SUSPENSIONS

Features Desired In Pharmaceutical Suspensions

- The suspended particles should not settle rapidly and sediment produced, must be easily re-suspended by the use of moderate amount of shaking.
- It should be easy to pour yet not watery and no grittiness.
- It should have pleasing odour, colour and palatability.
- Good syringeability.
- It should be physically, chemically and microbiologically stable.

  Parenteral/ophthalmic suspension should be sterilizable.

Theory of Suspensions

Velocity of sedimentation expressed by **Stoke's equation**

$$V = \frac{2r^2 (\rho_s - \rho_o) g}{9\eta} \quad \text{or} \quad V = \frac{d^2 (\rho_s - \rho_o) g}{18\eta}$$

- Where, $v_{sed.}$ = sedimentation velocity in cm / sec
- d = Diameterof particle
- r = radius of particle
- ρ_s = density of disperse phase
- ρ_o = density of disperse media
- g = acceleration due to gravity
- η = viscosity of disperse medium in poise

1. M.E.Aulton, Aulton's Pharmaceutics, The Design and Manufacture of Medicines, Third Edition, Churchill Livingstone Elsevier, 383-405.
2. Banker G.S., Rhodes C.T., Modern Pharmaceutics, Fourth Edition, Vol. 121, Marcel Dekker, Inc.,255-256.

Particle size diameter (d)

$V \alpha d^2$

Sedimentation velocity (v) is directly proportional to the square of diameter of particle.

Density difference between dispersed phase and dispersion media ($\rho_s - \rho_o$)

$V \alpha (\rho_s - \rho_o)$

Viscosity of dispersion medium (η)

$V \alpha 1/ \eta_o$

Sedimentation volume (F) or height (H) for flocculated suspensions

$$F = V_u / V_O \text{ ---------- (A)}$$

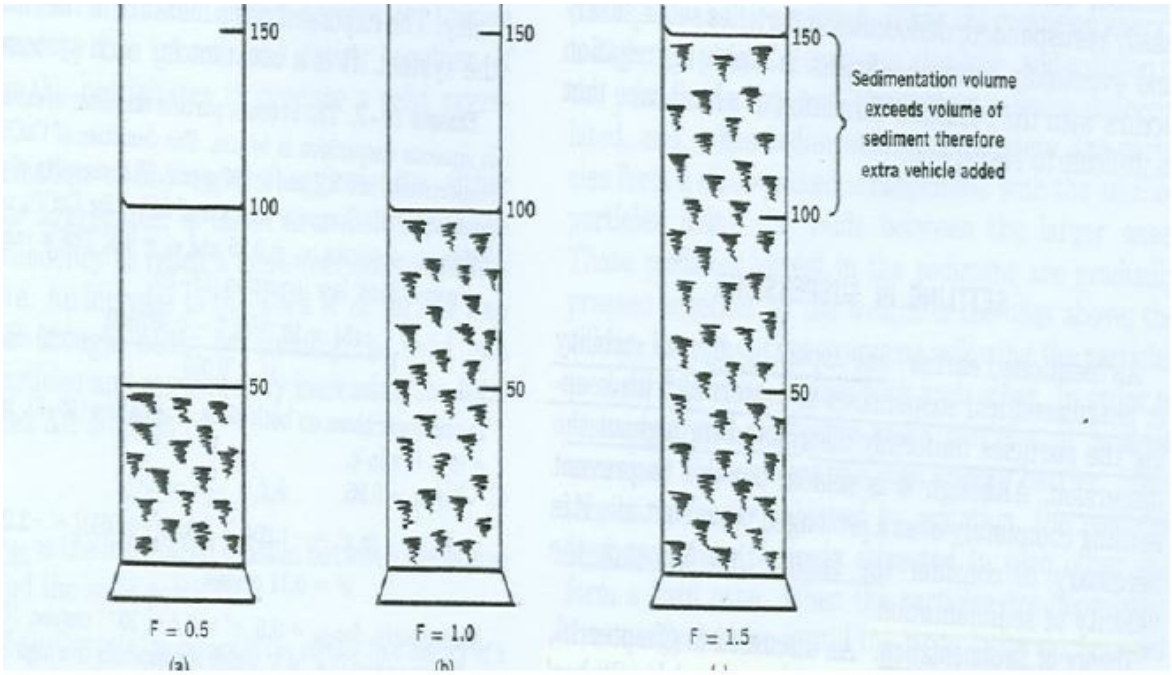
Where, V_u = final or ultimate volume of sediment

V_O = original volume of suspension before settling.

Sedimentation volume can have values ranging from less than 1 to greater than 1; F is normally less than 1.

F=1, such product is said to be in flocculation equilibrium and show no clear supernatant on standing.

1. Banker G.S., Rhodes C.T., Modern Pharmaceutics, Fourth Edition, Vol. 121, Marcel Dekker, Inc.,259-260



- **Degree of flocculation (β)**

It is a very useful parameter for flocculation

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

$$= \frac{V_u / V_O}{V_\infty / V_O}$$

$$= V_u / V_\infty$$

$$= \frac{\text{Ultimate sediment volume of flocculated suspension}}{\text{Ultimate sediment volume of deflocculated suspension}}$$

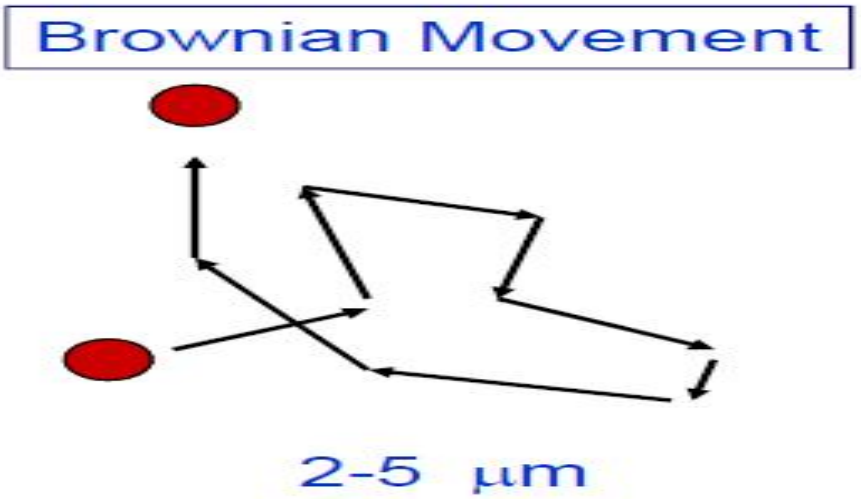
Alfred Martin, Physical Pharmacy, Physical Chemical principles in the Pharmaceutical Sciences, Chapter 20, Coarse Dispersion, Third Edition,544-556.

Brownian Movement (Drunken walk)

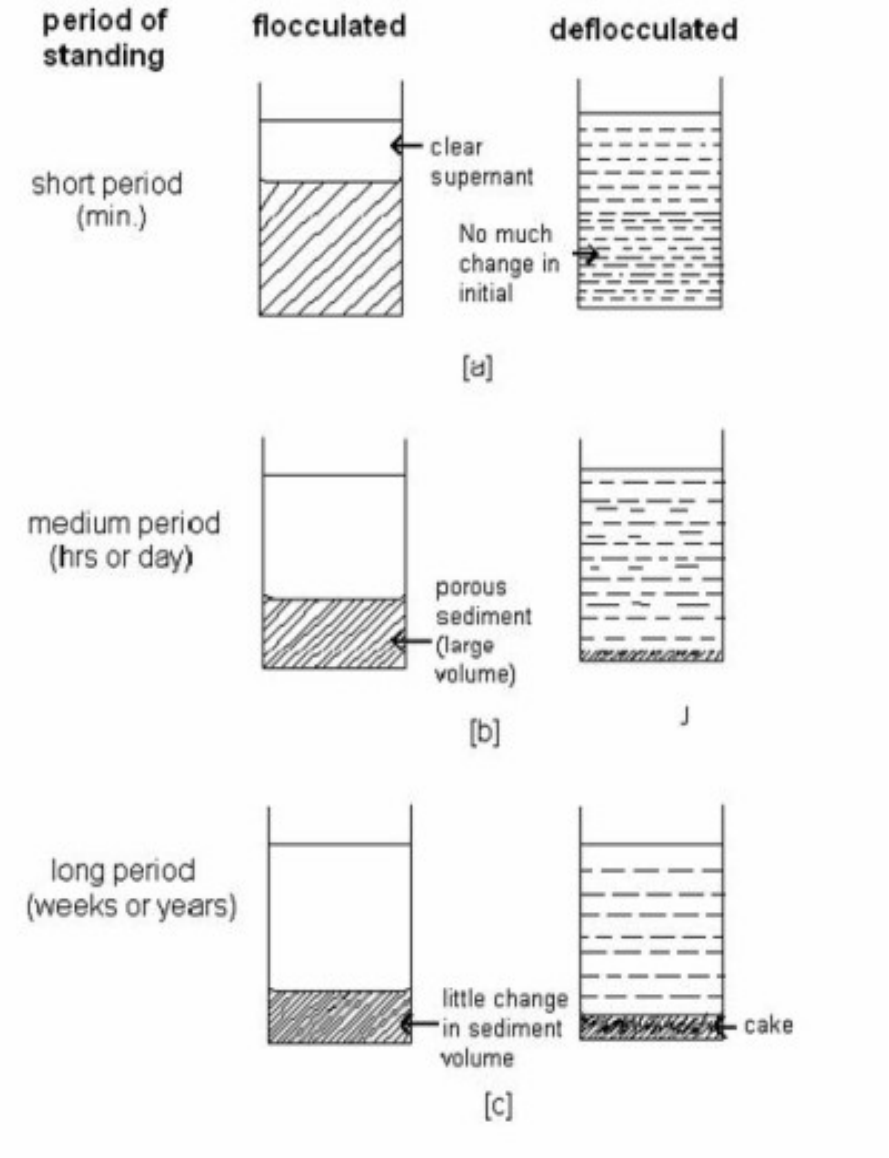
- Brownian movement of particle prevents sedimentation by keeping the dispersed material in random motion.
- Brownian movement depends on the **density of dispersed phase** and **the density and viscosity of the disperse medium**.
- The kinetic bombardment of the particles by the molecules of the suspending 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.



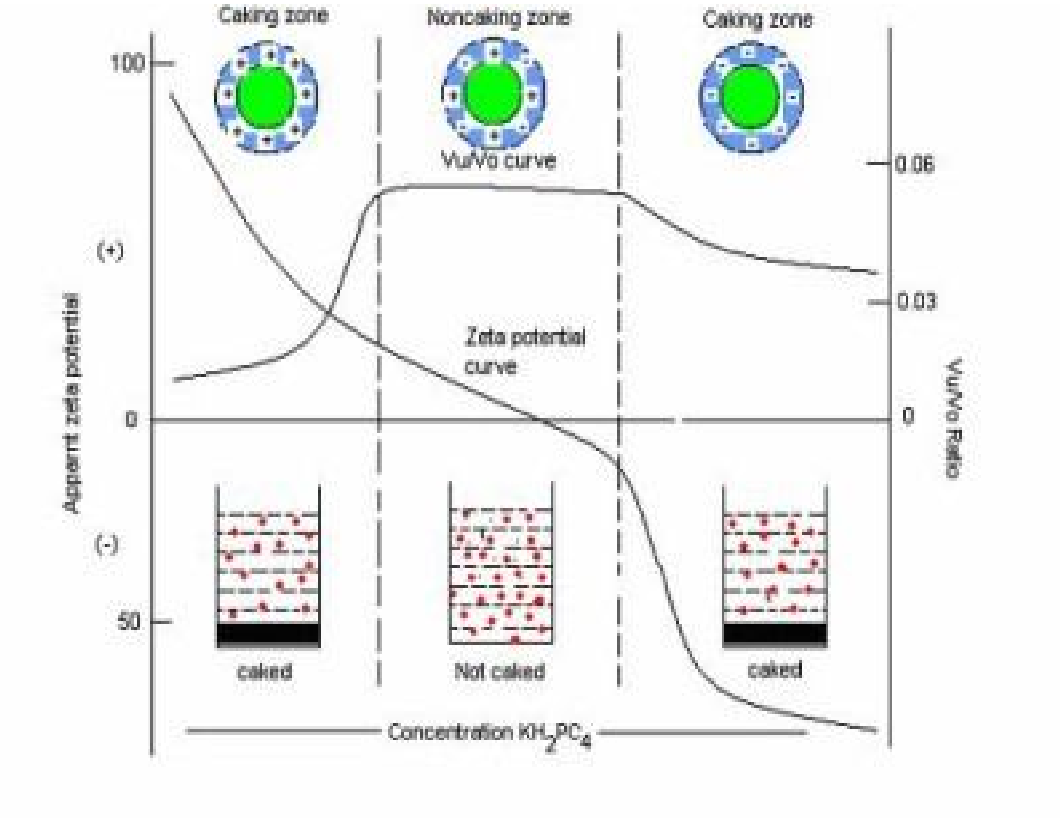
The Sedimentation Behavior of Flocculated and Deflocculated Suspensions



Alfred Martin, Physical Pharmacy, Physical Chemical principles in the Pharmaceutical Sciences, Chapter 20, Coarse Dispersion, Third Edition,544-556.

Method of Floccules Formation

1. Electrolytes



Caking diagram, showing the flocculation of a bismuth subnitrate suspension by means of the flocculating agent

2. Surfactants

3. Polymers

Alfred Martin, Physical Pharmacy, Physical Chemical principles in the Pharmaceutical Sciences, Chapter 20, Coarse Dispersion, Third Edition,544-556.

SMALL SCALE PREPARATION OF SUSPENSIONS

Suspensions are prepared by grinding (or) levigating the insoluble materials in the mortar 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 step1 to get slurry.

The slurry is transformed to a graduated cylinder, the mortar is rinsed with successive portion of the vehicle.

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.

FORMULATION DEVELOPMENT

Wetting agents	They are added to disperse solids in continuous liquid phase.
Flocculating agents	They are added to floc the drug particles
Thickeners	They are added to increase the viscosity of suspension.
Buffers and pH adjusting agents	They are added to stabilize the suspension to a desired pH range.
Osmotic agents	They are added to adjust osmotic pressure comparable to biological fluid.
Coloring agents	They are added to impart desired color to suspension and improve elegance.
Preservatives	They are added to prevent microbial growth.
External liquid vehicle	They are added to construct structure of the final suspension.

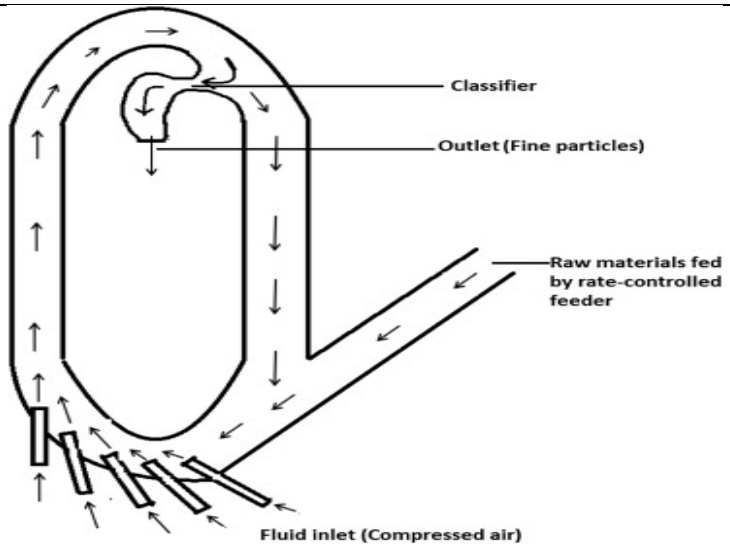
Alfred Martin, Physical Pharmacy, Physical Chemical principles in the Pharmaceutical Sciences, Chapter 20, Coarse Dispersion, Third Edition,544-556.

List of Suspending Agents

- Alginates
- Methylcellulose
- Hydroxyethylcellulose
- Carboxymethylcellulose
- Sodium Carboxymethylcellulose
- Microcrystalline cellulose
- Acacia, Tragacanth, Xanthan gum
- Bentonite ,Carbomer
- Powdered cellulose , Gelatin

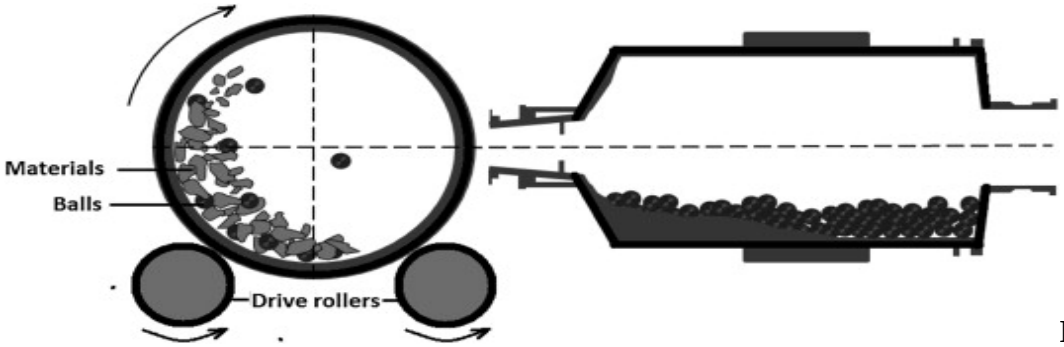
1. M.E.Aulton, Aulton's Pharmaceutics, The Design and Manufacture of Medicines, Third Edition, Churchill Livingstone Elsevier, 388-390.

Equipments used for milling of solid particle before dispersion into suspension



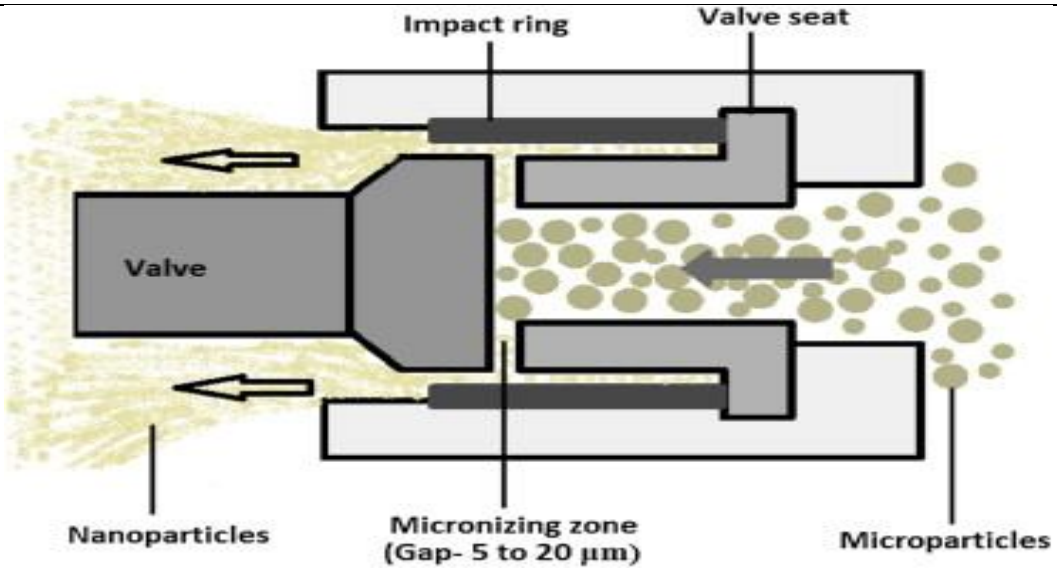
Fluid Energy Mill/ Jet mill

Air is introduced through specially-designed fluid inlets creating sonic or supersonic air streams. Raw materials are introduced into the violent and turbulent air stream in a confined space. High velocity collisions between the raw particles lead to effective pulverization of the feed into smaller particles particularly under 10 micrometers. This method is employed when the particles are intended for parenteral and ophthalmic suspensions.



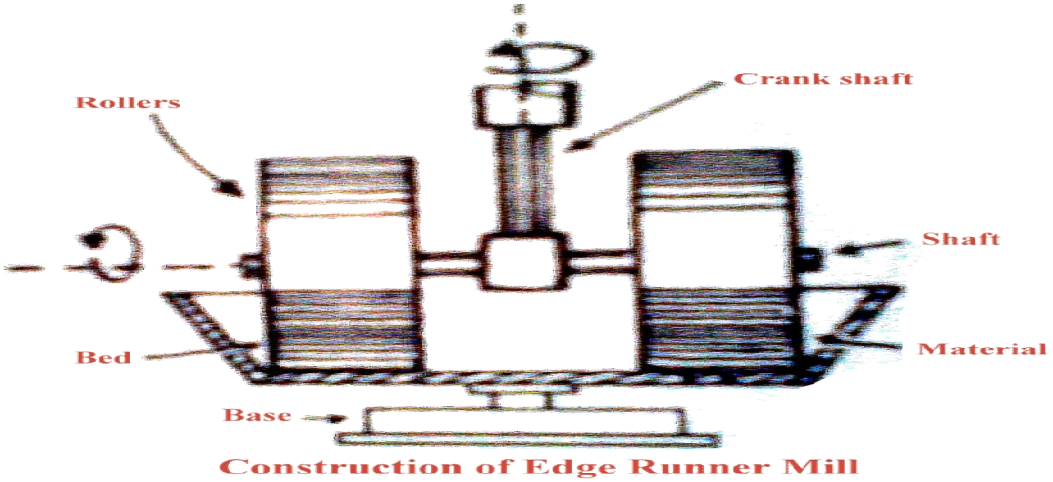
Ball Mill

The balls make up the grinding media and drive rollers help to rotate the milling chamber.



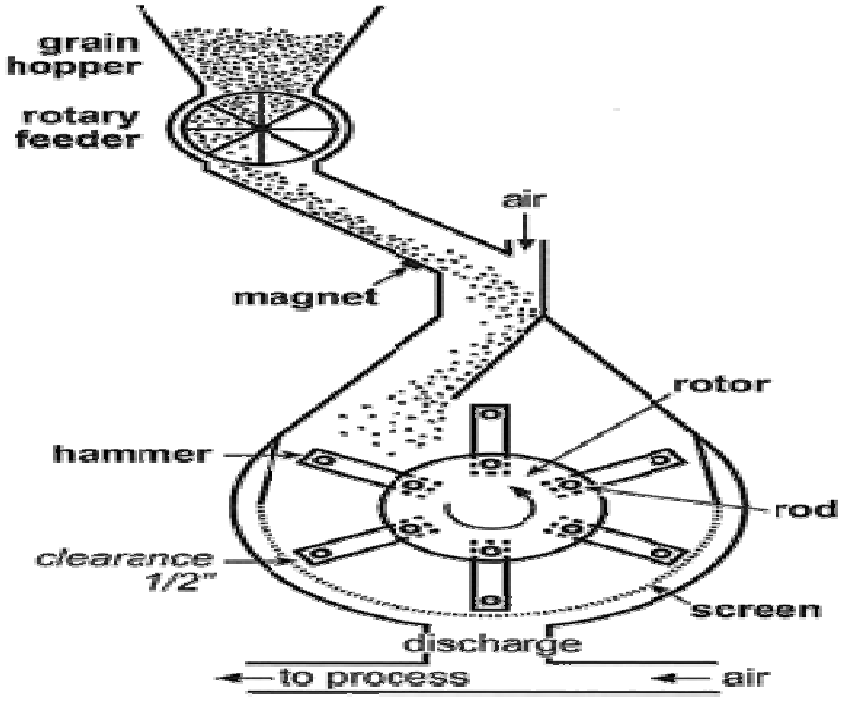
Micronizer

The microparticles are forced through a minute gap in the micronizing zone. This creates conditions of high turbulence and shear, combined with compression, acceleration, pressure drop and impact, leading to the formation of a nanosuspension.



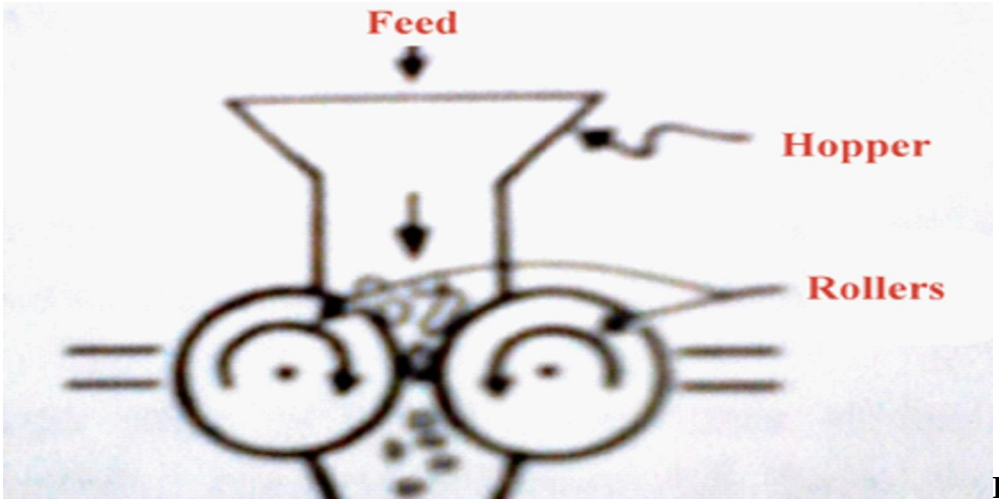
Construction of Edge Runner Mill

Size reduction is done by crushing due to heavy weight of stones.



Hammer Mill

Mill operates on principle of impact between rapidly moving hammers mounted on a rotor.



Roller Mill

Material is crushed by application of stress through rotating heavy rollers.

Quality Control of Suspensions

The following tests are carried out in the final quality control of suspension:

- Appearance, Color, odor and taste
- Physical characteristics such as particle size determination and microscopic photography for crystal growth
- Sedimentation rate and
- Zeta Potential measurement
- Sedimentation volume
- Redispersibility and Centrifugation tests
- Rheological measurement
- Stress test
- Freeze-Thaw temperature cycling
- Compatibility with container and cap liner

1. M.E.Aulton, Aulton's Pharmaceutics, The Design and Manufacture of Medicines, Third Edition, Churchill Livingstone Elsevier,
2. Leon Lachmann, Herbert A. Libermann; Joseph L.Kanig., The Theory and Practice of Industrial Pharmacy, Third Edition, Varghese Publishing House,

EMULSION

An emulsion is a thermodynamically unstable system consisting of at least two immiscible liquid phases one of which is dispersed as globules in the other liquid phase stabilized by a third substance called emulsifying agent.

Determination of type of simple emulsion

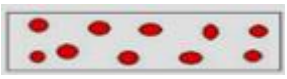
- Dilution test
- Dye solubility test
- Conductivity test
- CoCl2 filter test
- Fluorescence test

Factors affecting type of emulsion

- ✓ Type of emulsifying agent used
- ✓ Phase volume ratio
- ✓ Viscosity of each phase

1. M.E.Aulton, Aulton's Pharmaceutics, The Design and Manufacture of Medicines, Third Edition, Churchill Livingstone Elsevier,
2. Leon Lachmann, Herbert A. Libermann; Joseph L.Kanig., The Theory and Practice of Industrial Pharmacy, Third Edition, Varghese Publishing House,

Methods for the determination of type of emulsion are as follows,

Test	Observation	Comments
Dilution test	Emulsion can be diluted only with external phase.	Useful for liquid emulsions
Dye test	Water soluble solid dye tints only o/w emulsion and reverse.  o/w  w/o	May fail if ionic emulsifiers are present
Filter paper test/$CoCl_2$	Filter paper impregnated with $CoCl_2$ and dried, (blue) changes to pink when o/w emulsion is added.	May fail if emulsion is unstable or breaks in presence of electrolyte
Fluorescence test	Since oils fluoresce under UV light, o/w emulsion exhibit dot pattern, w/o emulsions fluoresce throughout.	Not always applicable
Conductivity test	Electric current is conducted by o/w emulsions, owing to presence of ionic species in water.	Fail in non-ionic o/w emulsion

Low energy emulsification

The principle of low energy emulsification has been established by Lin. In low energy emulsification, all of the internal phase, but only a portion of the external phase, is heated. After emulsification of the heated portions, the remaining external phase is added to the emulsion concentrate or the preformed concentrate is blended into the continuous phase. In those emulsions in which a phase inversion temperature exists, the emulsion concentrate is preferably prepared above the PIT, which results in emulsions having extremely small droplet size.

Theory of emulsification – interfacial films

- Mono molecular
- Multimolecular
- Solid particle films

Emulsifying agents

Added to an emulsion to prevent the coalescence of the globules of the dispersed phase.

Help in emulsion formation by

- Reduction in interfacial tension – thermodynamic stabilization
- Formation of a rigid interfacial film – mechanical barrier to coalescence
- Formation of an electrical double layer – electrical barrier to approach of particles

1. M.E.Aulton, Aulton's Pharmaceutics, The Design and Manufacture of Medicines, Third Edition, Churchill Livingstone Elsevier, 390-404.
2. Leon Lachmann, Herbert A. Libermann; Joseph L.Kanig., The Theory and Practice of Industrial Pharmacy, Third Edition, Varghese Publishing House, 502.

Synthetic

Surface active agents (Monomolecular films)

- Reduce interfacial tension and make the emulsion thermodynamically more stable.
- Form protective monomolecular film

Semi synthetic and natural

Hydrophilic colloids (Multimolecular films)

Finely divided solid particles (Particulate film)

Rule of Bancroft : Type of emulsion is a function of relative solubility of surfactant . The phase in which it is soluble becomes the continuous phase

1. M.E.Aulton, Aulton's Pharmaceutics, The Design and Manufacture of Medicines, Third Edition, Churchill Livingstone Elsevier,
2. Leon Lachmann, Herbert A. Libermann; Joseph L.Kanig., The Theory and Practice of Industrial Pharmacy, Third Edition, Varghese Publishing House,
3.

❖ **Synthetic (Surfactants) (Monomolecular films)**

➢ **Anionic**

- Soaps

  -Mono valent

  -Polyvalent

  -Organic

- Sulphates

  Sulphonates ($CH_3(CH_2)n\ CH_2SO_3 - Na^+$)

➢ **Cationic**

- Quaternary ammonium compounds

➢ Nonionic

- Polyoxy ethylene fatty alcohol ethers

  $C_{12}H_{25}\ (OCH_2CH_2)nOH$

- Sorbitan fatty acid esters
- Polyoxyethylene sorbitan fatty acid esters
- Polyoxyethylene polyoxypopylene block copolymers

  Lanolin alcohols and ethoxylated lanolin alcohols

Hydrocolloid Emulsifying agents

Provide a protective sheath (Multimolecular films)around the droplets

Impart a charge to the dispersed droplets (so that they repel each other

Swell to increase the viscosity of the system (so that droplets are less likely to change.)

- **Semi synthetic (Multi molecular films)**
  - Methyl cellulose
  - Carboxy methyl cellulose
- **Natural**
  - Plant origin Polysaccharides (Acacia, tragacanth, agar, pectin, lecithin)
  - Animal origin (Proteins (Gelatin), Lecithin, Cholesterol, Wool fat,Egg yolk)

M.E.Aulton, Aulton's Pharmaceutics, The Design and Manufacture of Medicines, Third Edition, Churchill Livingstone Elsevier, 395-397.

FINELY DIVIDED SOLIDS

Description :

Finely divided solid particles that are wetted to some degree by both oil and water act as emulsifying agents. This results from their being concentrated at interface, where they produce a particulate film around the dispersed droplets to prevent coalescence.

- **Finely divided solids (Particulate film)**

Colloidal Clays

- Bentonite,($Al_2O_3.4SiO_2.H_2O$),
- Veegum (Magnesium Aluminium silicate) ,
- Magnesium trisilicate.

Metallic hydroxides

- Magnesium hydroxide,
- Aluminium hydroxide,

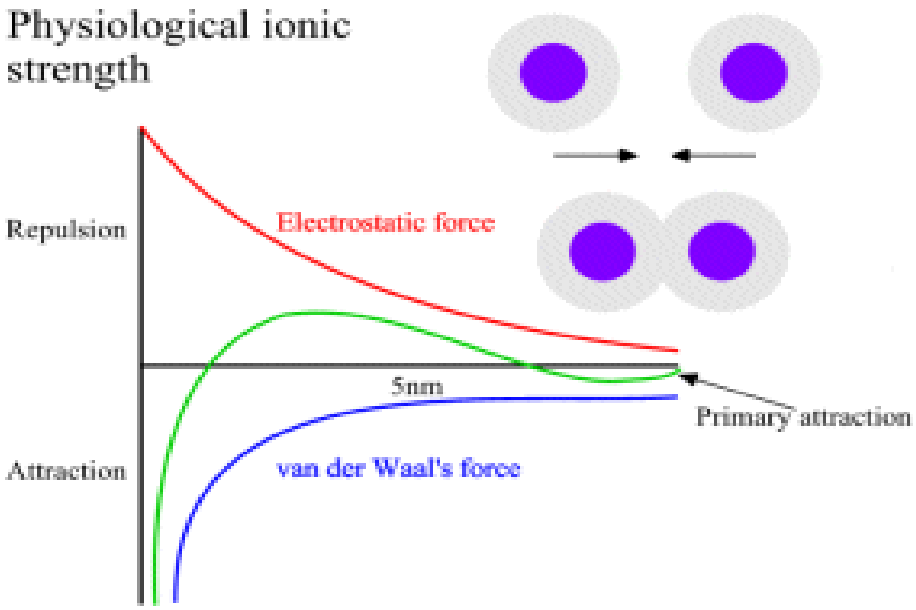
1. M.E.Aulton, Aulton's Pharmaceutics, The Design and Manufacture of Medicines, Third Edition, Churchill Livingstone Elsevier,
2. Leon Lachmann, Herbert A. Libermann; Joseph L.Kanig., The Theory and Practice of Industrial Pharmacy, Third Edition, Varghese Publishing House,
3. Alfred Martin, Physical Pharmacy, Physical Chemical principles in the Pharmaceutical Sciences, Chapter 20, Coarse Dispersion, Third Edition,544-556.

Extemporaneous (Laboratory scale) method of preparation

- Continental or dry gum method
- Wet gum method
- Bottle or Forbes bottle method
- Auxiliary method
- In situ soap method

1. M.E.Aulton, Aulton's Pharmaceutics, The Design and Manufacture of Medicines, Third Edition, Churchill Livingstone Elsevier, 409-411.

DLVO THEORY

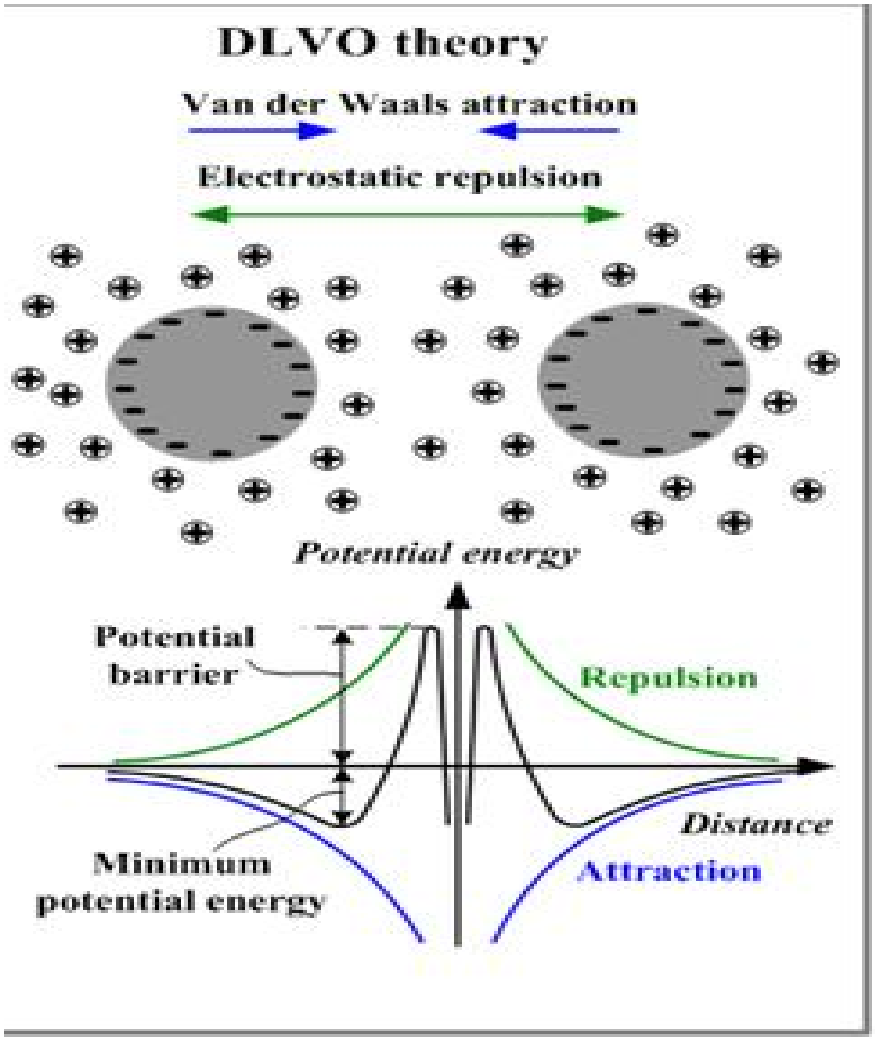


1. Leon Lachmann, Herbert A. Libermann; Joseph L.Kanig., The Theory and Practice of Industrial Pharmacy, Third Edition, Varghese Publishing House,
2. Alfred Martin, Physical Pharmacy, Physical Chemical principles in the Pharmaceutical Sciences, Chapter 20, Coarse Dispersion, Third Edition,544-556.

According To Theory:

- Electrostatic repulsive energy(VR)
- Vander Waals attractive-force(VA)
- total energy of interaction(VT)

VT =VR+VA



1. Alfred Martin, Physical Pharmacy, Physical Chemical principles in the Pharmaceutical Sciences, Chapter 20, Coarse Dispersion, Third Edition,544-556.

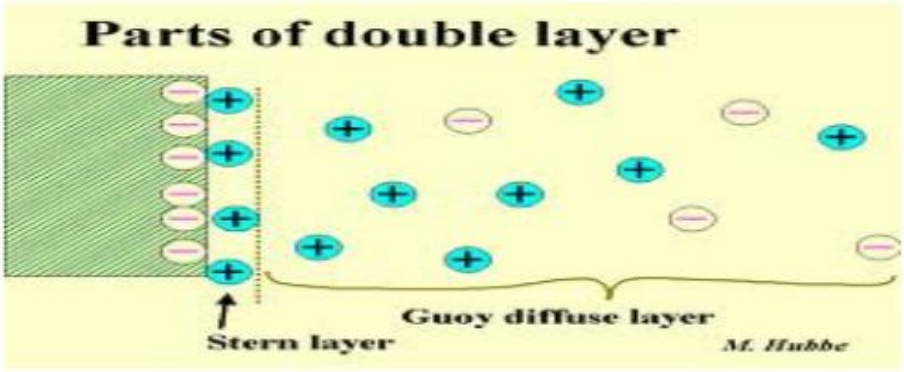
Tightly bound layer

- Also called Stern Layer
- once adsorption is complete

- Cations attract few anions and repel the cations
- At equilibrium some excess anions are present in this region
- Anions number less than cations, therefor layer have positive charge
- Anions are act as counter ions or gegenions(ions of opposite charge to that of the particle)
- Shear plane is present.

Diffuse Second Layer

- Excess of negative ions are present .
- Distribution of ions uniform after Diffuse second layer this region is called bulk liquid phase



Energy may be supplied in the form of

- Heat
- Homogenization
- Agitation

Heat

- Emulsification by vaporization
- Emulsification by phase inversion
- Low energy emulsification

Mechanical equipment for emulsification (Agitation)

- Mechanical stirrers
- Propeller type mixers

-Turbine mixers

- Homogenizers

- Colloid mills
- Ultrasonifiers

1. M.E.Aulton, Aulton's Pharmaceutics, The Design and Manufacture of Medicines, Third Edition, Churchill Livingstone Elsevier,
2. Leon Lachmann, Herbert A. Libermann; Joseph L.Kanig., The Theory and Practice of Industrial Pharmacy, Third Edition, Varghese Publishing House, 508-511.

Emulsion stability (Instability) – Types

- Physical instability
  - Flocculation
  - Creaming or sedimentation
  - Aggregation or coalescence
  - Phase inversion

Evaluation tests for emulsion

- Average globular size and size distribution
- Number of globules
- Rheological evaluation
- Zeta potential
- *In vitro* drug release
- *In vitro* stability study

1. M.E.Aulton, Aulton's Pharmaceutics, The Design and Manufacture of Medicines, Third Edition, Churchill Livingstone Elsevier,
2. Leon Lachmann, Herbert A. Libermann; Joseph L.Kanig., The Theory and Practice of Industrial Pharmacy, Third Edition, Varghese Publishing House, 426-427.
3. Alfred Martin, Physical Pharmacy, Physical Chemical principles in the Pharmaceutical Sciences, Chapter 20, Coarse Dispersion, Third Edition,544-556.

Assessment of emulsion shelf life

1- Aging and temperature

2- Centrifugation

3- Agitation

In case of o/w emulsions, flocculation of globules causes an immediate increase in viscosity. After this change, the consistency of the emulsion changes with time.

- In case of w/o emulsions, the dispersed phase particles flocculate quite rapidly resulting in a decrease in viscosity, which stabilizes after 5 to 15 days.

- As a rule, a decrease in viscosity with age reflects an increase of particle size due to coalescence.

1. M.E.Aulton, Aulton's Pharmaceutics, The Design and Manufacture of Medicines, Third Edition, Churchill Livingstone Elsevier, 400-401.
2. Leon Lachmann, Herbert A. Libermann; Joseph L.Kanig., The Theory and Practice of Industrial Pharmacy, Third Edition, Varghese Publishing House, 427-429.

Methods for Emulsion Formulation

1. Dry gum method (Continental method)

The continental method is used to prepare the initial or primary emulsion from oil, water and a hydrocolloid or "gum" type emulsifier (usually acacia). The primary emulsion or emulsion nucleus is formed from 4 parts of oil, 2 parts of water and one part of gum. The 4 parts of oil and 1 part of gum represent their total amount for the final emulsion.

In a mortar, one part of gum (acacia) is to be levitated with four parts of oil until the powder is thoroughly wetted; then the two parts water should be added all at once and the mixture is vigorously and continuously triturated until the primary emulsion is form, creamy white in appearance and produces a "crackling" sound as it is triturated (usually 3-4 minutes).

Additional water or aqueous solutions may be incorporated after the primary emulsion is formed. Solid substances (Example: active ingredients, preservatives, color, flavors etc.) are generally added as a solution to the primary emulsion; oil soluble substances in small amounts may be incorporated directly into the primary emulsion. Any substance which might reduce the physical stability of the emulsion, such as alcohol (which may precipitate the gum) should be added as near to the end of the process as possible to avoid breaking of the emulsion. When all agents have been incorporated, the emulsion should be transferred to a calibrated vessel, brought to final volume with water, then homogenized or blended to ensure uniform distribution of ingredients.

Ratio of oil: gum: water in primary emulsion for various types of oils is as,

Fixed oil = 4:1:2; Mineral oil = 3:1:2; Volatile oil = 2:1; 2 and Oleo gum resin = 1:1:2

2. Wet gum method (English method)

The proportion of oil and water and emulsifier (gum) are the same as in dry gum method, but the order and technique of mixing are different. The gum is triturated with water to form mucilage; then oil is to be added slowly in portions, while triturating. After all the oil is added, the mixture should be triturated for several minutes to form the primary emulsion. Then other ingredients are added as in continental method. This method is more difficult to perform successfully, especially with more viscous oils, but may result in a more stable emulsion.

3. Bottle method

This method is used to prepare emulsions of volatile oils, or oliogeneous substances of vary low viscosities. In this, gum is to be placed in a dry bottle and oil is added. Then the bottle is capped and should be shaken thoroughly. Into this the required volume of water is to be added all at once and the mixture is shaken thoroughly until the primary emulsion is formed. It is important to minimize the initial amount of time for the mixing of gum and oil. The gum will tend to imbibe the oil and will become water proof.

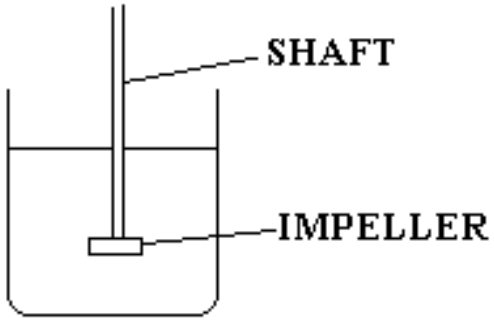
4. Beaker Method

When synthetic or non-gum emulsifiers are used, the proportions given in the previous methods become meaningless. The most appropriate method for preparing emulsions from surfactants or other non-gum emulsifiers is to begin by dividing components into water soluble and oil soluble components. All oil soluble components are dissolved in the oily phase in one beaker and all water soluble components are dissolved in the water in a separate beaker. Oleaginous components are melted and both phases are heated to approximately 70°C over a water bath. The internal phase is then added to the external phase with stirring until the product reaches room

temperature. The mixing of such emulsions can be carried out in a beaker, mortar, or blender; or, in the case of creams and ointments, in the jar in which they will be dispensed.

Equipments for Emulsion Manufacturising

1) Agitators: Agitation or shaking may be used to prepare the emulsion. This method frequently is employed by the pharmacist, particularly in the emulsification of easily dispersed, low viscosity oils. Under certain conditions, intermittent shaking is considerably more effective than ordinary continuous shaking. Continuous shaking tends to break up not only the phase to be dispersed but also the dispersion medium, thus impairing the ease of emulsification; laboratory shaking devices may be used for small scale production.



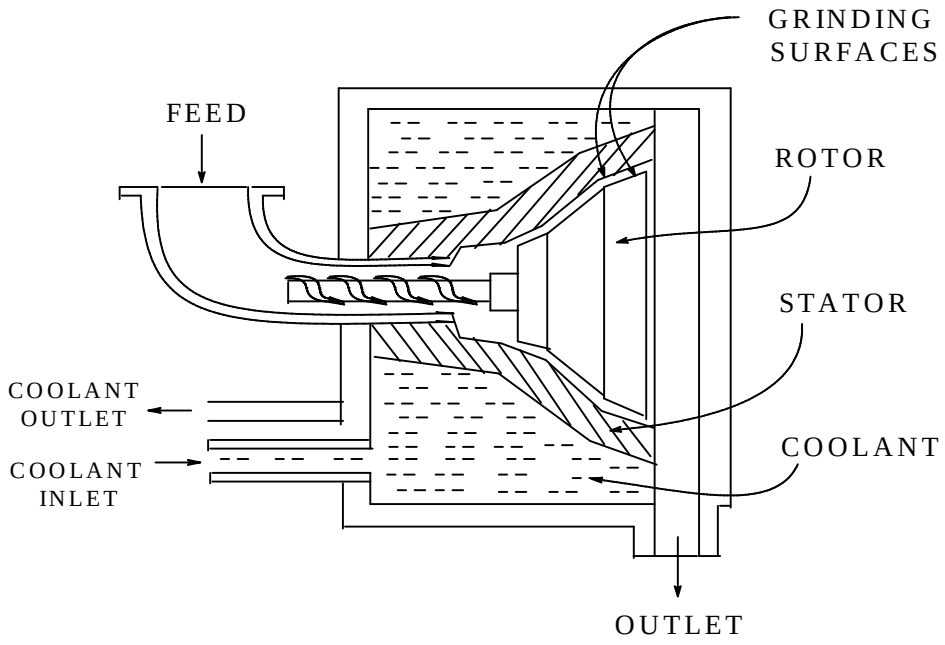
2) Mechanical Mixers: Emulsion may be prepared by using one of several mixers that are available. Propeller type mixers that have a propeller attached to a shaft driven by an electric motor are convenient and portable and can be used for both stirring and emulsification. This type operates best in mixtures that have low viscosity, that is, mixture with a viscosity of glycerine or less. They are also useful for preparing emulsions. Turbine mixers have a number of blades that may be straight or curved, with or without pitch, mounted on a shaft. The turbine tends to give a greater shear than propellers. The shear can be increased by using diffuser rings that are

perforated and surround the turbine so that the liquid from the turbine must pass through holes. The turbine can be used for both low viscosity mixtures and medium viscosity liquids, up to that of molasses. The degree of stirring and shear by propeller turbine mixers depends upon several factors, such as the speed of rotation, pattern of liquid flow, position in the container.

		
Mechanical Stirrers	Turbine Stirrer	Propeller Stirrers

		 Radial Flow Turbine  Axial Flow Turbine
Marine Propeller Mixer	Clamp Mounted Portable Mixer	

3) Colloid mills: In this, mixed phases of an emulsion formula are passes between a stator and a high speed rotor revolving at speeds of 2000 to 18,000 rpm. The clearance between the rotor and stator is adjustable, usually from 0.001in upward. The emulsion mixture, in passing between the rotor and stator, is subjected to a tremendous shearing action that effects a fine dispersion of uniform size. The shearing force applied in the colloid mill usually result in temperature rise within the emulsion. It may be necessary, therefore, to cool the equipment when the emulsion is being produced. Droplet size of emulsion was mainly determined by shear force within the gap between the spinning rotor and stationary rotor. Droplets size decreased with homogenization intensity and with decreasing viscosity of the dispersed phase.

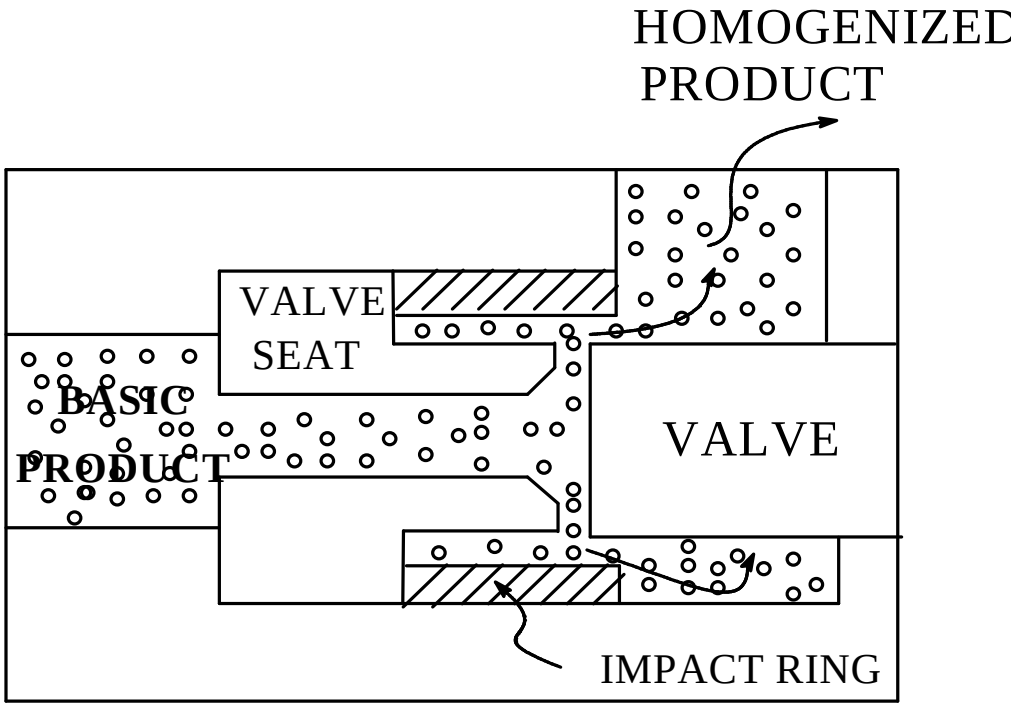


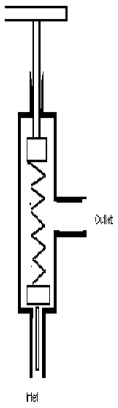
4) Homogenizers: Homogenizers may be used in one of two ways:

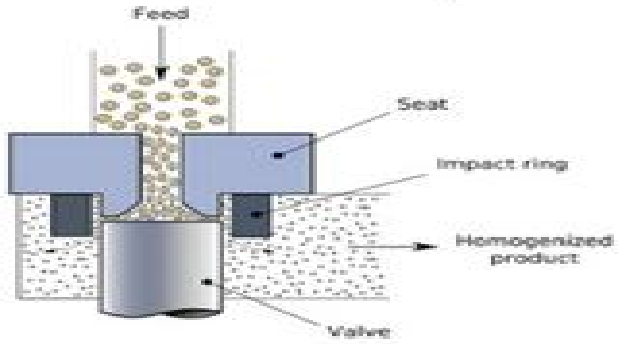
- The ingredients in the emulsion are mixed and then passed through the homogenizer to produced the final product

- A coarse emulsion 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.

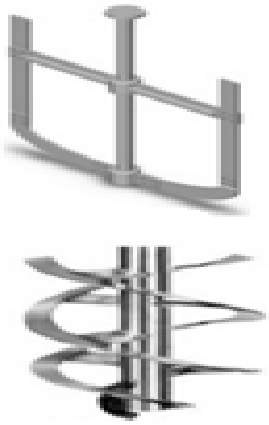
The mixed phases or the coarse emulsion are subjected to homogenization and are passed between a finely ground valve and seat under high pressure. This, in effect, produces an atomization that is enhanced by the impact received by the atomized mixture as it strikes the surrounding metal surface they operate at pressure of 1000-5000 psi and produced some of the finest dispersions obtainable in an emulsion. It is postulated that circulation and turbulence are responsible mainly for the homogenization. Two stage homogenizers are constructed so that the emulsion, after treatment in the first valve system, is conducted directly to another where it receives a second treatment.



		
Homogenizer	Colloid Mill	Colloidal Mill Rotor and Stator



Piston Homogenizer



Anchor and Helical Impeller

5) Ultrasonic Devices: Commercial products may be prepared using ultrasonic based upon the device known as the Pohlman whistle. In this apparatus, the premixed liquids are forced through a thin orifice and are allowed to impinge upon the free end of a knife-edge bar that is made to vibrate. Ultrasonic waves are produced and areas of compression and rarefaction are formed. Shock waves are produced by the collapse of bubbles that produce a shear effect, thereby producing fine particle sizes.

HOMOGENIZERS

Homogenization

It is a process in which coarse globules in emulsion are converted into smaller globules of uniform composition, so that each measured dose has the same composition.

Principle

It is based on the principle that when large globules in coarse emulsion are passed under high pressure through a narrow orifice is broken into smaller globules having a greater degree of uniformity and stability.

SIMPLE HOMOGENIZER

• It consist of a pump that rises the pressure of the dispersion to a range of 500-5000psi

• And an orifice through which the fluid strikes upon the homogenizing valve

• The homogenizing valve is held on valve seat by strong spring.

• As the pressure increases some of the dispersion escapes b/w valve and valve seat , and instantly pressure is released which subjects the product to intense turbulence and hydraulic shear

SILVERSON HOMOGENIZER:

- In silverson homogenizer the droplets are subjected to a high shear rates.
- It consists of an emulsifying head to which blades are attached, surrounded by a fine mesh sieve made up of a stainless steel . The emulsifying head is immersed in the liquid to be emulsified
- The head is rotated by a small motor at very high speed.

- The liquids to be mixed are sucked through fine mesh into the base of the emulsifying head where they are subjected to vigorous mixing by high speed rotation of blades.
- The mixed material is then expelled with a great force through the sieve band.
- This sucking in and forcing out sets up a pattern of circulation, and thus large size globules are reduced to small size globules.

HIGH PRESSUR HOMOGENIZER:

- It consist of a positive displacement pump that forces liquid into the valve area at high pressure.
- As the product is forced through the adjustable gap, its velocity increases tremendously .
- The emerging product then strikes on the ***impact ring*** **.**This sudden change in energy causes increased shear , turbulence resulting in droplet size reduction and uniform dispersion of particle.
- It provides mixing with homogenizing action.
- It also used in the production of microemuslion, cell disruption and also particle size reduction.
- It produces pressure ranges from 150-200 Mpa.

ULTRASONIC HOMOGENIZER:

- It uses positive displacement pump to force the premixed liquid through an elliptical opening at a speed of 100m/s or more.
- This high speed liquid strikes in the edge of a blade shaped obstacle, called ***vibrating knife.***
- In some design the blade is caused to vibrated at the ultrasonic frequency by the action of fluid, while in others, while in others this vibration is caused by electrically powered piezoelectric crystal.

- Ultrasonic vibration cause causes compression and refraction in different region of liquid and this result in high shear.
- It is used for low viscosity liquids.
- Not practical for large scale.

Semisolid dosage forms are dermatological preparations intended to apply externally on the skin to produce local or systemic effect.

Ex: Ointments, creams, pastes, gels etc

IDEAL PROPERTIES OF SEMISOLIDS PHYSICAL PROPERTIES

- Smooth texture
- Non dehydrating
- Non gritty and non greasy
- Elegant in appearance

PHYSIOLOGICAL PROPERTIES

- Non irritating
- Do not alter membrane or skin functioning
- Miscible with skin secretion

APPLICATION PROPERTIES

- Easily applicable with efficient drug release.
- High aqueous wash ability.

1. Leon Lachmann, Herbert A. Libermann; Joseph L.Kanig., The Theory and Practice of Industrial Pharmacy, Third Edition, Varghese Publishing House, 534-563.

PERCUTANEOUS ABSORPTION

FACTOR AFFECTING PERCUTANOUS ABSORPTION

BIOLOGICAL PARAMETERS

- Skin condition
- Skin age
- Blood flow
- Regional skin sites
- Skin metabolism

PHYSICOCHEMICAL PARAMETERS

- Physicochemical Attraction of Drug
- Mol wt Of Drug
- Hydration of Skin
- Temperature & pH
- Drug Concentrations
- Diffusion coefficient
- Partition coefficient
- Area of Applications
- Contact Time

1. Leon Lachmann, Herbert A. Libermann; Joseph L.Kanig., The Theory and Practice of Industrial Pharmacy, Third Edition, Varghese Publishing House, 534-563.

TYPES OF SEMISOLID BASES

The ointment base is the substance or part of ointment, which serves as carrier or vehicle for the medicament. Ointment bases are of following types

A) Oleaginous bases or Hydrocarbon base

Ex. Hard paraffin, Yellow soft paraffin.

B) Absorbent base

Ex. Hydrous wool fat, lanolin

C) Emulsion bases or water miscible bases

D) Water soluble bases

Ex. PEG, Polysorbate

1. Leon Lachmann, Herbert A. Libermann; Joseph L.Kanig., The Theory and Practice of Industrial Pharmacy, Third Edition, Varghese Publishing House, 534-563.

PASTES,GELS AND JELLIES

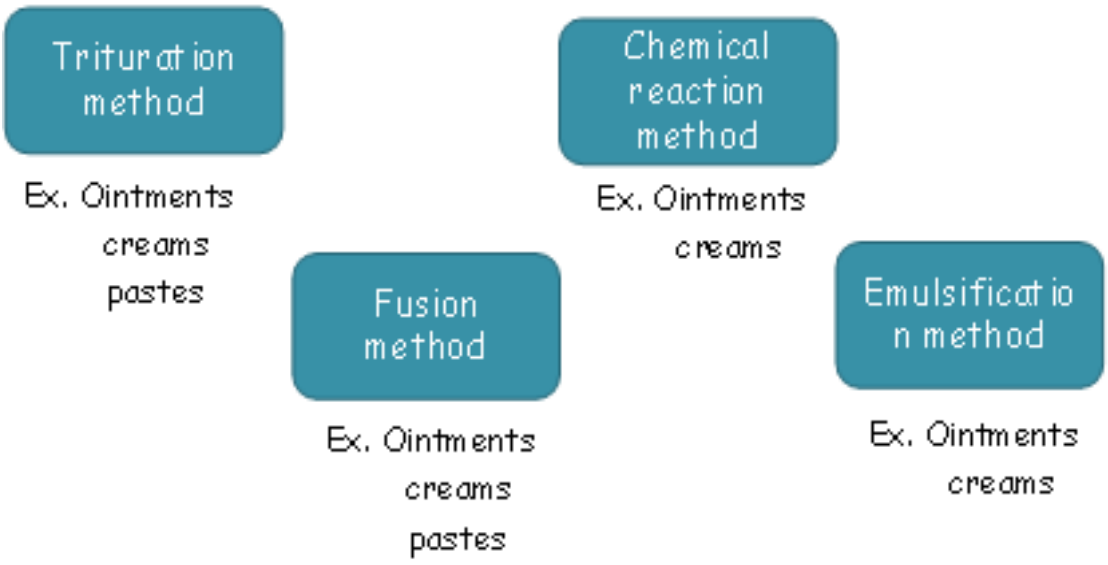
Pastes are dispersions of high concentrations of insoluble powdered substances (20 to 50%) in a fatty or aqueous base.

The fatty bases are less greasy as well as stiffer in consistency than ointments because of the large amount of powdered material present.

Jellies are water-soluble bases prepared from natural gums such as tragacanth, pectin and alginates.

Gels are usually clear transparent semisolids containing the solubilized active substances like hydroxypropylcellulose and HPMC.

PREPARATION OF SEMI SOLIDS



1. Leon Lachmann, Herbert A. Libermann; Joseph L.Kanig., The Theory and Practice of Industrial Pharmacy, Third Edition, Varghese Publishing House, 534-563.

Fusion method:

- Anhydrous ointments are prepared by fusion method.
- Active substances is dissolved in the melted fats and waxes and then mixed with base. The melted mass must mixed while cooling because the fatty alcohols, fatty acids, and waxes do not form true solutions, but crystallize from the melt as the temperature falls.

PREPARATION OF OIL AND AQUEOUS PHASES

- The components of the oil mixtures are placed into a stainless steel steam jacketed kettle,melted and mixed.
- Some of the solid components e.g. stearic acid,cetyl alchol are available in many different forms like cakes,flakes or powder. The flakes are more preferable because of the convenience of handling.
- Petrolatum is inconvenient to handle unless it is melted and transferred by pumping or pouring from its drum.
- The oil phase is then strained through several layers of cheese cloth to remove any foreign matter.

- If petrolatum is used as oil phase then it should be passed through filter medium particularly in ophthalmic preparations.
- The oil phase is transferred by gravity or pump to the emulsion mixing kettle.
- The components of the aqueous phase are dissolved in the purified water and filtered.
- A soluble drug may be added to this aqueous phase.

MIXING OF PHASES

- The phases are usually mixed at a temperature of 70 to 72^{0}C, because at this temperature intimate mixing of the liquid phases can occur.
- The properties of some emulsions depend on the temperature at which the phases are mixed.The initial mixing temperature must be raised above 70 to 72 ^{0}C.

Three ways of mixing the phases:

1.Simultaneous blending of the phases.

2.Addition of the discontinuous phase to the continuous phase.

3.Additon of the continuous phase to the discontinuous phase.

1. Leon Lachmann, Herbert A. Libermann; Joseph L.Kanig., The Theory and Practice of Industrial Pharmacy, Third Edition, Varghese Publishing House, 534-563.

- The simultaneous blending of the phases requires the use of a proportioning pump and a continuous mixer.
- This method is used for continuous or large batch operation.
- The second method is used for emulsion systems that have a low volume of dispersed phase.
- The third process is preferred for many emulsion systems.

Equipments used for mixing of phases:

1. Agitator mixers :Sigma mixer and planetary mixer.
2. Shear mixers: Triple roller mill and Colloidal mill.

Sigma blade mixer:

The mechanism of mixing is shearing.The sigma shaped blades creates high shear.

Colloidal mill:

It consists of two steel discs.Here one disc rotates and another one is stationary. When the material is passed through these discs they get sheared.Thus coarse particles are break down to small particles due to shear.

1. Leon Lachmann, Herbert A. Libermann; Joseph L.Kanig., The Theory and Practice of Industrial Pharmacy, Third Edition, Varghese Publishing House, 534-563.

COOLING THE SEMISOLID EMULSION:

- The rate of cooling is generally slow to allow for adequate mixing while the emulsion is still liquid.
- The temperature of the cooling medium in the equipment should be decreased gradually and at a rate consistent with the mixing of the emulsion and scrapping of the kettle walls to prevent formation of congealed masses of the ointment or cream.

- Perfume should be added at 43 to 45^0c to avoid chilling the emulsion in case of oil in water type emulsion.
- Perfume should be added at room temperature in water in oil type emulsion.
- If the drug is not added in the aqueous phase then it should be added in solution form or in the form of crystals.

1. Leon Lachmann, Herbert A. Libermann; Joseph L.Kanig., The Theory and Practice of Industrial Pharmacy, Third Edition, Varghese Publishing House, 534-563.

EVALUATION OF OINTMENTS

- **Content uniformity of drug**
- **Penetration**
- **Rate of release of medicament**
- **Absorption of medicament in blood stream**
- **Irritant effect**

- **Content uniformity of drug**

A known weight of ointment is taken and assayed for amount of the drug.

- **Penetration**

A weighed quantity of ointment is rubbed over skin for a given period of time and unabsorbed ointment is collected and weighed. The differences in weights represent the amount absorbed.

In Vitro Skin Penetration

- **Flow through cell**
- **Franz diffusion cell**

They mainly have two compartments

1) Donor

2) Receptor

Method:

- mouse skin or human cadaver skin.
- Placed in between the two compartments.
- The passage of semisolid preparation through the epidermal surface to receptor compartment is measured by,
- Detector (Flow through type)
- Sampling (Franz diffusion cell)

RATE OF RELEASE OF MEDICAMENT

 To assess rate of release of medicament, small amount of the ointment can be placed on the surface of nutrient agar contained in a Petri dish or alternately in a small cup cut in the agar surface. If the medicament is bactericidal the agar plate is previously seeded with a suitable organism like *s.aureus.* After a suitable period of incubation, the zone of inhibition is measured and correlated with the rate of release.

 Another method for finding out release rate is to smear internal surface of test tubes with thin layers of ointment, fill the tubes with saline/serum and after a gap of time estimating the amount of drug present in the serum/saline.

ABSORPTION OF MEDICAMENT INTO BLOOD STREAM

 The diadermatic ointment should be evaluated for the rate of absorption of drug into the blood stream. This test can be run in-vivo only.

 Definite amount of ointments should be rubbed through the skin. Under standard conditions and medicaments are estimated in the blood plasma or urine.