Pharmaceutical Technology

Electrostatic stability of suspension

By

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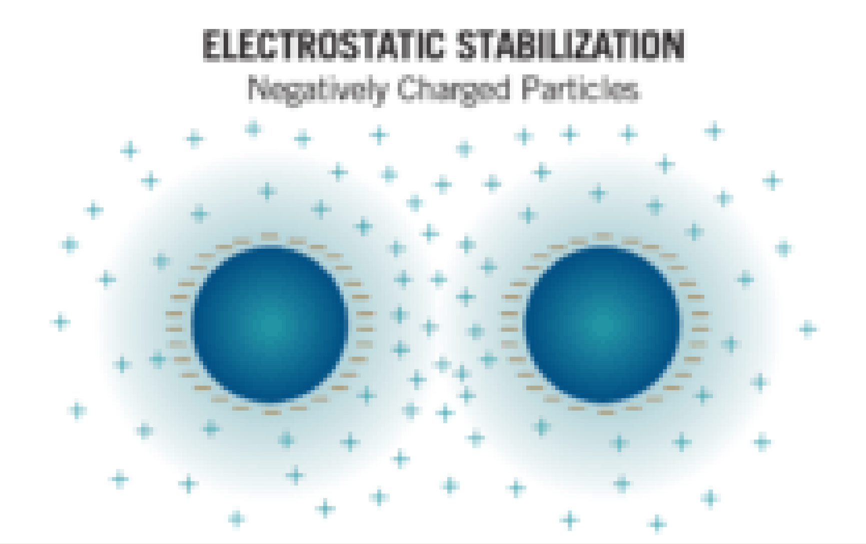
Effect of electrical charge on stability of suspension

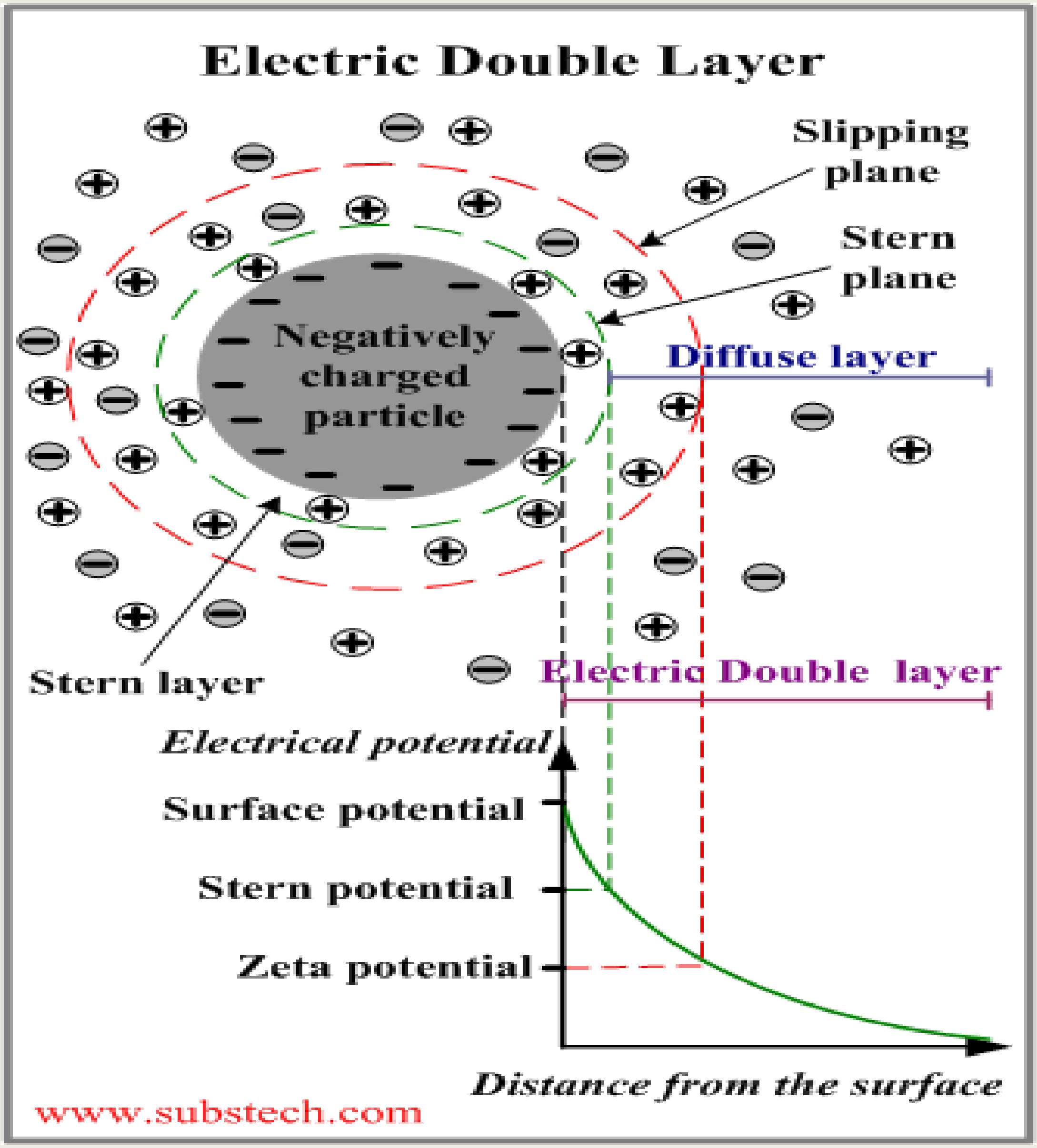
- If particles in the dispersion medium have similar electric charge then they preventing from coming together.
- It is usually for solid particles dispersed in aqueous media to carry the same type of charge.



- There are varies ways where charge can developed:

1. Ionization of groups on solid surface.
2. Adsorption of surfactant on solid surface.
3. Adsorption of electrolyte from solution.

- The last two methods are the most common. The sign of charge develop on the surface of particle can be predicted if the charge result from adsorption of sodium lauryl sulphate on the solid will make the solid carry negative charge.
- The sign of charge which develop from electrical charge adsorption depend on the ion adsorption from the solution and it is difficult to be predicated.
- The magnitude of charge is define as: the difference in electrical potential between the charge of solid surface and bulk of the solution.


Electric Double Layer
Slipping plane
Stern plane
Negatively charged particle
Diffuse layer
Stern layer
Electric Double layer
Electrical potential
Surface potential
Stern potential
Zeta potential
Distance from the surface
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Zeta potential

- Important potential for suspension is zeta potential, which is the difference of potential between surface of tightly bound layer and electro neutral portion of solution.
- In order to maintain a monodispersed system; the zeta potential must be great enough for particle to repel each other, the minimum value is called (the critical zeta potential) and it is specific for suspension.
- The electrostatic repulsion set up between adjacent like charge particle preventing them from adhering to each other.

- If particles have solvated surface, it will help to prevent particles from coming together, so in the presence of

1. a suitable vehicle,
2. a surface charge or
3. the possession of solvated sheath around the particles

➢ results in the dispersion of primary particles rather than aggregates.

- If the electrical or molecular barrier is very large then flocculation will be negligible.
- Note: Flocculation results from the collision and combination of primary particles in the suspension.

- The potential energy of two particles is plotted in Figure 17-1 as a function of the distance of separation. Shown are the curves depicting:

1. the energy of attraction,
2. the energy of repulsion, and
3. the net energy, which has a peak and two minima.

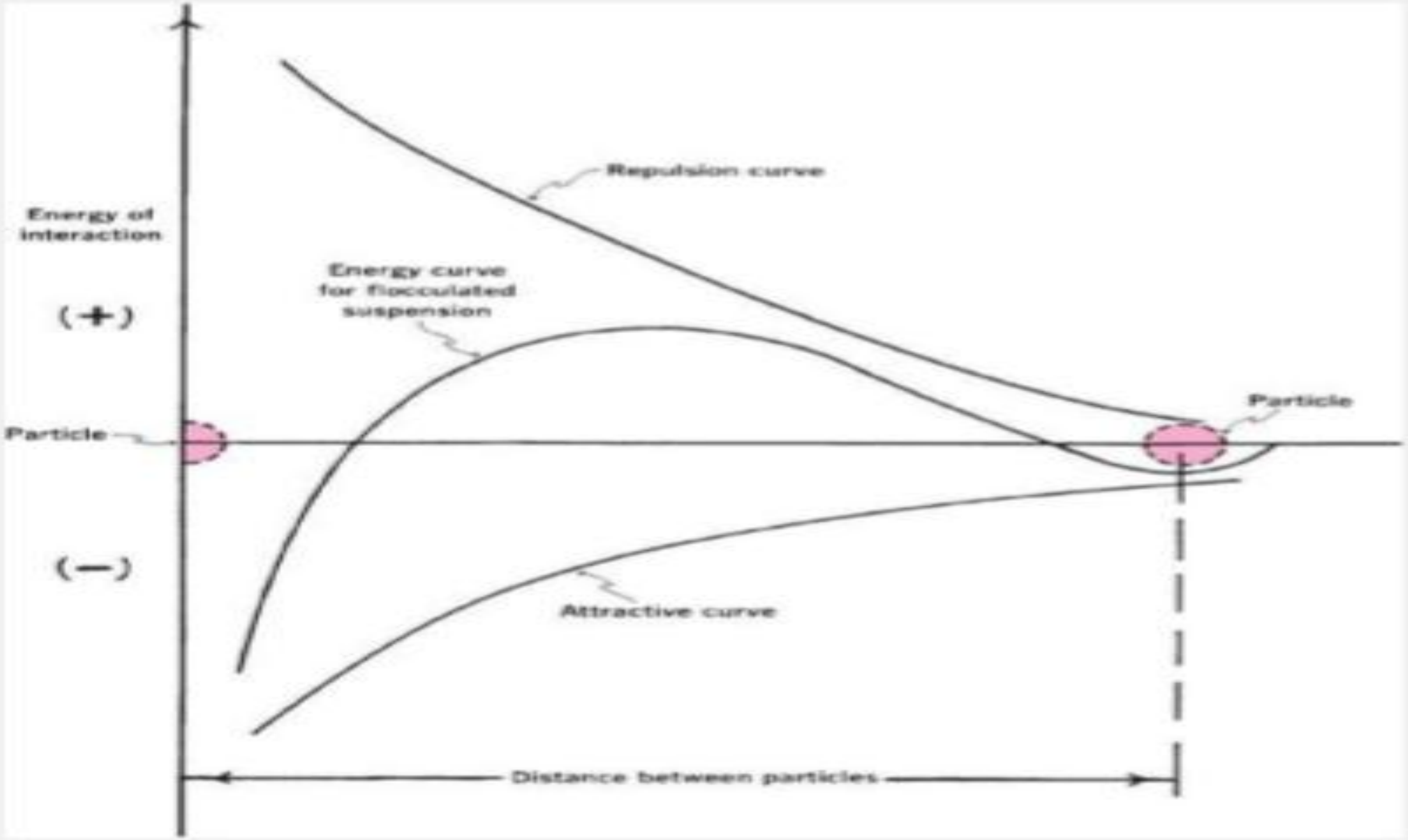
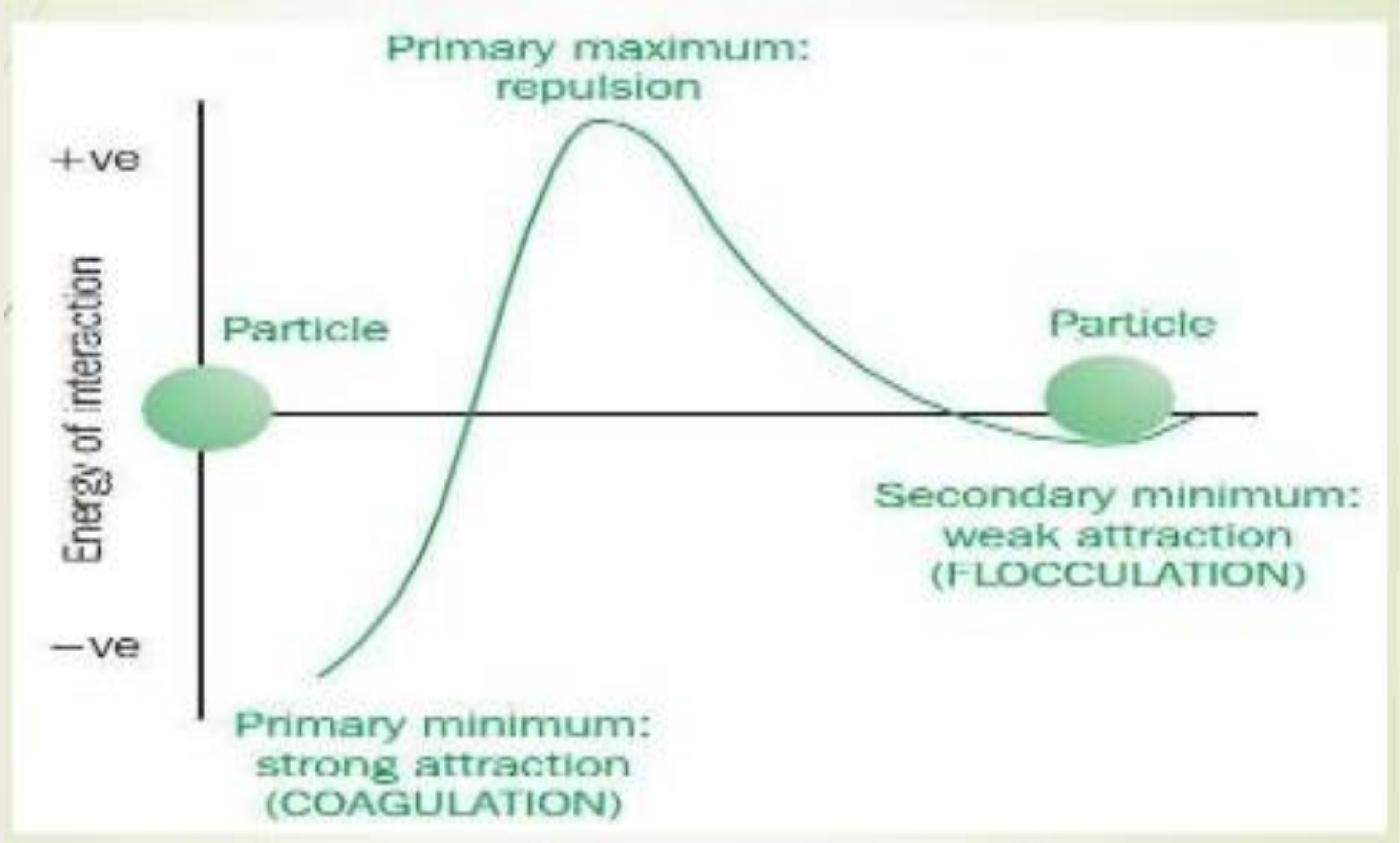


Fig. 17-1. Potential energy curves for particle interactions in suspension. (From A. Martin, J. Pharm. Sci. **50,** 514, 1961. With permission.)

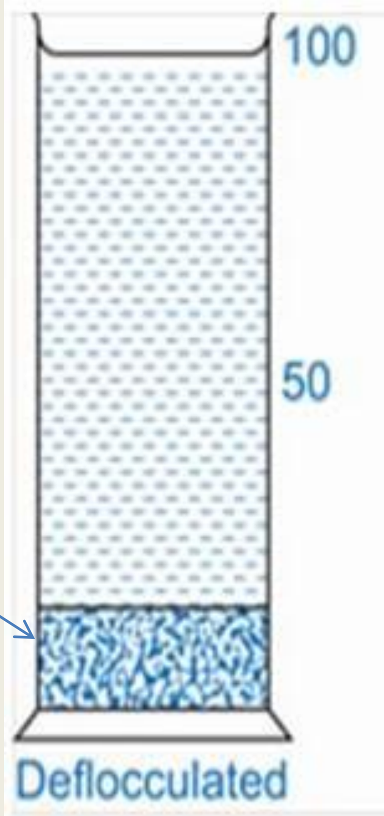


https://www.slideshare.net/deepakjadhav52/suspension-ppt

- When the repulsion energy is high, the potential barrier is also high, and collision of the particles is opposed.
- ➢ The system remains deflocculated, and 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.

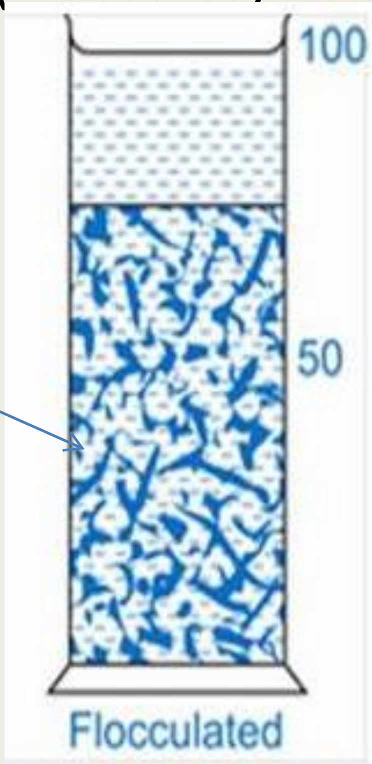
- To resuspend and redisperse these particles, it is again necessary to overcome the high-energy barrier. Because this is not easily achieved by agitation, the particles tend to remain strongly attracted to each other and form a hard cake.

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, (Floccules)

Loosely structural flocs



DLVO Theory

- These concepts evolve from the Derjaguin and Landau, Verwey and Overbeek (DLVO) theory for the stability of lyophobic sols.
- To summarize,

1. Flocculated particles are weakly bonded, settle rapidly, do not form a cake, and are easily resuspended;
2. 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.

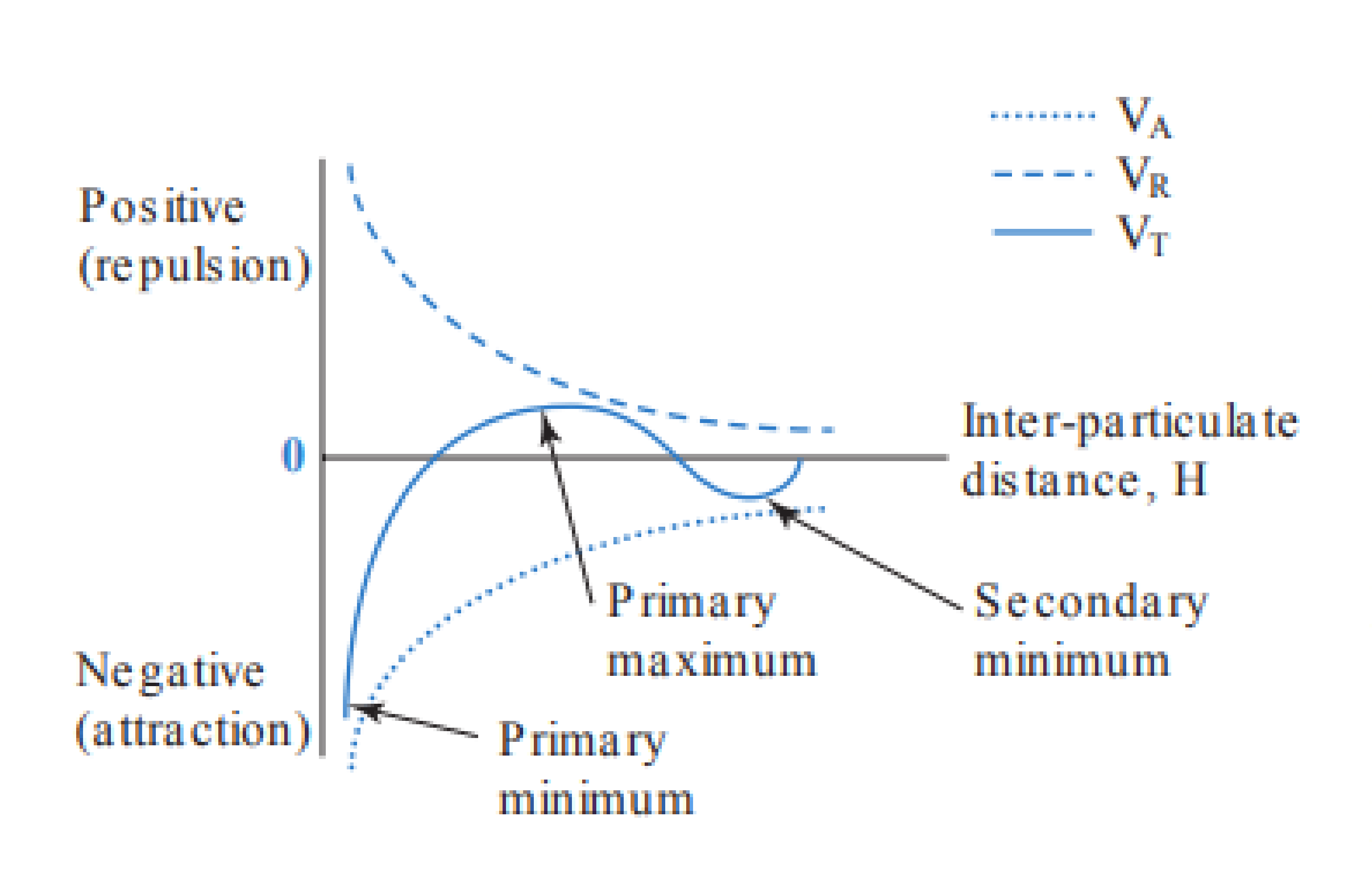
Properties of flocculated and deflocculated suspensions

Flocculated suspension	Deflocculated suspension
1. Particles form loss aggregate	1. Particles exist in suspension as separate entities
2. Rate of sedimentation is high, since particles settle as floc, which is a collection of particles	2. Rate of sedimentation is low, since each particle size is minimal.
3. A sediment is formed rapidly	3. A sediment is formed slowly
4. The sediment is loosely packed and possesses a scaffold like structure.	4. The sediment eventually becomes very closely packed, owing to weight of upper layers of sediment material.
5. The sediment does not form hard cake and easily re-disperse.	5. Hard cake is formed which is difficult to re-disperse
6. The suspension in some what unpleasant due to rapid sedimentation and presence of obvious clear supernatant region.	6. The suspension has a pleasing appearance since the suspended material remains suspended for a relative long time. The supernatant remains cloudy even when settling is apparent.
7. The floccules stick to the sides of the bottle	7. Particles do not stick to the sides of the bottle

- To calculate the total energy of interaction, V_T, between two particles, the values of V_A and V_R are summed, as shown in Equation shown below:

$$V_T = V_A + V_R$$

- V_R is the energy of electrical repulsion and by convention this carries a positive sign. VA is the energy of Van der Waals attractions and by convention is given a negative sign.
- Figure in the next slid shows the values of V_A, V_R and V_T for two similar particles suspended in a medium and interacting.



The energy of interaction between two similar particles, as described by the DLVO theory

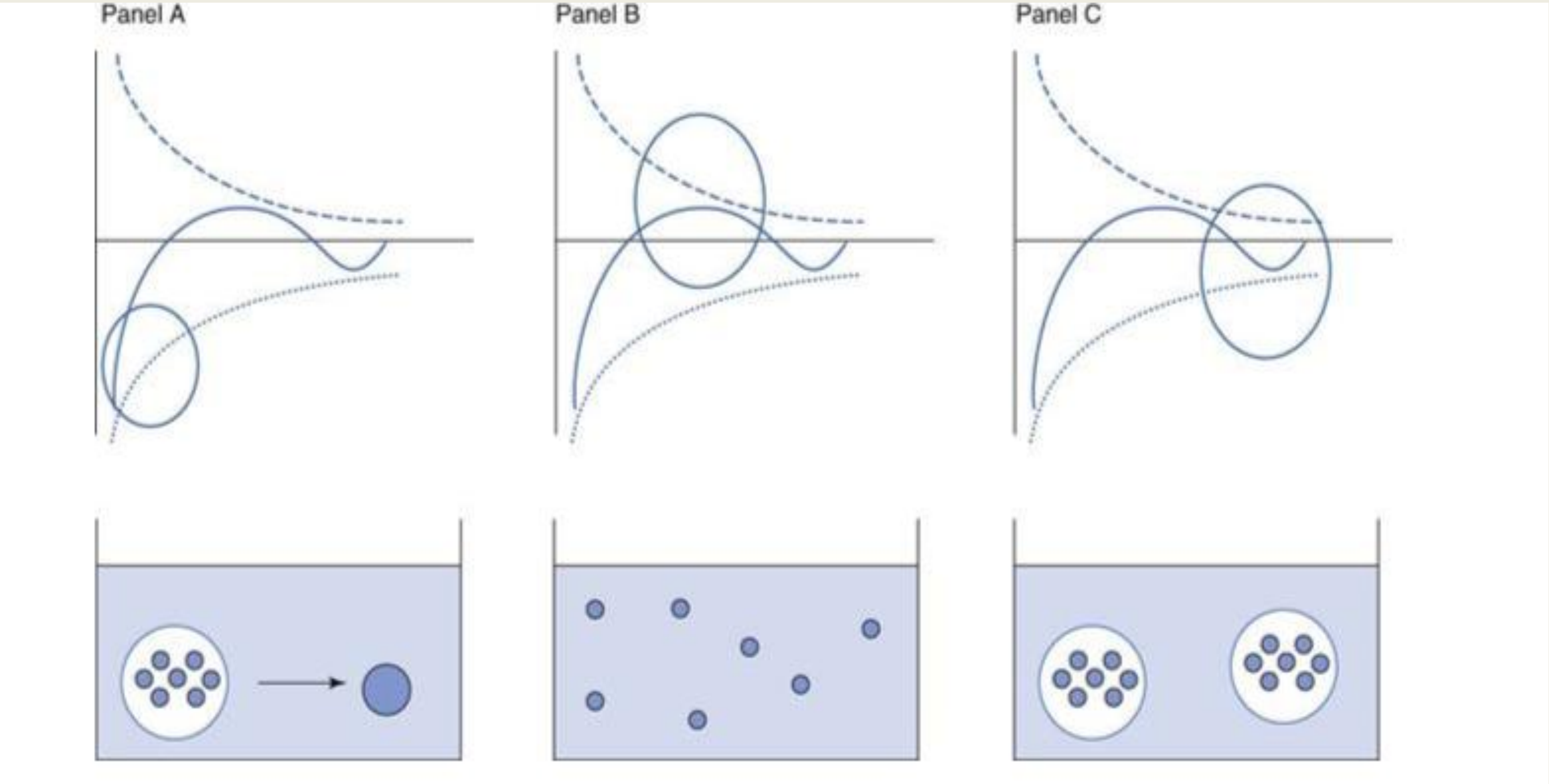
- The easiest way to consider what happens when two particles interact is to remember that the V_T line gives the overall energy of interaction and that this will change depending on the distance between the two particles.
- There are three important zones, or values of V_T in the DLVO diagram: the primary minimum, the secondary minimum and the primary maximum, and the behaviour of the suspension will be dependent on which zone the particles are in.
- It must also be remembered that all particles will have some thermal energy and will show some movement, whether caused by Brownian motion, the effects of gravity or by external agitation.

The primary minimum

- The ‘primary minimum’ zone is described as a ‘minimum’ because the total energy is calculated to be below zero (remember that repulsive energy is described as positive and attractive energy as negative).
- It is described as ‘primary’ because it is the largest negative deviation from zero.
- Particles in the primary minimum zone show a higher energy of attraction than repulsion and are therefore likely to move closer together.

- Imagine two particles are just far enough apart that the energy of attraction balances out the energy of repulsion, so that the overall energy of interaction is zero.
- Any movement of the particles which brings them closer together will result in an overall mathematical decrease in V_T, i.e. V_T is now attractive and the particles will continue to move closer together. As they do so, the strength of the overall attractive forces increases, moving the particles still closer together, resulting in a further increase in the attractive forces, and so on.

- The kinetic energy that the particles have (= kT, where k is the Boltzmann constant and T the temperature in Kelvin) is not high enough to overcome the attractive energy, V_T and therefore the particles will eventually aggregate irreversibly.
- Particles will initially show ‘flocculation’, whereby the individual particles are loosely attracted to each other, but still act independently; subsequently they will demonstrate ‘coagulation’ where particles will collide and form larger particles.
- Such behaviour is undesirable for pharmaceutical suspensions as it will have serious negative effects on the reproducibility of dosing from the system. These changes are illustrated in panel A of the following Figure.



Flocculation and deflocculation consequences of the DLVO theory for pharmaceutical suspensions

The primary maximum

- The naming of the ‘primary maximum’ zone follows the same conventions as for the primary minimum.
- The primary maximum zone is described as a ‘maximum’ because the total energy is calculated to be above zero (using the convention of repulsive energy being positive and attractive energy being negative).
- It is described as ‘primary’ because it is the largest positive deviation from zero.
- Particles in the primary maximum zone show a higher energy of repulsion than attraction and are therefore likely to remain separate or ‘deflocculated’. This is illustrated in panel B of the figure shown in previous slide.

- At first sight, this would appear to be a good formulation strategy for pharmaceutical suspensions, as if the particles can be forced into the primary maximum zone then they should remain independent and hence dosing would be expected to be reproducible.
- This is true when the kinetic energy of the particles is less than V_T and they are, if anything, more likely to move away from each other, which will have the effect of decreasing the magnitude of V_T but maintaining an overall repulsive effect.

- However, if the kinetic energy of the particles is high enough, for example if the temperature is increased, then this can overcome the energy barrier imposed by V_T with the result that the particles can then move closer together.
- In this case, V_T will initially decrease but remain repulsive, so the particles will still exist as independent entities. However, the magnitude of the difference between V_T and the particles' kinetic energy is now greater and therefore they are likely to move even closer together.

- At some point, the particles will be sufficiently close so that the overall energy of interaction becomes negative, i.e. it is now predominantly attractive, and the particles enter the primary minimum zone with the consequences described above.
- In summary, therefore, formulating pharmaceutical suspensions so that the particles are in the primary maximum zone can be considered to be risky.

The secondary minimum

- Panel C of the Figure, shows the behaviour within the secondary minimum zone.
- As its name suggests, the ‘secondary minimum’ gives rise to an overall attractive energy of interaction between particles, but of a lower magnitude than that seen in the primary minimum.
- The particles here show an overall limited attraction to each other and behave as ‘floccules’, loose aggregates of individual particles.

- Depending on the kinetic energy of the particles, their behaviour will vary slightly.
- If the kinetic energy is less than the V_T, then the particles will move closer together under the infuence of the V_T, but will not collide and coalesce as the V_T is still relatively weak.
- As the particles move further together, the attractive forces will reach their highest point (although not as strong as in the primary minimum zone) then decrease and overall V_T becomes weakly repulsive, which will have the effect of forcing the particles apart.
- At this stage, V_T once again dominates over the kinetic energy and the particles will be attracted weakly to each other.

- In essence, the particles are maintained in their flocculated state, that is they still exist as individual particles, but are loosely grouped together in floccules.
- If, however, the kinetic energy of the particles is greater than the V_T, then the particles will be able to move further apart.
- As they do this, the overall V_T will become less attractive and ultimately will become, to all practical purposes, zero.
- In this case, the particles will behave independently, will not flocculate and will not coalesce.
- In either case (kinetic energy greater to or less than V_T), coalescence and coagulation of particles is minimal, and hence this is usually the desired strategy for developing pharmaceutical suspensions.

5. Particle-vehicle interaction: these are significant in wetting and dispersion particle. When solid is reduced to small particle size, there is an increase in surface area ΔA and surface free energy ΔF, so the particle now is highly energetic and tend to come together to reduce the free energy.

- From thermodynamic point of view:

$$\Delta F = \Upsilon_{sL} \cdot \Delta A$$

- It is better to decrease ΔF by controlling the Υ_{sL} rather than ΔA. Controlling of Υ_{sL} is happen by adding surfactant which will result in dispersion of particle in the media. So these wetting agents will decrease the tendency of particle to flocculate by dispersing them.

- The wetability of lyophobic powder may increase by passing the material through colloid mills in presence of wetting agent like alcohol, glycerin, and other hygroscopic materials which are used as initial wetting agent in suspension manufacturing.
- These liquid cause:

1. Displace air
2. Disperse the particle
3. Allow the penetration of vehicle into powder