Suspensions

Suspensions may be defined as preparations containing finely divided drug particles distributed throughout water in which the drug exhibits a minimum solubility. Some suspensions are available in ready-to-use form, that is, already suspended in a liquid. Other preparations are available as dry powders to be suspended in liquid at the time of dispensing (reconstitution powders). The latter type of suspension is a powder mixture containing the drug and suitable suspending and dispersing agents to be diluted with a specified quantity of water. Drugs that are unstable in the presence of water (e.g., antibiotics) are frequently supplied as dry powder for reconstitution.

Suspensions can be used orally, applied topically to the skin, or given parenterally by injection. However, oral suspensions are our focus in this lecture.

Reasons for Suspension Preparation

There are several reasons for preparing suspensions. For example, certain drugs are chemically unstable in solution but stable when suspended. In this instance, the suspension ensures chemical stability while permitting the drug to be administered as liquid. For example, oxytetracycline HCl is used in solid dosage forms, but it rapidly decomposes in aqueous solution. A stable liquid dosage form has been made by suspending the insoluble calcium salt in a suitable aqueous vehicle.

For many patients, the liquid is preferred to the solid form of the same drug because of the ease of swallowing.

The disadvantage of unpleasant taste of certain drugs in solution form is avoided when the drug is administered as undissolved particles in a suspension. For example, erythromycin estolate is a less water-soluble prodrug of erythromycin and is used to prepare a palatable liquid dosage form of erythromycin.

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.

The Sedimentation Rate

The factors involved in the rate of settling of the particles of a suspension are present in the Stokes law equation:

$$\frac{dx}{dt} = \frac{d^2(p_1 - p_2)g}{18\eta}$$

Where:

$\frac{dx}{dt}$: sedimentation rate.

d : diameter of the particles.

p_1: density of the particles.

p_2: density of the medium.

g: gravity constant.

η: viscosity of the medium.

From the equation it is apparent that the velocity of fall of a suspended particle is greater for larger particles than it is for smaller particles. Reducing the particle size of the dispersed phase produces a slower rate of descent of the particles. Also, the greater the

density of the particles, the greater the rate of descent. If the particles were less dense than the vehicle, they would tend to float and floating particles would be quite difficult to distribute uniformly in water. The rate of sedimentation may be reduced by increasing the viscosity of the dispersion medium. However, a product having too high viscosity is not desirable, because it pours with difficulty and it is difficult to redisperse the suspended particles. Therefore, if the viscosity of a suspension is to be increased, it is done only to a moderate extent to avoid these difficulties.

The following table shows examples on the sedimentation rate of different particle sizes and vehicles (*not for save*):

CONDITION	RATE OF SETTLING (CM/S)
2.5 µm powder in water	1.02×10^{-4}
0.25 µm powder in water	1.02×10^{-6}
2.5 µm powder in glycerin	4.25×10^{-8}
0.25 µm powder in glycerin	4.25×10^{-10}

The most important consideration in suspensions is the size of the particles. In most good suspensions, the particle diameter is 1-50 µm. Generally, particle size reduction is accomplished by dry milling prior to incorporation of the dispersed phase into the dispersion medium.

One of the most rapid, convenient, and inexpensive methods of producing fine drug powders of about 10-50 µm is *micropulverization*. Micropulverizers are high-speed mills that are efficient in reducing powders to the size acceptable for most suspensions. For still finer particles, under 10 µm, *jet milling* (also called *micronization)*, is quite effective. Particles of extremely small dimensions may also be produced by *spray drying*. In spray dryer, a solution of a drug is sprayed and rapidly dried by a current of hot air. The resulting dry powder is very small in size.

Although the particle size of a drug may be small when the suspension is first manufactured, there is always a degree of crystal growth that occurs on storage,

particularly if temperature fluctuations occur. This is because the solubility of the drug may increase as the temperature rises, but on cooling, the drug will crystallize out.

As shown by Stokes' equation, the reduction in the particle size of the suspended material is beneficial to the physical stability of the suspension because the rate of sedimentation of the solid particles is reduced. However, one should avoid reducing the particle size too much, because fine particles have a tendency to form a compact cake upon settling to the bottom of the container. The result may be that the cake resists breakup with shaking and forms rigid aggregates that are larger and less suspendable than the original suspended particles.

Flocculated and deflocculated suspensions

In a deflocculated suspension, the dispersed particles remain as discrete separated units and settling will be slow. The supernatant of this suspension will continue to remain cloudy for an appreciable time after shaking, due to the very slow settling rate of the smallest particles in the product. The slow rate of settling prevents the entrapment of liquid within the sediment, which thus becomes compacted and can be very difficult to redisperse. This phenomenon is also called caking and is the most serious of all the physical stability problems encountered in suspension.

In contrast, the aggregation of particles in a flocculated suspension will lead to a much more rapid rate of sedimentation because each unit is composed of many individual particles (i.e., aggregates) and is therefore larger. One common method of preventing rigid cohesion of the small particles of a suspension (which are responsible for the formation of the cake) is the intentional formation of a less rigid or loose aggregation of the particles held together by weak bonds. Such an aggregation of particles is termed a *floc* or a *floccule*. The floccules have porous loose structure and the dispersion medium can flow through them during sedimentation. Also, they can entrap a large amount of the liquid phase. Therefore, the volume of the final sediment will still be large and will easily be redispersed by moderate agitation. Although flocs settle more rapidly than individual

discrete particles, flocculated particles forming a type of lattice that resists complete settling and thus are less prone to compaction and cake formation than unflocculated particles. The flocculated and deflocculated suspensions are shown in the following figure:

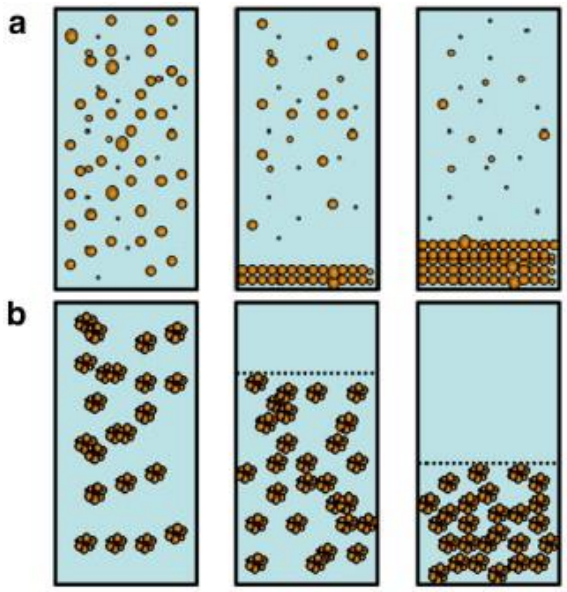

Figure: flocculated and deflocculated suspension.

a) deflocculated.

b) flocculated.

In a flocculated suspension, the supernatant quickly becomes clear, because of the large flocs that settle rapidly. The following figure shows the appearance of both flocculated and deflocculated suspensions at given time after shaking.

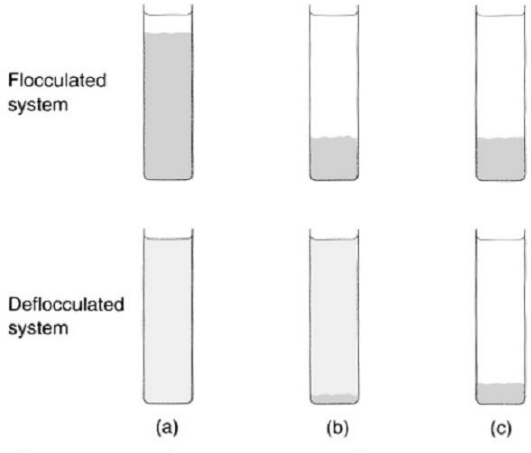

Figure: The flocculated and deflocculated suspensions. Within a few minutes of manufacture (a) there is no change within the deflocculated susp. compared to its initial appearance. Even after several hours (b) there is still little obvious change, except that the concentration of solids in the lower layers has increased owing to slow particle sedimentation. There is a small amount of sediment. After prolonged storage (c), the supernatant has cleared, leaving a compact sediment.

In a flocculated one at (a) there is some clear supernatant with a distinct boundary between it and the sediment. At (b) there is a larger volume of clear supernatant, which does not change further even after prolonged storage (c).

In summary, deflocculated suspensions have the advantage of a slow sedimentation rate, thereby enabling a uniform dose to be taken from the container, but when settling does occur the sediment is compacted and difficult to redisperse. Flocculated suspensions form loose sediments which are easily redispersible, but the sedimentation rate is fast and there is a danger of inaccurate dose being administered; also, the product will look inelegant.

Accordingly, to prepare an ideal suspension, one should prepare a suspension with ***partial flocculation***. That is, a compromise is reached in which the suspension is partially flocculated to enable adequate redispersion upon moderate shaking, and viscosity is controlled so that the sedimentation rate is at a minimum.

Flocculating agents

Whether or not a suspension is flocculated or deflocculated depends on size of particles and the forces of repulsion and attraction between the particles. In deflocculated suspension, the repulsive forces are dominant.

In many cases, after the incorporation of the wetting agent, a suspension will be deflocculated because of the hydrated layer around each particle forming a mechanical barrier that prevents aggregation.

The flocculating agents include electrolytes, surfactants and hydrophilic polymers.

Electrolytes: The addition of inorganic electrolyte to suspension will alter the zeta potential of the dispersed particles and, if this value is lowered sufficiently, flocculation may occur. The ability of an electrolyte to flocculate the particles depends on its valency. Although they are more efficient, trivalent ions are less widely used than mono- or divalent electrolytes because they are more toxic.

The most widely used electrolytes include sodium salts of acetates, phosphates and citrates. Care must be taken not to add excess electrolyte, otherwise charge inversion may occur on each particle, so forming a deflocculated suspension again.

Surfactants: Ionic surfactants may also cause flocculation by neutralizing the charge on each particle, thus resulting in a flocculated suspension.

Hydrophilic polymers: Starch, alginates, cellulose derivatives, tragacanth and carbomer are examples of polymers that can be used to control flocculation. Their branched-chain molecules form a gel-like network within the suspension and become adsorbed on to the surfaces of the dispersed particles, thus holding them in a flocculated state. Although some settling can occur, the sedimentation volume is large, and usually remains so for a considerable period.

Suspending Agents

The suspended particles settle too rapidly (especially in flocculated suspensions). The rapid settling prevents accurate measurement of the dose and from an esthetic point of view produces unsightly supernatant layer. Therefore, suspending agents are used commonly. Suspending agents are substances used to make the particles suspended in the vehicle for longer time and slow down their settling by ***increasing the viscosity of the medium***. Carboxymethylcellulose and xanthan gum are example on these agents. The amount of the suspending agent must not be very high to render the suspension too viscous to agitate or to pour.

Wetting Agents

In some instances, the suspended material has good affinity for water and is readily wetted by it. Other drugs are not penetrated easily by the water and have a tendency to clump together or to float on water. In the latter case, the powder must first be wetted to make it more penetrable by water. Alcohol and glycerin may be employed as wetting agents. They function by displacing the air on the surface of the particles thereby allowing penetration of water into the powder.

Evaluation of suspension stability

Sedimentation volume

Sedimentation volume is the ratio of the ultimate height (H_u) of the sediment to the initial height (H_0) of the total suspension. The larger this value, the better is the suspendibility.

$$\text{Sedimentation volume} = \frac{H_u}{H_0}$$

At zero time, the H_u=H_0 and the sedimentation volume equals to 1. On standing, the suspended solid particles begin to settle and thus sedimentation volume begins to decrease. In general, it is preferred that the suspension retains the same sedimentation volume, as possible.

Particle size changes

The freeze-thaw cycling technique is useful to stress suspensions for stability testing purposes. This technique promotes particle growth and may indicate the probable future state after prolong storage at room temperature.