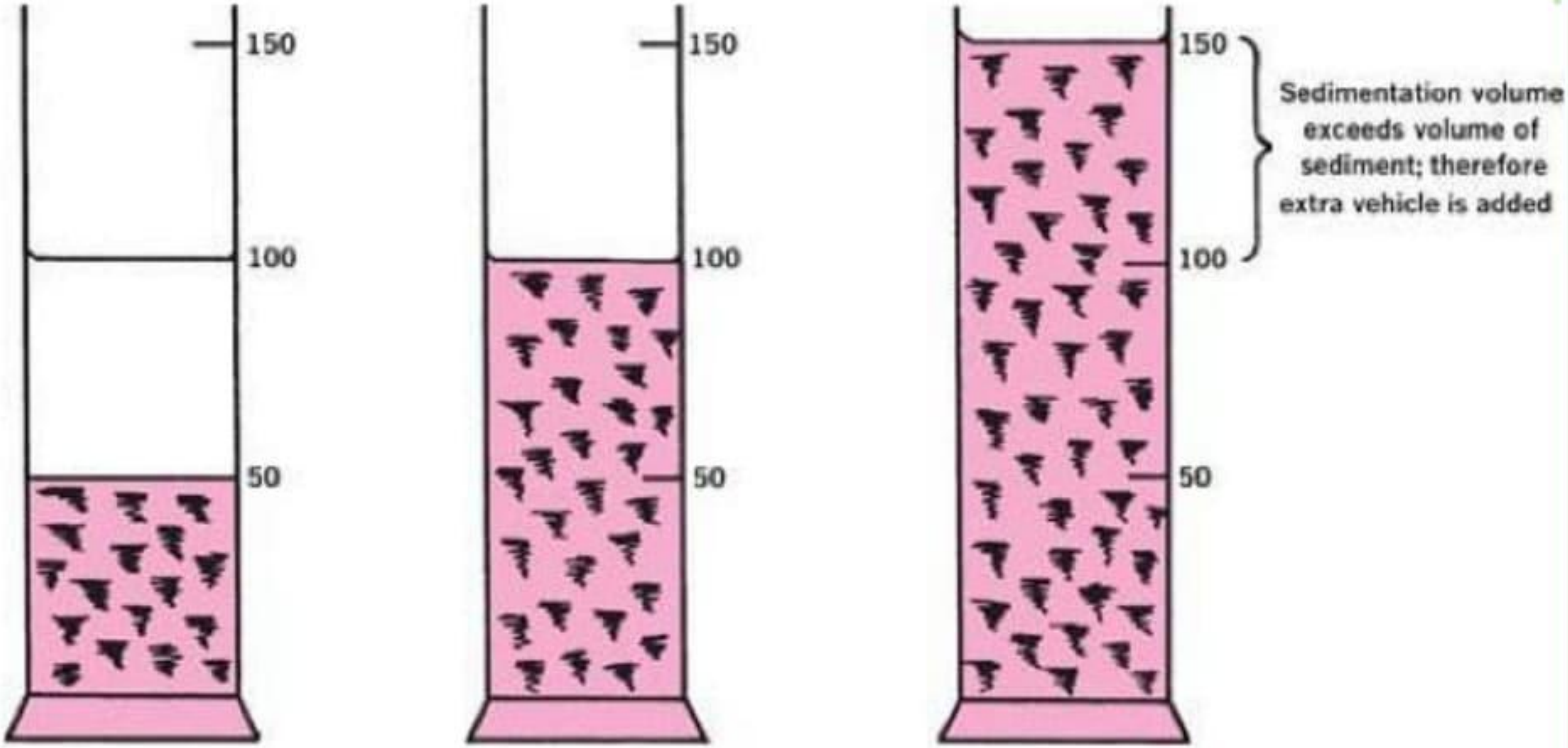
- For particles having a diameter of about 2 to 5 µm (depending on the density of the particles and the density and viscosity of the suspending medium), Brownian movement counteracts sedimentation to a measurable extent at room temperature by keeping the dispersed material in random motion.
- The *critical radius, r, below which particles will be kept in suspension by kinetic bombardment of the* particles by the molecules of the suspending medium (Brownian movement) was worked out by Burton.

- It can be seen in the microscope that Brownian movement of the smallest particles in a field of particles of a pharmaceutical suspension is usually eliminated when the sample is dispersed in a 50% glycerin solution, having a viscosity of about 5 centipoise.
- Hence, it is unlikely that the particles in an ordinary pharmaceutical suspension containing suspending agents are in a state of vigorous Brownian motion

Sedimentation of Flocculated Particles

- When sedimentation is studied in flocculated systems, it is observed that the flocs tend to fall together, producing a distinct boundary between the sediment and the supernatant liquid.
- The liquid above the sediment is clear because even the small particles present in the system are associated with the flocs.
- Such is not the case in deflocculated suspensions having a range of particle sizes, in which, in accordance with Stokes's law, the larger particles settle more rapidly than the smaller particles.

- No clear boundary is formed (unless only one size of particle is present), and the supernatant remains turbid for a considerably longer period of time.
- Whether the supernatant liquid is clear or turbid during the initial stages of settling is a good indication of whether the system is flocculated or deflocculated, respectively.
- The initial rate of settling of flocculated particles is determined by the floc size and the porosity of the aggregated mass.
- Subsequently, the rate depends on compaction and rearrangement processes within the sediment.
- The term *subsidence is sometimes used to describe* settling in flocculated systems.



$F = 0.5$
(a)

$F = 1.0$
(b)

$F = 1.5$
(c)

Sedimentation Parameters

- Two useful parameters that can be derived from sedimentation (or, more correctly, subsidence) studies are sedimentation volume, V, or height, H, and degree of flocculation.
- The sedimentation volume, F, is defined as the ratio of the final, or ultimate, volume of the sediment, Vu, to the original volume of the suspension, Vo, before settling. Thus,

$$F = V_u / V_o$$

- The sedimentation volume can have values ranging from less than 1 to greater than 1.
- *F is normally less* than 1, and in this case, the ultimate volume of sediment is smaller than the original volume of suspension. Figure a, in which $F = 0.5$.
- *If the volume of sediment in a flocculated* suspension equals the original volume of suspension, then $F = 1$ Figure b.
- Such a product is said to be in flocculation equilibrium and shows no clear supernatant on standing.
- It is therefore pharmaceutically acceptable.

- 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.
- This situation is illustrated in Figure c, in which sufficient extra vehicles have been added to contain the sediment($F = 1.5$).

- The sedimentation volume gives only a qualitative account of flocculation .
- A more useful parameter for flocculation is β, *the degree of flocculation.*
- If we consider a suspension that is completely deflocculated, the ultimate volume of the sediment will be relatively small.
- Writing this volume as $V\infty$, *based on equation*

$$F\infty = V\infty / V_o$$

Where

$F =$ *sedimentation volume of the deflocculated, or peptized, suspension.*

- The degree of flocculation, β, *is therefore defined as the ratio of F to F∞,*

$$\beta = F / F_\infty$$

- Substituting equations

$$\beta = \frac{V_u / V_o}{V_\infty / V_o}$$

$$\beta = V_u / V_\infty$$

- The degree of flocculation is a more fundamental parameter than *Fbecause it relates the volume of* flocculated sediment to that in a deflocculated system. We can therefore say that

$$\beta = \frac{\text{ultimate sediment volume of flocculated suspension}}{\text{ultimate sediment volume of deflocculated suspension}}$$

Formulation of Suspensions

- The approaches commonly used in the preparation of physically stable suspensions fall into two categories

  1. The use of a structured vehicle to maintain deflocculated particles in suspension

  2. The application of the principles of flocculation to produce flocs that, although they settle rapidly, are easily re-suspended with a minimum of agitation.

- A disadvantage of deflocculated systems is that formation of a compact cake when the particles eventually settle.
- It is for this reason that the formulation of flocculated suspensions has been advocated.
- Optimum physical stability and appearance will be obtained when the suspension is formulated with flocculated particles in a structured vehicle of the hydrophilic colloid type.
- Whatever approach is used, the product must

  (*a*) *flow readily* from the container

  (*b*) *possess a uniform distribution of particles in each dose.*

Wetting of Particles

- The initial dispersion of an insoluble powder in a vehicle is an important step in the manufacturing process and requires further consideration.
- 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 quantities of grease, and other contaminants.
- The powder is not readily wetted, and although it may have a high density, it floats on the surface of the liquid.

- Finely powdered substances are particularly susceptible to this effect because of entrained air, and they fail to become wetted even when forced below the surface of the suspending medium.
- The wettability of a powder can be ascertained easily by observing the contact angle that powder makes with the surface of the liquid.
- The angle is approximately 90° when the particles are floating well out of the liquid.
- A powder that floats low in the liquid has a lesser angle, and one that sinks obviously shows no contact angle.
- Powders that 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 that are readily wetted by water when free of adsorbed contaminants are called *hydrophilic*. *Zinc oxide, talc, and* magnesium carbonate belong to the latter class.

- Surfactants are quite useful in the preparation of a suspension in reducing the interfacial tension between solid particles and a vehicle.
- As a result of the lowered interfacial tension, the advancing contact angle is lowered, air is displaced from the surface of particles, and wetting and deflocculation are promoted.

Controlled Flocculation

- Assuming that the powder is properly wetted and dispersed, we can now consider the various means by which controlled flocculation can be produced so as to prevent formation of a compact sediment that is difficult to redisperse.
- *Electrolytes act as flocculating agents by reducing the electric barrier between the particles, as* evidenced by a decrease in the zeta potential and the formation of a bridge between adjacent particles so as to link them together in a loosely arranged structure.

- 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.
- By preparing a series of bismuth subnitrate suspensions containing increasing concentrations of monobasic potassium phosphate, it gives a correlation between apparent zeta potential and sedimentation volume, caking, and flocculation.

- The addition of monobasic potassium phosphate to the suspended bismuth subnitrate particles causes the positive zeta potential to decrease owing to the adsorption of the negatively charged phosphate anion.
- With the continued addition of the electrolyte, the zeta potential eventually falls to zero and then increases in the negative direction, as shown in Figure.
- Microscopic examination of the various suspensions shows that at a certain positive zeta potential, maximum flocculation occurs and will persist until the zeta potential has become sufficiently negative for deflocculation to occur once again.
- The onset of flocculation coincides with the maximum sedimentation volume determined.

- 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 because these compounds can also act as wetting and deflocculating agents to achieve dispersion.

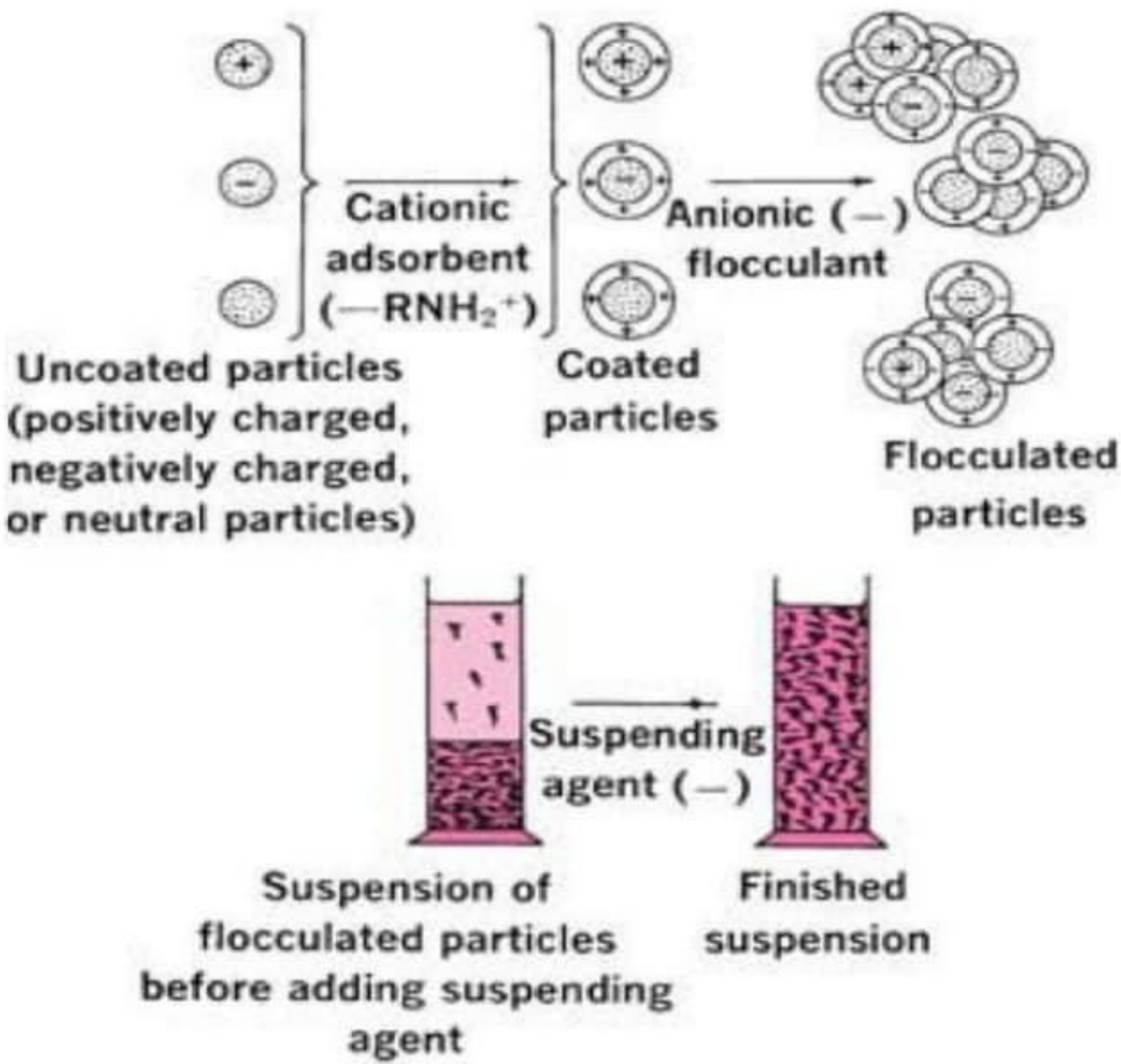
Flocculation in Structured Vehicles

- 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 or equal to 1.
- Consequently, in practice, a suspending agent is frequently added to retard sedimentation of the flocs.
- Such agents as carboxymethylcellulose, Carbopol 934, Veegum, tragacanth, and bentonite have been employed, either alone or in combination.
- This can lead to incompatibilities, depending on the initial particle charge and the charge carried by the flocculating agent and the suspending agent.

- For example, suppose we prepare a dispersion of positively charged particles that is then flocculated by the addition of the correct concentration of an anionic electrolyte such as monobasic potassium phosphate.
- We can improve the physical stability of this system by adding a minimal amount of one of the hydrocolloids .
- No physical incompatibility will be observed because the majority of hydrophilic colloids are themselves negatively charged and are thus compatible with anionic flocculating agents.

- If, however, we flocculate a suspension of negatively charged particles with a cationic electrolyte (aluminum chloride), the subsequent addition of a hydrocolloid may result in an incompatible product, as evidenced by the formation of an unsightly stringy mass that has little or no suspending action and itself settles rapidly.
- Under these circumstances, it becomes necessary to use a protective colloid to change the sign on the particle from negative to positive.

- This is achieved by the adsorption onto the particle surface of a fatty acid amine (which has been checked to ensure its nontoxicity) or a material such as gelatin, which is positively charged below its isoelectric point.
- We are then able to use an anionic electrolyte to produce flocs that are compatible with the negatively charged suspending agent.


Cationic
adsorbent
(—RNH₂⁺)
Anionic (—)
flocculant
Uncoated particles
(positively charged,
negatively charged,
or neutral particles)
Coated
particles
Flocculated
particles
Suspending
agent (—)
Suspension of
flocculated particles
before adding suspending
agent
Finished
suspension

Thank you