

Suspensions

Muhammad Adeel
Pharm-D
G.C University Faisalabad

Introduction

Definition:

A Pharmaceutical suspension is a heterogeneous system consisting of two phases in which internal phase is dispersed uniformly throughout the external phase.

- The internal phase consists of particulate matter that is essentially insoluble but dispersed uniformly throughout the continuous phase with aid of single or combination of suspending agent.
- The external phase (suspending medium) is generally aqueous in some instance, may be an organic or oily liquid for non-oral use.

Introduction

Classification:

Suspensions can be classified as:

1-Based on physical state:

- Suspension
- Aerosols
- Foams

2-Based on Proportion of Solid Particles:

- Dilute suspension (2 to 10% w/v solid). **For example** cortisone acetate, prednisolone acetate
- Concentrated suspension (50% w/v solid). **For example** zinc oxide suspension

3-Based on behavior of Dispersed Phase:

- Flocculated Suspension (Dispersed phase maybe a network of particle)
- Deflocculated Suspension (Dispersed phase may consist of discrete particles)

Introduction

4-Based on Size of Dispersed Particles:

- Molecular Dispersion (Particle size is less than 1 nm)
- Colloidal Dispersion (Particle size between 0.1-0.2 μm)
- Coarse Dispersion (Particle size is greater than 0.2 μm)

5-General classification of Suspension:

- Oral suspension (**Example** is Paracetamol suspension)
- Topical suspension (Dispersed phase is in high concentration often exceeds 20% w/v. **Example** is Calamine Lotion)
- Parenteral suspension (Solid Contents is between 0.5-5% w/v. Example includes Procaine penicillin G suspension.

Reference: Lachman/Lieberman's The theory and practice of industrial pharmacy 4th edition page no. 655

Properties of a Suspension

- A well formulated suspension should have:
- Easy and rapid redispersion of sedimented particles for uniformity of dose.
- No cake formation on sedimentation.
- Optimum viscosity for pouring.
- Physical and chemical stability.
- Free from gritting particles (in case of external use)

Advantages And Disadvantages:

Advantages:

- Suspension can improve chemical stability of certain drug. For example Procaine penicillin G.
- Drug in suspension exhibits higher rate of bioavailability than other dosage forms.

Solution > Suspension > Capsule > Compressed Tablet > Coated tablet

- Duration and onset of action can be controlled. For example Protamine Zinc-Insulin suspension.
- Suspension can mask the unpleasant/bitter taste of drug. For example Chloramphenicol

Disadvantages:

- Physical stability, sedimentation and compaction can causes problems.
- It is bulky. Sufficient care must be taken during handling and transport.
- It is difficult to formulate.
- Uniform and accurate dose may not be achieved.

Methods For Formulation of Suspension

1-Precipitation method:

Three precipitation methods are used:

➤ Organic solvent precipitation:

- Water insoluble drugs can be precipitated by dissolving them in water-miscible organic solvent and then adding organic phase to distilled water under standard conditions.
- Organic solvents used are ethanol, methanol, propylene glycol and polyethylene glycol.

➤ Precipitation by pH:

- The method of changing the pH of medium is more readily accomplished and does not present the same difficulties associated with organic solvent precipitation.
- This method is applicable only to those drugs in which solubility is dependent on pH value.
- **Examples** include Estradiol Suspension and Insulin Suspension.

➤ Double Decomposition:

- This method involves simple chemistry.
- Example includes White Lotion (NF XIII).

Methods For Formulation of Suspension

2-Dispersion Method:

- In this method, the vehicle must be formulated so that solid phase is easily wetted and dispersed.
- The use of surfactant is desirable to ensure uniform wetting of hydrophobic solid.
- The use of suspending agent such as synthetic polymer, natural gums and others maybe indicated depending upon specific application.
- The actual dispersing of solids may or may not cause particle size reduction. If particle size reduction occurs, the particles obtained may have different solubilities and this may lead to super saturation of the system.

3-Use of controlled flocculation:

- Controlled flocculation of particles is obtained by adding flocculating agents, which are:
 - Electrolytes
 - Surfactants
 - Polymers

Methods For Formulation of Suspension

4-Use of structured vehicle:

- Structured vehicles called also thickening or suspending agents.
- They are aqueous solutions of natural and synthetic gums.
- These are used to increase the viscosity of the suspension.
- These structured vehicles entrapped the particle and reduces the sedimentation of particles.
- Thus, the use of deflocculated particles in a structure vehicle may form solid hard cake upon long storage.
- Too high viscosity is not desirable as:
 - It causes difficulty in pouring and administration.
 - It may affect drug absorption since they adsorb on the surface of particle and suppress the dissolution rate.
 - Structured vehicle is not useful for parenteral suspension because they may create problem in syringeability due to high viscosity.

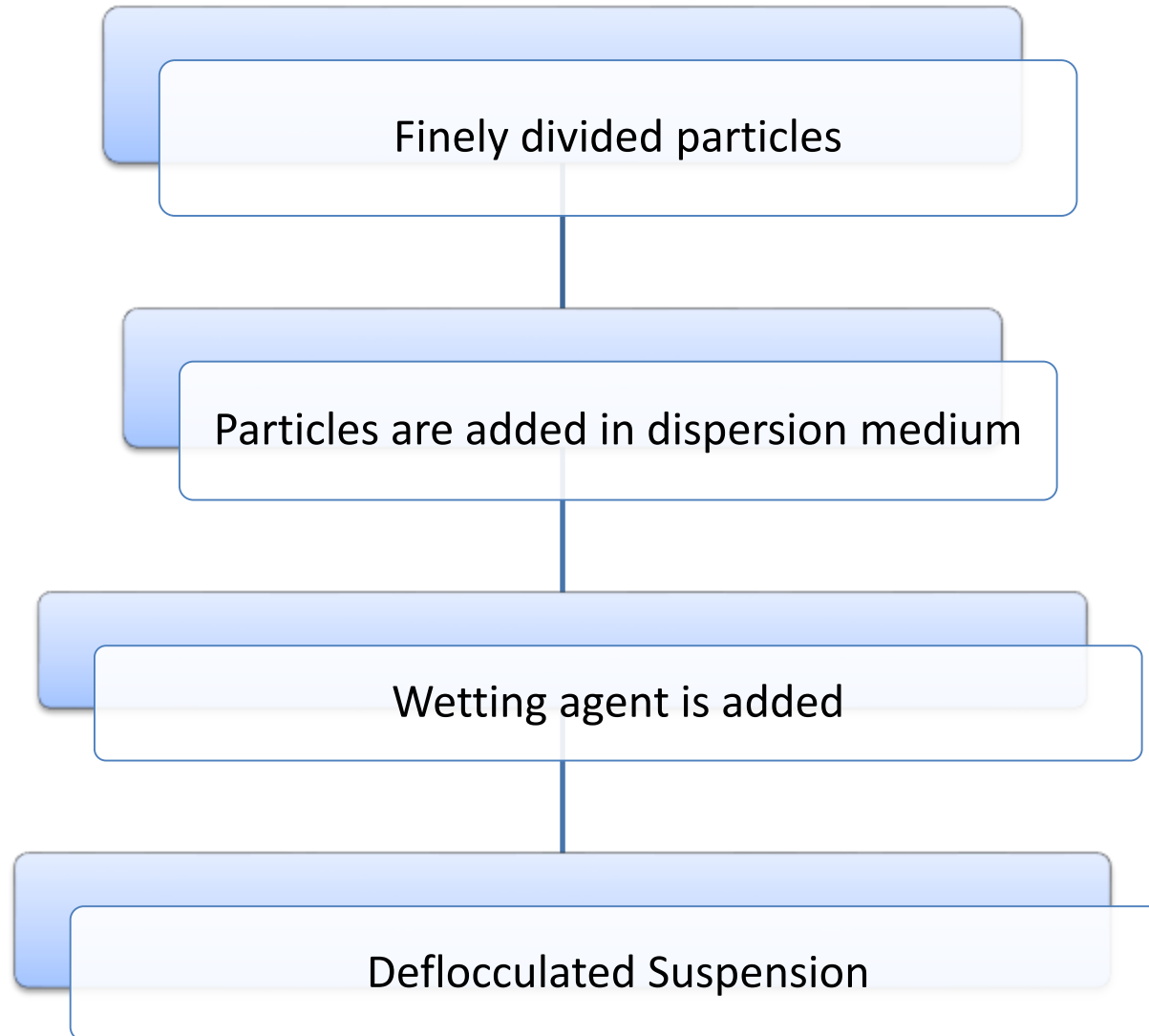
Reference: Lachman/Lieberman's The theory and practice of industrial pharmacy 4th edition page no. 655

Formulation of Suspension

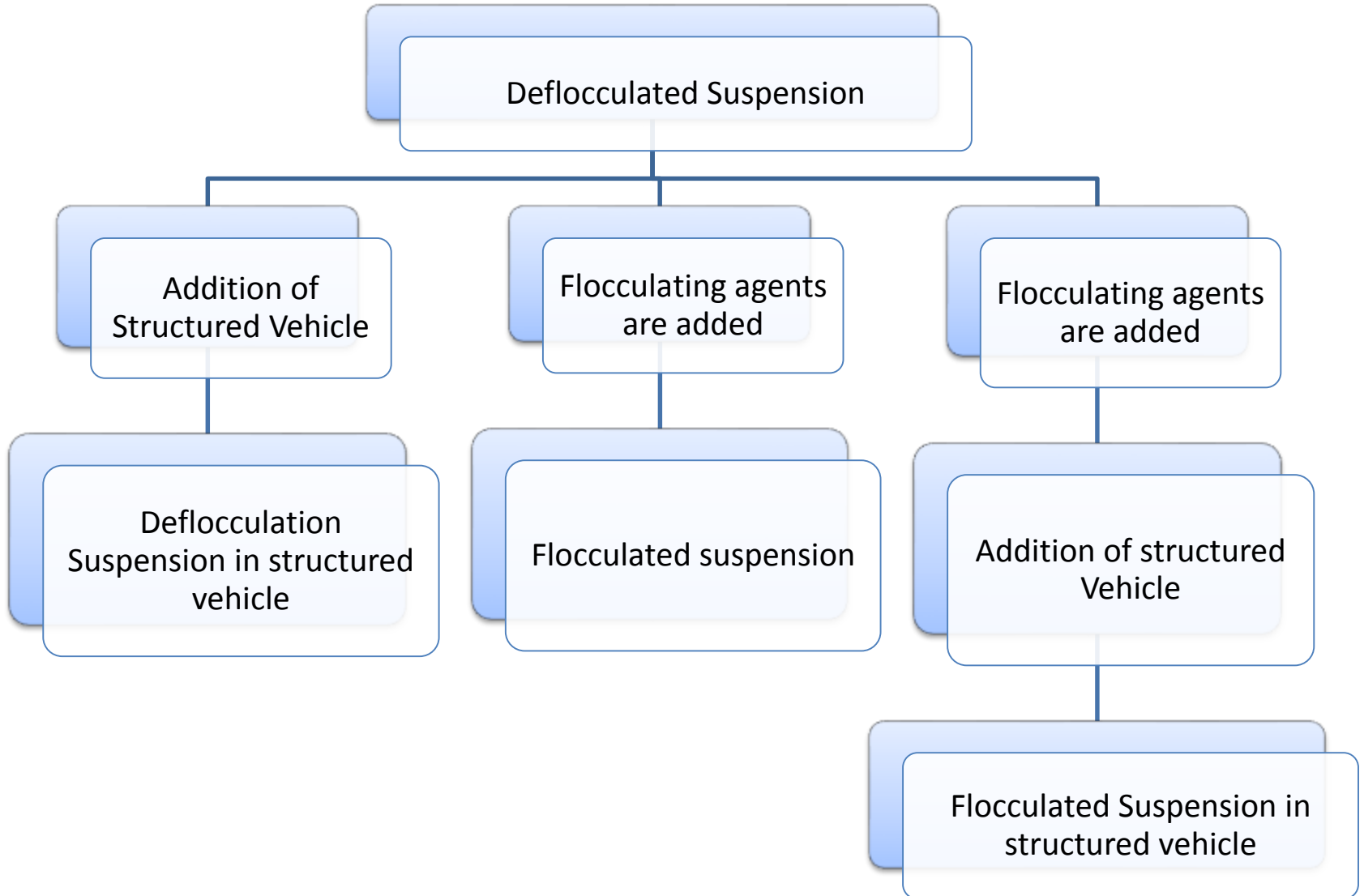
General Procedure

- First the particle size is reduced to a desired size with the help of mill or other equipments.
- The insoluble materials are levigated or grinded to a smooth paste with a vehicle containing the wetting agent.
- All soluble ingredients are dissolved in same portion of the vehicle and added to the smooth paste to get slurry.
- If preparing on small scale, the slurry is then transferred to a graduated cylinder and mortar is rinsed with successive portion of vehicle.
- If preparing on industrial scale, then slurry is transferred to a colloid mill or a disperser or any other equipment to completely wet the particles.
- Then a deflocculated suspension is obtained.
- Decide whether the solids are:
 - Suspended in a structured vehicle
 - Flocculated
 - Flocculated and then suspended
- Add the vehicle containing the suspending agent or flocculating agent.
- Make up the dispersion to the final volume.
- Thus suspension is prepared.

Flow Chart for formulation of Suspension



Flow Chart for formulation of Suspension



Formulation Components

1-Suspending agents:

- Suspending agent are also known as hydrophilic colloids which form colloidal dispersion.
- Suspending agent form film around particle and decrease interparticle attraction.
- Most suspending agents perform two functions i.e. besides acting as a suspending agent they also imparts viscosity to the solution.
- Sodium alginate, Methylcellulose (1-2%), Hydroxyethyl cellulose (1-2%), Hydroxypropyl cellulose(1-2%) Hydroxypropyl methylcellulose (1-2%)

2-Wetting Agents:

- Hydrophilic materials are easily wetted by water while hydrophobic materials are not.
- However hydrophobic materials are easily wetted by non-polar liquids.
- The extent of wetting by water is dependent on the hydrophilicity of the materials.
- The concentration used is less than 0.5 %.

Formulation Components

3-Surfactants:

- 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 ensures wetting.
- Generally, we use non-ionic surfactants but ionic surfactants can also be used depending upon certain conditions.
- **Polysorbate 80** is most widely used due to its following advantages:
 - It is non-ionic so no change in pH of medium.
 - No toxicity. Safe for internal use.

4-Hydrophilic colloids:

- Hydrophilic colloids coat hydrophobic drug particles in one or more than one layer.
- This will provide hydrophilicity to drug particles and facilitate wetting
- E.g. acacia, tragacanth, alginates, guar gum.

5-Solvents:

- The most commonly used solvents used are alcohol, glycerin, polyethylene glycol and polypropylene glycol.
- The mechanism by which they provide wetting is that they are miscible with water and reduce liquid air interfacial tension.
- Liquid penetrates in individual particle and facilitates wetting.

Formulation Components

6-Buffers:

- Buffers are the materials which when dissolved in a solvent will resist any change in pH when an acid or base is added.
- To encounter stability problems all liquid formulation should be formulated to an optimum pH.
- Generally pH of suspension preferably at 7.4-8.4.
- Most commonly used buffers are salts of weak acids such as carbonates, citrates, gluconates, phosphate

Formulation Components

7-Preservatives:

- Naturally occurring suspending agents such as tragacanth, acacia, xanthan gum are susceptible to microbial contamination.
- This leads to loss in suspending activity of suspending agents, loss of color, flavor and odor, change in elegance etc.
- Propylene glycol, Disodium EDTA (0.1%), Benzalkonium chloride (0.01-0.02%)
Benzoic acid (0.1%)

8- Flavoring and Coloring Agents:

- They are added to increase patient acceptance.
- Only sweetening agent are not capable of complete taste masking of unpleasant drugs therefore, a flavoring agents are incorporated.
- Examples include Acacia, Ginger, Sarsaparilla syrup, Anise oil, Glucose, Spearmint oil.

9-Coloring agents:

- Colors are obtained from natural or synthetic sources.
- The synthetic dyes should be used within range of(0.0005 % to 0.001%)
- Color aids in identification of the product.
- The color used should be acceptable by the particular country.
- Most widely used colors are as follows.
- Titanium dioxide (white), Brilliant blue (blue), Indigo carmine(blue), Amaranth (red), Tartarazine (yellow), Annatto seeds(yellow to orange)

Formulation Component

11- Sweetening Agents:

- They are used for taste masking of bitter drug particles.
- Sugars such as xylose, ribose, glucose, mannose.

12-Humectants:

- Humectants absorb moisture and prevent degradation of API by moisture.
- Examples of humectants most commonly used in suspensions are propylene glycol ,glycerol.
- Total quantity of humectants should be between 0-10 % w/w.

13-Antioxidants:

- Ascorbic acid derivatives such as ascorbic acid, erythorbic acid,
- Thiol derivatives such as thio glycerol, cytosine, acetyl cysteine,
- Tocopherols

Reference: Lachman/Lieberman's The theory and practice of industrial pharmacy 4th edition page no. 665, 666, 667.

Equipment for Suspensions

1-Mortar and pestle

- It consists of a glass or porcelain mortar and a pestle.

Advantages:

- (i) Small quantity suspensions can be prepared in the laboratory.
- (ii) Low cost
- (iii) Simplest operation among all other instruments.

Disadvantages:

- (i) Generally, the final particle size is considerable larger than in other equipment.
- (ii) It is necessary for the ingredients to have a certain viscosity prior to trituration in order to achieve a satisfactory shear.



Equipment for Suspensions

2. Agitators / Mechanical stirrers

- A suspension may be prepared by means of various impellers (propellers: produce axial movements; turbines produce radial and tangential movements) mounted on shafts.
- For low viscosity suspensions propeller type can be used but for higher viscosity turbine type is used.
- The degree of agitation is controlled by the rotational speed of impeller, by the patterns of the liquid flow and the resultant efficiency of mixing are controlled by the type of impeller, its position in the container, the presence of baffles, and the general shape of the container.

Advantages: Can be used for small-scale production and laboratory purpose.

Disadvantages: Continuous shaking tends to break up not only the phase to be dispersed but also the dispersion medium, in this way, impairs the ease of suspension.

Remedy: Slow the speed of agitator. Avoid continuous running.

**Propeller
agitator**



**Spiral Ribbon
agitator**



Turbine Agitator



Anchor agitator



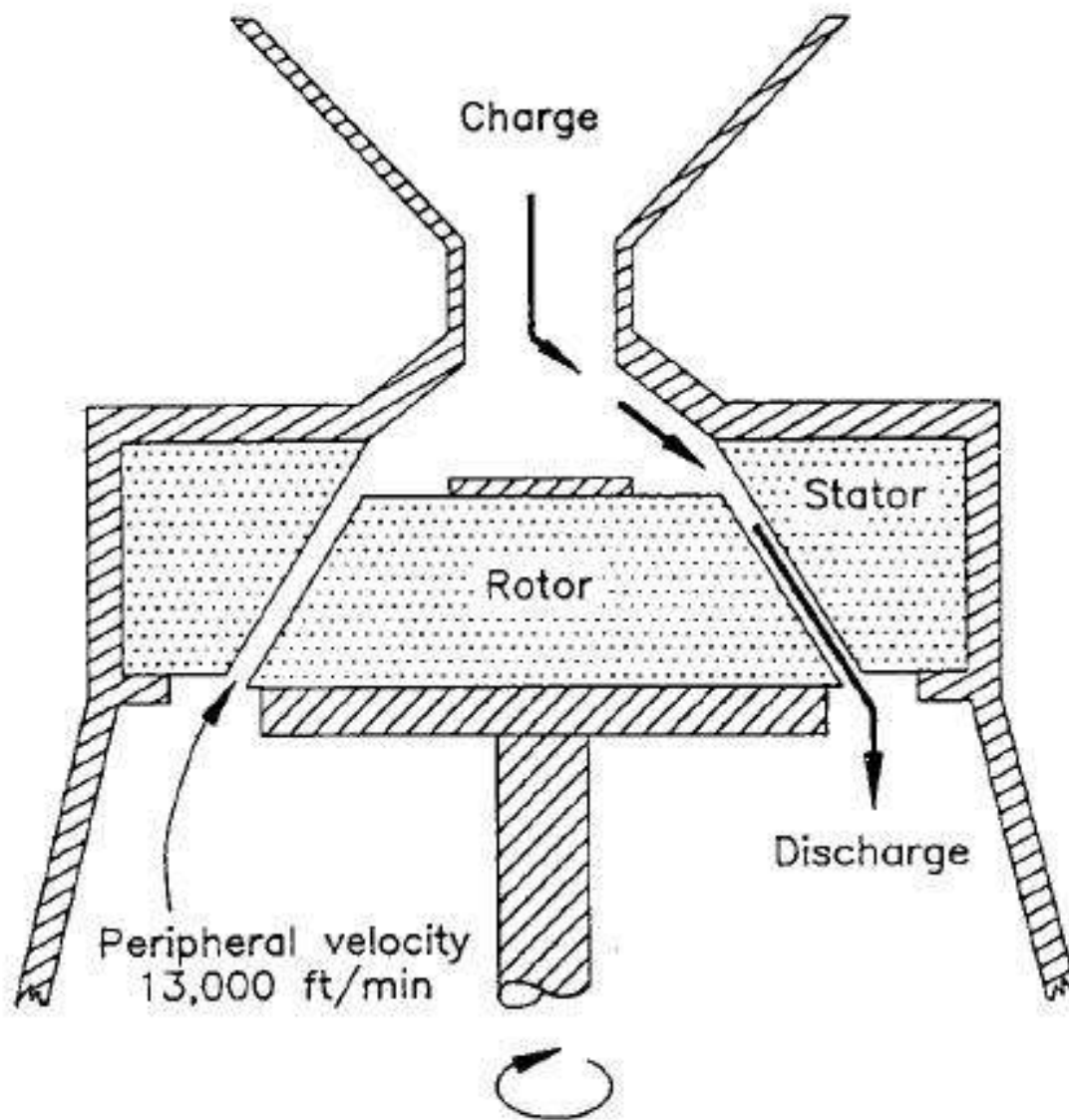
Equipment for Suspension

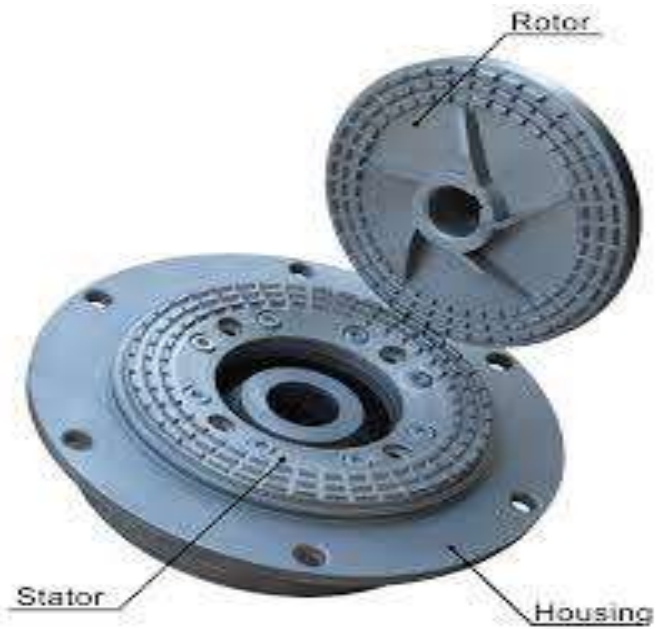


Equipments for suspension

3. Colloid mill

- The principle of operation of the colloid mill is the passage of the mixed phases of a suspension between a stator and a high speed rotor revolving at speeds of 2000 to 18,000 rpm.
- The clearance between the rotor and the stator is adjustable, usually from 0.001 inch upward. The suspension mixture, while passing between the rotor and the stator, is subjected to a tremendous shearing action which effects a fine dispersion of uniform size.
- The shearing forces applied in the colloid mill usually raises the temperature within the suspension. Hence, a coolant is used to absorb the excess heat.





Colloid Mill

Equipments for suspension

Advantage

- (i) Very high shearing force can be generated.
- (ii) Very fine particles can be prepared.
- (iii) Particularly useful in preparing suspensions containing poorly wetted solids.
- (iv) Useful for the preparation of relatively viscous emulsions.

Disadvantages:

- It has no wide applications in solids
- Wear of the rotating plates
- No fine grinding
- Consume energy

4. Homogenizers

- Impeller type of equipment frequently produce a satisfactory emulsion; however, for further reduction in particle size, homogenizers may be employed.
- Homogenizers may be used in one of two ways:
 - i) The ingredients in the suspension are mixed and then passed through the homogenizer to produce the final product.
 - (ii) A coarse suspension is prepared in some other way and then passed through a homogenizer for the purpose of decreasing the particle size and obtaining a greater degree of uniformity and stability.

Equipments for suspension

- The coarse suspension (basic product) enters the valve seat at high pressure (1000 to 5000 psi), flows through the region between the valve and the seat at high velocity with a rapid pressure drop, causing cavitation; subsequently the mixture hits the impact ring causing further disruption and then is discharged as a homogenized product. It is postulated that circulation and turbulence are responsible mainly for the homogenization that takes place.
- Sometimes a single homogenization may produce an emulsion which, although its particle size is small, has a tendency to clump or form clusters. Emulsions of this type exhibit increased creaming tendencies. This is corrected by passing the emulsion through the first stage of homogenization at a high pressure (e.g. 3000 to 5000 psi) and then through the second stage at a greatly reduced pressure (e.g. 1000 psi). This breaks down any clusters formed in the first step (it is a two stage homogenizer).

Equipment for suspension

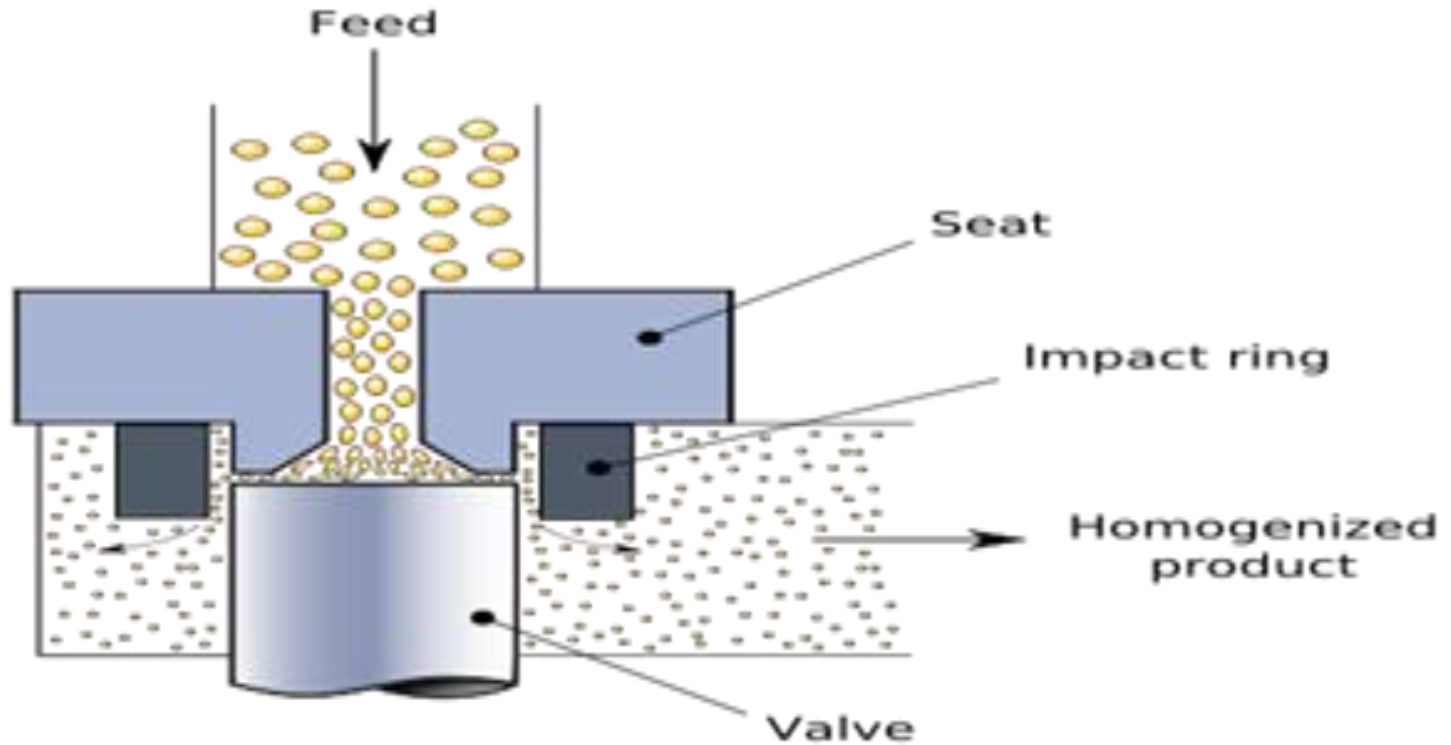


Equipment for suspension

Piston homogenizers:

- It is the most powerful device for producing emulsions and suspensions
- It uses high power positive displacement piston type pump to produce pressure of 3000-10,000 psig and then force the premixed product through a specially designed restricting wall where a extremely high shear forces are exerted
- Here turbulence and high shear are the major parameters in size reduction
- It having continuous Capabilities of 2500L/hr at 15hp to 50,000L/hr at 150hp.
- **Limitations:**
- They cannot handle the product feed above 200cps
- High maintenance cost and down time.

Equipment for suspension



Piston Homogenizer

Equipment for suspension

- **5. Ultrasonic devices**

- The preparation of emulsions by the use of ultrasonic vibrations also is possible. An oscillator of high frequency (100 to 500 kHz) is connected to two electrodes between which placed a piezoelectric quartz plate. The quartz plate and electrodes are immersed in an oil bath and, when the oscillator is operating, high-frequency waves flow through the fluid. Emulsification is accomplished by simply immersing a tube containing the emulsion ingredients into this oil bath.

- **Advantages**

- Can be used for low viscosity and extremely low particle size.

- **Disadvantages**

- Only in laboratory scale it is possible. Large scale production is not possible

Equipment for suspension



Equipment for suspension

Size Reduction Equipments:

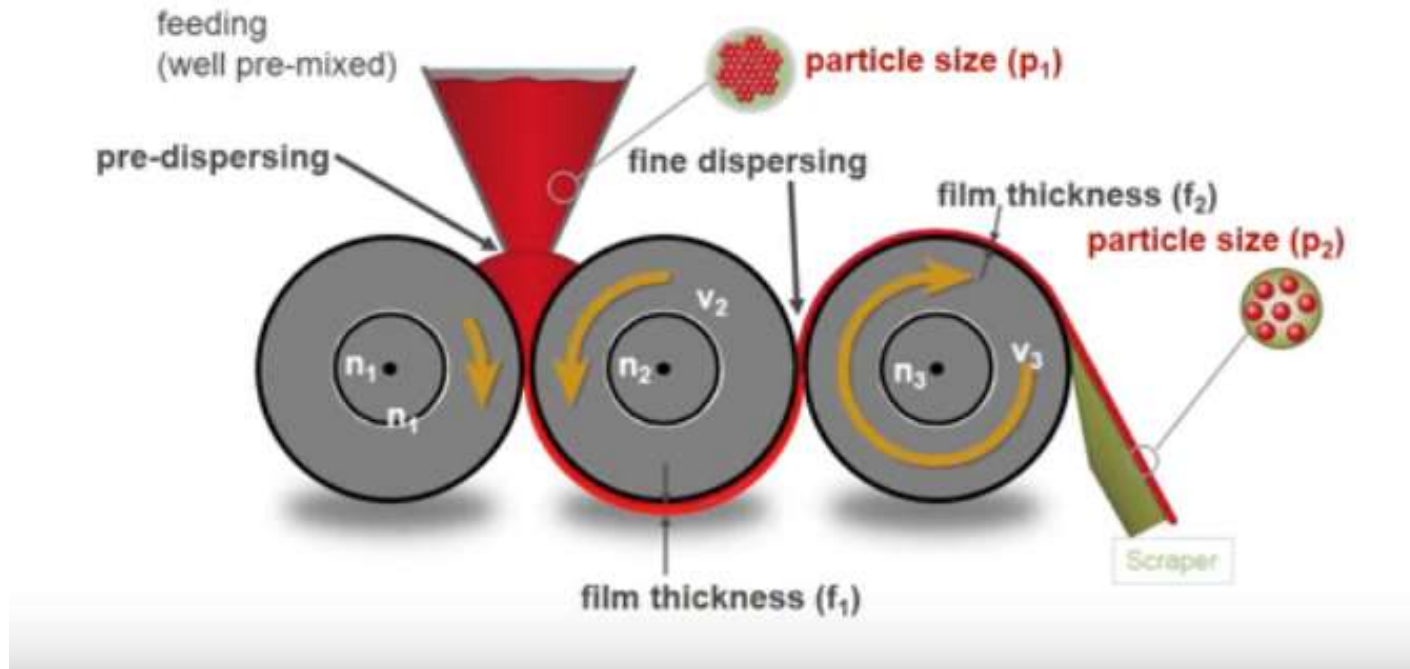
Triple roll mill:

- Disperse small tightly bound agglomerates and hard discrete particles.
- Particles are subjected to high shear, mechanical crushing.

Ball Mill:

- It is used for size reduction fine solid discrete particles or for deagglomeration of very tightly bound agglomerates.
- The machine consists of cylindrical drum into which a charge of heavy spherical balls usually metal or ceramic is loaded along with the components of the dispersion.

Equipment for suspension



Triple Roll Mill

REFERENCE: Pharmaceutical engineering(principles & practices) by C.V.S. Subrahmanyam.pg.no:155,161,229.

Equipment for suspension

Ball Mill



Triple Roll Mill



Stability Studies

1-Sedimentation Volume:

- Sedimentation volume (F) or height (H) for flocculated suspensions is a ratio of the ultimate volume of sediment (V_u) to the original volume of sediment (V_o) before settling.

$$F = V_u / V_o$$

- Where, V_u = final or ultimate volume of sediment V_o = original volume of suspension before settling
- F has values ranging from less than one to greater than one.
- When $F < 1$ then $V_u < V_o$
- When $F = 1$ then $V_u = V_o$
- The system is in flocculated equilibrium and shows no clear supernatant on standing.
- When $F > 1$ then $V_u > V_o$
- Sediment volume is greater than the original volume due to the network of flocs formed in the suspension and so loose and fluffy sediment
- The sedimentation volume gives only a qualitative account of flocculation.

Stability Studies

The sedimentation volume gives only a qualitative account of flocculation.

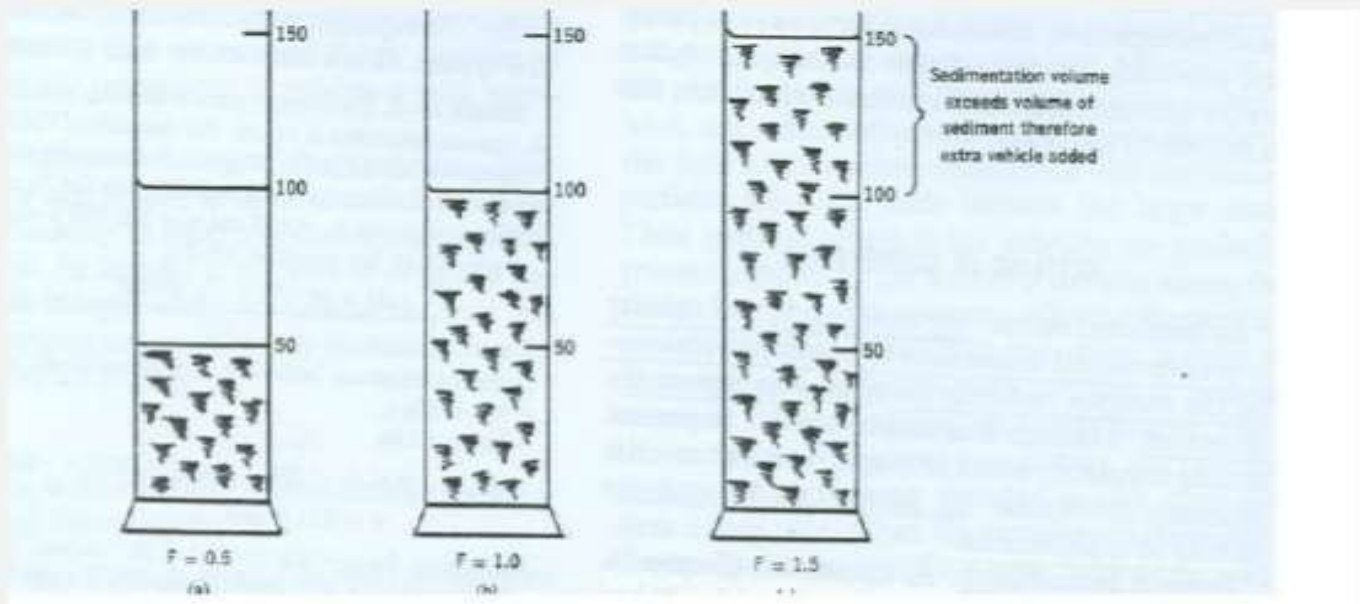


Fig : Suspensions quantified by sedimentation volume (f)

Stability Studies

2-Degree of Flocculation (β):

- It is the ratio of the sedimentation volume of the flocculated suspension, F , to the sedimentation volume of the deflocculated suspension, F_{∞}

$$\beta = F / F_{\infty}$$

- The minimum value of β is 1, when flocculated suspension sedimentation volume is equal to the sedimentation volume of deflocculated suspension.

3-Brownian Movement (Drunken walk):

Brownian movement of particle prevents sedimentation by keeping the dispersed material in random motion.

- Brownian movement depends on the density of dispersed phase and the density and viscosity of the disperse medium.
- The kinetic bombardment of the particles by the molecules of the suspending medium will keep the particles suspending, provided that their size is below critical radius (r).

Brownian movement can be observed,

- If particle size is about 2 to 5mm,
- When the density of particle & viscosity of medium are favorable.
- Brownian motion is given by equation:

$$Di^2 = RTt \div N3\pi \eta r$$

- Where, R = gas constant T = temp. in degree Kelvin N = Avogadro's number η = viscosity of medium t = time r = radius of the particle.

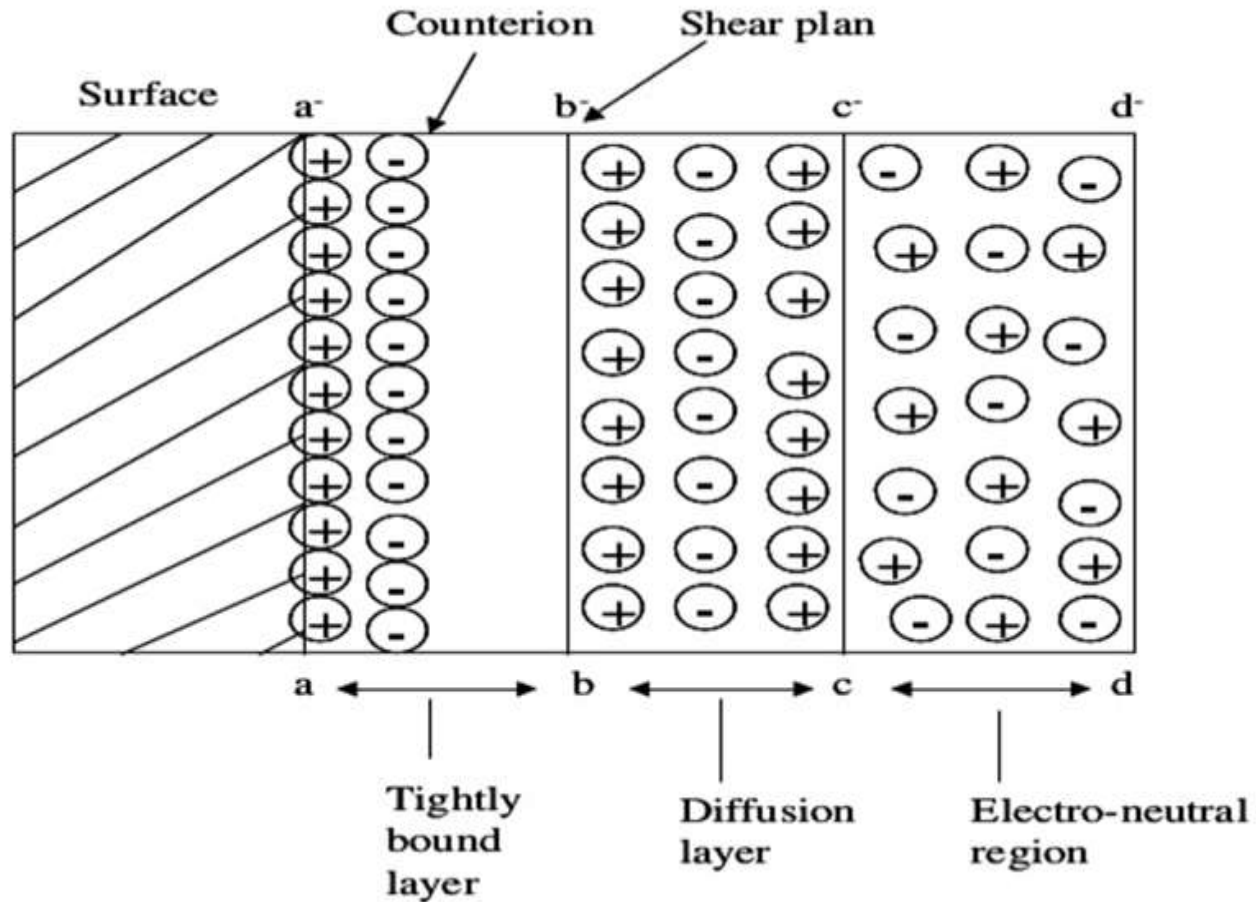
Stability Studies

4-Electro kinetic Properties:

Zeta Potential:

- The zeta potential is defined as the “difference in potential between the surface of the tightly bound layer (shear plane) and electro-neutral region of the solution”.
- As the potential drops off rapidly at first, followed more gradual decrease as the distance from the surface increases.
- 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 has practical application in stability of systems containing dispersed particles.
- Since this potential, rather than the Nernst potential, governs the degree of repulsion between the adjacent, similarly charged, dispersed particles.
- If the zeta potential is reduced below a certain value, the attractive forces exceed the repulsive forces, and the particles come together.
- This phenomenon is known as flocculation.
- The flocculated suspension is one in which zeta potential of particle is -20 to +20 mV.
- Thus the phenomenon of flocculation and de flocculation depends on zeta potential carried by particles.

Stability Studies



Stability Studies

Deflocculation and flocculation:

- **Flocculated Suspensions:**
- In flocculated suspension, formed flocs (loose aggregates) will cause increase in sedimentation rate due to increase in size of sedimenting particles.
- Hence, flocculated suspensions sediment more rapidly.
- Here, the sedimentation depends not only on the size of the flocs but also on the porosity of flocs.
- **Deflocculated suspensions:**
- In deflocculated suspension, individual particles are settling.
- Rate of sedimentation is slow, which prevents entrapping of liquid medium which makes it difficult to re-disperse by agitation.
- This phenomenon called 'caking' or 'claying'.
- In deflocculated suspension larger particles settle fast and smaller remain in supernatant liquid so supernatant appears cloud.

Stability Studies

