

**PHARMACEUTICS**  
**Chapter 4**  
**Unit Operation**  
**SIZE REDUCTION**

- The process in which the particle size of a substance is reduced from its smaller size to a finer state of subdivision (coarse or powdered state) is known as size reduction.
- Milling is the process in which the particle size of solid substance is reduced into coarse or powdered state by employing mechanical strength.
- In some cases, the process of size reduction is also known as comminution and grinding.
- Depending on the type of material used (solid or liquid), the methods employed for the reduction of particle size are broadly categorised into two classes:
  - 1) **Grinding and Cutting:** These methods are employed for reducing the size of solid substances.
  - 2) **Emulsification or Atomisation:** These methods are used for the liquid phase.

### **Advantages of Size Reduction**

- ✓ It maintains content uniformity and uniform flow of materials.
- ✓ It enables extraction and drying of drugs in an effective manner.
- ✓ It improves the absorption and dissolution rates and physical stability of the product.
- ✓ It enhances the viscosity and surface area of the drug.
- ✓ It improves the drug bioavailability.
- ✓ It aids in manufacturing of aerosols, inhalation and ophthalmic preparations, and parenteral suspensions.

### **Disadvantages of Size Reduction**

- ✘ It may degrade the drug.
- ✘ It leads to poor mixing.
- ✘ It may lead to product contamination.
- ✘ It may also lead to some instrumental problems like noisy environment.

### **Objectives**

- By reducing the size of particles, the surface area of the drug gets increased. Hence, in case of any chemical substance, this increased surface area helps in quick formation of the solution.

- By reducing the particle size of certain drugs, their therapeutic efficacy gets enhanced, e.g. the therapeutic effectiveness of Griseofulvin is increased by reducing its dose to half of the original of by requirement.
- If the particle size of different solid ingredients is reduced to the same size, their mixing becomes much easier and produces a uniform product.
- In order to increase the stability of emulsions, the size of oil globules should be reduced.
- By reducing the particle size of ointments, pastes, and creams, their physical appearance can be enhanced
- It facilitates drying of the wet masses by milling: as milling increases the surface area and hence the rate of drying increases.
- Size reduction reduces the bulkiness of drugs

### **Factor Affecting Size Reduction**

- ❖ **Toughness:** Those crude drugs are usually tough in nature which have high water content or are soft and fibrous. Problems are faced in the size reduction of soft but tough substances as compared to hard and fragile substances.
- ❖ **Hardness:** The size reduction of soft materials is comparatively easier than the hard substances. Hence the process of size reduction is also affected by the hardness of material.
- ❖ **Stickiness:** Sticky substances are resinous or gummy in nature. Therefore, during the process of size reduction, certain problems are faced as they stick to the grinding or sieve surfaces of the mill, which makes it difficult to break them into small pieces.
- ❖ **Moisture Content:** The process of particle size reduction is also affected by the moisture present in the material which affects different physical properties of the substance like stickiness, toughness, or hardness.
- ❖ **Softening Temperature:** During the process of size reduction, the material with a wax-like property (e.g. stearic acid or other drugs containing oils or fats) becomes soft because the temperature of the mill rises to a large extent.

### **Methods of Size Reduction**

- **Cutting:** In this method, the material is cut with the help of blades having a fine sharpness, e.g: cutter mill.

- **Compression:** In this method, pressure is applied on the material so that it gets crushed into smaller size particles, e.g., roller mill.
- **Impact:** In this method, the material is kept stationary and an object moving with high speed strikes the material in order to reduce its particle size. Impact also occurs when the particles in motion strike the non-moving surface of the mill.
- **Attrition:** In this method (similar to that compression in which pressure is applied on the material), both the surfaces (machine and material) move with respect to each other, and produces shear forces which reduces the size of particles, e.g., fluid energy mill. The size up to which the above mentioned methods reduce the particles are given in the

**TABLE**

Method/Mechanism	Common Equipment	Approx. Particle Size (Micron)
Cutting	Cutter Mill	100-80000
Compression	Roller Mill	50-10000
Impact	Hammer Mill	50-8000
Attrition	Colloid & Roller Mill	1-50
Impact and Attrition	Ball Mill	1-2000

## **EQUIPMENT FOR SIZE REDUCTION**

The common size reduction mills used in pharmaceutical industries are:

- ❖ Hammer mill,
- ❖ Ball mill,
- ❖ Fluid energy mill, and
- ❖ Disintegrator.

# Hammer Mill

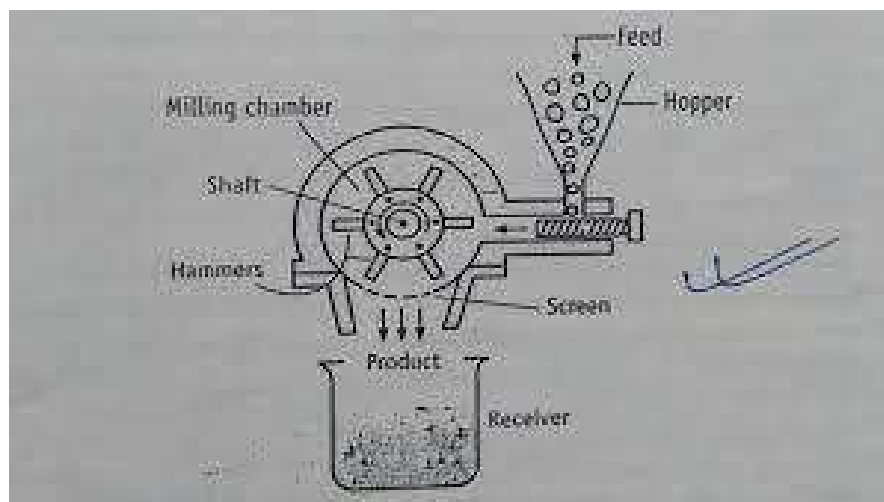
- Hammer mill is a type of crusher used for grinding and pulverising various materials.
- It is the device used for Crushing or milling agglomerates or large-sized particles into small-sized freely flowing particles (although the property of free flowing depends on the speed of the mill).

## Principle

- Hammer mill works on the principle of impaction, in which a speedily moving object is made to hit a stationary substance. Thus, the size of the particles is reduced by the mechanism of pulverisation or grinding.

## Construction

- ❖ The **hammer mill** consists essentially of a high speed rotor turning inside a cylindrical casing. The rotor is mounted on a shaft which is usually horizontal. The swing hammers are pinned to a rotor disk. The hammers are rectangular bars of metal with plain or enlarged ends. In this mill, the particles are broken by the sets of swing hammers. The product falls through a grate or screen which forms the lower portion of the casing.
- ❖ Several rotor disks each carrying four to eight swing hammers are often mounted on a single shaft. The rotor disk diameter ranges from 150 mm to 250 mm. As the hammers are hinged, the presence of any hard material does not cause damage to the equipment. The hammers can be readily replaced when they worn out.



## Working

- The material to be crushed is fed into the hopper connected to a drum.
- The fast rotating hammers powder the material into required size.
- The resultant powder is coarse to moderately fine and is collected beneath the screen.
- Hammer mill operates continuously because the hammers are not fixed, thus the chance of getting choked is less.
- The mill operates at a very high speed due to which heat is generated, which then affects the thermolabile materials.
- Also the mill may get damaged for the same reason if the feed contains foreign objects like stone or metal.

## Applications

- I. In pharmaceutical industries it is used in wet or dry granulations and to disperse powder mixtures.
- II. It is used to grind pharmaceutical raw materials, herbal medicines, and sugar.
- III. It is used to make powder of barks, leaves, and roots having medicinal properties.
- IV. It is used for milling Active Pharmaceutical Ingredients (APIS), excipients, etc.

## Merits

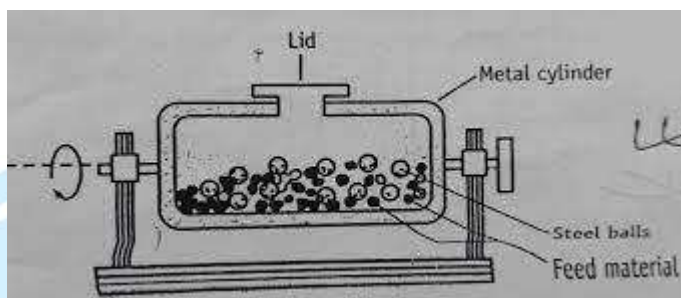
- ✚ Its reduction ratio and capacity are high for primary, secondary, or tertiary grinding.
- ✚ It requires moderate energy.
- ✚ It is used for milling variety of materials.
- ✚ It is easy to install, dismantle, and clean.
- ✚ It requires a small space for installation.

## Demerits

- ❖ It cannot be used for fine grinding of hard and abrasive materials due to excessive wear.
- ❖ It cannot be used for low-melting sticky or plastic-like materials due to heat generation.
- ❖ It may get choked and damaged in case of uncontrolled feed rate.
- ❖ It may damage the heat-sensitive materials due to heat generated when operating at a very high speed.

# Ball Mill

→ Ball mill is one of the types of grinders employed in grinding the drug substances into superfine powders. These powders are used in pyrotechnics, ceramics, and paints.



## Construction

Ball mill consists of the following parts:

### Hollow Cylinder

- The hollow cylinder is formed of metal and has a chromium lining.
- The metallic frame attaches the hollow cylinder in such a way that it can rotate at its longitudinal axis.
- About 30-50% volume of the mill remains the mill remain as occupied by the steel balls.

## Working

Working of a ball mill can be summarised in the following steps:

1. The cylinder of the mill is filled with the drug substance to be grinded and is then rotated.
2. In the whole process of size reduction, the speed of rotation plays a key role as

### At Low Speed (Sliding):

- The balls will only tend to roll and slide over each other.
- Very small quantity of material will be reduced to small particles.

### At High Speed (Centrifugation):

- Due to the centrifugal force the balls are moved towards the walls, and thus do not grind the material.
- This is because the compression force applied by the balls against the wall is not enough for size reduction of materials.

### **At Correct Speed (Cascading):**

- The centrifugal force causes the balls to move upto the roof of the mill and then fall off.
  - Thus, attrition and impact between the balls cause maximum size reduction of the particles.
3. Later, after a particular time period the material being grinded is withdrawn from the container and passed via suitable sieve in order to obtain the powder of desired size particles.

### **Applications**

- It is the key equipment for regrinding.
- It is widely used for cement, silicate product, new type building material, fire-proof material, chemical fertilisers, black and non-ferrous metals, glass, etc.
- It can grind ores or other materials either by wet process or by dry process.

### **Merits**

- It can be easily cleaned and operated.
- The grinding process can easily be seen.
- During the grinding process, there is minimum loss of material.
- Both dry and wet grinding can be processed.
- It can produce very fine powder.

### **Demerits**

- It has a large size.
- During the process of size reduction, strong vibrations and sounds are produced.
- Ball milling is a slow process.
- Due to frictional loss it consumes a large amount of Energy
- It has low efficiency.

# Size Separation

- A unit operation used to separate or categorise the particles on the basis of differences between the physical properties of the particles like density, shape, and size is termed as size separation (or screening or Sifting or Cassitying). Once the size of the material is reduced, it is Subjected to size separation techniques in order to obtain the powder of desired particle size range.
- Particle size distribution is defined as the number of particles in each size range present in a given powder of specified weight.

## Objectives

- The techniques of size separation particularly sieving is employed for the determination of average particle size and particle size distribution which is considered as the first step in the manufacturing of tablets and capsules.
- There are certain drugs which are needed in extremely fine state with the particle size of 10 $\mu$  so that they can get absorbed from the gastrointestinal tract rapidly and effectively. e.g., griseofulvin (antifungal) and aspirin (analgesic, antipyretic).
- Size separation is also essential for evaluation of the efficiency of different equipments used for the process of size reduction.

## Applications

- Release and Dissolution: Clinically, the particle size of a drug can affect its release from dosage form administered orally, parentally, rectally, and topically.
- Absorption and Drug Action: Drug absorption and its pharmacological response are affected by the size of particles. Higher the dissolution rate, faster the absorption rate, hence quicker and greater the drug action.
- Physical Stability: The physical stability of some pharmaceutical preparations like suspensions and emulsions are affected by the particle size. Depending upon the size of particle, the physical stability of the also changes; smaller the size of particles, drug greater will be the physical stability of the drug owing to the Brownian movement of the particles in the dispersion.

## Mechanism of Action

- I. **Agitation:** This mode of motion involves vigorous shaking of sieves in the following ways:



- II. **Oscillatory Motion:** In this type of motion, the movement of sieves takes place with the help of rotating shaft. In this, the sieves placed on the frame are moved in to and fro motion corresponding to the plane of sieve.
- III. **Vibrating Motion:** In this type of motion, the material is placed on the sieve which is then subjected to high speed vibration by employing either an electrical or a mechanical device.
- IV. **Gyratory Motion:** In this type of motion, an eccentric flywheel is used for rotating the sieve (placed on the rubber mounting) at a fixed axis in a circular motion.

### **Classification of Powders According to IP**

- Powders are generally termed as coarse and fine powders. But, it is necessary that they should be defined with some official specifications.
  - Pharmaceutical powders have been assigned some standards by the I.P., according to which degree of coarseness or fineness is expressed with reference to the aperture size of the sieve through which powder can pass
- i. **Coarse Powder (10/44):** All the particles of this powder pass through a sieve no. 10, having the nominal mesh aperture of 1,700 $\mu$ m but not more than 40% of the powder by weight must pass through the sieve no. 44, having the nominal mesh aperture of 355 $\mu$ m.
  - ii. **Moderately Coarse Powder (22/60):** All the particles of this powder pass through a sieve no. 22, having the nominal mesh aperture of 710 $\mu$ m but not more than 40% of the powder by weight must pass through sieve no. 60, having the nominal mesh aperture of 250 $\mu$ m.
  - iii. **Moderately Fine Powder (44/85):** All the particles of this powder pass through a sieve no. 44, having the nominal mesh aperture of 355 $\mu$ m but not more than 40% of the powder by weight must pass through sieve no. 85, having the nominal mesh aperture of 180 $\mu$ m.
  - iv. **Fine Powder (85/120):** All the particles of this powder pass through a sieve no. 85, having the nominal mesh aperture of 180 $\mu$ m but not more than 40% of the powder by weight must pass through sieve no. 120, having the nominal mesh aperture of 125 $\mu$ m.

- v. **Very Fine Powder (120/350):** All the particles of this powder pass through a sieve no. 120, having the nominal mesh aperture of 125µm but not more 40% of the powder by weight must pass through sieve no. 350 with the nominal mesh aperture of 45µm.)
- vi. **Microfine Powder (350):** The powder whose particles are not less than 90% by weight must pass through sieve no. 350, having the nominal mesh aperture of 45µm.
- vii. **Superfine Powder:** The powder in which the number of particles is not less than 90% and is less than 10µm in size.

## Sieves

- Normally, a sieve is used for separating the unwanted or useless material from that of the desired one with the help of different tools such as net, mesh, or other distillation and filtration techniques.
- For the separation of liquids from the solids, a particular type of sieve is used, known as strainer. Sieving is also used as an analytical technique for the measurement of size and classifying the powders according to the size of the particles.

### Types of Sieves

- The size and shape of sieve aperture is the main concern while setting standards. Square meshes are arranged as per the specifications. The following types of sieves are used mostly for pharmaceutical purposes:

Woven Wire Sieves: These sieves are of the following types:

- i) Plain weave, and ii) Twilled weave

### Standards of Sieves

Common standards used for sieves are as follows.

- 1) Tyler standard sieve series (in U.S.A.),
- 2) US standard sieve series (in U.S.A.),
- 3) British standard sieve series (in U.K.),
- 4) German DIN (Deutsche Industrie-Normen) (in Germany and Europe).
- 5) I.P. standard sieve series (in India),
- 6) International test sieve series (ISO) (Worldwide)

**The specifications given below should be matched by the sieves used for Pharmacopoeial testing:**

- 1) **Sieve Number:** This is the number of meshes present per linear length of 25.4mm.
- 2) **Nominal Aperture Size:** This is the distance between the two adjacent wires, representing the side of a square aperture. The nominal mesh aperture size for most of the sieves is given in the I.P. 1996 (either in mm or in  $\mu\text{m}$ ).
- 3) **Nominal Wire Diameter:** The wire used in wire mesh sieves has a specified diameter which provides a suitable aperture size and sufficient strength so that sieve distortion can be avoided.
- 4) **Approximate Percentage Sieving Area:** This is the mesh area expressed as a percentage of the total sieve area. It depends on the wire size used for a sieve. The sieving area is appropriately maintained within 35- 40% to provide the required strength to the sieve.
- 5) **Aperture Tolerance Average Size:** Some variations which the aperture size undergoes cannot be avoided, Such variations are termed aperture tolerance average, expressed as a percentage.

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# Cyclone Separator

→ The method used to remove particulate matter from air, gas, or water stream with the help of vortex rather than filters, is known as cyclonic separation. Gravity and rotational effects are helpful in the separation of solid mixtures from those of the fluids.

## Principle

- ★ Cyclone separator is a type of sedimentation technique which works on the principle of centrifugal force rather than the gravitational force.
- ★ Thus, based on the fluid velocity, cyclone enables the separation of all the particles or only the coarse particles can be removed, leaving behind the fine particles which are then carried away by the fluid.

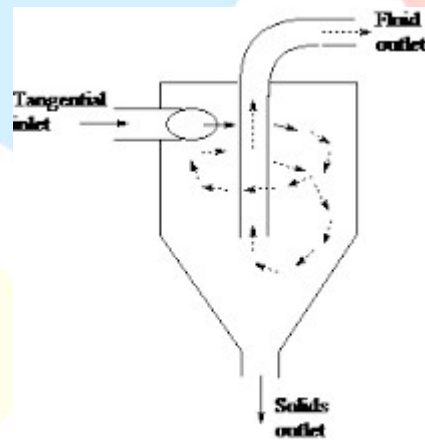


Fig. Cyclone separator

## Construction

- Cyclone separator consists of a cylindrical vessel having a conical base., The vessel is divided into two parts:
- The upper part consists of a tangential inlet and a fluid outlet at the centre of the top portion and extending inwardly into the separator, and
- The lower part or the base is fitted with the outlet for the solid particles.

## Working

- The suspension is introduced into the cylindrical vessel through the tangential inlet at high speed in order to provide the rotary movement inside the vessel.
- The fluid outlet located at the top of the vessel helps in removing the fluid.
- The solid particles are thrown out towards the cyclone walls due to the rotary movement occurring inside the cyclone which causes the movement of particles by the centrifugal force. The particles thrown out then fall down on the conical

base which is removed ultimately from the solid outlet at the bottom of the cylinder.

### **Applications**

- 1) It is used for the separation of suspensions of solids in liquids with the preference for suspension of a solid in a gas (air).
- 2) It is also used for separating the heavy or coarse fraction from fine dust.

### **Merits**

- 1) It involves low capital costs.
- 2) It can operate at high temperatures.
- 3) It can be used for liquid mists or dry materials.
- 4) Its maintenance requirements are less.
- 5) It requires a small space for installation.

### **Demerits**

- 1) Its operating cost is high due to pressure drop.
- 2) It shows low efficiency for small particles.
- 3) It cannot be used for sticky materials

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# Mixing

- Mixing is one of the most important processes of unit operation and is used in many industries. It involves mixing of solids, liquids, or gases having two or more than two components.
- Mixing may be defined as the process in which two or more ingredients are treated so that every particle of any one ingredient lies as near as possible to the particle of the other ingredient.
- There are several factors, which affect the process of mixing, like density of the material, particle size, shape, and proportion of the constituents.
- Mixing is thought to be an important process in the field of pharmacy because at different steps it might affect the preparation's efficiency.

## Objectives of Mixing

- ◆ **Chemical Reaction Enhancement:** In chemical industries, it uses mixing to continue a reaction appropriately which require a close contact among reacting substances.
- ◆ **Simple Physical Mixtures:** It is a mixture of two or more miscible liquids, homogeneously divided solids, etc. can be
- ◆ **Physical Changes:** They are carried out by mixing such as from supersaturated solution crystals are formed.
- ◆ **Achieving Dispersion:** It is also an objective of mixing in which two or more immiscible liquids and one or more liquids with finely divided solids are mixed to produce a quasi-homogenous substance.

## In order to obtain the following types of product usually the process of mixing operation

- **True Solutions:** These solutions are formed when two or more miscible liquids are mixed with each other.
- **Emulsions:** These are formed when two immiscible liquids are mixed together with the addition of an emulsifying agent.
- **Solutions:** These are formed when any solute (solid) is dissolved in a solvent (vehicle).
- **Suspensions:** These are formed when an insoluble solid (solute) is mixed with the solvent or vehicle.
- **Ointments or Suppositories:** These are formed when any liquid or a solid is mixed with a semisolid base.
- **Capsules:** These are formed when two or more solid materials are mixed with each other to form a powder which is then filled into the gelatin capsule shells.

- **Tablets:** These are formed when two or more solid substances are mixed with each other to form a powder which is then compressed under heavy pressure to obtain tablets.

## **Applications**

- During tablet and capsule manufacturing, wet mixing is done in the granulation stage.
- For easy compression of tablets, various components are mixed by dry mixing.
- In the manufacturing of capsules, compound powders, and dry syrups, dry blending of powder is done
- For capsule manufacturing, pellets are formed.
- In tablet manufacturing, powder mixing is an important step because many additives are added to this process

## **Factors Affecting Mixing**

- ◆ Surface Nature
- ◆ Particle Density
- ◆ Particle Size
- ◆ Particle Shape
- ◆ Particle Charge
- ◆ Material Proportion

## **Equipments for Mixing**

- For mixing and homogenisation process such mixer should be used which facilitates random mixing, and also prevents the conditions which may result in segregation. Thus, the operational conditions should be critically optimised.

### Mixing Equipments

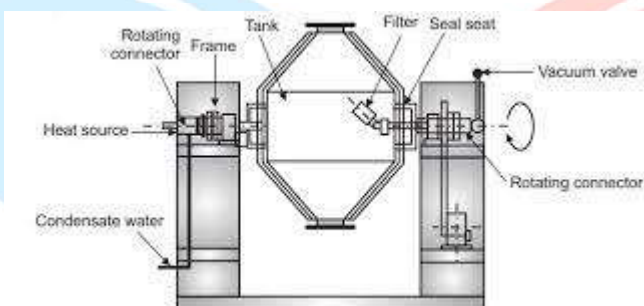
- Double cone mixer
- Turbine mixer
- Triple roller mill
- Silverson mixer (homogenizer)

# Double Cone Blender

- Double cone blender is a competent and versatile machine used for uniform blending of granules and dry powders.
- It is made up of stainless steel.
- It is available in a wide range of working capacities ranging from 5- 500 litres.

## Principle

- Double cone blender produces a homogeneous solid-solid mixture.
- This equipment involves axial mixing as the powder moves in different sections.
- This blender provides thorough mixing depending on its speed of rotation.



## Construction

- ◆ The body of double cone blender consists of two coneshaped sections.
- ◆ These are joined to a central cylindrical section at their bases.
- ◆ The rotational axis is perpendicular to the cone axis and passes through the cylindrical section.
- ◆ The blender body is held by two lateral supports.
- ◆ One of these supports is fitted with the driving motor.

## Working

- The autoclaved double cone blender's angle is adjusted with the help of a moving wheel so that the material can be conveniently loaded.
- After loading, the lid of the blender is closed, and the lid is secured by fitting the safety pin within its groove.
- Then the safety guard is put and the equipment is switched on.
- After the blending process is complete, the safety guard is put is removed (only after switching the equipment off), the blender is adjusted to an angle (so that the material can be conveniently unloaded), the safety pin is unlocked, and the lid is opened.



## Applications

- It is employed in different industries for the preparation of different products such as pharmaceutical, food, chemical, cosmetic products, etc.
- It is used for uniform mixing of granules or dry powders.
- It is used for the preparation of pharmaceuticals, food, and chemical products.
- It is suitable for homogeneous mixing of small amount of powders.
- It is used for providing heating and cooling effect with the help of jacketed construction.

## Merits

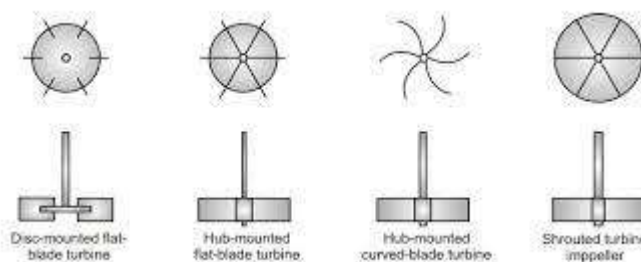
- 1) Large quantity of material can be easily handled.
- 2) It requires minimum maintenance cost.
- 3) It can be easily cleaned and maintained.
- 4) It can be easily operated with easy charging and discharging of the material.

## Demerits

1. It requires large headspace for installation.
2. Due to insufficient shearing force, it is not suitable for materials having large differences in particle size distribution or for systems containing fine particles.

## Turbine Mixer

- ◆ Turbines are mechanical devices used for mixing different types of fluids with different types of blades and impellers.
- ◆ Turbines are used for mixing high viscosity liquids because of the greater shear forces produced by them as compared to the propellers.
- ◆ They are used especially for the preparation of emulsion. For preventing vortex formation, baffles are often used.



## Construction

- ◆ Turbines consist of a circular disc having short blades attached to it. Their diameter is 30-50% of the vessel diameter. They rotate at 50-200rpm speed (lesser than the propellers). Different turbines have blades of different shapes, like straight, curved, pitched, or vertical.

## Working

- ◆ Turbines operate similar to a centrifugal pump working in a vessel against negligible back pressure.
- ◆ Mixing is accomplished by the turbine blades which constrain and discharge the liquid.

## Applications

- Due to high shear forces, they are effective for high viscous solutions, e.g., syrups, glycerine, etc.
- They are suitable for liquids of large volume and high viscosity.

## Merits

- ✓ They provide greater shearing forces than propellers, So the pumping rate is less; therefore, are suitable for emulsification.
- ✓ They do not damage dispersed particles at economical speeds.

## Demerits

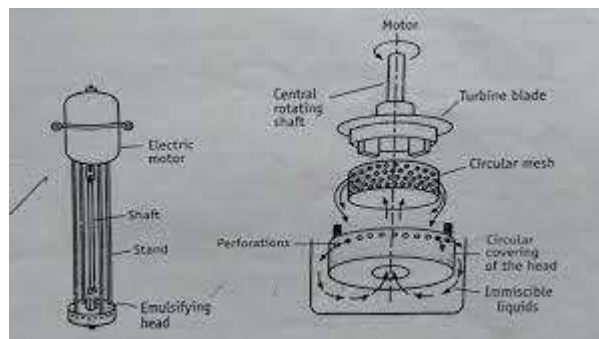
- ◆ Due to the absence of vertical flow, they are less suitable for suspension.
- ◆ They are expensive to fabricate, and are restricted to a narrow range of speeds
- ◆ They are expensive.

# Silverson Mixer Homogeniser

→ Silverson emulsifier is used for mixing or homogenising coarse particles in the emulsion and suspension to the fine form of reduced particles. Its capacity ranges from 1ml to 12lt, and its ability to mix in-line with flow rates is up to 20lt/min.

## Principle

- Silverson emulsifier works on the principle of shearing forces and turbulence produced by the high-speed rotors.
- The fluid passes through fine spaces formed by closely placed perforated metal sheets under the influence of turbulence.
- The material circulates through the head by the suction produced in the inlet at the head bottom.
- As the material circulates, the dispersed fluid rapidly breaks down into smaller globules.



## Construction

- Silverson emulsifier consists of long supporting columns connected to a motor providing support to the head.
- It has a centrally located shaft with one end connected to the motor and the other end connected to the head.
- Turbine blades are present in the head.
- These blades are surrounded by a mesh enclosed by a cover having openings.

## Working

- The head of Silverson emulsifier is placed in the vessel (containing immiscible fluid or coarse emulsion) in such a way that it gets completely immersed in the fluid.
- On starting the motor, the central rotating shaft rotates the head at a very high speed, which further rotates the turbine blades at the same speed; thus creating a pressure difference.
- As a result, fluid in the centre of the base is sucked into the head and subjected to intense mixing action.
- The contents of the head are forcefully expelled through the mesh and onto the cover by the centrifugal forces. A fine emulsion is obtained through the openings of the outer cover.
- This intake and expulsion of mixture set up (such a circulation pattern) rapidly breaks the bigger globules into smaller ones.

## Application

- ◆ It is used for mixing creams, ointments, sauces, flavouring emulsions, and pharmaceutical suspensions of globule or droplet size ranging from 2-5 $\mu$

## Merits

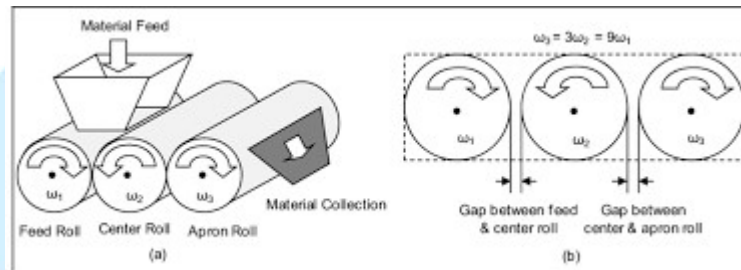
- It is available in different sizes, thus making handling of liquids ranging from a few millilitres to several thousand litres possible.
- Its mixing action reduces the processing time and also reduces the mixing time by up to 90%.

## Demerit

- It may clog pores of mesh.
- It consumes high operating power.
- It requires high shear force.

# Triple Roller Mill

- Triple roller mill is used for mixing semisolids while preparing ointments, creams, pill masses and wet mass for making granules, etc.
- Principle
- The material experiences a high shear developed by the differential speed and the narrow space between the rollers.
- Under the influence of this shear, aggregates and particles get crushed, and also the drug gets distributed uniformly throughout the semi-solid base.



## Construction

- A triple roller mill consists of three rollers of equal diameters and made up of hard abrasion resistant material (stainless steel usually).
- These rollers are arranged parallelly, and are horizontally fixed to a rigid frame.
- The pressure and gap between the rollers can be adjusted.
- A hopper is fixed between the first two rollers, and the last roller has a scrapper attached to it.

## Working

- ❖ The last two rollers are adjusted such that the distance between them is less than the distance between the first two rollers.
- ❖ The first roller is the receiving-roller, which rotates at a speed slower than that of the second roller, which itself rotates at a speed slower than that of the third roller, which is the discharge roller.
- ❖ The feed introduced is made to pass through the gap between the first and second rollers.
- ❖ The aggregates and particles are crushed and abraded by the rubbing action of the rollers; this action develops due to different rotation speed.
- ❖ A film of the feed of desirable thickness is produced.
- ❖ The feed introduced passes from the slow rotating roller to the fast rotating one.
- ❖ The gap between the second and third roller is small, thus a thinner film of feed is produced. Speed of the third roller can be increased to compensate the reduction of cross-sectional area.

- ❖ Finally the material removed by the scrapper from the last roller is collected in a receiver or transported through a suitable conveyor.

### **Application**

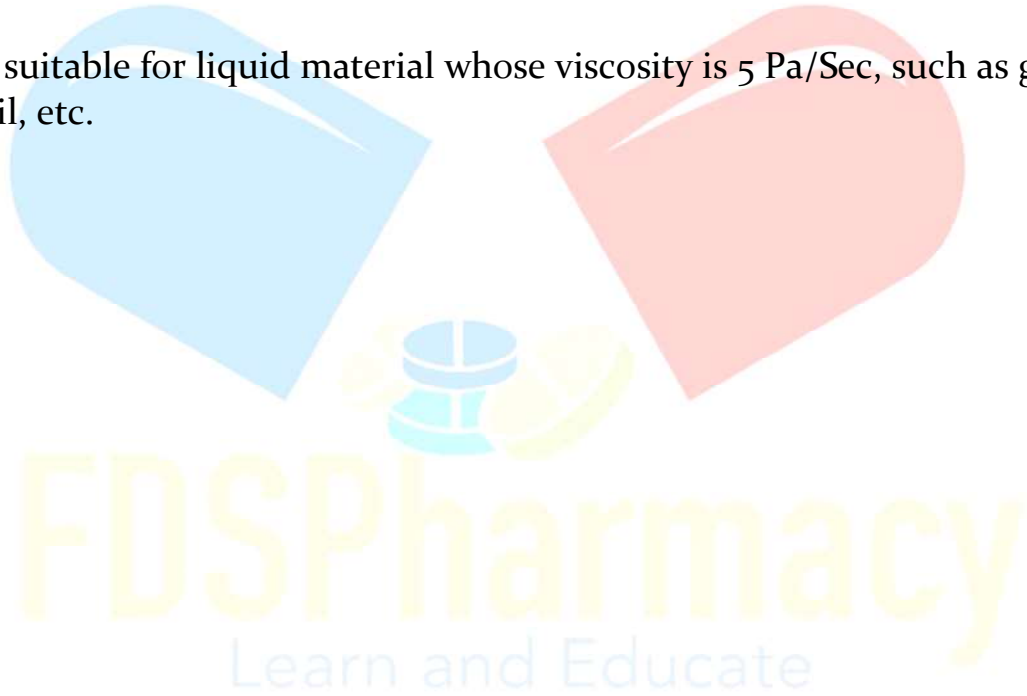
- It is used for mixing solid powders with an ointment base.

### **Merits**

- ◆ It is used in pharmaceutical industries for preparing uniform dispersion of the semisolid drugs and bases.
- ◆ It is also used in continuous processes for preparing semisolid dosage forms.

### **Demerits**

- ✚ It is not suitable for liquid material whose viscosity is 5 Pa/Sec, such as glycerin, castor oil, etc.



# Filtration

- The process in which a heterogeneous mixture of a fluid and solid particles are separated by a filter medium which permits the passage of fluid but retains the solid particles, is termed filtration.
- Oversize solids in the fluid are retained but the separation is not complete as filtrate may be contaminated with solid particles smaller in size than pore size of filter media. The suspension of solid or liquid to be filtered is known as slurry.
- The porous medium used to retain the solids is known as filter medium.
- The accumulated solids on the filter media are referred to as filter cake, while the clear liquid passing through the filter is the filtrate.
- Filtration is also used to separate particles and fluid in a suspension where the fluid can be a liquid, a gas, or a supercritical fluid.
- Depending on the application either one or both of the components may be isolated.

## Objectives

- ✚ It aims to clarify liquor purification.
- ✚ It aims to separate the solids recovered.
- ✚ It aims to separate both the liquids and solids recovered.
- ✚ It aims to facilitate or improve other plant operations.

## Applications

- ✓ It is used for improving the appearance of various pharmaceutical preparations like solutions, mouthwashes, etc.
- ✓ It is used for removing potential irritants; for example, various irritants are removed from eye drops or solutions used on mucous membrane
- ✓ It is used for removing the turbid products obtained after various unit operations: for example, filtration is performed to separate the turbid product with a small quantity of fine suspended colloidal matter obtained by the extraction of vegetable drugs with a solvent.
- ✓ It is used for detecting microorganisms present in liquids by using a filter which retains the bacteria. The efficiency of preservatives can also be evaluated by this method.

## Theories

- The liquid flowing through a filter follows the basic rules governing the flow of any liquid through a medium which offers resistance.
- The rate of flow is expressed as: Rate = Driving force / Resistance
- Theory of filtration can be explained by the following equations:
  - 1) Poiseuille's equation,
  - 2) Darcy's equation, and
  - 3) Kozeny-Carman equation

## Poiseuille's Equation

- According to Poiseuille, filtration is similar to the streamline flow of a liquid under pressure through capillaries, thus Poiseuille's equation is expressed as:

$$V = \frac{\pi \Delta P r^4}{8L\eta}$$

- V= Rate of flow, i.e., liquid volume flowing in unit time (m<sup>3</sup>/s)
  - ΔP= Pressure difference across the filter media (Pa)
  - r= Radius of the capillary in filter bed (m)
  - L= Thickness of the filter cake (m)
  - η= Viscosity of the filtrate (Pa S)
- ❖ If a bulky mass of particles form a cake and the liquid flows in between the spaces (correspond to a multiplicity of capillary tubes), the flow of liquids is expressed by the Poiseuille's equation.

## Darcy's Equation

- Poiseuille's equation considers that non-uniform and highly irregular capillaries are present in the filter. So, if the capillary length is assumed to be the bed (filter medium) thickness, a correction factor for radius is applied to approximate and simplify the rate equation.
- Therefore, Darcy incorporated the factor influencing the filtration rate into an equation which is expressed as:

$$V = \frac{KA\Delta P}{\eta L}$$

Where,

- V= Volume of liquid flowing in unit time (m<sup>3</sup>s)
- K=Permeability coefficient of the cake (m<sup>2</sup>)
- A = Surface area of the porous bed (m<sup>2</sup>)
- ΔP = Pressure difference across the filter (Pa)
- η= Viscosity of the filtrate (Pa.S)
- L=Thickness of the filter cake (capillary length) (m)

## Kozeny-Carman Equation

→ Poiseuille's equation is applicable to porous bed, based on a capillary type structure and other parameters. Thus, Kozeny-Carman equation is expressed as:

$$V = \frac{A}{\eta S^2} \cdot \frac{\Delta P}{KL} \cdot \frac{\varepsilon^3}{(1-\varepsilon)^2}$$

Where,

- A = Area of filter medium
  - S = Specific surface area of the particles comprising the cake (m<sup>2</sup>/m<sup>3</sup>)
  - ΔP = Pressure drop across the filter medium and the filter cake
  - K = Kozeny constant
- ε = Porosity of the cake (bed) Since the flow rate and  $\varepsilon^3/(1-\varepsilon)^3$  are directly proportional, 10% change in porosity can change V up to 3-folds.

## Factors Affecting Filtration

- ◆ Pressure
- ◆ Viscosity
- ◆ Surface area of Filter Media
- ◆ Temperature
- ◆ Particle Size
- ◆ Thickness of Cake
- ◆ Characteristics of slurry



## FILTRATION EQUIPMENT

- In the bulk drug industry, solid is the desired product.
- Its Size, physical properties, and purity are important
- A filter is a device (usually a membrane or layer) that is designed to physically block certain objects or substances while letting others to pass through. Filters are often used to remove solid substances suspended in fluids.

### Sintered filters

- ☞ Sintered filters consist of a filtering medium made up of jena or pyrex ground glass particles fused in the form of a disc by heating to its sintering point.
- ☞ The liquids pass through the spaces existing between the fused particles.

#### Applications

- 1) These are used for coarse, fine, and bacterial filtration.
- 2) These are used for parenteral injection, ophthalmic solution, and solution of potent drugs

#### Merits

- They are easily cleanable.
- No foreign body can enter the filtrate.
- A very small amount of medicament is absorbed.
- Negligible volume of filtrate is retained in the medium.

#### Demerits

- 1) They are expensive.
- 2) They cannot be used for large volume as it provides a small area of filtration.
- 3) They are fragile.

# Membrane Filters

- Membrane filter consists of microporous plastic films of specific pore sizes, therefore it is also known as screen, sieve, or microporous filter.
- Membrane present in these filters retains particles or microorganisms (larger than the pore size) by surface capture.

## Principle

- ✓ Membrane filter functions like a sieve and traps the particles on its surface.
- ✓ Construction
- ✓ Membrane filter consists of membranes of cellulose acetate, cellulose nitrate or mixed cellulose ester.
- ✓ The pore size of filter is in the micron or submicron range. Many grades of membrane filters are available with pore sizes ranging from  $0.010 \pm 0.002\mu$  to  $5.0 \pm 1.2\mu$ .)

## Working

- ❖ The membrane filter functions like a sieve and thus removes particles.
- ❖ The filter of  $0.010-0.10\mu$  pore sizes remove even viruses from water or air, and filter of  $0.30-0.65\mu$  pore sizes remove bacteria.
- ❖ Filter with largest pore sizes ( $0.8, 1.2, 3.0-5.0\mu$ ) is used in aerosol radioactivity and particle sizing applications.

## Applications

- 1) It is used for enhanced recovery of particular gram- positive organisms.
- 2) It is used for filtration of enzyme solution.
- 3) It is used for diagnostic cytology.
- 4) It is used for receptor binding studies.
- 5) It is used as a clarifying filter.

## Merits

- 1) It does not allow bacterial growth.
- 2) It can be easily disposed off.
- 3) It does not allow any cross-contamination.
- 4) Since adsorption is negligible, it does not impart any fibres or alkali into the filtrate.
- 5) Its filtration rate is rapid.

## Demerits

- 1) It may get clogged.
- 2) If ordinary, it is less resistant to solvents like chloroform.

# Drying

- The process in which water and other solvents are removed from a substance by applying heat is called drying.
- Removal of liquid from the solids can be done either mechanically (by using filter press or centrifuge) or thermally (by vaporisation).
- The mechanical method is more favourable and Inexpensive compared to the thermal process. Hence, before drying, the amount of liquid must be reduced to minimum

## Objective

- It decreases food decomposition caused by the moisture present.
- It prevents decomposition by the microbes so the product can be used for longer duration.
- It is used for reducing transportation and storage cost by reducing bulk and weight.
- Manufacturers get more benefit because dried goods of superior quality will also have more market value.
- It aids in granule formation.
- It is used in material processing, while preparing spray-dried lactose, dried aluminium hydroxide, and also in scale preparation of ferric ammonium citrate.
- It enables size reduction.
- It prevents bacterial and mould growth, thus increases product stability.
- In dry state, some substances like aspirin, penicillin, ascorbic acid, etc. are stable.

## Application

- Preparation of Bulk Drugs:
- Preservation of Drug Products:
- Improved Handling:
- Reduction transportation cost:
- Easy Handling and Storing:
- Provides Properties:

## Factors Affecting Drying

- Particulate Diameter
- Mechanism Involved in Drying Operation
- Size Uniformity

- Physical Properties of Wet and Dry Solid Particles
- Product mass flow rate

## EQUIPMENT DRYING

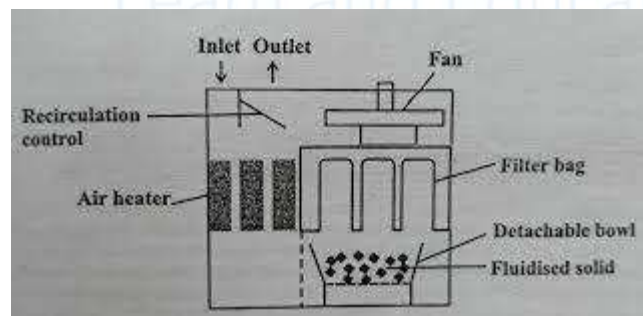
- Dryers are classified on the basis of the material being dried, i.e., solids, pastes, and solutions.
- Some of the commonly used dryers discussed below are
  1. Fluidized bed dry,
  2. Freeze dryer.

### Fluidised Bed Dryer

- When a solid material present in a holding vessel is placed under suitable conditions for the solid/fluid mixture to act as a fluid, a fluidised bed is formed.
- This is possible by exposing the material to pressurised fluid.

#### Principle

- ★ In fluidised bed dryer hot air or gas (at high pressure) is introduced within a container through its perforated bottom.
- ★ The container is filled with granules to be dried.
- ★ The gas introduced lifts up the granules from the bottom and suspends them in the air stream, thus, resulting in a fluidised state.
- ★ This dryer is useful for uniform drying of the material as the hot gas surrounds all the granules completely.



#### Construction

- Vertical fluid bed dryer and horizontal fluid bed dryer are the two types of bed dryers.
- A vertical fluidised bed dryer is made up of stainless steel or plastic.
- At the bottom of the dryer, a detachable bowl used for charging and discharging is present.

- This bowl has a perforated bottom with a wire mesh which supports the materials to be dried.
- The upper part of the dryer is equipped with a fan for circulating hot air.
- The air is heated up to the desired temperature with the help of fresh air inlet, pre-filter, and heat exchanger connected in a series.
- Temperature of the air at the inlet and outlet are monitored. Filter bags are placed above the drying bowl to recover the fines.

### **Working**

- The wet granules to be dried are put in the detachable bowl, which is then placed into the dryer.
- The fresh air introduced is allowed to pass through a pre-filter, and then through a heat exchanger after which its gets heated.
- The hot air flows through the bottom of the bowl and the fan is allowed to rotate.
- Velocity of the air is increased gradually and when it exceeds the settling velocity of granules, the granules remain partially suspended in the gas stream.
- At a point of pressure, the frictional drag on the particles equals the gravity force.
- At this point, the granules rise in the container because of high velocity gas (1.5-7.5m/min) and then fall back in a random boiling motion. This condition is the fluidised state.
- The hot air completely dries the material by surrounding each and every granule.
- The air passes through the filter bags and exits the dryer.
- The particles trapped in the filter bags remain adhered to their inside surface which can be removed by shaking the bags at frequent intervals.
- Intense mixing of granules and hot air give uniform conditions of temperature, composition, and particle size distribution.
- Drying is achieved at a constant rate and a short falling rate period.
- The residence time for drying is 40 minutes.
- The material reaches the ambient temperature when left for some time in the dryer.
- Thereafter, the bowl is pulled out for discharging the free flowing end product.

### **Applications**

- ★ It is used for drying granules to be punched into tablets.
- ★ It is used for mixing, granulation, and drying.

- ★ It is used for coating granules.
- ★ It is used for mixing ingredients.

### **Merits**

- ❖ It is less time-consuming and is 15 times faster than the tray dryer (as it takes 20-40 minutes for drying in comparison to tray dryer which takes 24 hours).
- ❖ Its handling of material is simple and demands reduced labour as the drying containers are mobile.
- ❖ It is available in different sizes with 5-200kg/hour drying capacity.
- ❖ Its mixing efficiency is high.
- ❖ Its temperatures for drying can be higher than that of the tray dryer and truck dryer.
- ❖ It occupies a small floor space.

### **Demerits**

- ✚ Drying of organic powders results in electrostatic charges which can be avoided by electrical earthing of the dryer.
- ✚ Fine particles get entrapped, therefore, should be collected using filter bags.

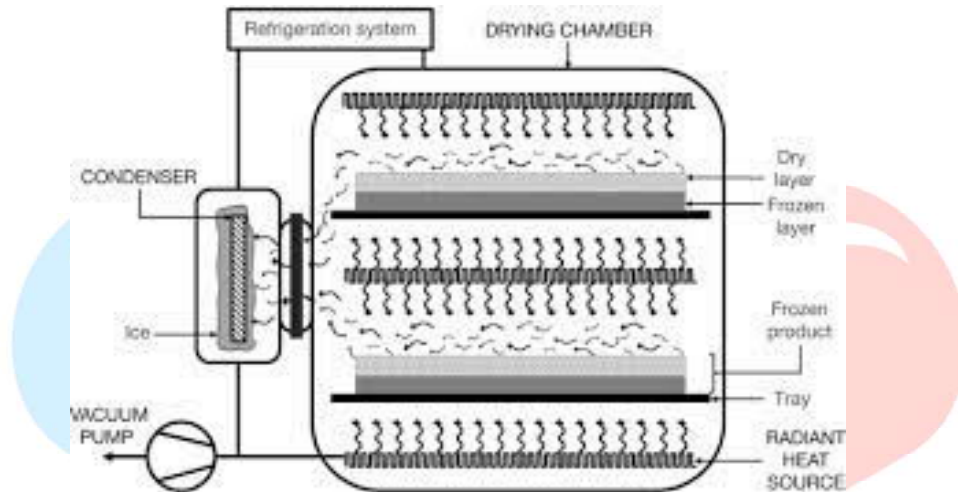
## **Freeze Dryer**

- The freeze drying involves freezing of the material and then warming in a vacuum so that the ice sublimates.
- This method is used for drying food, blood plasma or tissues, and pharmaceuticals without affecting their physical structure.

### **Principle**

- ❖ The principle of freeze drying involves removal of water from the frozen material by Sublimation.
- ❖ The experimental conditions required for freeze drying can be decided by the solid-liquid-vapour equilibrium phase diagram of water.
- ❖ Exposing the material to temperature and pressures the below the triple point, results in drying.
- ❖ Under these Conditions, the heat transferred is used as latent heat and ice sublimates (i.e., changes to vapour state directly ).

- ❖ The water Vapour is removed by condensation in a cold trap maintained at a temperature lower than the frozen material.
- ❖ Freeze drying is also known as lyophilisation Which means that for the removal of solvent, the system is made solvent loving.



## Construction

Freeze dryer consists of the following parts

- 1) Drying chamber for loading trays,
  - 2) Radiation source or heating coils for supplying heat,
  - 3) Vapour condensing or adsorption system, and
  - 4) Vacuum pump, or steam ejector, or both.
- ◆ The vacuum chamber (suitable for batch operation The batch operation) consists of shelves for loading the material to be freeze dried.
  - ◆ The distance between the subliming surface and condenser should be less than the molecules' mean path, thus, increasing the drying rate.
  - ◆ The condenser has a large surface area, which is cooled by solid carbon dioxide slurred with acetone or ethanol.
  - ◆ The condenser temperature should be less than the evaporated surface of frozen material.
  - ◆ This condition can be maintained by frequent cleaning of the condenser surface.

## Application

- ★ It is used for manufacturing injections, solutions, and suspensions
- ★ It can be also be used for drying:
- ★ Blood plasma and its fractionated products,

- ★ Bacterial and viral cultures,
- ★ Human tissue (arteries and corneal tissue),
- ★ Antibiotics and plant extracts, and
- ★ Steroids, vitamins, and enzymes.
- ★ Food items like prawns, mushrooms, meat and poultry products, coffee and tea concentrates, and citrus fruit juices can also be dried.

### **Merits**

- ❖ It is used for drying thermolabile materials.
- ❖ The porous and uniform product obtained retains its bulk volume as reconstitution of the material is easy.
- ❖ Product denaturation does not occur.
- ❖ Migration of salts and other solutes does not occur.
- ❖ Less volatile material is lost.

### **Demerits**

- ✚ Equipment and running costs are high.
- ✚ Solutions containing non-aqueous solvents cannot be dried by this method.
- ✚ It is a time-consuming process (it takes around 10 hours) and the time cannot be shortened.



# Extraction

- The process of separating medicinally active constituents of plant and animal tissues with the help of selective solvents and standard procedures is termed extraction.
- Methods of Extraction
- Extraction of crude drugs can be carried out by various processes, and the selection of process depends on the chemical properties of the drug's active constituents.

## Various extraction methods employed are:

- 1) Maceration,
- 2) Digestion, and
- 3) Percolation

## Maceration

- ☞ The word maceration denotes softening. The maceration process (or Process M) is used for producing tinctures, extracts, and concentrated infusions.
- ☞ It is the simplest method of crude drug extraction, which was official in I.P., 1966.

## Classification

- 1) Simple Maceration: A method for preparing tinctures from organised drugs, e.g., roots, stems, leaves, etc.
- 2) Modified Maceration: A method for preparing tinctures from unorganised drugs, eg., oleo-resins and gum resins.
- 3) Multiple Maceration: A method for preparing concentrated extracts. This method includes: i) Double maceration, ii) Triple maceration.

## Simple maceration

- Simple maceration involves extraction of organised drugs having specific cell structures, e.g., roots, stems, leaves, flowers, etc.
- It is a very simple method and does not require trained operators.
- Tincture of myrrh and compound tincture of benzoin are examples of products prepared by simple maceration.

## Principle

- In simple maceration, solid ingredients and the solvent are taken in a stoppered container, and left undisturbed for at least 3-7 days with frequent agitation.
- When the soluble matter dissolves in the solvent, the resultant mixture is passed through sieves or nets.
- The marc retained in the sieves is pressed, the liquids are combined, and filtered or decanted after standing.

## Apparatus

- Simple maceration is performed using a wide mouthed bottle or any other container which can be closed tightly to prevent evaporation of the menstruum.

## Procedure

- In simple maceration, the crude drug to be extracted and the menstruum are placed in close contact in a closed vessel for 7 days with frequent agitation. After 7 days, the resultant mixture is strained through sieves, the marc retained is pressed, the liquids are combined, and filtered. The drug should be properly comminuted.
- The menstruum penetrates the cellular structure of drug, and softens and ultimately dissolves the soluble portions.
- A closed vessel is used for preventing menstruum loss by evaporation.
- Occasional shaking is recommended to maintain a rapid equilibrium between the intra- and extra-cellular fluids.
- The degree of pressing the marc may vary, thus the final product is not adjusted to a fixed volume.
- Simple maceration process may take around 14 days to complete.
- The ratio of drugs to menstruum should be 1:10.
- When the drug and menstruum are left undisturbed, sediment may form, which can be avoided by standing the fluid product for a few days prior to use.
- Simple maceration method cannot be used for extracting all the drugs, thus other maceration processes have to be employed.

## Digestion

→ Digestion is a modified maceration process. It involves extraction at such a high temperature which does not put adverse effects on the active ingredients. Higher temperature enhances the solvent action of menstruum and constant mechanical agitation of the system speed up the attainment of equilibrium. If at the used temperature the menstruum gets volatilised easily, a reflux condenser should be attached to the vessel in which the digestion process is being performed; this facilitates the condensation of menstruum, so that it can be recovered and returned back to the container.



# THANK YOU