

UNIT - II.

MIXING AND HOMOGENISATION

MIXING: It is defined as the process in which two (or) more than two components in a separate/roughly mixed condition are treated in such a way, that each particle of one ingredient lies as nearly as possible to the adjacent particles of another ingredient.

- Mixing is one of the most common pharmaceutical operation

- Each & Every pharmaceutical product will be undergone mixing at one stage (or) other

- It may involve mixing of gases/liquids/solids in any combination (or) ratios.

Objectives

→ To ensure uniform composition of all the ingredients, which can be tested by taking samples and analyzing them, which represents the entire batch.

→ To enhance the physical/Chemical reaction

Eg: Diffusion, Dissolution.

Mixing is done to obtain following products:

- 1) 2 (or) more miscible liquids → True solution.
- 2) 2 (or) immiscible liquids + Emulsifying agent (oil + water) → Emulsion.
- 3) Solid + vehicle → solution
- 4) Insoluble solid + vehicle → suspension
- 5) Solid/liquid + Semisolid base → ointment
- 6) 2/Solid substances → capsule filling.
more than 2

Types of...

- 1) True solution
- 2) Suspension
- 3) Emulsion
- 4) Ointment
- 5) Capsule

HOMOGENISATION:

✓ also called as micronization

It is the process of reducing the particle sizes of pharmaceutical products under high pressure to make them stable and clinically effective

- This process is used for various types of suspensions & emulsions

- For homogenisation, machines like homogenizers are used.

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

LIQUID MIXING:

- 2 Groups.

- (a) Mixing of liquids & liquids / mixing of 2 miscible liquids
" " " immiscible
- (b) Mixing of liquids & solids / mixing of liquids & soluble solids
" " " & insoluble "

(a) Mixing of liquids & liquids:

- (1) Mixing of 2 miscible liquids
(Homogenous mixtures)
Eg: solution

✓ It is easy & occurs by diffusion
✓ Done by simple shaking/
stirring

✓ If not miscible → electric stirrer is used

- (2) Mixing of 2 immiscible liquids
(Heterogenous mixtures)
Eg: Emulsions.

✓ 2 Immiscible liquids + Emulsifying agent
↓
stable Emulsion.

✓ Mixing should not stop
✓ Continuous mixing should be done

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(b) Mixing of liquids and solids:

(i) Mixing of liquids & soluble solids
(Homogenous mixtures)
Es: Solutions.

- ✓ Solid + liquid $\xrightarrow{\text{stirring}}$ solution (Soluble)
- ✓ It is physical change

(ii) Mixing of liquids & insoluble solids
(Heterogenous mixtures)
Es: Suspensions

- ✓ Solid + liquid \rightarrow suspension (Insoluble)
- ✓ Done with motor & pestle
- ✓ can add suspending agent to get good suspension.

Equipments:

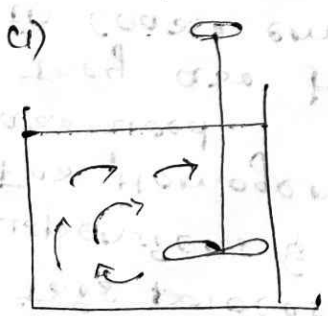
(i) Shaker Mixers:
The material is agitated by oscillatory movement
- similar to Ball Mills
- less used in industries

oscillatory (or) rotating
 \downarrow
small scale large scale

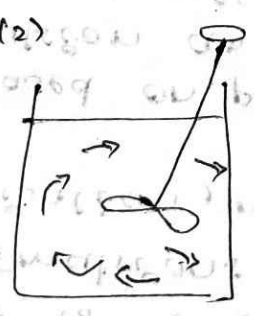
(ii) Propeller Mixers: widely used for low viscosity liquids
- Not suitable for glycerine, castor oil etc.

- The propeller is small when compared to container in which it is present
- The propeller rotates at 5000 rpm.
- Due to this high speed, there may be formation of vortices.

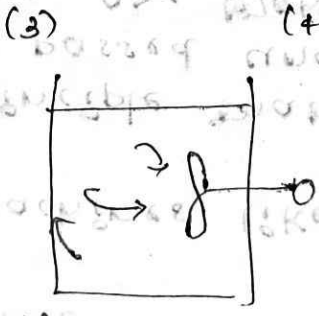
This problem can be avoided by several ways



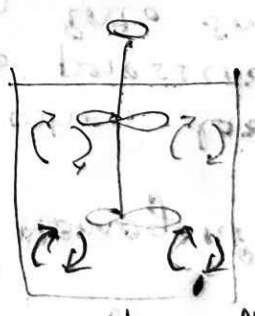
(1) attaching propeller away from centre



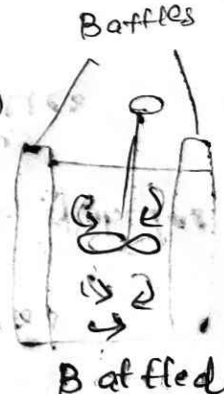
(2) placing propeller at an angle



(3) At side of the vessel propeller is placed



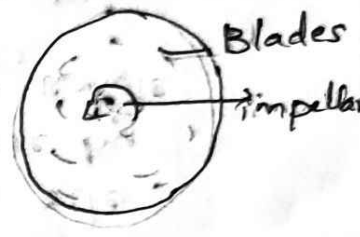
(4) push-pull



(5) Baffled

(iii) Turbine Mixers:

- It has a circular disc like impeller to which a no. of curved blades are attached
- They are rotated at low speed than propellers
- It produces great shear forces, hence they are useful for high viscosity liquids.
- It can be used in the prep. of emulsions



Mixing of Semisolids:

- Semi-solids form neutral mixtures because they do not segregate after mixing.
- All the ingredients are mixed using high shear mixers/agitator mixtures at high temperatures.

Equipments:

- 1) Agitator mixers: used for mixtures which are viscous
- used for creams and ointments.
 - they operate high pressure.
 - small quantities are mixed because of their greater thickness.
 - The most commonly used agitated mixers are Planetary mixer & sigma blade mixer.

2) Planetary mixer: Construction

- It consists of a stationary bowl containing all the mixing ingredients at the base
- A set of beaters/mixers are placed at the top
- A chopper is also present which helps in crushing the material

Working:

- The mixer blade will be dipped in the bowl containing material and mixer
- This process is continued until the mixing process is completed.
- It is used for homogenous semi-solid mixtures

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(3) Sigma-Blade Mixer:

- It consists of 2 mixing blades - sigma shaped (Σ)
- The 2 blades rotate towards each other at diff speeds
- The material to be mixed is introduced from the top and reaches the blades
- The blades move at high speed with help of motor
- The material moves up and down due to the shear between the blades
- At the bottom a discharge tube is present from where material is withdrawn.
- Planetary & Sigma-blade mixers are used for wet granulation.

Powder Mixing

- It is the process in which 2 (or) more solid substances are intermingled in mixer by continuous movement.
- It is a neutral type of mixing
- Bulk mixture \rightarrow when divided into diff doses every dose must contain equal/correct amount of each ingredient.
- Powder mixing is used for the formulation of powders, tablets and capsules.
- The following factors are taken into consideration

(a) Mixing Factors:

- (1) Volume: The mixer should not be filled up to top
- sufficient empty space must be provided.
- Overfilling reduces the efficiency, hence should be avoided
- (2) Mixing Mechanism: Mechanism plays a major role
- The mixer selected must serve its purpose by applying suitable shear force and passing the whole material through the mixing area
- (3) Duration: The mixing must be done for optimum time
- (4) Handling: After mixing, they should be handled carefully so that mixed material should not be separate

SILVERSON-MIXER-HOMOGENISER

Principle: Works on the principle of shear force which acts parallel to the surface of the material.

Construction:

- It consists of an emulsifying head to which blades are attached.
- The head is surrounded by mesh sieve made of stainless steel.
- The head is rotated with the help of motor which is connected to the head with the help of shaft.

Working:

- The head is immersed into the liquid that is to be mixed.
- The liquid is sucked through fine mesh into the head where there is vigorous mixing of liquids at high speed with the help of blades.
- The mixed material is forced out through sieve band.
- This process continues like a pattern of circulation of sucking in and forcing out of liquid.
- The whole liquid is passed through the head repeatedly where the large globules are reduced to small globules.
- Silverson mixer mixes liquids about 9-9000 litres.

Advantages:

- used in the prep of emulsions & creams.
- used for batch operations.

Hand Homogeniser

Construction:

- It is the most common equipment used in the laboratory scale.
- It consists of hopper, through which the material to be mixed is placed.
- A small orifice is present below the hopper.

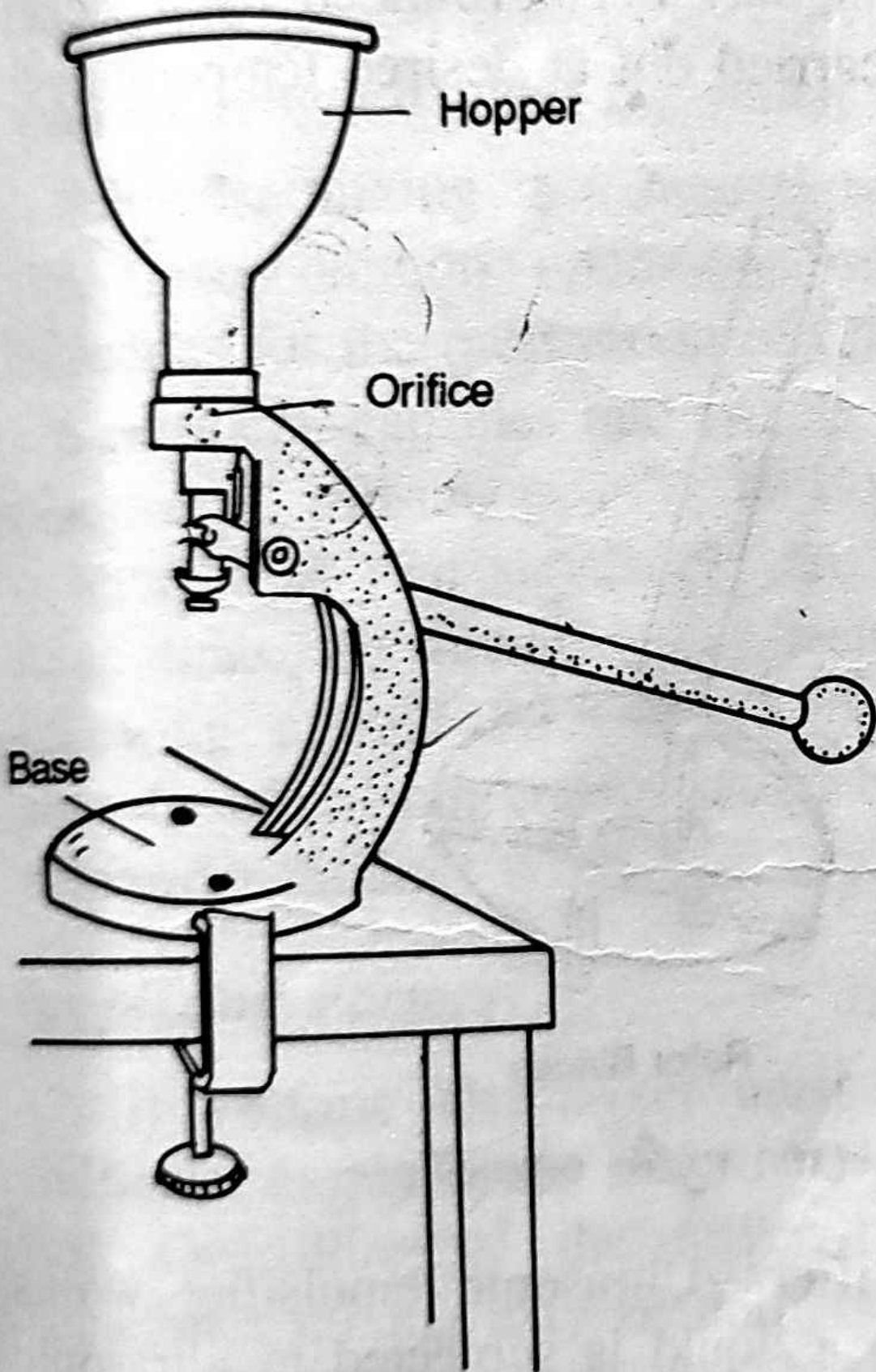


Fig. 7.2 Q.P. emulsifier

- A Handle is present which is moved upward and downward, helps in reducing the size

Working:

- A pre-boomed emulsion which is prepared by using motor & pestle is placed in the Hopper
- The emulsion is forced to pass through narrow orifice by the upward & downward movement of handle
- This results in the reduction of size of large sized globules to small globules

Triple Roller Mill:

Principle: Three roller mill / Triple roller mill uses shear forces created by 3 horizontally placed rollers rotating at opposite direction at various speeds.

Construction:

- It consists of three rollers which are made up of hard abrasion-resistant material.
- They are arranged in such a way that they come very close to each other.
- These rollers rotate at different speed.
- The material that comes between the rollers is crushed depending on the gap between them.

Working:

- The material after passing through Hopper (A) comes between roller B and C where it is reduced in size
- Then it will pass through C and D where the gap is less than B and C to crush and smoothen the mixture
- A scraper is placed such that it can remove the material and is collected

- Advantages: - used for ^{homogenisation} mixing of ointments, pastes, creams
- used in pharmaceuticals, Herbal medicals, food, agriculture.

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Double-cone Blender

Principle. Mixing occurs due to tumbling motion.
- Tumbling is the process of mixing powders by shaking & rotating them in a closed container.

Construction:

- All the parts of the equipment are made up of stainless steel.
- The equipment consists of 2 cones joined as a cylinder.
- The cones is rotated about an axis.
- The conical shape helps in easy mixing & discharge.

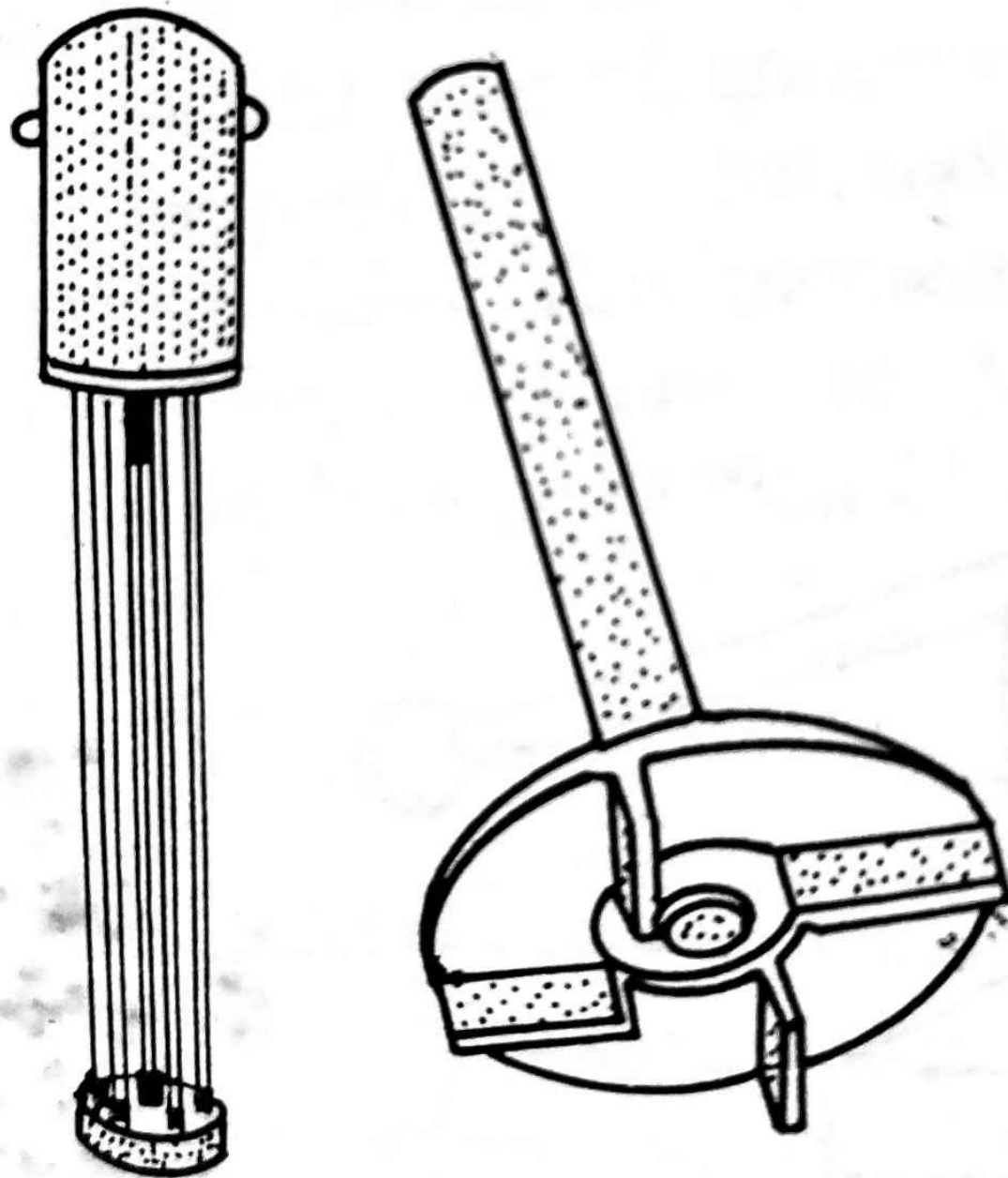
Working:

- The powder to be mixed is filled upto $\frac{2}{3}$ rd volume of cylinder to ensure proper mixing.
- The cylinder is rotated upto 30-100 revolutions/minute.
- On rotation, mixing occurs due to tumbling motion.
- The product after mixing can be discharged from the bottom of the cylinder.

Advantages:

- Easy to clean & maintain.
- No chances of clogging of material.
- Large amounts can be easily handled.

So that



Rotor Blades

Fig. 7.4 Silverson mixer emulsifier

(iv) Ultrasonic

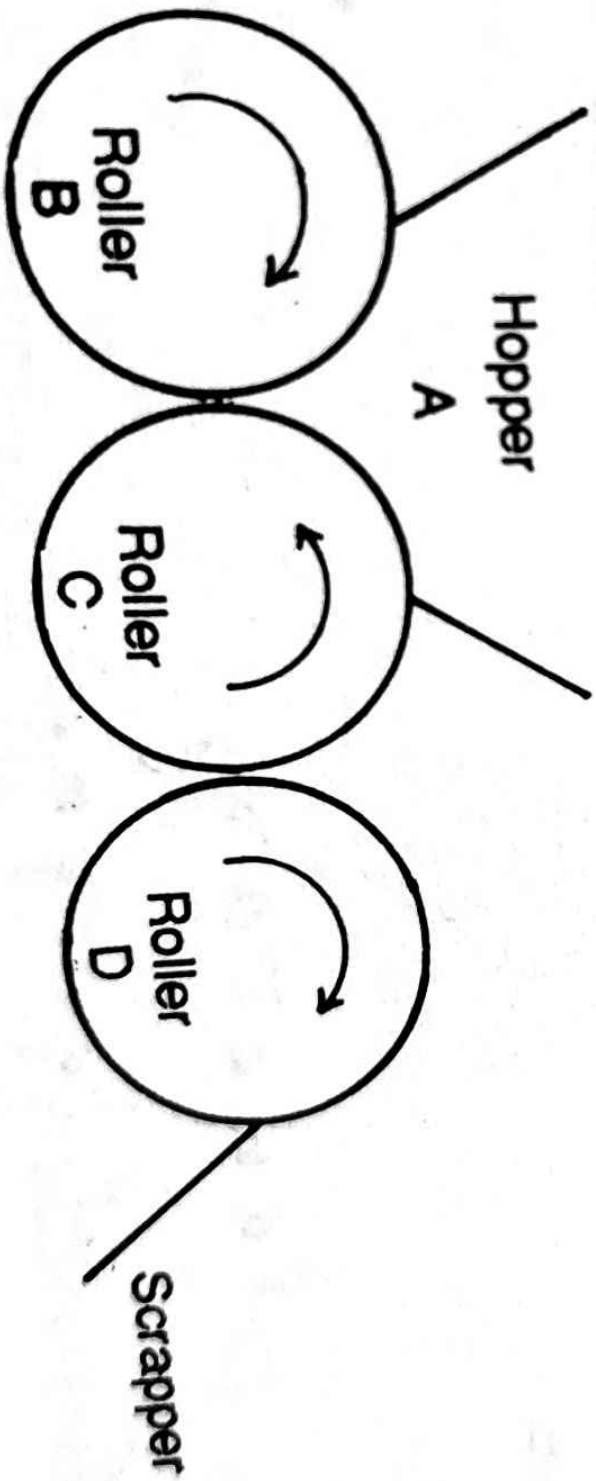


Fig 7.7 Triple roller mill

... than the

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Filtration and Clarification

Filtration may be defined as the process in which solids are separated from liquids by means of a porous medium which retains the solids but allows the liquid to pass through it and optically transparent liquid free from insoluble solids, colloidal hazes, or insoluble liquid drops is obtained.

The term clarification is used when the solids present in the liquid is very small and they do not exceed 1.0 per cent and filtrate is the required product.

The suspension of solids and liquids to be filtered is known as feed or slurry and the porous medium through which the slurry is forced to pass is called filter medium, the solids collected on the filter medium is referred to as filter cake and clear liquid which passes through the filter is called filtrate. When solids collected on the filter medium is the desired product then the process is known as cake filtration.

The mechanism of filtration is based on two operations that is

- (i) the flow of solids is resisted by the filter medium while the liquid is allowed to pass.
- (ii) as the filtration proceeds the retention of solids on the filter media goes on increasing which acts as a secondary and sometimes more efficient filtering medium.

Theory of
Filtration 130

Factors Affecting Rate of Filtration

The factors which affect the rate of filtration of any liquid is expressed by Darcy's law which is stated as under :

$$\frac{dV}{dt} = \frac{KA \Delta P}{\eta l}$$

where V = volume of filtrate

t = time of filtration

K = constant for the filter medium and filter cake.

A = area of filter medium

ΔP = pressure difference above the filter medium and below the filter medium i.e. on the filtrate.

η = viscosity of the filtrate.

l = thickness of the filter bed i.e. thickness of the filter cake and filter medium.

The above law represents the rate of flow through the capillaries of the filter medium and filter cake. From the above equation it is clear that the rate of filtration depends upon a number of factors and not only the liquid which is undergoing filtration.

The factors which govern the rate of filtration are as follows:

1. Area of Filter Surface

Rate of filtration is directly proportional to the area of filter surface. Greater the filtering surface greater will be the rate of filtration e.g. with the use of pleated filter paper filtration is increased.

2. Particle Size of the Solids to be Removed

Rate of filtration is directly proportional to the particle size of the solids to be removed.

3. Pore Size of the Filter Media

Rate of filtration is directly proportional to the pore size of the filter media.

4. The Resistance of the Filter Cake and Filter Media

The rate of flow will be greatest at the beginning of the process because there is minimum resistance but as the process

proceeds the filter cake is formed which goes on increasing and adding thickness to the cake which slows down the rate of filtration but this cake also acts as a secondary filter medium.

5. *Viscosity of the Liquid to be filtered*

The rate of filtration is inversely proportional to the viscosity of the liquid to be filtered. Liquids with low viscosity get filtered quickly whereas thick liquids get filtered slowly. The rate of filtration of such liquids can be increased by applying pressure on the viscous liquids or by increasing the temperature of liquid to be filtered.

6. *Temperature*

Increased temperature reduces the viscosity of thick liquids such as syrup, glycerin, liquid paraffin etc. thus they can be filtered quickly.

In some cases filter presses are so constructed that they can be maintained at high temperatures through which viscous liquids are to be filtered.

7. *Pressure Difference Across the Filter*

The rate of filtration is directly proportional to the pressure difference across the filter bed. The rate of filtration can be increased by increasing the pressure on the liquid to be filtered (cake filtration) or by reducing the pressure under the filter media i.e. in the receiver (vacuum filtration).

8.1 *Filter Media*

The surface or medium upon which solids are retained in the process of filtration is known as filter media.

An ideal filter media should have the following properties:

- (i) It should be chemically inert.
- (ii) It should have high retention power for the solids but should allow the maximum passage of the liquids.
- (iii) It should have sufficient mechanical strength to withstand filtration pressure.
- (iv) It should absorb negligible amounts of dissolved material.

- (v) It should be resistant to the corrosive action of the liquid.

While selecting the filter media the following factors must be taken into consideration.

- (i) Size of the particles to be filtered.
- (ii) Amount of the liquid to be filtered.
- (iii) Nature of the product to be filtered i.e. a solution, suspension or a viscous preparation.
- (iv) Purpose of filtration i.e. only to get clear preparation or to get a clear sterile preparation.

There are a wide range of filter media used for pharmaceutical processes which are discussed below :

1. Filter Paper

Filter paper is the most commonly used media for filtration. Different grades and qualities of filter paper are available. Depending on the pore size they are referred to as coarse, medium and fine. Only high quality filter paper should be used to get maximum filtering efficiency.

Though filter papers are widely used as filter media but they shed very fine particles to the filtrate moreover they have the tendency to absorb small quantity of liquid.

2. Woven Materials

Woven materials such as cloth made from cotton, silk, wool, rayon, nylon or glass act as filter media. Fine muslin made from cotton is widely used for removing very coarse particles but it can shed particles to the filtrate; has a great tendency to absorb liquid and can be destroyed by certain chemicals. Nylon cloth is also used for coarse filtration. It is superior to cotton cloth for pharmaceutical use in that the nylon is not affected by mold, fungus or bacteria and has negligible absorption properties. Nylon cloth is extremely strong as compared to cotton cloth. Due to above mentioned reasons synthetic cloth is preferred for filtration in pharmaceutical processes.

Woven wire cloth particularly made from stainless steel is quite durable, long lasting and easily cleaned which can be

reused. They are resistant to chemicals and can be easily sterilized. Wire cloth filter media afford good surface for cake filtration and are generally used with filter aids.

3. Cotton wool

Cotton wool is commonly used for filtering the coarse particles. A small tuft of cotton wool is placed in the neck of the funnel and the liquid is poured over it. The cotton wool has disadvantage that small filaments are detached from it which are carried to the filtrate. This difficulty can be reduced to a minimum by using cotton wool prepared from high quality cotton with long staple and by wetting the cotton with the menstruum before inserting it in the funnel.

4. Glass Wool

Glass wool is used for filtering highly corrosive chemicals such as strong acids, strong alkalies and oxidising agents e.g. solutions of potassium permanganate and chromic acid. Filter paper and cotton wool can't be used for filtering above mentioned substances because both these filters get destroyed. Although glass wool provides very effective filter medium but it may contaminate the filtrate with glass fibres.

5. Asbestos

Asbestos is also used for filtering the corrosive liquids. Asbestos pads are prepared by compressing shredded asbestos tightly under pressure. These pads have disadvantages in that (i) they impart alkalinity to the filtrate (ii) certain substances like alkaloids may get adsorbed on them (iii) asbestos fibres may contaminate the filtrate.

6. Kraft paper

Kraft paper is mainly used in plate and frame filters and horizontal plate filters. They offer controlled porosity, limited absorption properties and are quite cheap. White papers are preferred for pharmaceutical work. When used in large filter presses they require a support of cloth or wire mesh, to prevent rupture of the paper with pressure.

7. Sintered Glass

Sintered glass filters consists of pyrex glass powdered and sifted to produce granules of uniform size which are then heated to fuse them. The interstices between the particles form a connective system through which liquid can pass. The sintered glass can be fused in an ordinary funnel or in a Buchner funnel for filtration under reduced pressure. Various shapes and grades of these funnels are available.

These filters are used for filtering parenteral preparations and solutions meant for eyes. They are also useful for filtering corrosive liquids and oxidizing agents. Sintered glass filters do not shed particles, do not absorb any liquid and can be easily washed for re-use. For cleaning they may be scrubbed gently with a soft brush and a stream of water is introduced through the reverse direction or by chemical methods.

Note : For discussion of sintered glass funnel please refer to 'Sterilization' chapter.

8. Membrane Filters

These are thin porous membranes made from cellulose esters or similar polymeric materials or from nylon, teflon or polyvinylchloride. They are mainly used for filtration of parenteral solutions or preparations meant for ophthalmic use.

Note : Please refer to 'Sterilization' chapter also.

9. Cartridge Units

Different types of filter media are also available as cartridge units. They are used for removing low percentage of solids ranging from 100 microns to less than 1 micron in size. Two types of cartridge units are available (i) surface type and (ii) depth type. The surface type cartridges are made up of porcelain or kieselguhr in the form of candles. They can be cleaned easily for reuse by backflushing. The depth type cartridges consist of fibrous media like cotton, asbestos or cellulose. These can be used only once because they are difficult to clean and they have the tendency to shed fibres.

8.2 Filter Aids

While filtering liquids containing slimy compressible materials, the filter media soon get clogged and it becomes necessary to add a material which will check this problem, such type of substances are known as filter aids.

Filter aids may be defined as the substances which when added to the liquid to be filtered, reduce the resistance of the filter cake and increase the filtration. These substances form a porous, non-compressible cake which can retain the solid particles but allow the liquid to flow through it. A concentration of 0.1 to 0.5% of filter aid is added to the preparation before filtration. They may be added directly to the suspension to be filtered or a suspension of filter aid is first prepared in a suitable liquid which is then added to the liquid to be filtered. An ideal filter aid should have the following characteristics :

- (i) It should be chemically inert.
- (ii) It should have low specific gravity.
- (iii) It should be insoluble in the liquid to be filtered.
- (iv) It should form a porous cake.
- (v) It should be readily recoverable from the liquid.

The substances which are used as filter aids include kieselguhr, talc, charcoal, asbestos, paper pulp, kaolin, chalk, magnesium carbonate and bentonite.

8.3 Methods and Equipment Required for Filtration

The selection of a method and equipment required for filtration of a liquid depends on the nature of the material and quantity to be filtered as well as the object of the operation. Various types of equipment used for filtration are discussed below :

1. Filter Funnels

Funnels are conical shaped devices which help in pouring the liquids in narrow mouth containers. They are widely used for supporting the filter media. Funnels are generally made up of glass, polythene, copper, aluminium, stainless steel or any other suitable metal. Glass funnels made from neutral glass are most commonly used for small scale filtration.

Generally funnels with plane surface are used but they may be fluted, grooved or ribbed to increase the downward flow of the filtrate. A white filter paper of suitable pore size is selected which is folded in such a way that it fits in the funnel. To increase the rate of filtration a pleated filter paper is used by which effective filtration surface will be increased to a considerable extent. Polythene funnels are not suitable for corrosive substances.

2. Buchner Funnels

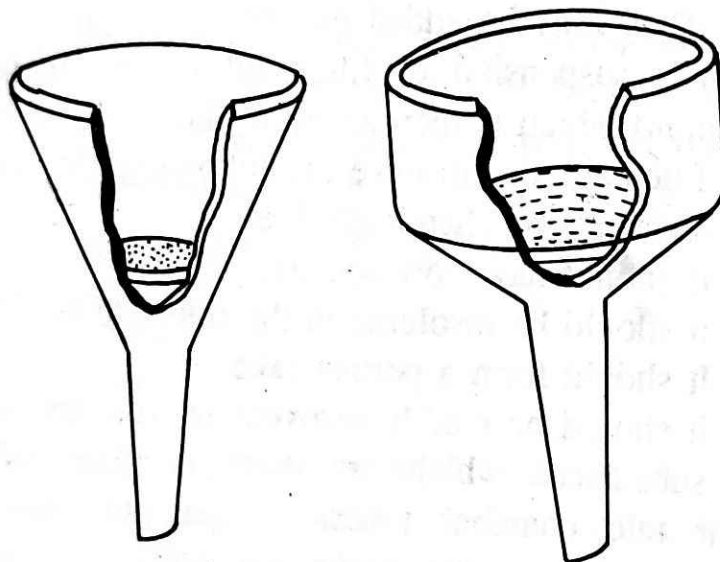


Fig. 8.1 Buchner funnels

Buchner funnels also known as Hirsch funnels are made up of porcelain which are modified in such a way that a disc of filter paper is supported on a perforated plate. These funnels are especially used for filtration under reduced pressure. They are also used for washing the precipitates.

3. Hot Water Funnels

Hot water funnels or Jacketed funnels are double walled funnels made up of a metal. Viscous substances such as liquid paraffin, glycerin, castor oil and fatty substances like wool fat, bees wax, soft paraffin, hard paraffin, ointments and creams etc. are difficult to filter at ordinary temperature but they can be filtered easily if the temperature of the funnel is maintained at a higher level throughout the process which is done by

using hot water funnels. Boiling water or steam is circulated in the jacketed funnel.

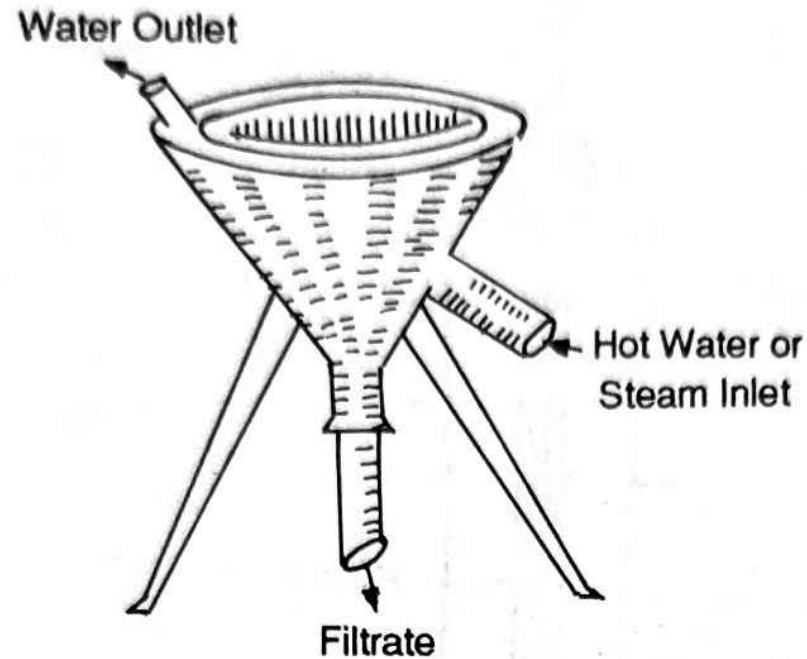


Fig. 8.2 Hot water funnel

4. Sintered Glass Funnels

These funnels are used for filtering parenteral products, ophthalmic preparations, solutions of potent substances, corrosive liquids and oxidizing agents.

FILTRATION & CLARIFICATION:

Metafilters:

Principle metafilter acts as a pressure filter, the product is fed into the filter at higher pressure and that is produced by gravity.

For particles separation, metafilter acts as strainer

Construction:

- Metafilter is a row of metal rings arranged on drainage rod
- these rings are made up of stainless steel having diameter 15mm, interior diameter 22mm, outer diameter 22mm and thickness 0.8mm
- when packed on the rod, these rings are separated by the gap of 0.2mm.

Working:

- this unit is placed in a vessel containing the slurry to be filtered.
- the slurry is either forced into the filter under reduced pressure (or) sometimes pressure is applied to the output side of filter
- when required force is applied, liquid passes through the drainage rod and ultimately reaches the receiver
- the clear liquid rises and collects at the receiver
- metafilter is only capable of straining coarse particles, but for finer particles separation a bed of kieselguhr/charcoal is deposited on the pack of rings.

Advantages: 1. There is no filter media, hence operation cost is low.

- 2) small particles can be filtered
- 3) sterile liquids can also be filtered
- 4) metafilter is strong and can withstand high pressures

Sintered Glass filters

Principle: It works on the principle of surface filtration

Construction:

- It consists of funnel, which is fitted with sintered glass filter which is made up of borosilicate glass.

- The sintered glass filter is fused with a funnel of suitable size & shape

- The sintered glass filters are available in different pore sizes and has greater mechanical strength

Working: Take the mixture to be filtered

↓
pass it through sintered glass filter
under reduced pressure

↓
particles larger than pore size retain
on the filter

↓
liquid passed through the sintered
glass

↓
Collect the filtrate in a suitable
container

↓
Repeat until liquid is clear

Advantages:

- 1) It is used for the filtration of parenteral and ophthalmic substances
- 2) It is used for the filtration of potent drugs.

Filter Candles:

Construction:

These are ceramic filters and are made up of porcelain/Kieselguhr.

- The Kiesel-guhr filters are usually softer than porcelain.

- These candles are available in the cylindrical shape with an opening which is connected to vacuum pump for reducing the pressure.

- These candles are available in different pore sizes.

Working:

- The candle is placed in the solution to be filtered.

- When vacuum is applied, the liquid will pass through the thick wall of the candle and gets collected inside the candle and filtered.

- The filter candle gets blocked by continuous use. This can be cleaned by scratching the external surface.

Uses & Advantages:

- 1) It is used for sterilization of solutions.
- 2) It is economical.

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Plate and Frame Press / Filter press:

Principle:

The mechanism is surface filtration

The slurry enters the frame

↓
Passed through filter media

↓
Filtrate is collected in plates

↓
Sent to outlet

Construction: It is made up of 2 units

Plates Frames

- They are usually made up of Aluminium alloy because it is protective against corrosive materials and suitable for steam sterilization
- The plate has a grooved surface to support the filter cloth and has outlet
- Filter media is filter cloth placed between plate & frame
- plate → Filter media → frame → Filter media → plate

Sequence of arrangement

- A no. of plates & frames are arranged in sequence

Working: 2 steps

1) Filtration operation:

- The slurry enters the frame and passed through filter media under pressure
- The solid forms a filter cake and remain in frame
- The filtrate is escaped through the outlet

2) Washing operation:

- Filtration stops when the frame is filled with the cake
- To wash the frame, wash water is pumped into it
- The wash water after cleaning, escapes through outlet

Advantages:

- 1) Construction is simple
- 2) provides large area for filtration
- 3) Efficient washing is possible
- 4) operation & maintenance is easy
- 5) Filter cloth can be easily replaced

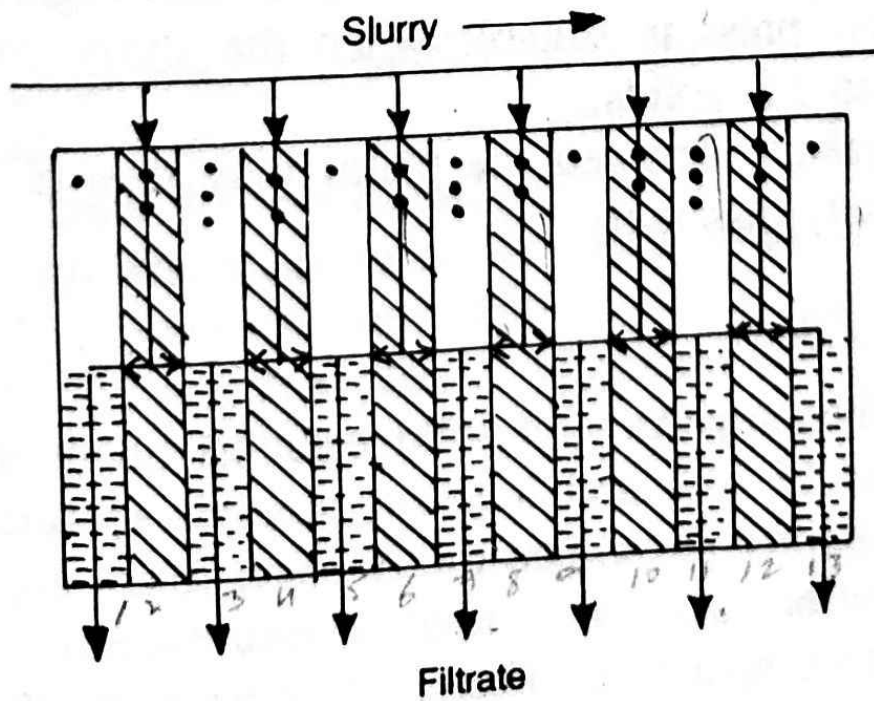
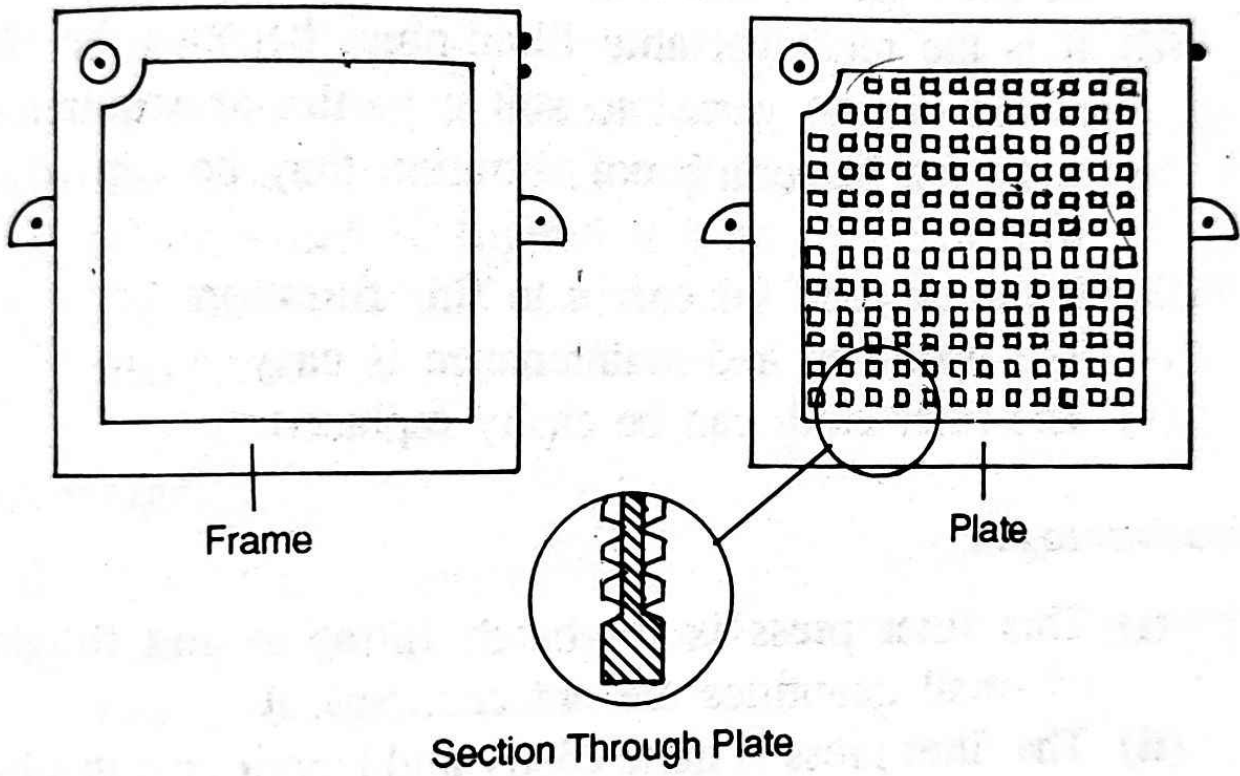


Fig. 8.4 Frame, plate and filter press showing operation

the frame