Coarse Dispersions

Learning Outcomes

At the end of this chapter the students should be able to:

- Describe pharmaceutical suspensions and its roles in the pharmaceutical sciences.
- Discuss the desirable qualities of pharmaceutical suspensions.
- Discuss the factors that affect the stability of suspensions and explain flocculation, deflocculation.
- Define and calculate the two useful sedimentation parameters - sedimentation volume and degree of flocculation.
- Define pharmaceutical emulsion and emulsifying agent and identify the main types of emulsions.
- Explain the theories of Emulsification.
SUSPENSIONS

A suspension is a heterogeneous (biphasic) system consisting of a solid phase in a liquid phase.

The solid phase is subdivided into small particles and dispersed in the liquid medium in which the solid is insoluble or sparingly (or slightly) soluble.

Suspensions being coarse dispersions, the size of the greater number of particles may exceed 0.1µ.

A pharmaceutical suspension: defined as a coarse dispersion of finely subdivided insoluble solid drug suspended in a suitable liquid (usually aqueous) medium.

A suspension may be for internal, external or parenteral use.

Suspensions for oral administration is a better means of administration when swallowing is difficult.

Surface’ area is large and this is taken advantage of for drugs which are adsorptives or antacids. Example: kaolin, magnesium trisilicate etc.

Bitter drugs - administered in their insoluble form as a suspension to mask the taste.

For example insoluble Chloramphenicol palmitate is used in the form of suspension to reduce the bitter taste of the Chloramphenicol base.
Suspensions for external use are mainly lotions. This facilitates the drug application in the form of liquid which provides a fine coating of the drug to promote the action of the drug on the affected part of the skin.

It is not messy to use in the form of suspensions as in the case of ointments. 
*Eg*: Calamine lotion.

Parenteral suspensions are of particular importance in the field of depot therapy.

This is based on the slow release of the drug for extended action.

This is made possible due to the size of the particle whose solubility is low and takes more time providing for sustained action. *Eg*: Insulin zinc suspension.

---

**Desirable Properties of Suspensions**

1. The color & odor should be acceptable and pleasing for oral & external uses.

2. No rapid settling of suspended particles

3. If the particles do settle, they must not form a hard cake at the bottom of the container & should be easily re-dispersible into uniform mixture when shaken.

4. Suspension should be easily pourable.

5. Parenteral preparations: it should flow through the syringe needle.

6. External preparations: spread easily on the surface of the skin & must not be too fluid to run off the skin surface.
Interfacial Properties

Two factors must be taken into account, when the interfacial properties between the solid phase and the liquid are considered:

- **Surface free energy** increase resulting from increase in surface area of suspended particles due to reduction in size of particles
- **Presence of electrical charges** on the surface of the dispersed solid particles in a liquid medium.

The increase in surface free energy due to a reduction in size of the particles is given by the relation: $\Delta G = \gamma \Delta A$ \hspace{1cm} (1)

Where $\Delta G = \text{increase in surface free energy in ergs}$, $\Delta A = \text{increase in surface area in cm}^2$, $\gamma = \text{interfacial tension in dynes/cm}$.

Electrical Properties at the surface of the dispersed particles

Both attraction and repulsion forces exist between particles dispersed in a liquid medium.

The particle-particle interaction (due to attraction and repulsion) may be given as follows.

The various electrostatic contributions: They may be ion-ion, ion- dipole, dipole-dipole and dipole-induced dipole. They have both attractive (between dissimilar charges) and repulsive forces (between similar charges)

The London dispersion forces (between atoms of one particle with those of the other. It is induced dipole-induced dipole interaction (attraction)

The covalent bonds (attractive)

Born repulsion forces (repulsive). It is due to overlapping of electron clouds of the atoms present in a molecule or ion
The region in which the influence of the surface charge (i.e. potential) of the particle is appreciable is termed the electric double layer region. The electric double layer is considered to comprise:

- **The Stern layer** consisting of counter ions: The thickness is of the ionic dimension. The potential drop across the stern layer from the surface of the particle is sharp.

- **The diffuse double layer**: The potential drop across this layer is somewhat gradual and it drops to zero at the end of its surface where it meets electro-neutral region.

**Flocculation and Deflocculation in suspensions**

The overall (or resultant) charge existing on the suspended particle is called as zeta potential and it is a measurable indication of the charge.

Therefore, flocculation and deflocculation may be considered in terms of zeta potential.

When the zeta potential is high, the particles remain dispersed and are said to be deflocculated.

These particles resist collision due to the high zeta potential even if the particles are brought close by way of random motion or agitation.
The zeta potential can be progressively lowered by the addition of an electrolyte (whose ion which is oppositely charged to that of the suspended particles is preferentially adsorbed).

At some concentration of the electrolyte, the forces of attraction dominate over the electrical forces of repulsion slightly.

Under these conditions (i.e. when the zeta potential is sufficiently lowered), the particles when they approach each other, form loose aggregates commonly called flocs.

Then such a suspension is said to be flocculated.*

---

**Flocculated & Deflocculated Suspensions**

<table>
<thead>
<tr>
<th>Period of Standing</th>
<th>Flocculated</th>
<th>Deflocculated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short period (min.)</td>
<td><img src="image1.png" alt="Diagram" /></td>
<td><img src="image2.png" alt="Diagram" /></td>
</tr>
<tr>
<td>Medium period (hrs or day)</td>
<td><img src="image3.png" alt="Diagram" /></td>
<td><img src="image4.png" alt="Diagram" /></td>
</tr>
<tr>
<td>Long period (weeks or years)</td>
<td><img src="image5.png" alt="Diagram" /></td>
<td><img src="image6.png" alt="Diagram" /></td>
</tr>
</tbody>
</table>
Flocculated Suspension | Deflocculated Suspension
--- | ---
Particles form light fluffy conglomerates called flocs. | The particles in the suspension remain individually.
Since the flocs are groups of particles, rate of sedimentation is fast. | Since the particles are small and remain separately, the rate of sedimentation is slow.
Formation of sediment is quick. | Formation of sediment at the bottom of the container takes a long time.
The sediment is loosely packed and presents a scaffold like structure with entrapped liquid. The sediment does not form a dense hard cake. | The sediment formed becomes eventually a hard cake.
Sediment volume is high. | Sediment volume is small.
The supernatant liquid becomes clear at a shorter time since small particles are entrapped within the flocs and settle along with flocs rapidly. | The supernatant liquid remains cloudy for a longer time as very small particles approaching colloidal dimensions) take very long time to settle.
Redistribution of the sedimanted particles by shaking the container is easy. | Redistribution of the sedimanted particles by shaking the container is difficult.
The suspension has a pleasing appearance.

Settling & its control

The sedimentation velocity of particles in a suspension is related to
1. size of the particles
2. density of the particles
3. viscosity of the dispersion medium.

The effect of these factors can be given by Stoke's law

\[ v = \frac{d^2(\rho_s - \rho_l)g}{18\eta_l} \]

where
- \( v \) = average velocity of sedimentation of particles (cm/sec)
- \( d \) = diameter of the particle in cm.
- \( \rho_s \) and \( \rho_l \) = densities of the dispersed phase (solid) and the dispersion medium (liquid) respectively
- \( g \) = acceleration due to gravity
- \( \eta_l \) = viscosity of the dispersion medium.
Stoke's law is applicable to dilute suspensions containing spherical particles and the settling of particles should be slow with less turbulence i.e. the settling should be streamline.

Pharmaceutical suspensions being concentrated, there is disturbance for the settling of particles and hence Stoke's law cannot be effectively applied.

However, these factors may be expected to influence the rate of settling.

According to Stoke's law, settling rate for the particles may be reduced by decreasing the particle size provided the particles are deflocculated.

The rate of sedimentation may be delayed by increasing the viscosity of the medium (by adding suitable suspending agents) as it is inversely related to the viscosity of the dispersion medium.

This approach to reduce the rate of sedimentation is frequently used. However there is an optimum level for this approach as too much increase in viscosity may hinder the flow of the suspension out of the container.

That is, pourability is affected and the viscosity increase may also make the redistribution of the particles uniformly throughout the dispersion medium difficult.

The other approach that may be applied is to narrow down the density difference between the dispersed particles and the dispersion medium.

This is seldom possible as the density of solid particles is always greater than the liquid.
Brownian movement

When the size of the dispersed particles approach that of colloidal dimensions, Brownian motion sets in. Such a Brownian motion may be observed if the size of the particle is reduced approximately to 2\(\mu\).

However the Brownian movement depends on the density of the particles and the density and viscosity of the dispersion medium.

Considering the size of the particles normally found in most of the pharmaceutical suspensions it is unlikely that the particles will undergo Brownian movement.

Effect of flocculation on sedimentation rate

In a deflocculated suspension, the larger particles settle relatively at a faster rate than the smaller particles.

As a result, a clear boundary is not easily discernible and the supernatant liquid remains cloudy for a considerable period of time.

In the case of flocculated suspension, groups of particles are aggregated into flocs and the flocs tend to fall together while settling and there is a clear boundary formed between the sediment and the supernatant liquid.

Settling in a flocculated suspension depends on size and porosity of the flocs. However, the rate of settling in a flocculated suspension is faster.
Sedimentation volume & degree of sedimentation

Useful: In assess a formulation of suspension in terms of amount of flocculation

The **sedimentation volume**, \( F \), is defined as the ratio of the final, or ultimate, volume of the sediment, \( V_u \), to the original volume of the suspension, \( V_o \), before settling.

The **degree of flocculation** is a more fundamental parameter than \( F \) because it relates the volume of flocculated sediment to that in a deflocculated system.

\[
\beta = \frac{\text{ultimate sediment volume of flocculated suspension}}{\text{ultimate sediment volume of deflocculated suspension}}
\]

Compute the sedimentation volume of a 5% w/v suspension of magnesium carbonate in water.

The initial volume is \( V_o = 100 \text{ mL} \) and the final volume of the sediment is \( V_u = 30 \text{ mL} \). If the degree of flocculation is \( \beta = F/F_\infty = 1.3 \), what is the deflocculated sedimentation volume, \( F_\infty \)?

\[
\begin{align*}
\bullet \ F &= \frac{30}{100} = 0.30 \\
\bullet \ F_\infty &= \frac{F}{\beta} = \frac{0.30}{1.3} = 0.23
\end{align*}
\]
Surfactants
• Flocculation brought by using both ionic and non-ionic surfactants.

Polymers
• Polymers act as flocculating agents by forming a ‘bridge’ between particles.
• The sedimentation volume is higher in a suspension in which polymers have been used to bring about flocculation.
• e.g. Xanthumgum

Pharmaceutical applications of suspensions

For oral use

• A suspension provides convenient means of administering an insoluble drug as compared to tablets or capsules as far as swallowing is concerned.
• For adsorptive or antacid properties, usually suspensions are fast acting because of more surface area. e.g. Kaolin, magnesium carbonate, calcium carbonate and magnesium trisilicate.
• Insoluble derivatives of drugs are often used to reduce the unpleasant taste. e.g. Chloramphenicol palmitate.
• Insoluble drugs which are susceptible to hydrolysis are dispensed as dry syrups and are reconstituted with water at the time of use. e.g. Ampicillin dry syrup.
For external use

- Number of lotions are of suspension type (e.g. calamine lotion for protective action on the skin).
- Semisolid suspensions are pastes (e.g. Magnesium sulfate paste, Zinc and salicylic acid paste, Tooth paste etc). The performance and acceptability of these preparations depend upon the sedimentation and rheological properties.

For injections

- Insoluble drugs which are susceptible to hydrolysis are dispersed as sterile powders in vials.
- At the time of their use, they are reconstituted with sterile water for injection. e.g. Penicillin injection.
- Suspension injections provide for sustained action. e.g. Streptomycin oily injections.

EMULSIONS

An emulsion is a dispersion of a liquid as globules in another liquid, both the liquids being immiscible with each other.

- Example: dispersion of oil in water or dispersion of water in oil.
The diameters of the globules usually vary from 0.1 to 10 µm, although globule diameters as small as 0.01 µm and as large as 100 µm are possible in some emulsions.

Emulsions having globules of mean diameter about 5 µm are called fine emulsions and emulsions with large globules are referred to as coarse emulsions.

The emulsion is thermodynamically unstable since the globules coalesce and the phases will ultimately separate. To stabilize an emulsion, a third substance called emulgent or emulsifier or emulsifying agent is invariably added to the emulsion.

The emulsion may be a dilute dispersion, a concentrated dispersion or semisolid. The liquid emulsions are opaque, milky white, and viscous. The semisolid emulsions are called creams.

Types of emulsion

- Oil-in-Water-type emulsion
- Water-in-oil type emulsion
- Multiple emulsion or complex emulsions
- Micro emulsions
- Complex emulsions
Multiple emulsion of the type w/o/w stabilized by Silica Nanoparticles

Applications of Emulsions

Medicinal agents which have objectionable taste and odour (for example, shark liver oil, castor oil, olive oil etc) may be formulated into o/w emulsions to mask the taste and to make palatable.

Oil soluble vitamins (A, D, E and K) are absorbed more completely when they are made into fine emulsions than when they are administered as oily solutions.

O/w type emulsions are used as a dosage form for intravenous administration of oils and fats with high calorific value to patients who can not ingest food by other means and the globules in this emulsion should be similar to the size of chylomicrons (nearly colloidal size).

• The choices of emulsifying agent for intravenous emulsions are restricted to gelatin, lecithins and some non-ionic surfactants. Only edible oils are used as oily phase.

Radio-opaque emulsions are being used as diagnostic agents in X-ray examination.
Emulsions of both the types (o/w and w/o) are extensively used to prepare pharmaceutical preparation for external use and as cosmetic preparations. Such a product should be easily spreadable, water washable non-staining and more acceptable to the patients. E.g., Cold cream and vanishing cream.

Emulsification is used in aerosol products to produce foams. The propellant that forms the dispersed liquid phase within the container vaporizes when the emulsion is discharged from the container.

Emulsions afford protection to drugs susceptible to oxidation or hydrolysis.

Liquid paraffin is used as purgative when taken orally and is not absorbed. It should not be made into fine emulsion since fine globules may be absorbed.

Some enemas are made as emulsions either for local action (E.g., soap enemas) or to influence drug action.

Solid drugs which show poor solubility may be dissolved in the oil and emulsified. From this emulsion, the bio-availability is more (as compared to tablet or suspension. E.g., non-steroidal antifungal agents).
Theories of Emulsification

**Viscosity theory**

- As per this theory, an increase in viscosity of an emulsion will lead to an increase in stability. This theory failed to explain about the milk which shows considerable stability even though its viscosity is less.

**Film theory or Adsorption theory**

- As per this theory, the added emulsifying agent forms a mechanical film by getting adsorbed at the interface of the liquids (i.e. at the interface between the dispersed globules and the dispersion medium) and offers stability to the emulsion. However, this theory could not explain the formation of type of emulsion.

**Wedge theory**

- According to this theory, monovalent soaps like sodium stearate give o/w type emulsion and divalent soaps like calcium stearate give w/o type emulsion.
- This was explained by the successful accommodation of the, soaps at the interface and subsequent possible orientation of the soap molecules to give the type of emulsion.
- For example, sodium stearate may be represented as follows:
  - C\textsubscript{17}H\textsubscript{35}COONa or \begin{figure}[h] \centering \includegraphics[width=0.5\textwidth]{sodium_stearate.png} \end{figure} and its accommodation is possible only in o/w type emulsion.
- In the case of divalent soap, calcium stearate, the representation may be presented as follows: \begin{figure}[h] \centering \includegraphics[width=0.5\textwidth]{calcium_stearate.png} \end{figure} Its accommodation is possible in w/o type emulsion. This theory could not explain the stability of an emulsion. Another defect in this theory is that calcium stearate will ionize and will not exist as a wedge.
Interfacial tension theory

• In accordance with this theory, the added emulsifying agent reduces the interfacial tension between the oil and water phases and thus a stable emulsion is formed. This theory could not explain the formation of type of emulsion.

Thus there is no universal theory of emulsification. Any theory, to be meaningful, should be capable of explaining

• (a) type of emulsion formed
• (b) stability of emulsion

Emulsifying agents

<table>
<thead>
<tr>
<th>Type</th>
<th>Type of film</th>
<th>Examples</th>
</tr>
</thead>
</table>
| Synthetic surfactants | Monomolecular | 1. Anionic  
Soaps: Potassium laureate and triethanolamine stearate. 
Sulphates: Sodium lauryl sulphate and alkyl poly oxyethylene sulphate  
Sulphonates: Dioctyle sodium sulphosuccinate  
2. Cationic: Quaternary ammonium compounds Cetyltrimethyl ammonium bromide  
3. Nonionic  
polyoxyethylene dathy alcohol ethers  
sorbitan fatty esters  
poly oxyethylene sorbitan fatty acid esters. |
| Natural            | Multimolecular | Hydrophilic colloids: Acacia, gelatin  
Cholesterol, Lecithin |
|                   | Monomolecular | Colloidal clays: Bentonite veegum |
| Finely divided solids | Solid particle (particulate layer) | Metallic hydroxides: magnesium hydroxide. |
Stability of Emulsions

Stability of emulsions is characterized by

- absence of coalescence of internal phase
- absence of creaming
- maintenance of elegance with respect to color, odour and other physical properties.
Instabilities of the Emulsions

Flocculation & Creaming  Coalescence & Breaking  Phase Inversion

Preparation of Emulsions

Small scale method: Mortar and pestle method

- It is used for emulsions which are stabilized by a multimolecular film at the interface.
- Consequently the emulgents used are acacia, tragacanth, agar, cellulose derivatives, etc.
- There are two basic methods (wet gum method and dry gum method) for the preparation of such emulsions.
- The emulsions produced show polydisperse globules with wide range of sizes.
**Wet Gum Method**

In this the emulgent is placed in the mortar and dispersed in water to form mucilage.

The oil is added in small amounts with continuous trituration, each portion of the oil is emulsified before adding the next increment.

The optimum ratio of fixed oil; water and acacia is 4:2:1 to prepare initial emulsion called primary emulsion.

The ratio of volatile oil, water and gum is 3:2:1. The ratio varies with emulgents.

The primary emulsion should be triturated at least for five minutes. Then sufficient water is added to produce the final volume.

**Dry Gum Method**

In this, the gum is added to the oil and dispersed in a mortar and pestle.

The water is added in little quantities at a time with trituration to produce the primary emulsion.

Preparations of emulsions by wet gum method and dry gum method may be carried out by shaking or agitation in bottles rather than in a mortar and pestle.
Thank You