Disperse systems

Disperse systems include many types of 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 disperse system.

Dispersed phase may be:

1. Solid materials that are insoluble in the dispersing phase like suspension.
2. Liquid that is neither soluble nor miscible with the liquid of dispersing phase like an emulsion.
3. Small air bubbles throughout a solution like an aerosol, dispersion 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 down to particles of colloidal dimension between 1 nm and 0.5 µm, so we have:

- Coarse dispersion: dispersion containing coarse particles 10 to 50 µm, they include suspensions and emulsions.
- Fine dispersion: dispersion containing smaller particles 0.5 to 10 µm.
- Colloidal dispersion: dispersion containing particles in colloidal range 1nm to 0.5 µm they include Magmas and gels.

Particles in coarse dispersion have greater tendency to separate from the dispersion medium than do particles of a fine dispersion, this because of their greater density than the dispersion medium so complete and uniform redistribution of the dispersed phase is essential to the accurate administration of uniform doses, this should be accomplished by moderate agitation of the container.
Suspensions

Preparations containing finely divided drug particles distributed uniformly throughout a vehicle (usually aqueous) in which the drug exhibits a minimum degree of solubility, it is a coarse dispersion.

They are available either in in ready to use form that is already distributed through a liquid vehicle with or without stabilizers and other additives or as dry powder intended for suspension in liquid vehicles.

Depending on nature of drugs we have:

- For oral suspension: dry powder mixtures for reconstitution at the time of dispensing e.g many antibiotics.
- Oral suspension: prepared suspensions not requiring reconstitution at the time of dispensing

Reasons for suspensions:

1. Chemically unstable drugs in solution can be stable when suspended.
2. Drugs that are insoluble in the delivery vehicle can be suspended effectively.
3. The disadvantage of disagreeable taste of certain drugs in solution can be overcome when the drug is administered as undissolved particles of an oral suspension.
4. To achieve controlled/sustained drug release.

Features desired in a pharmaceutical suspension:

1. Suspension should settle slowly and should be readily redispersed upon gentle shaking of the container.
2. The particle size of the dispersed phase should remain constant throughout long periods of undisturbed standing.
3. The suspension should pour readily and evenly from its container.
Classification of suspensions:

- Based on general classes
  1. Oral suspension e.g antacids, anthelmintic
  2. Externally applied suspension e.g Calamine lotion.
  3. Parenteral suspension e.g procaine penicillin G, Insulin zinc suspension.

- Based on proportion of solid particles
  1. Dilute suspension (2 to 10% w/v solid) e.g cortisone acetate, prednisolone acetate.
  2. Concentrated suspension (50% w/v solid) e.g zinc oxide suspension.

- Based on electrokinetic nature of solid particles
  1. Flocculated suspension.
  2. Deflocculated suspension.

- Based on size of solid particles
  1. Coarse suspension > 1 micron.
  2. Colloidal suspension < 1 micron.
  3. Nano suspension 10 nm

Theoretical consideration in the formulation of suspension:

- Particle size control.
- Wetting.
- Sedimentation.
- Electrokinetic

1. Particle size control:

Particle size of any suspension is critical and must be reduced within the range, in most good pharmaceutical suspensions the particle diameter is 1 to 50 µm.

Generally particle size reduction is accomplished by dry milling prior to incorporation of the dispersed phase into the dispersion medium, however, we 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 which resist breakup with shaking.
2. Wetting:
Hydrophilic materials (talc, ZnO, Mg₂Co₃) are easily wetted by water while hydrophobic materials (sulphur, charcoal) are not due to the layer of adsorbed air on the surface, thus particles even with higher density float on the surface of the liquid until the layer of air displaced completely.

The using of wetting agents allow removing the air from the surface and to easy penetration of the vehicle into the particles.

3. Sedimentation
It means settling of particles or floccules which occur under the effect of gravitational force in liquid dosage form.

*Sedimentation rate and Stokes solution:*
The various factors involved in the rate of settling of the particles of a suspension are described in the equation of Stokes law:

\[
\frac{dx}{dt} = \frac{d^2(\rho_1 - \rho_e)g}{18\eta}
\]

Where
\( dx/dt \) is the rate of settling.
\( d \) is the diameter of the particles.
\( p_1 \) is the density of the particle.
\( p_e \) is the density of the medium.
\( g \) is the gravitational constant, and
\( \eta \) is the viscosity of the medium.

The equation showed that the velocity of sedimentation is greater for larger particles than its for smaller particles, also the greater the density of the particles the greater rate of sedimentation.
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, this can be solved by increasing the viscosity of the dispersion medium; however, a product having too high viscosity is not generally desirable because it pours with difficulty and it is difficult to redisperse the dispersed phase.

**Sedimentation parameters:**

- Sedimentation volume (F) or height (H).
- Degree of flocculation ($\beta$).

*Sedimentation volume (F):* is the ratio of the ultimate volume of sediment ($V_u$) to the original volume of sediment ($V_o$) before settling.

$$F = \frac{V_u}{V_o}$$

Where

$V_u$ is the final or ultimate volume of sediment.

$V_o$ is the original volume of suspension before settling.

$F$ has values ranging from less than 1 to greater than 1.

When $F < 1 \quad V_u < V_o$

When $F = 1 \quad V_u = V_o$

The system is in flocculated equilibrium and show no clear supernatant on standing.

When $F > 1 \quad V_u > V_o$

Sediment volume is greater than the original volume, due to the network of floccules formed in suspension and so loose and fluffy sediment.
The sedimentation volume gives only a qualitative account of flocculation.

Degree of flocculation ($\beta$): it is the ratio of the sedimentation volume of the flocculated suspension $F_1$ to the sedimentation volume of the deflocculated suspension $F_\infty$.

$$\beta = \frac{F_1}{F_\infty}$$

$$\beta = \frac{\frac{V_u}{V_0} \text{ flocculated}}{\frac{V_u}{V_0} \text{ deflocculated}}$$

The minimum value of $\beta$ is 1, when flocculated suspension sedimentation volume is equal to the sedimentation volume of deflocculated suspension.

4. Electrokinetic properties:

Zeta potential is defined as the difference in potential between the surface of the tightly bound layer and the electroneutral region of the solution.
As potential drops off rapidly at first followed more gradual decrease in as the distance from the surface is increased, this is because the counter ions close to the surface acts as a screen that reduce the electrostatic attraction between the charged surface and those counter ions further away from the surface.

Zeta potential is important in stability of systems containing dispersed particles, if the Zeta potential reduced below a certain value the attractive forces exceed the repulsive forces and particles come together, this phenomenon known as flocculation.

Thus the phenomenon of flocculation and deflocculation depend on zeta potential of the particles.
**Flocculated suspension**

- In flocculated susp. (loose aggregate) will cause increase in sedimentation rate due to increase in size of sedimenting particles.
- Flocculated susp. Sediment more rapidly.
- Sedimentation depend not on the size of the particles but also on the porosity of floccules.

**Deflocculated suspension**

- Individual particles are settling.
- Rate of sedimentation is slow which prevent entrapping of liquid medium that makes it difficult to redispense by agitation, this phenomenon called caking or claying
- Larger particles settle faster and smaller one remain in supernatant so the supernatant appear cloudy.
**Formulation of suspension**

The formulation depend on whether susp. is flocculated or deflocculated.

Three approaches:
1. Use of structured vehicle.
2. Use of controlled flocculation.
3. Combination of both methods.

1. **Structured vehicle:** it also called thickening or suspending agents, they are aqueous solutions of natural and synthetic gums, these are used to increase the viscosity of suspension.

   It is only applicable to deflocculated suspension e.g methyl cellulose(MC), NaCMC, acacia, gelatin and tragacanth.

   Disadvantages:-cause difficulty in pouring and administration.
-may affect drug absorption since they may adsorb on particle surface and suppress dissolution.

-Not useful for parenteral susp. Because of problem in syringability due to high viscosity.

2. Controlled flocculation: it is obtained by adding flocculating agents which are:
   a. Electrolytes.
   b. Surfactants.
   c. Polymers.

3. Flocculation in structured vehicles: sometimes suspending agent can be added to flocculated susp. To retard sedimentation e.g CMC, carbopol 934, veegum and bentonite.

**Ingredients for formulation of suspension:**

1. Suspending agents

Also known as hydrophilic colloids which form colloidal dispersion with water and increase the viscosity of continuous phase.

Most suspending agents have two functions act as suspending agent and increase viscosity of solution.

Preferred suspending agents are those that give thixotropy to the media e.g xanthan gum, NaCMC/MC, Avicel and carrageenan.

2. Wetting agents

Used for hydrophobic substances include many types which are:

a. Surfactants: decrease the interfacial tension between drug particles and liquid thus, liquid is penetrated in the pores of drug particle displacing air from them and thus ensure wetting e.g polysorbate 80.

May be ionic or non ionic, non ionic is preferred because it does not change the pH, no toxicity, safe for internal use.

b. hydrophilic colloids: they coat hydrophobic drug particles so facilitate wetting, they produce deflocculated susp. Because force of attraction is declined e.g acacia, alginate, tragacanth and guar gum.

c. Solvents: most commonly used are alcohol, glycerin, poly ethyleneglycol and propyleneglycol. The mechanism involve that they are miscible with water and reduce liquid interfacial tension.
3. Buffers
All liquid formulations should be formulated to an optimum pH to encounter stability problems, generally pH of suspension between 7.4-8.4 e.g carbonate, phosphate, citrate and gluconate.

4. Osmotic agents
These are added to produce osmotic pressure comparable to biological fluids when susp. Is intended for ophthalmic or injectable purposes. e.g dextrose, sorbitol, mannitol, sodium chloride and sodium sulfate.

5. Preservatives
Naturally occurring agents such as acacia, xanthan gum are susceptible to microbial contamination so we use preservative e.g methylparaben, benzalkonium chloride, disodium EDTA, benzoic acid.

6. Flavoring and coloring agents
This to increase patient acceptance e.g titanium dioxide (white), brilliant blue (blue), tartarzine (yellow), amaranth (red).
Sweeting agent like sorbitol, mannitol, mannose.

7. Humectant
These absorb moisture and prevent degradation of API by moisture e.g glycerol, propylene glycol, total quantity should be 0-10%

9. Antioxidants
Ascorbic acid, tocopherol, sodium bisulfate, butylated hydroxyl toluene (BHT), butylated hydroxyl anisole (BHA).

**Preparation of suspension:**
We must know the characteristics of dispersed phase and dispersion medium (hydrophilic or hydrophobic).
1. Suspension are prepared by grinding or levigating the insoluble materials in the mortor to a smooth paste with a vehicle containing the wetting agent.

2. All soluble ingredients are dissolved in same portion of the vehicle and added to the smooth paste in step 1 to get slurry.

3. The slurry is transferred to graduated cylinder, the mortor is rinsed with successive portion of the vehicle.

4. Decide whether solids are:
   - Suspended in a structured vehicle
   - Flocculated
   - Flocculated and then suspended

Add the vehicle containing the suspending agent or flocculating agent

5. Make up the dispersion to the final volume.

**Packaging and storage of suspensions:**

All suspensions should be packaged in wide mouth container having adequate airspace above the liquid to permit thorough mixing by shaking and ease of pouring.

Should be stored in tight container protected from freezing, excessive heat and light.

Should be shaken before each use to ensure a uniform distribution of solid in the vehicle and thereby uniform and proper dosage.