SUSPENSIONS

6th week

-**Pharmaceutical suspensions** may be defined as uniform dispersions containing finely divided insoluble material suspended in a liquid medium.

-A suspension containing particles between 1 nm to 0.5 μm in size is called **colloidal suspension**.

-When the particle size is between 1 to 100 μm, the suspension is called coarse suspension.

-Most of the pharmaceutical suspensions are coarse suspension.

Suspensions are heterogeneous systems consisting of two phases:

- The external phase, which is also referred to as the continuous phase or dispersion medium, and the internal or dispersed phase is made up of particulate matter, which is practically insoluble in the external phase.

Most pharmaceutical suspensions consist of an aqueous dispersion medium, although organic or oily liquids are also used in some instances.

Pharmaceutical Applications of Suspensions

1) Insoluble drugs or poorly soluble drugs which required to be given orally in liquid dosage forms can be formulated as suspensions (in case of children, elderly and patients have difficulty in swallowing solid dosage forms).

2) Suspensions can be prefered to overcome the instability problem of certain drugs in aqueous solutions.

3) Suspensions can be used to mask the unpleasant taste of some active substances.

4) Some materials are needed to be present as finely divided forms to increase the surface area (e.g. Mg carbonate and Mg trisilicate are used to adsorb some toxins)

5) Suspensions can be used in topical applications (Calamine lotion BP)

6) Suspensions can be used for parenteral administration; intramuscular (i.m.) or subcutaneous (s.c.)

7) Suspensions can be used as X-ray contrast media (e.g. oral and rectal administration of propyliodone)

8) Aerosol formulations can be formulated as the suspension of active agents in the mixture of propellants

Depending on their intended route of delivery, pharmaceutical suspensions can be broadly classified as;

-Parenteral suspensions

-Topical suspensions

-Oral suspensions

Also, pharmaceutical suspensions can be applied intranasally, inhaled into the lungs or used for ophthalmic purposes in the eye.

There are certain criteria that a well-formulated suspension should meet:

1) The dispersed particles should not settle readily and the settle should redispersed immediately.

* Ideally, the particles in a suspension should not sediment at any time during the storage period. Unfortunately, the present technology does not allow us to prepare such a suspension. Since the sedimentation of particles cannot be completely avoid, it is desirable that the particles should settle slowly.

** The easy redispersion of sedimented particles in a suspension is important for the uniformity of dose.

2) The particles should not form a cake on settling.

3) The viscosity should be such that the preparation can be easily poured. A highly viscous suspension would make pouring difficult.

4) It should be chemically and physically stable.

5) It should be palatable (for oral suspensions).

6) It should be free from gritting particles (external use).

Basic Principles in Preparing Suspension Formulations

The three major concerns associated with suspensions are;

- Ensuring adequate dispersion of the particles in the vehicle.

- Minimizing settling of the dispersed particles.

- Preventing caking of these particles when a sediment forms.

A) Wetting of the particles

- 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.

* The use of wetting agent allows removing this air from the surface and to easy penetration of the vehicle into the pores.

** Alcohol, glycerin, and propylene glycol are frequently used to remove adsorbed air from the surface of particles when aqueous vehicle is used to disperse the solids.

*** When the particles are dispersed in a non-aqueous vehicle, mineral oil is used as wetting agent.

!!! Solid particles that are not easily wetted by aqueous vehicle after the removable of the adsorbed air are referred to as hydrophobic particles. It is necessary to reduce the interfacial tension between the particles and the vehicle by using surface active agents to improve the wettability.

Sodium lauryl sulfate is one of the most commonly used surface active agents.

!!! Hydrophilic particles are easy to disperse in the aqueous vehicle once the adsorbed air is removed.

Hydrophilic particles do not require the use of surface active agents.

B) Particle Size

Controlling the size of the particles is very important for suspension stability.

- Finely divided particles are necessary to reduce sedimentation. However, improper control of particle size can create several undesirable consequences.

- Most pharmaceutical suspensions contain polydisperse solids. A narrow particle size distribution is desirable as it yields uniform sedimentation rate, which ultimately will provide better predictability of suspension properties from batch to batch of finished suspensions.

- Very fine particles sediment as hard cake if the suspension is not flocculated.

- For a concentrated suspension, there is a significant particle–particle interaction, which may lead to more viscous or thixotropic dispersions.

- Smaller particles can have a greater effect on increasing the viscosity of the system because they have a higher specific surface area than the larger particles.

- Particle size can also significantly affect the drug bioavailability.

- Suspensions are used to deliver poorly soluble drugs. The absorption of these drugs is primarily controlled by the dissolution rate. In such cases, using smaller particles may provide a better rate and extent of drug absorption due to their higher specific surface area.

- Suspensions containing particles greater than 5 µm in diameter will be gritty and unsuitable for parenteral or ophthalmic preparations due to the possibility of irritation.

- Particles larger than 25 µm in diameter may clog the hypodermic needle, especially when the particles are acicular in shape.

C) Sedimentation

Sedimentation of particles in a suspension is governed by several factors;

- Particle size
- Density of the particles
- Density of the vehicle
- Viscosity of the vehicle

!!! The velocity of sedimentation of particles in a suspension can be determined by using the Stoke's law.

C) Sedimentation

Stoke's law

$$V = \frac{2\, r^2(\rho_1 - \rho_2)\, g}{9\eta}$$

V: Terminal velocity (cm/sec)
r: Radius of the particles (cm)
ρ_1: Density of the dispersed phase (g/cm^3)
ρ_2: Density of the dispersion medium (g/cm^3)
g: Acceleration due to gravity (980.7 cm/sec^2)
η: Viscosity of the dispersion medium (g/cm.sec)

!!! A single parameter or a combination of the parameters in Stokes' equation can be altered to reduce settling.

1) The most important parameter is the particle size because it is presented as square form in the equation. Smaller particles yield a low rate of sedimentation.

2) Viscosity of the medium can be increased in order to reduce settling. Common viscosity-increasing agents are cellulose derivatives (e.g., methylcellulose and hydroxypropyl methylcellulose). Other examples would be natural gums (e.g., acacia and tragacanth).

3) The difference in density between the dispersed phase and dispersion medium can affect the rate of settling. A difference of zero means no sedimentation. Since, the density of the dispersed phase cannot be changed, it would be necessary to increase the density of the medium. However, it is rarely possible to increase the vehicle density; therefore, the difference cannot be completely eliminated. However, by using some density modifiers (e.g., sorbitol and mannitol), the difference can be reduced. These agents may also increase the viscosity of the medium.

D) Electric Double Layer

Dispersed solid particles in a suspension may have charge in relation to their surrounding vehicle.

These solid particles may become charged through one of two situations.

1) **Selective adsorption of a particular ionic species present in the vehicle.** This may be due to the addition of some ionic species in a polar solvent. A solid particle which is in contact with an electrolyte solution may become positively or negatively charged by selective adsorption of either cations or anions from the solution.

2) Ionization of functional group of the particle.

In this situation, the total charge is a function of the pH of the surrounding vehicle.

If the adsorbed species is an anion, the particles will be overall negatively charged. The ions that give the particle its charge, anions in this case, are called potential-determining ions or co-ions.

Remaining ionic species in the solution are the rest of the anions and the total number of cations added. This means, there will be excess cations than anions in the dispersion medium. These cations having a charge opposite to that of the potential-determining ions are known as counter-ions.

Counter-ions are attracted to the negatively charged surface by electric forces. They also repel the approach of any further anions to particle surface, once the initial adsorption is complete. These electric forces and thermal motion keeps an equal distribution of all the ions in solution. It results in an equilibrium condition where some of the excess cations approach the surface and the rest of the cations will be distributed in decreasing the amounts as one moves away from the charged surface.

The part of the solvent immediately surrounding the particles will almost entirely comprise of the counter-ions. This part of the solvent, along with these counter-ions is tightly bound to the particle surface and is known as the Stern layer.

Surrounding the Stern layer is the diffuse layer that contains more counter-ions than co-ions. The ions in this layer are relatively mobile and, because of thermal energy, they are in a constant state of motion into and from the main body of the continuous phase. Electric neutrality occurs where the mobile diffuse layer ends. Beyond the diffuse layer, the concentrations of co- and counter-ions are equal, that is, conditions of electric neutrality prevail throughout the remaining part of the dispersion medium.

Thus, the electric distribution at the solid–liquid interface can be visualized as a double layer of charge. The Stern layer, the first layer is tightly bound to the solid surface and contains mostly the counter-ions. The second layer is more mobile containing more counter-ions than co-ions. These two layers are commonly known as the electric double layer.

The thickness of the double layer depends upon the type and concentration of ions in solution.

It is important to note that the suspension, as a whole is electrically neutral despite the presence of unequal distribution of charges in the double layer.

E) Nernst and Zeta Potential

The difference in electric potential between the actual surface of the particle and the electroneutral region is referred to as Nernst potential. Thus, Nernst potential is controlled by the electrical potential at the surface of the particle due to the potential determining ions.

The potential difference between the ions in the tightly bound layer and the electroneutral region, referred to as zeta potential, has significant effect in the formulation of stable suspension.

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

** If the zeta potential is reduced below a critical value, the force of attraction between particles due to van der Waals' force, overcome the forces of repulsion and the particles come together to form floccules. This phenomenon is known as flocculation. The magnitude of surface and zeta potentials is related to the surface charge and the thickness of the double layer.

DLVO Theory

- Derjaguin, Landau, Verwey and Overbeek described the stability of lyophobic colloids. This is the classic DLVO theory, which explains the result of particle interaction in lyophobic colloids.

- According to this theory, the potential energy of interaction between particles (V_T) is the result of repulsion due to electrical double layer (V_R) and attraction due to van der Waals' force (V_A) and can be shown by

$$V_T = V_R + V_A$$

V_R depends on several factors including the zeta potential of the system, the particle radius, the interparticular distance, the dielectric constant of the medium, whereas the factors that affect V_A includes the particle radius, and the interparticular distance.

Electrical repulsion due to the electric double layer and the attraction due to van der Waals’ force are shown in the opposite direction due to their opposite nature of force.

At any distance from a particle (h), the net energy (V_T) is calculated by subtracting the smaller value from the larger one.

When the net energy curve remains above the baseline, it represents repulsion. On the other hand, attraction can be shown by the curves below the baseline.

When V_R is much larger than V_A ($V_R >> V_A$), the dispersion will be highly stable because of the high net repulsive force. This dispersion is resistant to aggregation (i.e., flocculation or coagulation) as long as the particles do not sediment under gravity.

High energy barrier, V_M, must be overcome by the particles to form aggregates. If V_M greatly exceeds the mean thermal energy of the particles, these particles will not enter P, the primary energy minimum.

The minimum value of V_M that can create this situation corresponds to a zeta potential of more than 50 mV. A very small interparticular distance is found at P.

The high magnitude of energy at P causes the particles to bond tightly together. Consequently, it is possible that it will compact into a hard cake, which will be very hard to redisperse.

Occasionally, there occurs a secondary minimum at S, which is far from the surface of the particle.

Loose aggregates can be created at this point and this aggregate can usually be broken easily by shaking or dilution.

Where attractive forces predominate over repulsion forces all the time (VA >> VR); and rapid aggregation will occur.

In addition to electric stabilization, steric stabilization can also be applied to prepare a stable dispersion. Substances such as nonionic surfactants, when adsorbed at the particle surface, can stabilize a dispersion, even when there is no significant zeta potential. Therefore, the term for steric stabilization, V_S, should be added to the equation obtained in DLVO theory, which gives rise to:

$$V_T = V_R + V_A + V_S$$

F) Flocculation and Deflocculation

When zeta potential is relatively high (25 mV or more), the repulsive forces between two particles exceed the attractive London forces. Accordingly, the particles are dispersed and are said to be deflocculated.

Even when brought close together by random motion or agitation, deflocculated particles resist collision due to their high surface potential.

The addition of a preferentially adsorbed ion whose charge is opposite in sign to that on the particle leads to a progressive lowering of zeta potential. At some concentration of the added ion, the electrical forces of repulsion are lowered sufficiency and the forces of attraction predominate.

Under these conditions the particles may approach each other more closely and form loose aggregates, termed *flocs*. Such a system is said to be *flocculated*.

The continued addition of the flocculating agent can reverse the former process, if the zeta potential increases sufficiently in the opposite direction. Thus, the adsorption of anions onto positively charged deflocculated particles in suspension will lead to flocculation. The addition of more anions eventually can generate a net negative charge on the particles. When this has achieved the required magnitude, deflocculation may occur again.

The only difference from the starting system is that the net charge on the particles in their deflocculated state is negative rather than positive.

Relative Properties of Flocculated and Deflocculated Particles in Suspension

Deflocculated	Flocculated
1. Particles exist in suspension as separate entities.	1. Particles form loose aggregates.
2. Rate of sedimentation is slow, as each particle settles separately and particle size is minimal.	2. Rate of sedimentation is high, as particles settle as a floc, which is a collection of particles.
3. A sediment is formed slowly.	3. A sediment is formed rapidly.
4. The sediment eventually becomes very closely packed, due to weight of upper layers of sedimenting material. Repulsive forces between particles are overcome and a hard cake is formed that is difficult, if not possible, to redisperse.	4. The sediment is packed loosely and possesses a scaffold-like structure. Particles do not bond tightly to each other and a hard, dense cake does not form. The sediment is easy to redisperse, so as to reform the original suspension.
5. The suspension has a pleasing appearance, as the suspended material remains suspended for a relatively long time. The supernatant also remains cloudy, even when settling is apparent.	5. The suspension is somewhat unsightly, due to rapid sedimentation and the presence of an obvious, clear supernatant region. This can be minimized if the volume of sediment is made large. Ideally, volume of sediment should encompass the volume of the suspension.