Clarification

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Credit: Prof. Nizar Al-Zoubi

Clarification

It is the processes that involve the separation of a solid from a fluid, or a fluid from another fluid.

The main reasons for clarification are:

- To remove unwanted solid particles droplets from either a liquid product or air.
- To collect the solid as the product itself (crystallization, precipitation).

Clarification can be achieved by filtration or centrifugation.

Filtration is frequently the method of choice for sterilization of solutions that are unstable under heating conditions.

Sterile filtration of liquid and gases is a commonly used method in pharmaceutical industry.

Filtration

The following terms are used in filtration:

- The mixture of solid and liquid intended for filtration is referred to as *feed*, *suspension*, *dispersion*, *influent* or *slurry*.
- The clarified liquid passing through the filter is known as *effluent* or *filtrate*.
- The accumulation of solid over filter is known as *cake*.

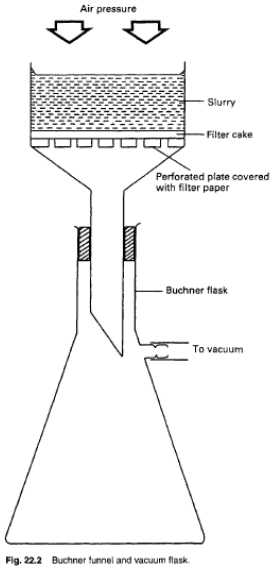

Fig. 22.2 Buchner funnel and vacuum flask.

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Types of Filtration

Solid/fluid filtration

- The separation of an insoluble solid from a fluid by means of a porous medium that retains the solid but allows the fluid to pass.
- It is the most common type of filtration encountered during the manufacture of pharmaceutical products.
- It may be divided to:
  - ***Solid/liquid filtration***
  - ***Solid/gas filtration***

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Types of Filtration

Solid/liquid filtration

The applications of solid/liquid filtration in pharmaceutical processing include:

A. Improvement of the appearance of solution, mouthwashes etc.
B. Removal of solid particles that may block certain instruments like HPLC columns
C. Removal of potential irritants (ex. from eye drops).
D. Recovery of desired solid material from a suspension or slurry (ex. after crystallization process).
E. Sterilization of liquid or semisolid products.
F. Detection of microorganisms present in liquids by analyzing a suitable filter on which the bacteria is retained.

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Types of Filtration

Solid/gas filtration

The applications of solid/gas filtration in pharmaceutical processing include:

- The removal of suspended solid particles from air in order to supply air of the required standard for:
  - processing equipment (ex. fluidized-bed, film coating and bottle cleaning equipment)
  - manufacturing areas (sterile and clean areas).
- The removal of suspended solid particles from air in order to prevent the material being vented to the atmosphere (ex. Filtering of exhaust air from fluidized-bed and coating processes).

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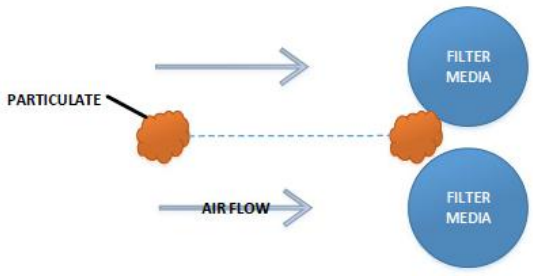
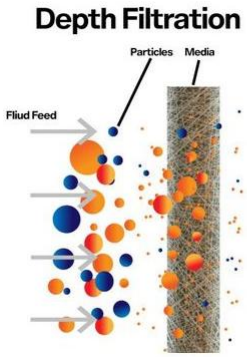
Types of Filtration

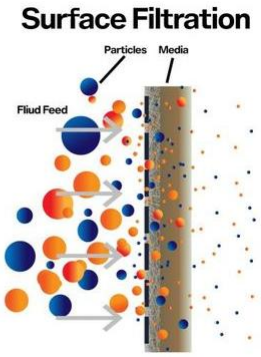
Fluid/fluid filtration

The applications of fluid/fluid filtration in pharmaceutical processing include:

- Removal of turbidity due to flavoring oil droplets.
- Filtration of air from entrained oil or water droplets.







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Mechanisms of filtration

Straining/sieving

- This occurs when the material to be removed has a larger particle size than the pores of the filter.
- Filtration occurs on the surface of the filter and therefore the filter can be very thin.
- Filter media of this type are referred as membrane filter.
- There is a tendency for them to become blocked unless the filter is carefully designed.
- Filters using straining mechanism are used where the contaminant level is low or for filtration of small volumes. (ex. The removal of bacteria and fibers from parenteral preparations).

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Mechanisms of filtration

Impingement

- Suspended solids may have sufficient momentum that they do not follow the fluid path but impinge on the filter fiber and are retained.
- Some particles (small particles that have low momentum and can pass through the pores between fibers) may follow the fluid streamlines and miss the fiber.
- To ensure the removal of all unwanted material, filter media using the impingement mechanism must be sufficiently thick so that materials not trapped by the first fiber in its path is removed by a subsequent one.
- These type of filter are referred to as depth filters.
- The fluid should flow through the filter in a streamline manner to ensure the filter works effectively.
- Depth filters are the main type of filters for filtration of gases.

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Fig. 3 SEM of the random fiber matrix of a depth filter. (Courtesy of Sartorius AG.)

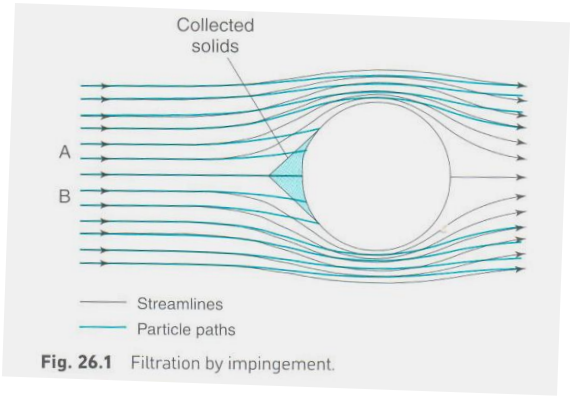

Fig. 26.1 Filtration by impingement.

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Mechanisms of filtration

Attractive forces

- Electrostatic forces and other surface forces may exert sufficient hold on the particles to attract and retain them on the filter medium.
- Air can be freed from dust particles in an electrostatic precipitator by passing the air between highly charged surfaces that attract the dust particles

Autofiltration

- It is the term when filter cake acts as a filter medium.

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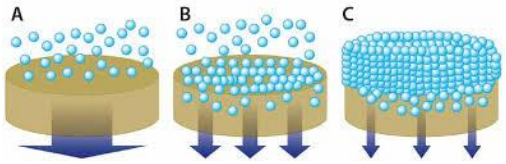
Factors affecting the rate of filtration

The rate of filtration depends on the following factors:

1. The area available for filtration (A, m^2)
2. The pressure difference (ΔP, Pa) across the filter bed (filter medium and any cake formed).
3. The viscosity of the liquid passing through the filter (μ, Pa s). A viscous fluid will filter more slowly than a mobile one.
4. The thickness of the filter medium and any deposited cake (L, m).

The above factors are combined in the Darcy equation:

$$\frac{V}{t} = \frac{KA\Delta P}{\mu L}$$



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Factors affecting the rate of filtration

- The proportionality constant (K, m^2) expresses the permeability of the filter medium and cake and increases as the porosity of bed increases.
- K is given by:

$$K = \frac{e^3}{5(1-e)^2 S^2}$$

where e is the porosity of the cake and S is the surface area of the particles comprising the cake

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Methods used to increase the filtration rate

Increase the area available for filtration

- The total volume of filtrate flowing through the filter will be directly proportional to the area of filter.
- Also, the distribution of cake over a large area means a decrease of thickness, L.
- The rate of filtration can be increased by either larger filters or a number of small units in parallel.

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Methods used to increase the filtration rate

Increase the pressure difference across the filter cake

- The gravitational force is often two low for a sufficiently quick filtration.
- If a vacuum is pulled on the far side of the filter medium then the pressure difference can be increased to a value limited practically by the boiling point of the liquid.
- Vacuum filtration is used in the laboratory when there are safety advantages when using glassware.
- Most industrial filters have positive-pressure feed using pumps. The pressure used is limited by pump efficiency and the ability of the filter to withstand high pressure.
- Pressures up to 15 bar are commonly used.

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Methods used to increase the filtration rate

Increase the pressure difference across the filter cake

- Too high applied pressure may cause the particles to deform and therefore decrease the bed porosity (e) which leads to a large (amplified) decrease in cake permeability (K).
- The effect of decreasing K greatly overweighs any increase in filtration rate arising from a thinner cake.
- There is also a danger of blinding the filter medium at high pressure by forcing particles into it, especially in the early stages before cake formation.

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Methods used to increase the filtration rate

Decrease the filtrate viscosity

- To increase the filtration rate the viscosity of the filtrate can be reduced by heating (unsuitable for thermolabile and volatile materials) or by dilution (providing that the increase in filtration rate exceeds the effect of increasing the total volume).

Decrease the thickness of filter cake

- In some cases if the cake is allowed to build up the filtration slows or may almost stop. In these situations it may be necessary to remove the cake periodically or maintain it at a constant thickness.

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Methods used to increase the filtration rate

Increase the permeability of cake

- The cake permeability can be increased by including filter aids, which is a material that forms a more porous cake when included in the dispersion to be filtered.
- Examples: diatomite and perlite.
- The use of filter aid is not appropriate when the filtered material is the intended end product.

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Filtration equipments

The equipment used for filtration should be:

- Fast
- Cheap
- Easily cleaned
- Resistant to corrosion
- Capable of filtering large volumes of product before cleaning or replacing the filter.

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What to consider when selecting filtration equipment's

a) The type of filtration and type of fluid (gas or liquid)
b) The chemical nature of the product (The product should not react, be adsorbed by or cause degradation of the filter)
c) The volume to be filtered and the required rate of filtration
d) The operating pressure needed.
e) The operating temperature.
f) The amount of material to be removed
g) Whether the filtration for sterilization or not
h) The degree of filtration required
i) The product viscosity

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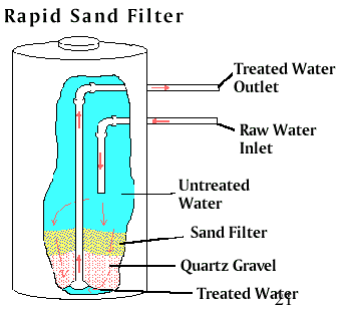
Industrial filtration equipment

Filters can be organized into three classes, namely gravity, vacuum and pressure

Gravity filters

- Gravity filters are common in water treatment, where a sand filter may be used to clarify water prior to deionization or distillation.
- Also in laboratory filtration, where volumes are small and a low filtration rate is relatively unimportant.



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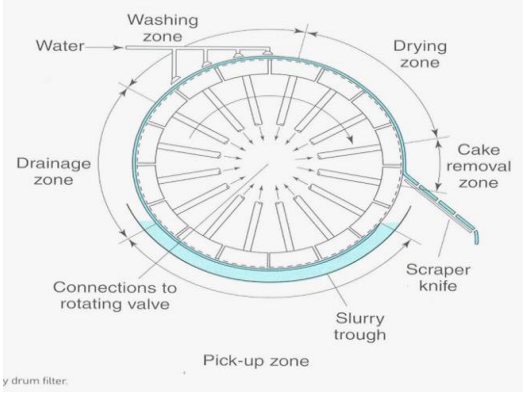
Industrial filtration equipment

Vacuum filters

Rotary vacuum filter

- The rotary vacuum filter is continuous in operation and can be run for long periods handling concentrated slurries.
- It consists of two concentric cylinders with an annular space between them divided into a number of septa by radial partitions.
- The outer cylinder is perforated and covered with a filter cloth.
- Each septum has a radial connection to a complicated rotating valve.



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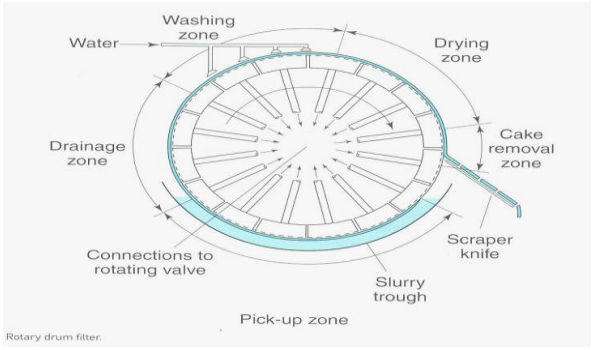

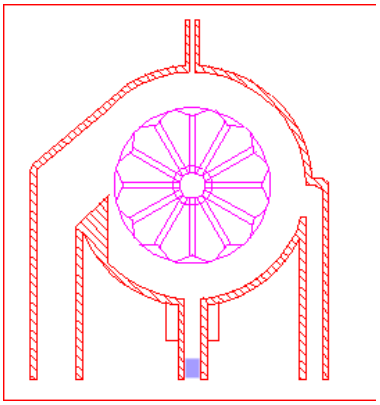

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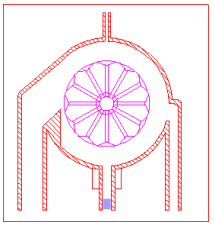
Industrial filtration equipment



Vacuum filters

Rotary vacuum filter

Operation:

- The cylinder rotates slowly in the slurry and a vacuum applied to the segments draws filtrate into the septa, depositing cake on the filter cloth.
- When the deposited cake leaves the slurry bath, vacuum is maintained to draw air through the cake, thus aiding drainage.
- This followed by washing then further drainage in the drying zone.
- The cake is removed by the scraper blade aided by the compressed air forced into the septa.
- The function of rotary valve is to direct the services into the septa where they are required.

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Industrial filtration equipment

Vacuum filters

Rotary vacuum filter

Operation:

- Rotary filters can be up to 2 m in diameter and 3.5 m in length with a filtration area of about 20 m^2.
- Difficult solids which tend to block the filter cloth necessitate a preliminary precoat of a thickness of filter aid to be deposited on the cloth prior to filtration of the slurry.
- If removal of the cake presents problems, a ***string discharge filter*** may be employed.

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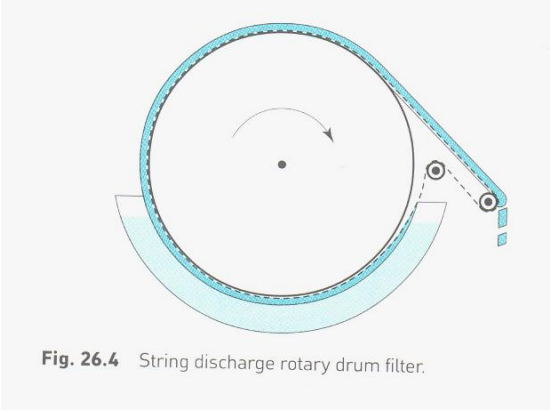
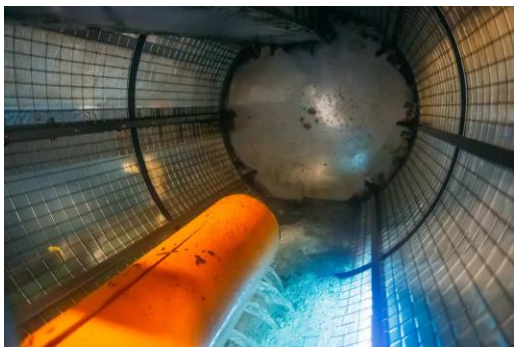


Fig. 26.4 String discharge rotary drum filter.



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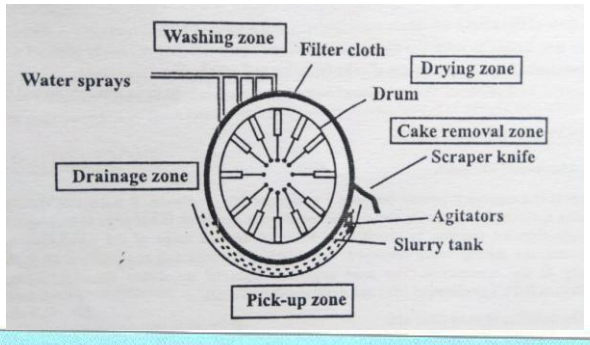

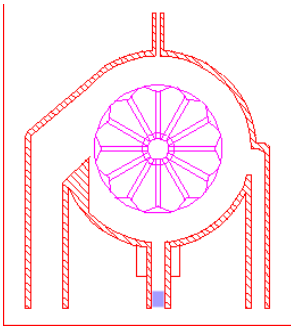

Table 26.1 Rotary vacuum filter operation

Zone	Position	Service	Connected to
Pick-up	Slurry trough	Vacuum	Filtrate receiver
Drainage	–	Vacuum	Filtrate receiver
Washing	Wash sprays	Vacuum	Wash water receiver
Drying	–	Vacuum	Wash water receiver
Cake removal	Scraper knife	Compressed air	Filter cake conveyor

In some cases, for example when the solid is the required product, the same receiver may be used for filtrate and for wash water.

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Industrial filtration equipment

Rotary vacuum filter

Advantages

- It is automatic and continuous in operation, so that labor costs are very low.
- The filter has a large capacity.
- Cake thickness can be controlled by variation of the speed of rotation.

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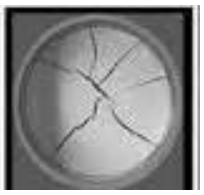
Industrial filtration equipment



Rotary vacuum filter

Disadvantages

- Complex, expensive and require ancillary equipments.
- The cake tends to crack because of the air drawn through by the vacuum system so that washing and drying are not efficient.
- The pressure difference is limited to 1 bar and hot filtrates may boil.
- The rotary vacuum filter is less satisfactory if the solids form an impermeable cake or will not separate cleanly from the cloth.

Industrial filtration equipment

Rotary vacuum filter

Uses

- The rotary vacuum filter is most suitable for continuous operation on large quantities of slurry, especially if the slurry contains considerable amounts of solids (15 –30 %).
- Examples of pharmaceutical applications include the collection of calcium carbonate, magnesium carbonate and starch.

Industrial filtration equipment

Pressure filters

Metafilter

- The metafilter consists of a grooved drainage rod on which is packed a series of metal rings.
- These rings are about 15 mm inside diameter, 22 mm outside diameter and 0.8 mm thickness, with a number of semicircular projections on one surface.
- The height of the projections and the shape of the section of the ring are such that when the rings are packed together and tightened on the drainage rod with a nut, channels are formed that taper from about 250 µm to 25 µm.

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Industrial filtration equipment

Pressure filters

Metafilter

- One or more of these packs is mounted in a vessel, and filter operated by pumping the slurry under pressure.
- For removal of finer particles a bed of a suitable material (such as filter aid) is first built up over the rings, and the pack of rings serves essentially as a base on which the true filter medium is supported.

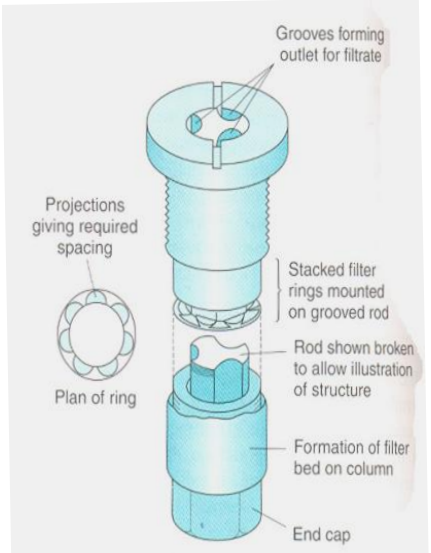

Fig. 26.5 Metafilter. Construction of the filter element.

Industrial filtration equipment

Metafilter

Advantages

- The running cost is low since there is no filter medium
- High pressures can be used with no danger of bursting
- It can be made of materials, such as stainless steel, that provide resistance to corrosion and avoidance of contamination.
- By selecting of a suitable grade of material to form a filter bed it is possible to remove very fine particles.

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Industrial filtration equipment

Cartridge filters

- They consist of a cylindrical cartridge, containing highly pleated material (ex. Polytetrafluoroethylene (PTFE) or nylon) or string-wound material, fitted in a metal supporting cylinder.
- The product is pumped under pressure into one end of the cylinder surrounding the filter cartridge.
- The filtrate is forced through the filter cartridge from the periphery to the inner hollow core from where it exits through other end of the support cylinder.

Cartridge filters

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Industrial filtration equipment

Pressure filters

Plate and frame filter press

- Material to be filtered enters the apparatu under pressure through a pipe at the botton and is forced into one of the many chambers A filter cloth is positioned on both sides o each chamber.
- As the material passes through the filter cloth, solids remain behind in the chamber and the clear filtrate passes through and out of an opening located on the top of the apparatus.

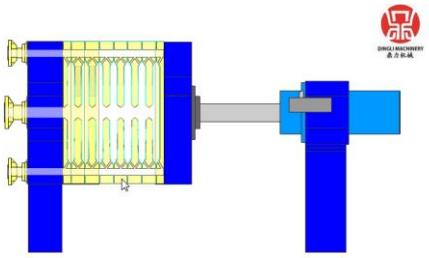

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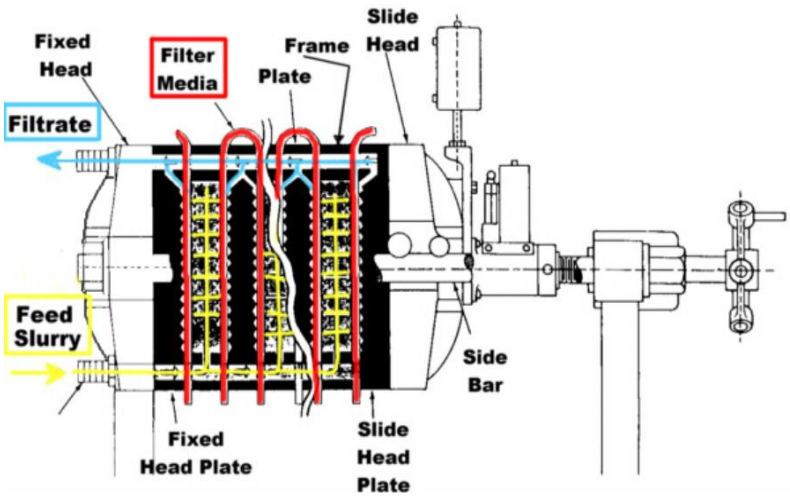
Plate and frame filter press



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Industrial filtration equipment

Plate and frame filter press

Advantages

1. Construction is very simple and a wide variety of materials can be used.
2. It provides a large filtering area in a relatively small floor area.
3. It is versatile, the capacity being variable according to the thickness of the frames and the number used.
4. Maintenance is easy and the filter cloths are renewable.

Disadvantages

a. It is a batch filter
b. The press is relatively expensive and labor costs are high
c. The filter is used for slurries containing less than 5 % solids.

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Industrial filtration equipment

Cross flow microfiltration

- It is possible to form membrane filters within hollow fibers The membrane may consist of polysulphone, acrylonitrile or polyamide is laid down within a fiber which forms a rigid outer porous support.
- A large number of fibers can be contained in a surrounding shell to form a cartridge which have a high effective area for filtration.
- The liquid to be treated is pumped through the cartridge in a circulatory system so that it passes through many times.
- The filtrate (permeate) flows radially through the membrane and porous support.

Uses:

- For fractionation of biological products.
- The process has been suggested for recovery of antibiotics from fermentation media

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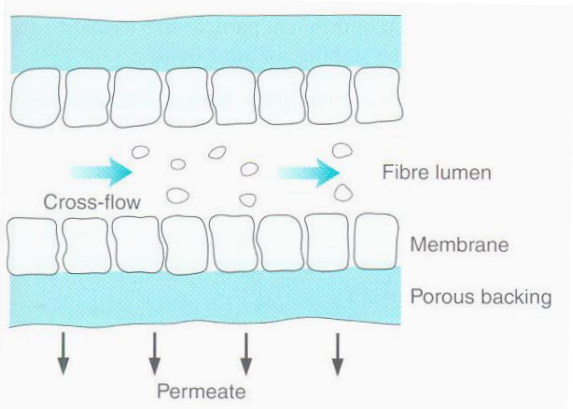

Fig. 26.6 Cross-flow microfiltration through an individual fibre.

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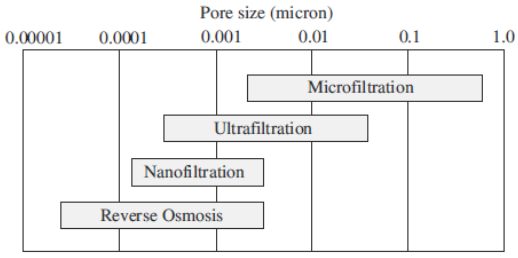
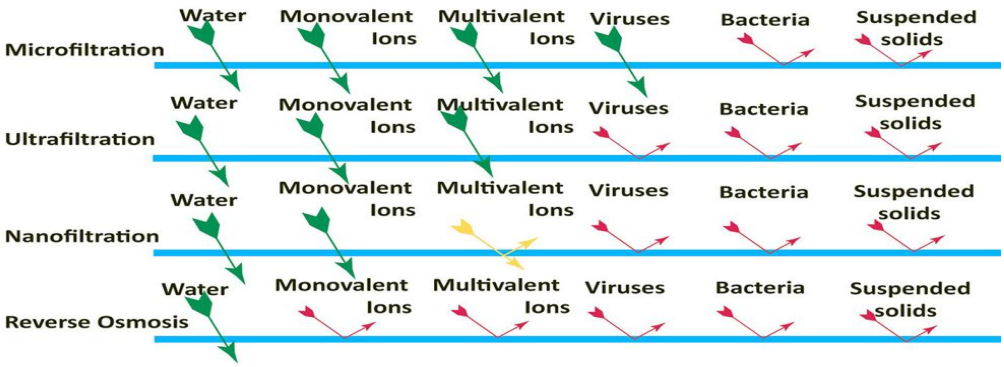


Fig. 1 Typical pore sizes for membranes used in reverse osmosis, nanofiltration, ultrafiltration, and microfiltration.



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Centrifugation

- Centrifugal force can be used either to provide the driving force for filtration or to replace the gravitational force in sedimentation.

Principles of centrifugation

- If a particle (mass = m, Kg) spins in a centrifuge (radius r, m) at a velocity (v ms^{-1}) then the centrifugal force (F, N) acting on the particle is equal to m v^2/r.
- The same particle is affected by gravitational force (G, N) = mg (g = gravitational constant).
- The centrifugal effect (C) is the ratio of these two force (C = F/G).
- If velocity is taken to be πdn (n: rotation speed s^{-1}, d: diameter of rotation, m), then:

$$C = 2.01 d\, n^2$$

- In order to increase the centrifugal effect it is more efficient to increase the centrifuge speed (n) than to use large diameter (d).

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Industrial centrifuges

There are two main types of industrial centrifuges used to achieve separation:

- Centrifuges using perforated baskets, which perform a filtration-type operation (work like spin drier)
- Centrifuges with solid walled vessel, where particles sediment towards the wall under the influence of centrifugal force.

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Industrial centrifuges

Perforated-basket centrifuges (centrifuge filters)

- This centrifuge consists of a stainless steel perforated basket lined with a filter cloth.
- The basket rotate at speed which is typically less than 25 S^{-1}.
- The filtrate is forced through the cloth while the solid material is retained on the cloth.
- The cake can be washed if required by spraying water into centrifuges

Advantages:

A. It is compact and efficient

B. It can handle concentrated slurries which might block other filters.

C. It gives products with a very low moisture content (typically around 2%) which saves energy during drying.

D. Continuous centrifuges are available for large-scale work, which have means for automatic discharge of the cake from a basket.

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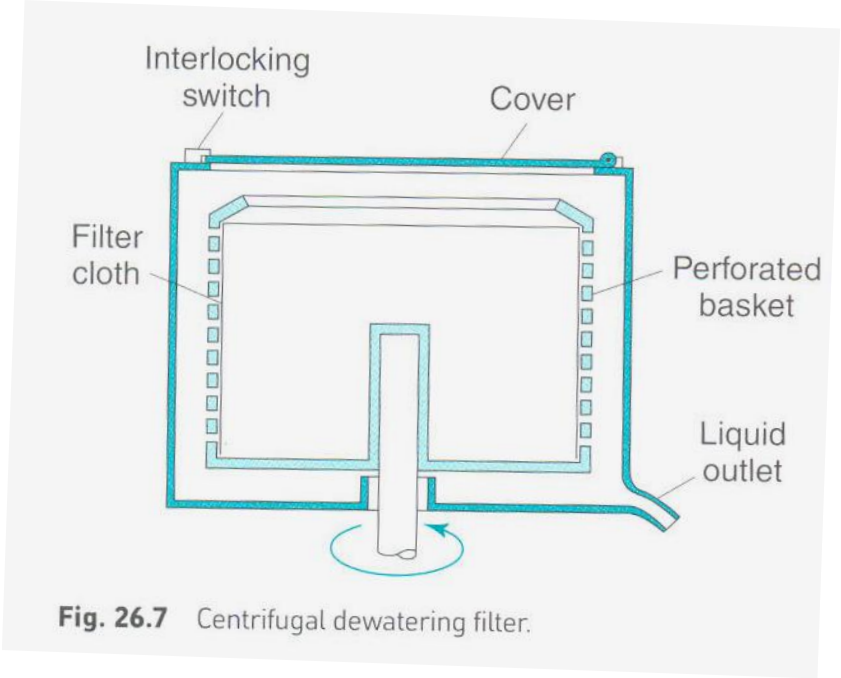

Fig. 26.7 Centrifugal dewatering filter.

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Industrial centrifuges

Tubular bowel centrifuges (centrifugal sedimenters)

- These consist of a cylindrical bowl, typically around 100 mm in diameter and 1 m long, which rotates at 300 - 1000 s^{-1}.
- The product enters at the bottom and the centrifugal force causes solids to be deposited on the wall as it passes up the bowl, the liquid over flowing from the top.
- This type of centrifuges can be adapted to separate immiscible liquids.
- The inlet rate should be controlled in order to allow sufficient time for sedimentation to occur before the product leaves the bowl.

Advantages

- Compact efficient and rapid
- Solids can be classified by control of the speed of rotation and the flow rate.
- Suitable for difficult solids that would block the filter medium.

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Industrial centrifuges

Tubular bowel centrifuges (centrifugal sedimenters)

Uses:

1. Liquid/liquid separation
2. The removal of very small particles
3. The removal of solids that are compressible or those which easily block the filter medium.
4. The separation of different particle size fractions
5. Examining the stability of emulsions
6. The separation of blood plasma from the whole blood
7. The removal of dirt and water from oils

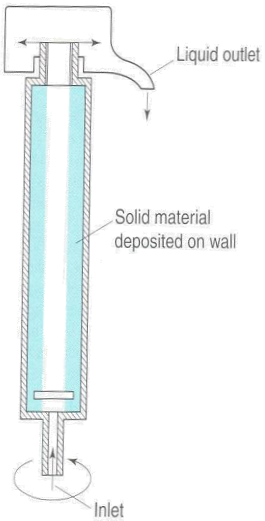

Fig. 26.8 Tubular-bowl centrifuge.

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Filter media

- The surface upon which solids are deposited in a filter is called the filter medium
- The filter medium must
  1. be strong
  2. have low resistance to flow
  3. be unaffected by the substances in the slurry
  4. Retain solids without plugging
- Filter media are available in different materials and forms:
- Woven materials
  - Filter fabrics woven from natural fibers (ex. cotton), synthetic fibers, glass, or metal (ex. stainless steel).

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Filter media

- Nonwoven filter media
  - Felts, bonded fabrics and Kraft papers
- Membrane filter media
  - They are used commonly in the preparation of sterile solutions.
  - They are made of various esters of cellulose or from nylon, Teflon, PVC, polyamide or polysulphone.
  - The filter is a thin membrane, about 150 microns thick , with 400 to 500 million pores / cm^2 of filter surface.
  - The pores are extremely uniform in size and occupy about 80% of filter volume.

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Filter Aids

- Usually, the resistance to flow due to the filter medium is very low, but will increase as a layer of solids (cake) is build up.
- The object of filter aid is to prevent the medium from becoming blocked and to form an open porous cake.
- Filter aid may be used in two ways:
  - Precoating: Application as a precoat over the medium by filtering a suspension of the filter aid.
  - Body-mix: Adding a small proportion of the filter aid (0.1 –0.5 %) to the slurry.
- Filter aid may be used intentionally to adsorb certain solutes (ex. Decolorising sugar solutions by means of charcoal).

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Filter Aids

- Important characteristics of filter aid:
  a. It should be a structure that permits formation of pervious cake
  b. It should have a particle size distribution suitable for retention of solids, as required.
  c. It should be able to remain suspended in the liquid
  d. It should be inert
  e. It should be free from moisture in cases that the addition of moisture to the liquid is undesirable.

Examples:

- Talc: Nonadsorbent, chemically inert
- Charcoal: Adsorbent for many active constituents.
- Clays: ex. fuller's earth, Kaolin
- Chalk and Magnesium carbonate: react with acids and possess a finite solubility in water and aqueous fluids, with the production of alkalinity in the filtrate.
- Bentonite, diatomaceous earth, perlite, asbestos. cellulose, silica gel.

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