Dispersion Systems

Liquid preparations containing undissolved or immiscible drug distributed throughout a vehicle. In these preparations, the substance distributed is referred to as the *dispersed phase*, and the vehicle is termed the *dispersing phase* or *dispersion medium*. Together, they produce a *dispersed system*.

In the case of suspensions, the particles of the dispersed phase are usually solid materials that are insoluble in the dispersion medium. In the case of emulsions, the dispersed phase is a liquid that is neither soluble nor miscible with the liquid of the dispersing phase. In the case of an aerosol, the dispersed phase may be small air bubbles throughout a solution or an emulsion. Dispersions also consist of droplets of a liquid (solution or suspension) in air.

The particles of the dispersed phase vary widely in size, from large particles visible to the naked eye down to particles of colloidal dimension, falling between 1.0 nm and 0.5 µm.

Dispersions containing coarse particles, usually 10 to 50 µm, are referred to as *coarse dispersions*; they include the *suspensions* and *emulsions*. Dispersions containing particles of smaller size are termed *fine dispersions* (0.5 to 10 µm), and if the particles are in the colloidal range, *colloidal dispersions. Magmas* and *gels* are fine dispersions.

SUSPENSIONS

Generally Suspensions may be defined as preparations containing finely divided drug particles (the *suspensoid*) distributed somewhat uniformly throughout a vehicle in which the drug exhibits a minimum degree of solubility. A pharmaceutical suspension is a coarse dispersion in which insoluble particles, generally greater than 1µm in diameter, are dispersed in a liquid medium, usually aqueous.

Some suspensions are available in ready-to-use form that is, already distributed through a liquid vehicle with or without stabilizers and other additives. Other preparations are available as dry powders intended for suspension in liquid vehicles.

Aqueous suspensions are most commonly used for oral administration of insoluble drugs but may also be used for parenteral, topical and ophthalmic administration.

Largely because of their greater size, particles in a coarse dispersion have a greater tendency to separate from the dispersion medium than do the particles of a fine dispersion. Most solids in dispersion tend to settle to the bottom of the container because of their greater density than the dispersion medium, whereas most emulsified liquids for oral use are oils, which generally have less density than the aqueous medium in which they are dispersed, so they tend to rise toward the top of the preparation. Complete and uniform redistribution of the dispersed phase is essential to the accurate administration of uniform doses. For a properly prepared dispersion, this should be accomplished by moderate agitation of the container.

Drugs that are unstable if maintained for extended periods in the presence of an aqueous vehicle (e.g., many antibiotic drugs) are most frequently supplied as dry powder mixtures for reconstitution at the time of dispensing.

REASONS FOR SUSPENSIONS (Advantages of Suspensions)

1- Certain drugs are chemically unstable in solution but stable when suspended. In this instance, the suspension ensures chemical stability while permitting liquid therapy.
2- The ease of swallowing liquids and the flexibility in administration of a range of doses.
3- The disagreeable taste of certain drugs in solution form is overcome when the drug is administered as undissolved particles of an oral suspension.
4- It's a method for delivering liquid medication for drugs with low solubility that prevent formulating them as solutions.

FEATURES DESIRED IN A PHARMACEUTICAL SUSPENSION

There are many considerations in the development and preparation of a pharmaceutically elegant suspension. In addition to therapeutic efficacy, chemical stability of the components of the formulation, permanency of the preparation, and esthetic appeal of the preparation— desirable qualities in all pharmaceutical preparations— a few other features apply more specifically to the pharmaceutical suspension:

1. A properly prepared pharmaceutical suspension should settle slowly and should be readily re-dispersed upon gentle shaking of the container.
2. The particle size of the suspensoid should remain fairly constant throughout long periods of undisturbed standing.
3. The suspension should be of suitable viscosity & pour readily and evenly from its container.

SEDIMENTATION RATE OF THE PARTICLES OF A SUSPENSION

The various factors involved in the rate of settling of the particles of a suspension are embodied in the equation of Stokes law, which was derived for an ideal situation in which uniform, perfectly spherical particles in a very dilute suspension settle without producing turbulence, without colliding with other particles of the suspensoid, and without chemical or physical attraction or affinity for the dispersion medium. Obviously, Stokes' equation does not apply precisely to the usual pharmaceutical suspension in which the suspensoid is irregularly shaped and of various particle diameters, in which the fall of the particles *does* result in both turbulence and collision, and also in which the particles may have some affinity for the suspension medium. However, the basic concepts of the equation do give a valid indication of the factors that are important to suspension of the particles and a clue to the possible adjustments that can be made to a formulation to decrease the rate of sedimentation.

Stokes' Equation:

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

where

dx/dt is the rate of settling,
d is the diameter of the particles,
ρ_i is the density of the particle,
ρ_e is the density of the medium,
g is the gravitational constant, and
η is the 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, all other factors remaining constant. 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, provided the density of the vehicle is not altered. Because aqueous vehicles are used in pharmaceutical oral suspensions, the density of the particles is generally greater than that of the vehicle, a desirable feature. 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 the vehicle. The rate of sedimentation may be appreciably reduced by increasing the viscosity of the dispersion medium, and within limits of practicality this may be done. However, a product having too high a viscosity is not generally desirable, because it pours with difficulty and it is equally difficult to re-disperse the suspensoid.

The viscosity characteristics of a suspension may be altered not only by the vehicle used, but also by the solids content. As the proportion of solid particles in a suspension increases, so does the viscosity.

The particle shape of the suspensoid can also affect caking and product stability. It has been shown that symmetrical barrel-shaped particles produced more stable suspensions than did asymmetrical needle-shaped particles of the same agent. The needle-shaped particles formed a tenacious sediment cake on standing that could not be redistributed, whereas the barrel-shaped particles did not cake upon standing.

Probably the most important single consideration in a discussion of suspensions is the size of the particles. In most good pharmaceutical suspensions, the particle diameter is 1 to 50µm.

As shown by Stokes' equation, the reduction in the particle size of a suspensoid is beneficial to the stability of the suspension because the rate of sedimentation of the solid particles is reduced as the particles are decreased in size. The reduction in particle size produces slow, more uniform rates of settling. 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.

One of the most rapid, convenient, and inexpensive methods of producing fine drug powders of about 10 to 50µm size is ***micropulverization***. Micropulverizers are high-speed attrition or impact mills that are efficient in reducing powders to the size acceptable for most oral and topical suspensions. For still finer particles, under 10µm, *fluid energy* grinding, sometimes referred to as ***jet milling*** or ***micronizing***, is quite effective. By this process, the shearing action of high-velocity compressed airstreams on the particles in a confined space produces the desired ultrafine or micronized particles. The particles to be micronized are swept into violent turbulence by the sonic and supersonic velocities of the airstreams. The particles are accelerated to high velocities and collide with one another, resulting in fragmentation. This method may be employed when the particles are intended for parenteral or ophthalmic suspensions.

Particles of extremely small dimensions may also be produced by ***spray drying***. A spray dryer is a cone-shaped apparatus into which a solution of a drug is sprayed and rapidly dried by a current of warm, dry air circulating in the cone. The resulting dry powder is collected. It is not possible for a pharmacist to achieve the same degree of particle-size reduction with such comminuting equipment as the mortar and pestle.

The concept of Flocculation

Basically; the electro-repulsive forces between sedimenting particles will determine the behavior of the particles and whether the system is going to be flocculated or not.

If the electrical repulsive forces between the particles were high, it will allow the particles to slip past one another to form a close packed arrangement at the bottom of the container, with the small particles filling the voids between the larger ones. The supernatant liquid may remain cloudy after sedimentation due to the presence of colloidal particles that will remain dispersed. Those particles lowermost in the sediment are gradually pressed together by the weight of the ones above. The repulsive barrier is thus overcome, allowing the particles to pack closely together and Physical bonding occurs leading to 'cake' or 'clay' formation.

On the other hand, if the electrical repulsive forces between the particles were low, particles flocculated form a loosely bonded structure, called a *flocculate* or *floc*. A suspension consisting of particles in this state is said to be flocculated. Although sedimentation of flocculated suspensions is fairly rapid, so loosely packed high-volume sediment is obtained in which the flocs retain their structure and the particles are easily re-suspended. The supernatant liquid is clear because the colloidal particles are trapped within the flocs and sediment with them.

The rate of flocculation also depends on the number of particles present, so that the greater the number of particles, the more collisions there will be and flocculation is more likely to occur.

Deflocculated and flocculated suspensions

Deflocculated suspensions

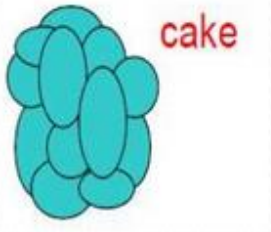
- In this system solids as present as individual particles . they also exhibit aggregation but comparatively low than flocculated .
- Pleasant appearance because of uniform dispersion of particles .
- Particles exhibit repulsive forces
- Particles settle independently

Flocculated suspensions

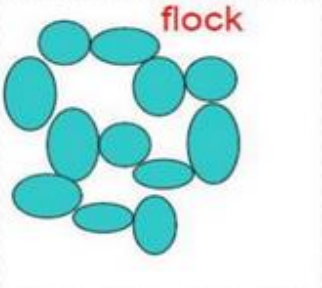
- In this system solids aggregate by forming chemical bridges .
- Un slightly sediment and supernatant layer is formed.
- Particles exhibit attractive forces
- They settle as flocs

Deflocculated and flocculated suspensions

- Rate of sedimentation is slow and size of particle is small.
- Particles exist as separate entities
- Bioavailability is relatively high



- Rate is high as flocs are collection of smaller particles.
- Particles form loose aggregates
- Bioavailability is comparatively less

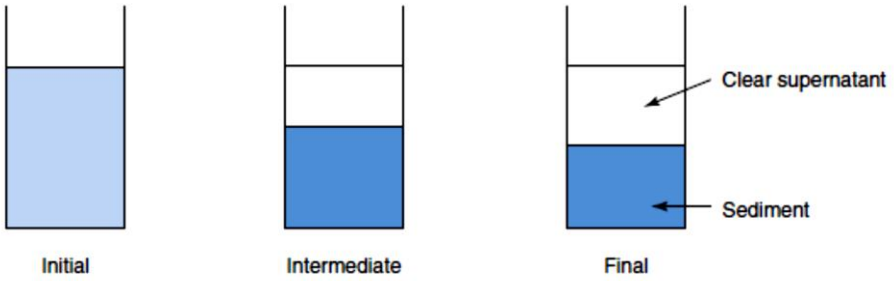


Measuring Sedimentaion Rate

Bulk sedimentation is a very easy process to observe. A known volume of the suspension with the solid particles dispersed as optimally as possible is placed in a graduated cylinder and left to stand, allowing sedimentation to occur. And at certain time intervals, the volume of sediment is measured and the sedimentation volume ratio*(F*) calculated; the value of *F* is in the range of 0 to 1.

$F = V_f / V_0$ where V_F is the final volume of sediment and V_0 is the initial volume of suspension

The sedimentation patterns of flocculated and deflocculated systems are different. In a flocculated system, the particles are arranged in loose aggregates or floccules, which behave as large, porous individual particles. These floccules will begin to sediment quickly, generally within a period of minutes, leaving a clear supernatant, and sedimentation will reach a maximum within a few hours or days. The sediment formed is loose and fluffy and can be easily redispersed by shaking, as both the individual floccule and the bulk sediment formed has the solvent medium incorporated into it. A high volume of sediment is observed, with calculated values of the sedimentation volume ratio, *F*, being up to 0.6.

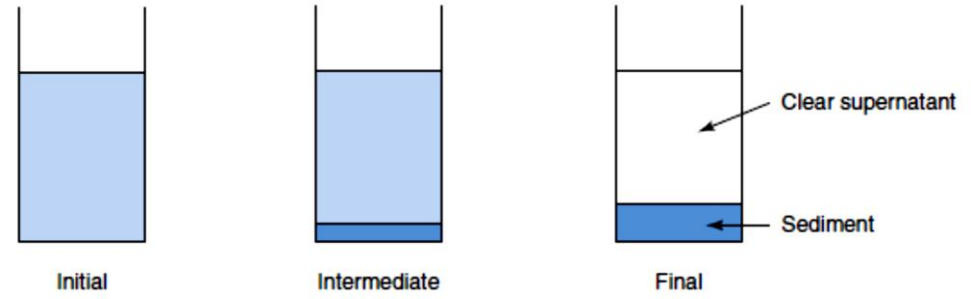


• The sedimentation behaviour of a flocculated suspension. Pale blue colouration indicates the initial

showing the initial condition, an 'intermediate' condition after a short period of time and the 'final' condition after a prolonged period.

Deflocculated systems show a different pattern of sedimentation. As the particles behave independently, they will sediment slowly, reflecting their small size. Sedimentation takes some time, measured in days and weeks rather than minutes. In the initial stages of sedimentation, a small amount of compact sediment is observed at the base of the cylinder, with no, or limited clear supernatant being observed. Subsequently, the volume of sediment and the volume of clear supernatant both increase. The sediment formed is dense and compacted, described as being 'caked'. Redispersion of the caked sediment is difficult, as little, if any, of the solvent medium can penetrate into it. A low final volume of sediment

is observed, with calculated values of the sedimentation volume ratio, *F*, being as low as 0.1.



• The sedimentation behaviour of a deflocculated suspension. Pale blue colouration indicates th

Above illustration is showing the initial condition, an 'intermediate' condition after a short period of time (although longer than for flocculated systems) and the 'final' condition after a prolonged period.

Wetting agents

One of the problems encountered in dispersing solid materials in water is that the powder may not be readily wetted. This may be due to entrapped air or to the fact that the solid surface is hydrophobic.

Wetting agents are used to improve the flow of the liquid vehicle across the particle surface, which in turn improves the homogeneity of distribution of the drug particles throughout the formulation. They do this by reducing the interfacial tension between the solid particle and liquid medium, as discussed earlier. Wetting agents are typically surfactants below their critical micelle concentration (CMC). Above the CMC, micelles are formed with a hydrophobic core and the hydrophobic drug will begin to dissolve into this region, thus affecting the structure of the system. Hence, the level of the surfactant is kept below the CMC.

Dispersion Medium

Oftentimes, as with highly flocculated suspensions, the particles of a suspension settle too rapidly to be consistent with what might be termed a pharmaceutically elegant preparation. The rapid settling hinders accurate measurement of dosage and from an esthetic point of view produces too unsightly a supernatant layer. In many commercial suspensions, suspending agents are added to the dispersion medium to lend it structure. Carboxymethylcellulose, methylcellulose, microcrystalline cellulose, polyvinylpyrrolidone, xanthan gum, and bentonite are a few of the agents employed to thicken the dispersion medium and help suspend the suspensoid.

Preparation of Suspensions

In the preparation of a suspension, the pharmacist must be acquainted with the characteristics of both the intended dispersed phase and the dispersion medium. In some instances, the dispersed phase has an affinity for the vehicle to be employed and is readily wetted by it. Other drugs are not penetrated easily by the vehicle and have a tendency to clump together or to float on the vehicle. In the latter case, the powder must first be wetted to make it more penetrable by the dispersion medium. They function by displacing the air in the crevices of the particles, dispersing the particles, and allowing penetration of dispersion medium into the powder. In large scale preparation of suspensions, wetting agents are mixed with the particles by an apparatus such as a colloid mill; on a small scale in the pharmacy, they are mixed with a mortar and pestle. Once the powder is wetted, the dispersion medium (to which have been added all of the formulation's soluble components, such as colorants, flavorants, and preservatives) is added in portions to the powder, and the mixture is thoroughly blended before subsequent additions of vehicle. A portion of the vehicle is used to wash the mixing equipment free of suspensoid, and this portion is used to bring the suspension to final volume and ensure that the suspension contains the desired concentration of solid matter. The final product is then passed through a colloid mill or other blender or mixing device to ensure uniformity.

EXTEMPORANEOUS COMPOUNDING OF SUSPENSIONS

Unfortunately, not all medicines are available in a convenient, easy-to-take liquid dosage form. Consequently, patients who are not able to swallow solid medicines, such as infants and the elderly, may present a special need. Thus, the pharmacist may have to use a solid dosage form of the drug and extemporaneously compound a liquid product. A difficulty that confronts the pharmacist is a lack of ready information on stability of a drug in a liquid vehicle. It is known that drugs in liquid form have faster decomposition rates than in solid form, and some are affected by the pH of the medium. Typically, in formation of an extemporaneous suspension, the contents of a capsule are emptied into a mortar or tablets crushed in a mortar with a pestle. The selected vehicle is slowly added to and mixed with the powder to create a paste and then diluted to the desired volume.

DRY POWDERS FOR ORAL SUSPENSION

A number of official and commercial preparations consist of dry powder mixtures or granules that are intended to be suspended in distilled water or some other vehicle prior to oral administration. These official preparations have “for Oral Suspension” in their official title to distinguish them from prepared suspensions.

Most drugs prepared as a dry mix for oral suspension are antibiotics. The dry products are prepared commercially to contain the antibiotic drug, colorants (FD&C dyes), flavorants, sweeteners (e.g., sucrose or sodium saccharin), stabilizing agents (e.g., citric acid, sodium citrate), suspending agents (e.g., guar gum, xanthan gum, methylcellulose), and preserving agents (e.g., methylparaben, sodium benzoate) that may be needed to enhance the stability of the dry powder or granule mixture or the liquid suspension. When called on to reconstitute and dispense one of these products, the pharmacist loosens the powder at the bottom of the container by lightly tapping it against a hard surface and then adds the label-designated amount of purified water, usually in portions, and shakes the slurry until all of the dry powder has been suspended. It is important to add precisely the prescribed amount of purified water to the dry mixture if the proper drug concentration per dosage unit is to be achieved. Also, the use of purified water rather than tap water is needed to avoid the possibility of adding impurities that could adversely affect the stability of the resulting preparation. Generally, manufacturers provide the dry powder or granule mixture in a slightly oversized container to permit adequate shaking of the contents after the entire amount of purified water has been added. Pharmacists must realize that an oversized bottle is provided with each of these products, and they must carefully measure out the required amount of purified water.