

Pharmaceutical Technology

Coarse Dispersion
Suspensions

Suspensions

- Suspension is a coarse dispersion containing finely divided insoluble material suspended in a liquid medium or available in a dry powder to be distributed in the liquid when desired, this in case the stability of powder is low.
- Suspension consist of two phases; solid dispersed phase and dispersion medium, which is liquid and may be oil or water.
- The particle size of coarse particles usually 10-50 μm in size.
- Suspension could be administer orally, topically, parenterally (except I.V), and for ophthalmic administration.

- Some suspensions preparations are available in:
 1. Ready-to use form- that is, already distributed through a liquid vehicle with or without stabilizers and other pharmaceutical additives.
 2. Other preparation are available as dry powders intended for suspension in liquid vehicles. This type of product generally is a powder mixture containing the drug and suitable suspending and dispersing agents, which upon dilution and agitation with a specified quantity of vehicle (generally purified water) results in the formation of a suspension suitable for administration.
- This type of preparation is designated in the USP by a title of the “**drug powder for oral suspension**”.
- Prepared suspensions not requiring reconstitution at the time of dispensing are simply designated as “**drug oral suspension**”

Examples of suspension preparations





FIGURE 14.2 Commercial antibiotic preparation for oral suspension following reconstitution with purified water. *Left*, dry powder mixture. *Right*, suspension after reconstitution with the specified amount of purified water.

Reasons for suspensions

- There are several reasons for preparing suspensions
 1. Certain drugs are chemically unstable when in solution but stable when suspended. In instances such as this, the suspension insures chemical stability while permitting liquid therapy.
 2. For many patients, the liquid form is preferred over the solid form of the same drug because of the ease of swallowing liquids and flexibility in the administration of a range of dose. This particularly advantageous for infants, children and the elderly.
 3. The disadvantage of a disagreeable taste of certain drugs when given in solution form is overcome when the drug is administered as undissolved particles of an oral suspension.

- Suspension given as intramuscular injection, because absorption from a suspension is normally slower than from solution at the injection site, and thus prolong the time of action of drug.
- By using an oil further slower down absorption and provide sustained or prolong action.
- Externally used suspension are either formulated in aqueous or oily vehicle depending on the intended of their use.
- For parenteral and ophthalmic use suspension should be sterile, and smaller particle size (less than $10\mu\text{m}$)

Features desired in a pharmaceutical suspension

1. A properly prepared pharmaceutical suspension should settle slowly and should be readily redispersed upon the gentle shaking of the container.
2. The characteristics of the suspension should be such that the particle size of the suspensoid remains fairly constant throughout long periods of undisturbed standing.
3. The suspension should pour readily and evenly from its container.

What are the properties of ideal suspension

- The properties of acceptable ideal suspension are:
 1. It should have a uniform particle size so that each particle acts as other particles producing constant behavior for the suspension as a whole.
 2. No particle-particle interaction (no aggregation) and no clumping should occur; such suspension is called monodispersed suspension.
 3. There should be no sedimentation, the particles should either be stationary or moved randomly through out the dispersion so that there is always uniform dispersion of the drug.
 4. The suspension should not be too viscous and pour freely.
 5. It should have an agreeable odor, color, and taste.
 6. It must not be decomposed or support microbial growth during storage.

- In other words suspension must provide a uniform therapeutically active pleasant dose that is convenient to take by the patient.
- The properties or parameters that could be controlled in an attempt to reach ideal behavior are:
 1. Particle size: it is desirable to have small particle size.
 - In colloidal system Brownian movement keeps the particles movement, while in coarse dispersion as in suspension the particle size are too large for the terminal energy to keep them suspended and their will be always some degree of sedimentation.

- The terminal velocity with which particles settle in a coarse dispersion is expressed by stokes law:

$$\frac{dx}{dt} = V = \frac{d^2(\rho - \rho_0) g}{18 \eta}$$

- Where, V is the terminal velocity or sedimentation rate of fall of an average particle in the dispersion (perfectly spherical particles).
- d is the mean particle diameter.
- ρ is the density of the particles
- ρ_0 is the density of the dispersion medium.
- G is acceleration constant due to gravity
- η is the viscosity of the dispersion medium.

- Diameter is important factor because it is raised to the 2nd power.
 - So by reducing the diameter by reducing particle size using mortar and pestle the terminal velocity is decreased. Thus decrease sedimentation of particles.
 - Mills is used for hard substances like crystals.
2. Particle movement and density and viscosity of medium.
- A. If the density of solid equal the density of the dispersion medium then the rate of sedimentation V equal zero, which means ideal condition; **but this condition is hard to get, because**
- it is difficult to prepare a suspension with density great enough to match the density of a solid.
 - Also the density of a solution is affected by the temperature, so density matching is useful only at control temperature.

- B. Viscosity adjustment is better control of movement of sedimentation that by increasing it to a certain extent will decrease the sedimentation rate because there is an inverse proportion between them referring to Stokes' law, and this done by
- adding a thickening or suspending agent to increase the viscosity of the dispersion medium.
 - Hydrophilic colloids are commonly used specially gums; cellulose, clays.

Example

- A powder has a density of 1.3 g/cc and is available as a powder with an average particle diameter of 2.5 microns (assuming the particles to be spheres). According to Stokes Equation, this powder will settle in water (viscosity of 1cps assumed) at a rate of:

$$V = \frac{(2.5 \times 10^{-4})^2 (1.3 - 1.0) (980)}{18 \times 0.01} = 1.02 \times 10^{-4} \text{ cm/sec}$$

- If the particle size of the powder is reduced to 0.25μ and water is still used as the dispersion medium, the powder will now settle at a rate of:

$$v = \frac{(2.5 \times 10^{-5})^2(1.3 - 1.0)(980)}{18 \times 0.01} = 1.02 \times 10^{-6} \text{ cm/sec}$$

- As is evident, a decrease in particle size by a factor of 10 results in reduction in the rate of settling by a factor of 100,
- This enhanced effect is a result of the “d” factor in stokes’ equation being squared.

- Now, if a different dispersion medium, such as glycerin is used in place of water, a further decrease in settling will result.
- Glycerin has a density of 1.25g/cc and a viscosity of 400 cps. The larger particle size powder (2.5 μ) will settle at a rate of:

$$v = \frac{(2.5 \times 10^{-4})(1.3 - 1.25)(980)}{18 \times 4} = 4.25 \times 10^{-8} \text{ cm/sec}$$

- The smaller particle size (0.25μ) powder will now settle at a rate of:

$$v = \frac{(2.5 \times 10^{-5})(1.3 - 1.25)(980)}{18 \times 4} = 4.25 \times 10^{-10} \text{ cm/sec}$$

- A summary of these results is shown in the following table:

Condition	Rate of settling (cm/sec)
2.5 μ powder in water	1.02×10^{-4}
0.25 μ powder in water	1.02×10^{-6}
2.5 μ powder in glycerin	4.25×10^{-8}
0.25 μ powder in glycerin	4.25×10^{-10}

- As is evident from this table, a change in dispersion medium results in the greatest change in the rate of settling of particles. Particle size reduction can contribute significantly to suspension stability. These factors are important in the formulation of physically stable suspensions.

3. Concentration of solid:

- High concentration of solid increase the possibility of particle-particle collision, but will also promote particle-particle interaction.
- The concentration of solid is usually fixed in prescription and can not be changed to affect the stability purpose.

4. Particle-particle interaction

- Particle-particle interaction controls the deflocculation and flocculation system. Particle-particle interaction must be avoid because the aggregation of small particle will behave as single large particle and tend to settle at increase rate of flocculation.
- If particle 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 various ways where charge can be 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 developed on the surface of a particle can be predicted if the charge results from adsorption of sodium lauryl sulphate on the solid will make the solid carry a negative charge.
- The sign of charge which develops from electrical charge adsorption depends on the ion adsorption from the solution and it is difficult to be predicted.
- The magnitude of charge is defined as: the difference in electrical potential between the charge of solid surface and bulk of the solution.

- Important potential for suspension is zeta potential, which is the difference of potential between surface of tightly bound layer and electroneutral 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 a suitable vehicle, a surface charge or 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 the energy of attraction, the energy of repulsion, and the net energy, which has a peak and two minima.
- 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

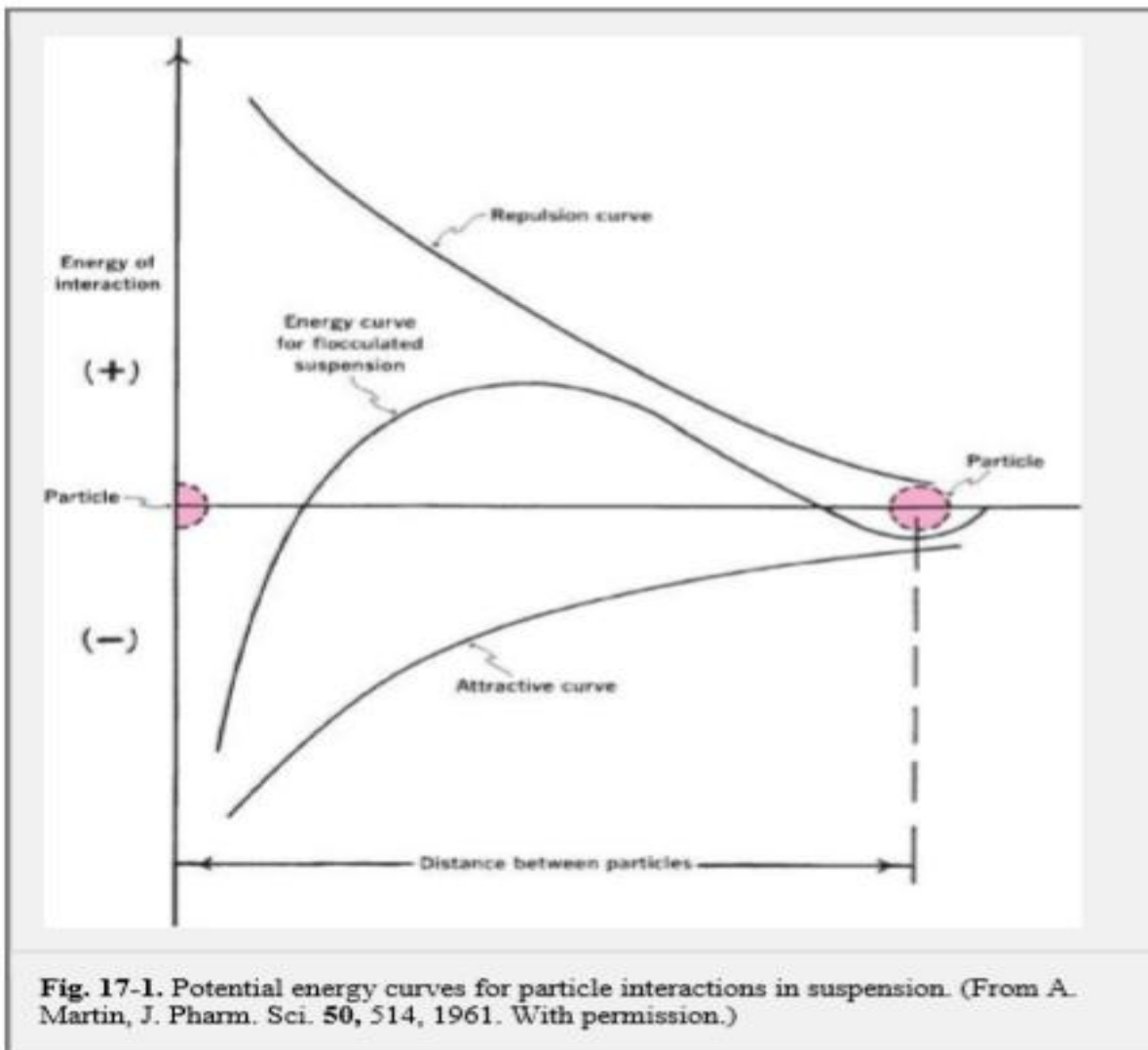
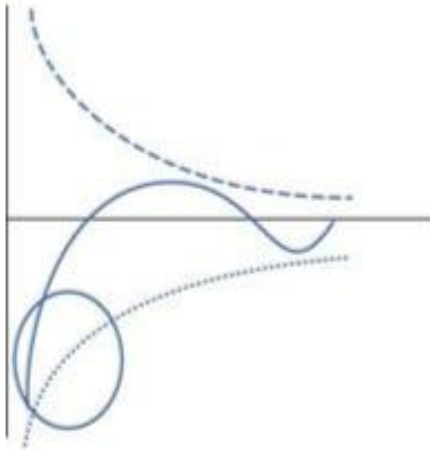


Fig. 17-1. Potential energy curves for particle interactions in suspension. (From A. Martin, *J. Pharm. Sci.* **50**, 514, 1961. With permission.)

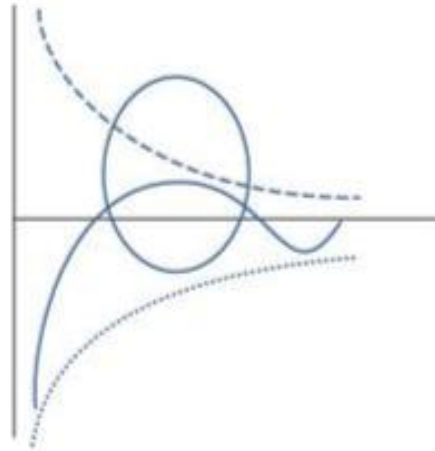
- To resuspend and redisperse these particles, it is again necessary to overcome the high-energy barrier. Because this is not easily achieved by agitation, the particles tend to remain strongly attracted to each other and form a hard cake.
- When the particles are flocculated, the energy barrier is still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

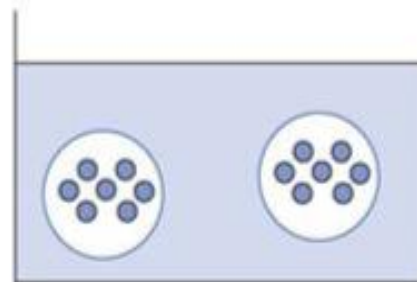
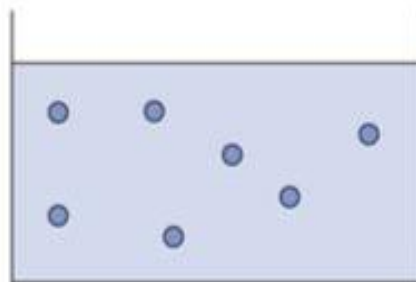
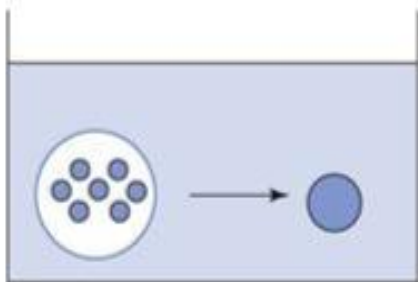
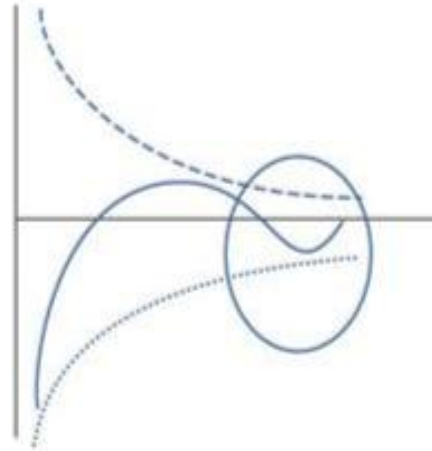
Panel A



Panel B



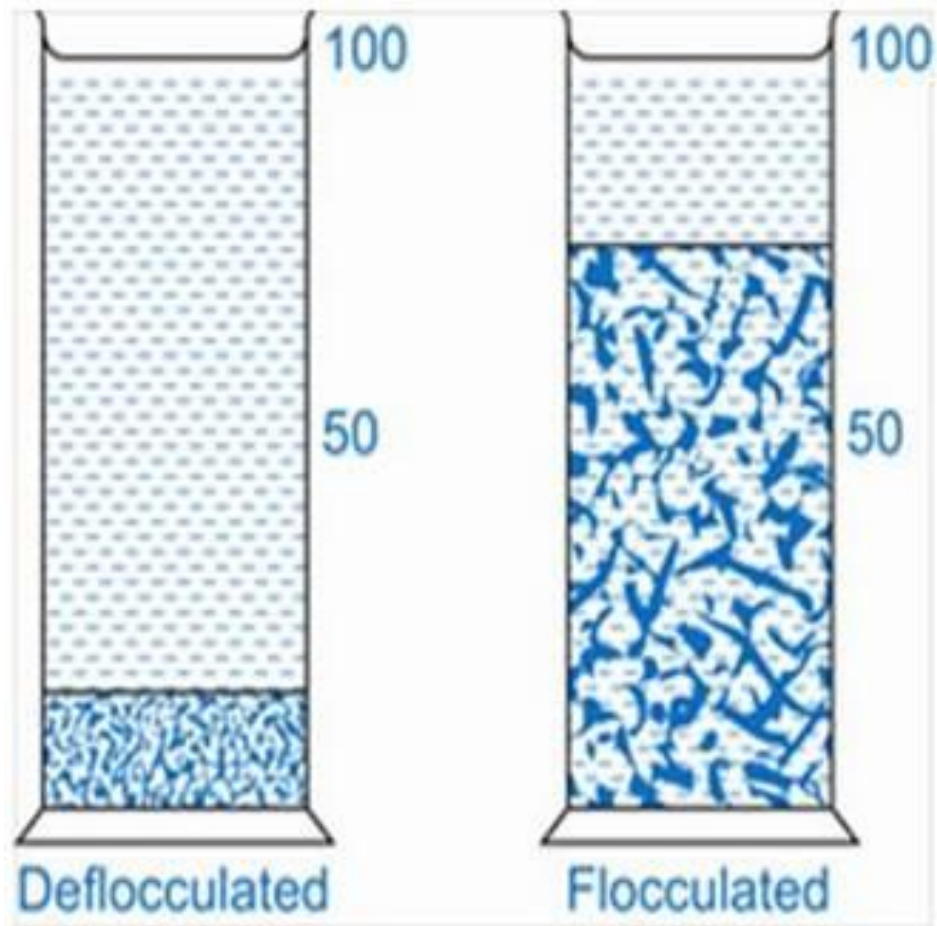
Panel C



Flocculation and deflocculation consequences of the DLVO theory
for pharmaceutical suspensions

Properties of flocculated and deflocculated suspensions

Flocculated suspension	Deflocculated suspension
1. Particles form loose 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 is somewhat 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 flocs stick to the sides of the bottle	7. Particles do not stick to the sides of the bottle



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:
$$\Delta F = \gamma_{sL} \cdot \Delta A$$
 - It is better to decrease ΔF by controlling the γ_{sL} rather than ΔA . Controlling of γ_{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 watability 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