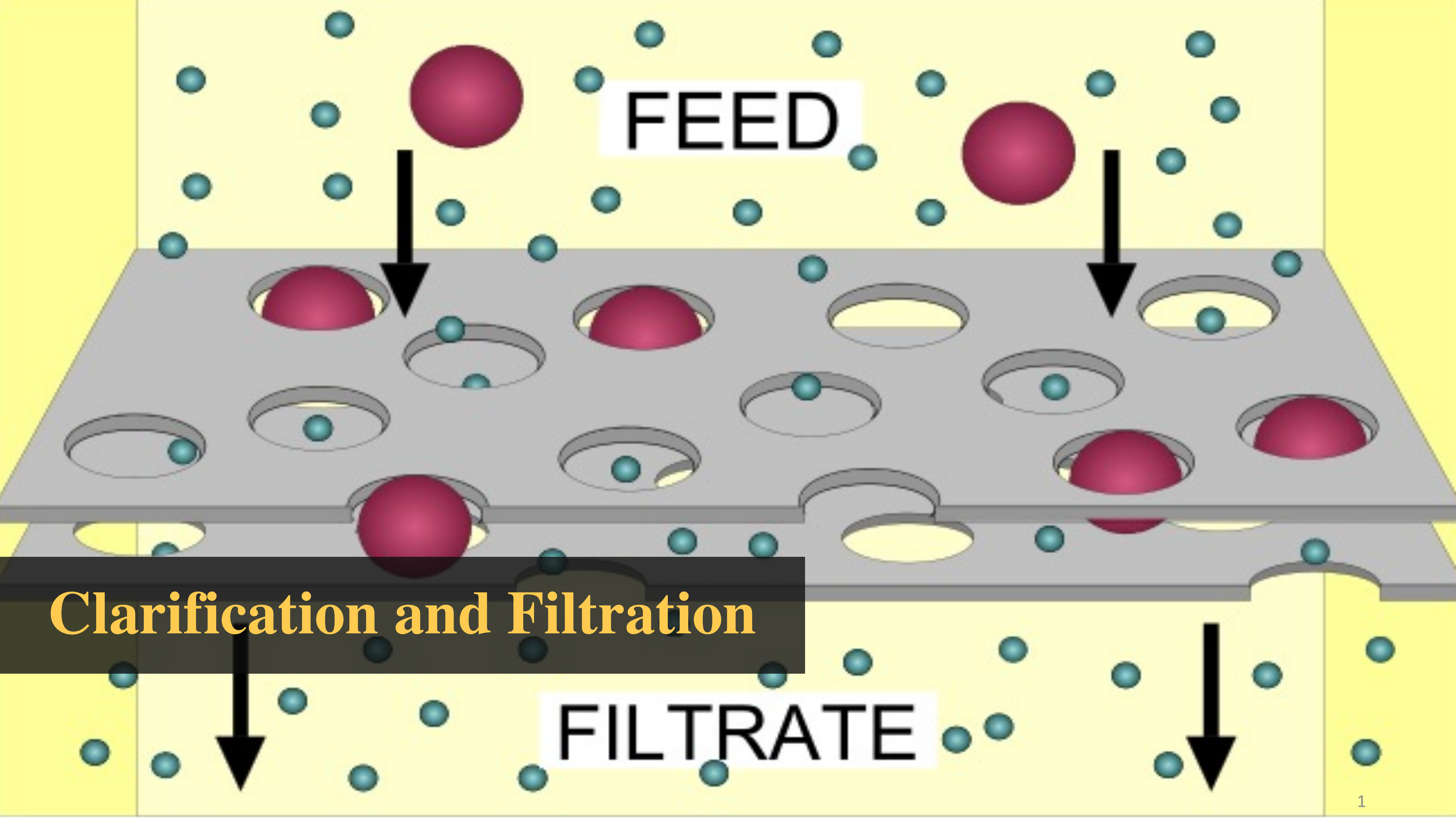


Clarification and Filtration

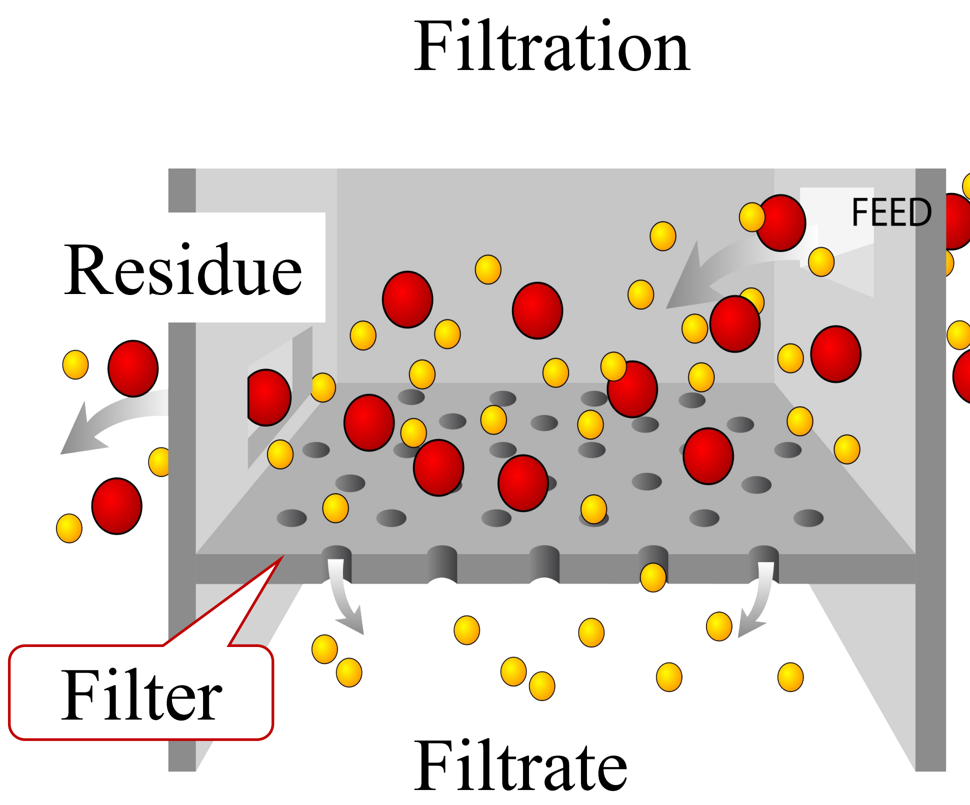
Definitions

- **Clarification**: process that involves the **removal or separation** of a solid from a liquid, or a fluid from another fluid.
- The term “fluid” involve both **liquids and gases**.
- Clarification can be achieved using either **filtration or centrifugation techniques**.
- In **pharmaceutical processing** there are two main **Goals** for such processes:

1. To **remove unwanted solid** particles from either a liquid product or from air
2. To **collect the solid** as the product itself (e.g. following crystallization).

Definitions

- **Filtration**: the process in which particles are separated from a liquid by passing the liquid through a permeable material.
- **Filter**: is the permeable material that separates particles.
- The mixture of solids and liquid is called : **feed, suspension, dispersion, or slurry.**
- After passing of the suspension through the filter, solid will retain in/on the filter and form a **cake** that called **residue**.
- The liquid will pass through the filter and it is called **filtrate or effluent.**



Application of Filtration in Pharmaceutical Processing

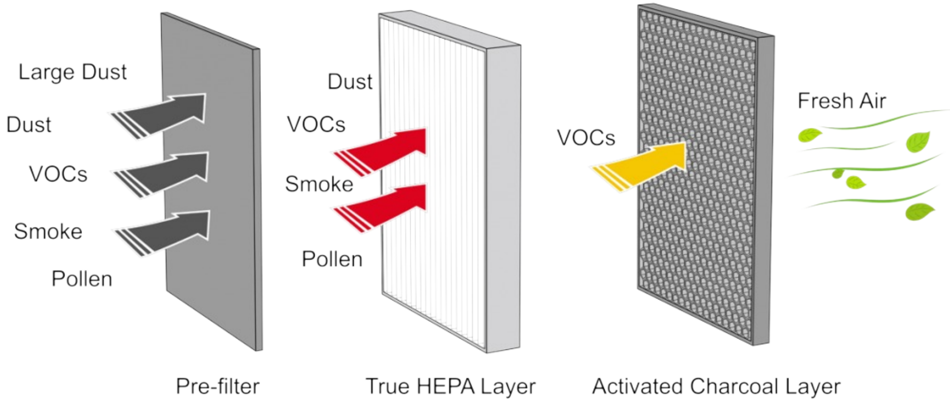
1. **Improvement of the appearance** of solutions, mouthwashes, etc, to give them a 'sparkle' or 'brightness'.
2. **Removal** of **potential irritants**, e.g. from eye-drop preparation or solution applied to mucous membranes.
3. **Recovery of desired solid** material from a suspension or slurry, e.g. to obtain a drug or excipient after a crystallization process.
4. Production of **water of appropriate quality** or pharmaceutical uses such as Nanopure® water.

Application of Filtration in Pharmaceutical Processing

5. **Sterilization of liquid** or semi-solid products where processes involving heat (such as autoclaving) are not appropriate. This process called **sterile filtration**.

6. **Detection of microorganisms present** in liquids. This can be used to assess the **efficiency of preservative** added to the pharmaceutical product.

7. **Improve air quality** for various application by using air filters of various types. This is can have a great impact of workers, product, and environment for example by filtering the exhaust air in factories.

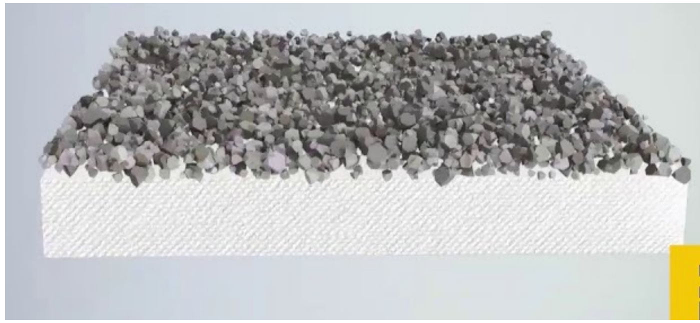


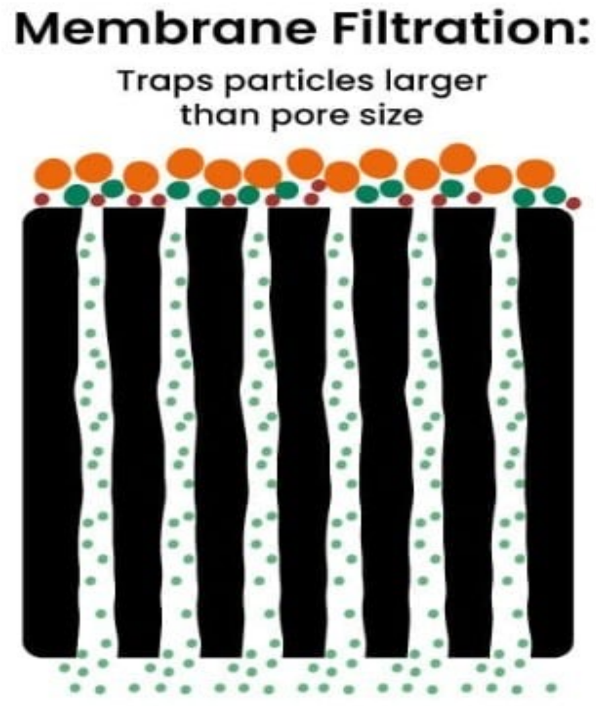
Mechanisms of Filtration

- **Four** different mechanisms of filtration according to the way in which the suspended material is trapped by the filter medium are as follow:

1. **Surface straining/ sieving**: any particle that is larger in size than the pores of the medium deposits on the surface, and stays there until it is removed.

- Particle that are smaller in size than the pores pass quickly through the medium.
- Filtration occurs on the surface of the filter so **called membrane filters.**
- Because filtration occurs on the surface, there is a tendency for them to become **blocked** unless the filter is carefully designed.
- So, Filters employing the straining mechanism are used where the **contaminant level is low** or small volumes need to be filtered.

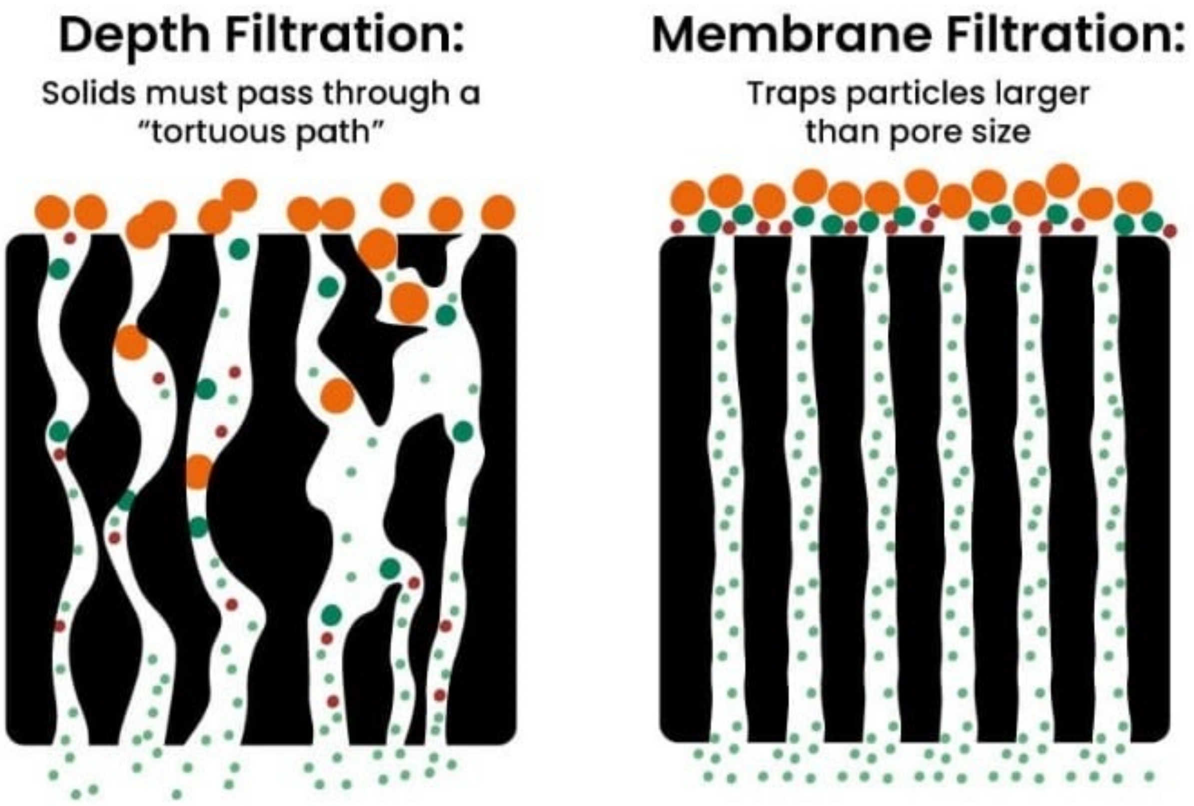




Mechanisms of Filtration

2. **Depth straining**:

- Similar to previous mechanism in which is governed by the particle size or shape.
- However, the filter medium here is **thick** and the particle **will travel along the pore** until they reach a point where the pore narrows down to a size too small for the particle to go any further.



3. Depth filtration (impingement):

- Involve different mechanisms.
- As a flowing fluid approaches and passes an object, for example a filter fiber, the fluid flow pattern is disturbed. ➔:
- **Suspended solids** may, however, have sufficient momentum so that they **do not follow the fluid** path but **impinge** on the filter fiber and are retained, **owing to attractive forces between the particle and the fiber**.
- The action of **attractive forces such** as (van der Waals) even small particle will be entrapped in the filter even if it was smaller than the pores.

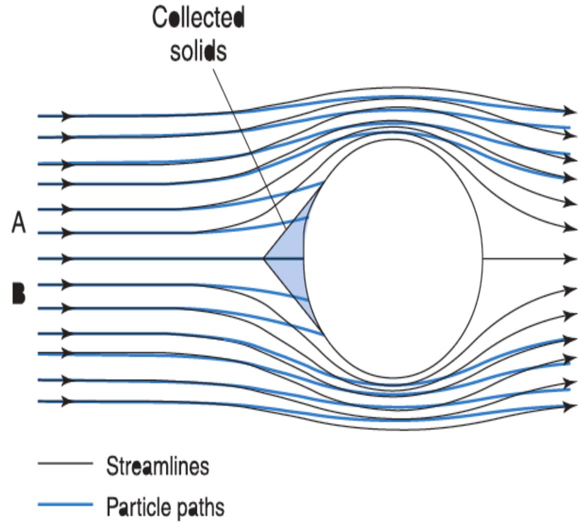
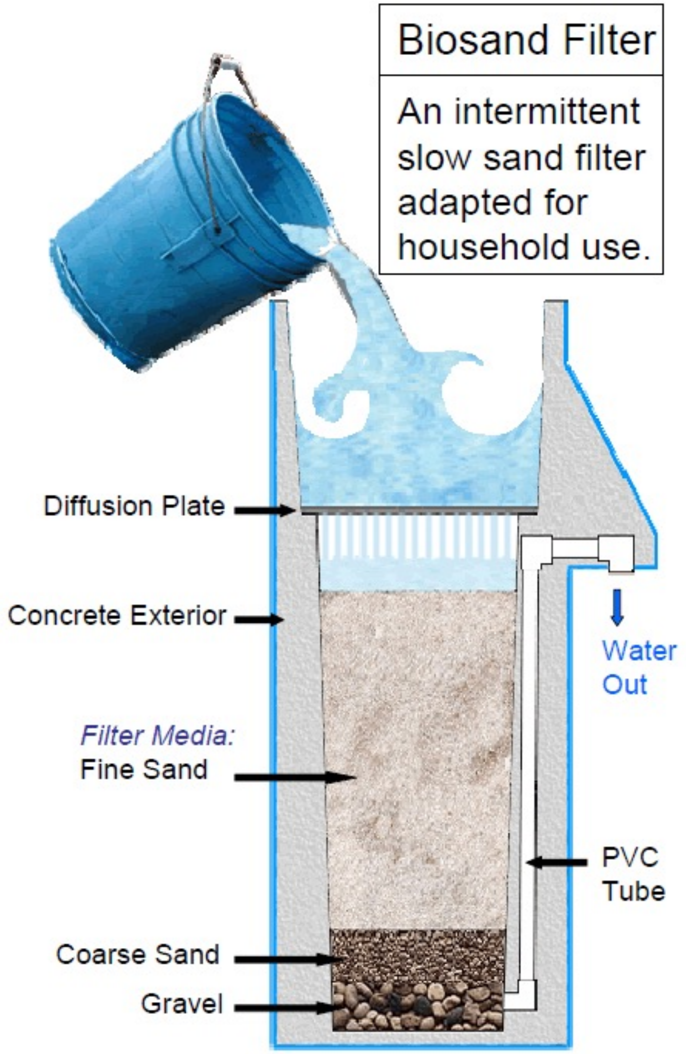


Fig. 25.1 • Filtration by impingement.

Mechanisms of Filtration

- <u>Impingement mechanism (continue)</u>

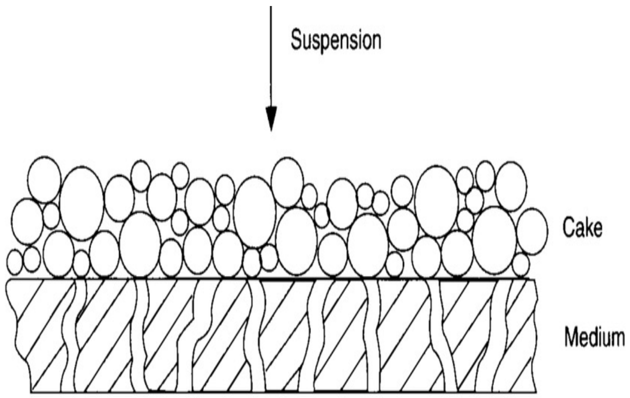
- To help in entrapment of small particles that may escape the pores, the filter is thick and the particle escape the first layer will be held in the subsequent layers. That's why it is called **depth filtration**.
- This mechanism is most important in air filters and sand filters.
- Other examples of impingement filters are air filters, fuel filters and oil filters used in cars.



Mechanisms of Filtration

4. Cake Filtration (auto filtration):

- The filtered material **acts as its own filter medium**.
- **Starts** with the formation of **a layer of particles** on the surface of the filter medium, with **larger pores bridged by a group of smaller particles.**
- On this layer , a **cake of particles accumulated** to act as the filter medium for subsequent filtration.
- In this mechanism the **solid is the goal** of the process.
- This process requires the **solution to contain a large amount** of suspended solids.
- This is **widely used in pharmaceutical** processing.



Factors Affecting Filtration

1. The **properties of the liquid** , such as density, viscosity, and corrosiveness.
2. The **properties of the solid**, for example, particle shape, particle size, particle size distribution, and the rigidity or compressibility of the solid.
3. The **proportion of solids** in the slurry.
4. Whether the **goal** is to collect the solid, the liquid ,or both.
5. Whether the **solids** have to be **washed free** from the liquid or a solute.

Filtration Theory

- It is complex to know the exact mathematical model of filtration process.
- We can **estimate** resistance to flow of **empty filter** but it will be more complicated when we have a suspension in it **since additional resistance and pressure drop** will happened which will be variable for example with the thickness of the cake formed on the top of the filter.
- However, we can study some expressions:
- The Flow rate may be expressed as:

$$rate = \frac{driving\ force}{resistance}$$

- The **rate** may be expressed as **volume per unit time (rate change dV/dT)** and Driving force (**pressure differential**).
- **But**: **Resistance** is **not constant** since it increases as solids are deposited on the filter medium.

Filtration Theory

- Another equation called **Darcy's equation** that counts for the change in resistance to flow during filtration as follow:

$$\frac{dV}{dT} = \frac{KA\,\Delta P}{\eta L}$$

- where (dV/dT rate change, A= filter area, P= pressure **drop** through filter medium, η =filtrate viscosity, L bed thickness, K permeability coefficient and depends on the nature of the precipitate to be filtered and filter medium itself.

- So

$$rate\ of\ filtration = \frac{(Area\ of\ filter)x\ (pressure\ difference)}{(viscocity)\ x\ (resistance\ of\ cake\ and\ filter)}$$

Interpretation of Flow Rate Equation
How to Change the Flow Rate

$$rate\ of\ filtration = \frac{(Area\ of\ filter)\ x\ (pressure\ difference)}{(viscocity)\ x\ (resistance\ of\ cake\ and\ filter)}$$

a. **Pressure increases** → increase in flow unless the cake is highly compressible.

- **Change pressure difference** by using a **vacuum** (pull) on the far side (under) the filter which will increase the pressure difference up to atmospheric pressure.
- **Note**: this **also** can be done by **pumping** the fluid into the filter (industrial scale).
- **Note**: high pressure may cause dense cake that block the filter, so care must be taken during vacuum filtration.

Interpretation of Flow Rate Equation
How to Change the Flow Rate

$$rate\ of\ filtration = \frac{(Area\ of\ filter)\ x\ (pressure\ difference)}{(viscocity)\ x\ (resistance\ of\ cake\ and\ filter)}$$

b. **Increase in area** → increases flow since cake thickness and thus resistance are also **reduced**).
- Can be done by using **larger filter** of a number of small units in parallel.
- **Note:** flow is proportional to A^2 because **L** term has area in its equation → small increase in area will results in a bigger increase in flow rate.

Interpretation of Flow Rate Equation
How to Change the Flow Rate

$$rate\ of\ filtration = \frac{(Area\ of\ filter)\, x\, (pressure\ difference)}{(viscosity)\ x\ (resistance\ of\ cake\ and\ filter)}$$

c. **Viscosity is inversely** proportional to the flow rate, increase in viscosity will decrease the flow rate.

- To increase filtration rate →
- **Decrease in filtrate viscosity**: the viscosity of the filtrate can be reduced in most cases **by heating** the formulation to be filtered.
- If the liquid is **highly volatile or there is a thermolabile material → dilution** of the formulation with water may be an alternative means of reducing the viscosity.

Interpretation of Flow Rate Equation
How to Change the Flow Rate

$$rate\ of\ filtration = \frac{(Area\ of\ filter)\ x\ (pressure\ difference)}{(viscocity)\ x\ (resistance\ of\ cake\ and\ filter)}$$

d. **Cake resistance:** is function of cake thickness, and flow will decrease when the cake **become thicker**.

- **Particle size** of the cake will affect cake resistance;
- **Decrease** in particle size → cake will become more packed → **increase** resistance → **decrease** the flow.
- **In cake filtration**, because the cake is the main obstacle → resistance of the filter under the cake is **negligible**, but if filter under the cake has some resistance → it will be inversely proportional to the flow because it will increase resistance.
- **Decrease the cake thickness**: this can be decrease by removing some of the cake periodically.

Filter Aid

- **Cake resistance** (and hence the flow rate) can be **increased by using filter aid**.
- A **filter aid** is a material that, when included in the formulation to be filtered, forms a cake of a **more open, porous nature**.
- In addition, it may **reduce the compressibility** of the cake and/ or prevent the filtered material blocking the filter medium.
- These materials must be **inert, insoluble, incompressible and free of impurities**. Examples are diatomite, Perlite (aluminum silicate) and cellulose filter aids.
- These materials is applied by either a **pre-coating** of the filter medium by filtering a suspension of the filter aid, **or** by a body mix technique in which a small proportion of the filter aid (0.1-0.5 %) is added to the slurry to be filtered.
  - **Note**: The use of filter aids is obviously **not appropriate** if the filtered material is the **intended end product**.

Filter Media

- **Filter medium**: the **surface upon** which solids are deposited in.
- **The filter fabrics (filter material)** are commonly woven from natural fibers such as cotton and from synthetic fivers and glass or metal.
- **Ideal Filter medium**:

1. Must **retain the solids**: **without plugging** and without **excessive bleeding** of particles at the start of the filtration.
2. Chemically and physically **inert**.
3. Should have **sufficient mechanical strength** during filtration.

Types of Filter Media
Woven Filters

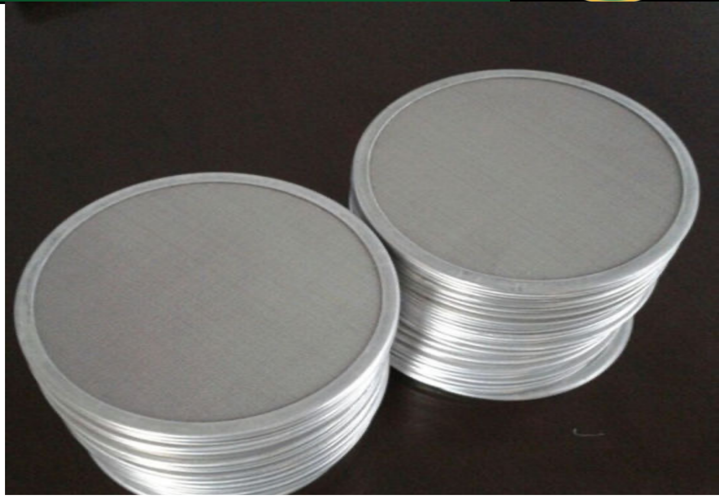
1) **Woven Filters: → two types:**

   A. **Filter Cloth**: (surface type medium) is woven from either natural or synthetic fiber. They are as follow:

- **Natural: Cotton fabric** (most common and widely used as a primary medium), as backing for paper or felts in plate and frame filters.
- **Synthetic fiber**: **Nylon** is superior for **pharmaceutical use** since it is **unaffected** by molds, fungi, or bacteria, and provides an extremely smooth surface for good cake discharge and has negligible absorption properties).
  - **Note:** Both cotton and nylon are suitable for coarse straining in aseptic filtrations: since they can be sterilized by autoclave.
- **Teflon** (superior for most liquid filtration)…chemically inert, provides sufficient strength, and can withstand elevated temp.

Types of Filter Media
Woven Filters

B. **Woven wire cloth (stainless steel):** it is **durable**, resistant to plugging, and easily cleaned.



- Properties of woven wire cloth:
- **Metallic filter media**: Provide **good surfaces** for cake filtrations and used with filter aids.
- **Wire screens**: used as **support elements** for disposable media since they may be cleaned rapidly and returned to service.
- **Wire mesh filters**: installed in **filling lines** of packaging equipment. Here it will **act as a security against** the presence of **large foreign particles**.

Types of Filter Media
Non-Woven Filter Media

2) **Non Woven Filters**: three types:

a) **A felt:** free from bonding agents and **mechanically interlocked** to yield specific pore diameters that have controlled particle retention.

- They are a **fibrous mass** that is either natural or synthetic material **Function as depth media.**
- Primary characteristic: **High flow rate with low pressure drop.**

b) **Bonded fabrics are** made by binding textile fibers with resins, solvents, and plasticizers.

- **Not used widely** in dosage form production because of interactions with the additives.

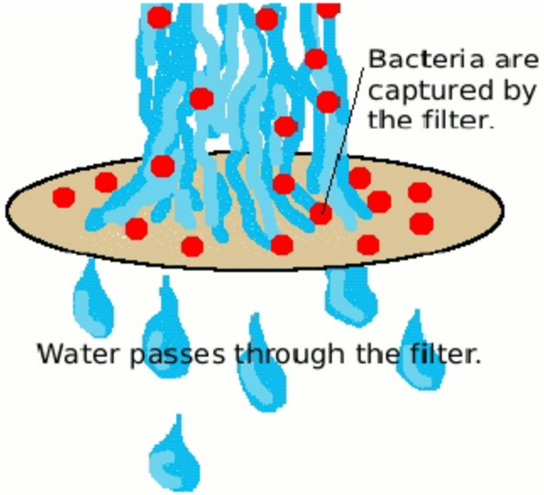
Types of Filter Media
Non-Woven Filter Media

c) Kraft paper (pharmaceutical standard).

- Uses: limited use in plate and frame filters and horizontal-plate filters.
- Offers a **controlled porosity**, **limited absorption** characteristic, **low cost and disposable medium**.
- Example: White papers (preferred, due to crinkles that produce **greater** filtration area).
- Note: **support** of cloth or wire mesh is necessary in large filter presses to prevent rupture of the paper with pressure.

3) Membrane filter:

- Basic tools for microfiltration and ultrafiltration, nanofiltration and reverse osmosis.
- Uses: in the **preparation of sterile solutions**.
- Classified as a surface or screen filters and are made of various materials such as **nylon, Teflon, etc.**
- The filter is a thin membrane (150 μm thick) with millions of pores/cm^2.
- The pores are **extremely uniform** in size and occupy about 80% of filter volume.
- Due to high porosity, these filters permit flow rates **40 times faster** than other media.
- Because of the surface screening: **Pre-filtration** is required to avoid rapid clogging of a membrane.



Filtration Equipment

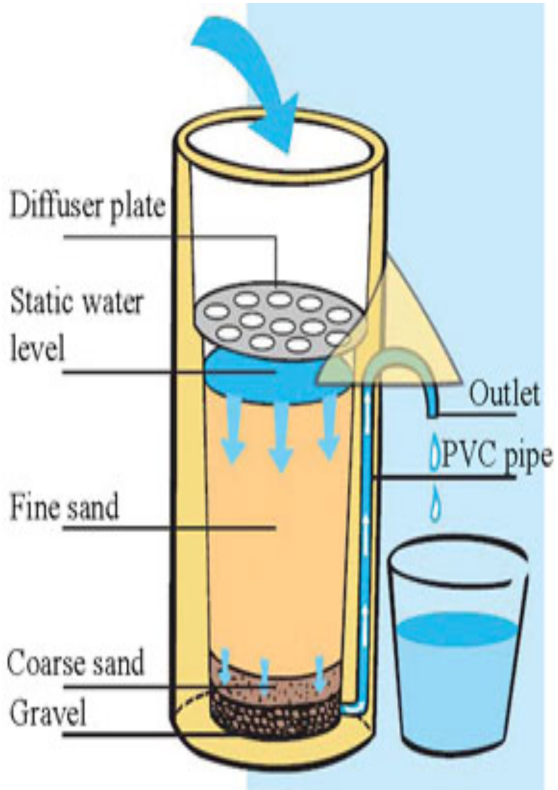
- Equipment can be classified according to:
- **The end product desired** (filtrate or cake solids).
- **Type of operation** (non sterile, sterile filtration , centrifugation filtration)
- **The driving force** (gravity, vacuum, pressure and centrifugation). This is the most important classification.

- Choosing equipment will depend on:

1. The chemical nature of the product. Interactions with the filter medium may lead to leaching of the filter components, degradation or swelling of the filter medium or adsorption of components of the filtered product onto the filter.
2. The volume to be filtered and the filtration rate required.
3. The operating pressure needed.
4. The amount of material to be removed.
5. The degree of filtration required.

Gravity Filters

- Filters that rely on gravity only generate **low pressures** .
- Employing thick granular beds are widely **used in water filtration** e.g. Sand Filter.
- **Advantage**:
- Simple and non expensive.
- **Disadvantage**:
- **Flow rate is low** unless using **very large surface area** which **limits their commercial use**.



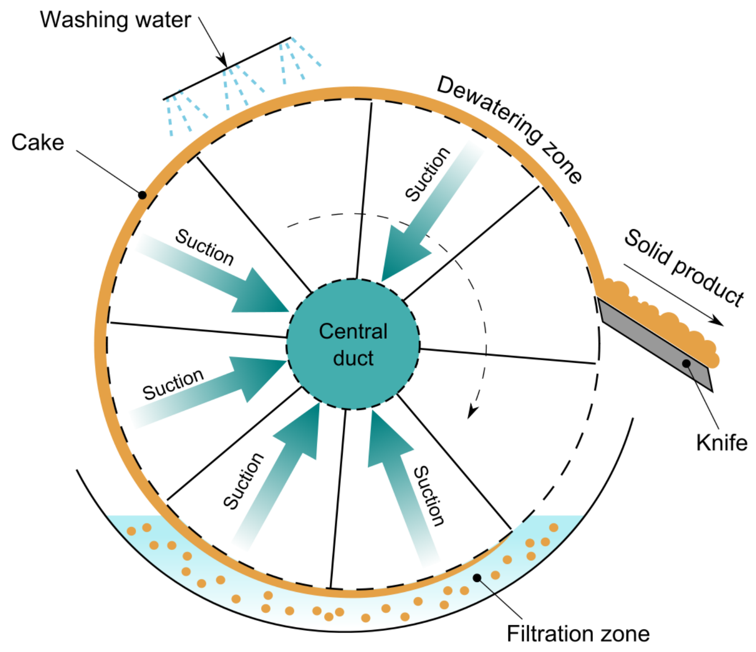
- Used in laboratory filtration where small volume and low filtration rate are insignificant.

Vacuum Filters

- Vacuum filters operate **practically at higher pressure** differentials than gravity filters.
- Can be used in **large scale** which they are relatively low cost compared to the filtration output.
- **Rotary vacuum** filter and the **leaf filter** are most extensively used:

The rotary vacuum filter.

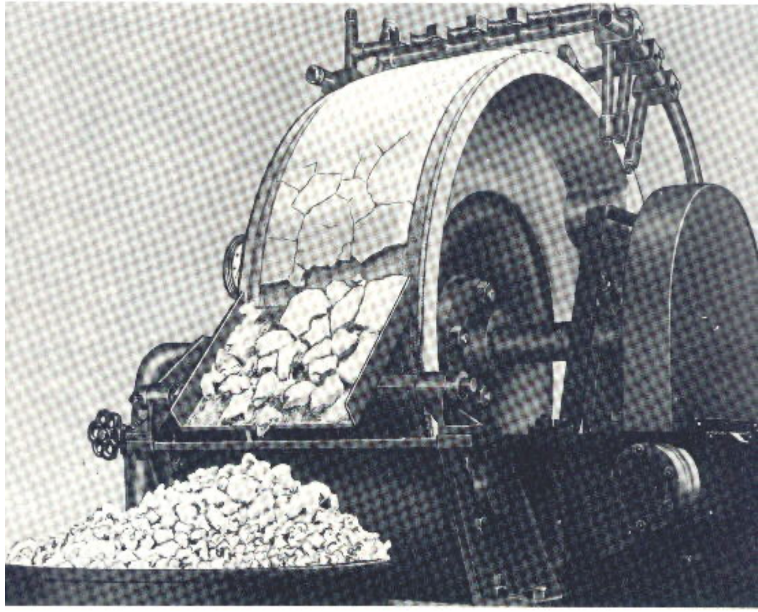
  - The rotary vacuum filter is **continuous in operation** and has a system for removing the cake so that it can be run for long periods handling concentrated slurries, so **it is desirable in large-scale**.



https://youtu.be/MjJ-0kcZab8

Rotary Vacuum Filter

- The cylinder rotates slowly in the slurry and a vacuum applied depositing cake on the filter medium.
- This is followed by washing and then further drainage in the drying zone. The cake is removed by the **scraper knife**.
- Due to the continuous removal of the cake → The rotary filter is most **suitable for continuous operation** on large quantities of slurry.
- Examples of pharmaceutical applications include the collection of and starch.



https://youtu.be/GAhJAgQn3sU
Starch collection

Rotary Vacuum Filter

- **Advantages**:
- It is **automatic and continuous** in operation, so that labor is very low.
- The filter has a **large capacity**.
- Variation of the speed of rotation enables the **cake thickness to be controlled**.

- **Disadvantages**:
- The rotary filters are **complex equipment** with many moving parts and are very expensive.
- The filter is made from cloth which **may be ruptured**.

Pressure Filter

- This is the most common type of filter used in the processing o pharmaceutical products.

- Due to the formation of cakes of **low permeability**, many types of slurry require **higher pressure difference** for effective filtration than can be applied by compression and **vacuum** techniques.
- Pressure filters are used for such operations.
- However, high operational pressures, may **prohibit continuous operation** because of the difficulty of discharging the cake whilst the filter is under pressure.
- Examples are the Filter leaf, plate and frame filter press.

1. Filter Leaf

https://youtu.be/gkmB0VaACSI

- The leaf filter is consisting of a **frame enclosing a drainage screen** or grooved plate , the whole unite being covered with filter cloth.
- **The operation**:
- The slurry is pumped under pressure into a vessel that is fitted with a stack of leaves that serves as filter elements.
- The leaf filter is immersed in the slurry and a receiver and a vacuum system connected to the filtrate outlet.
- **Advantages:**
- The slurry can be filtered from any vessel.
- The cake can be washed simply by immersing the filter in a vessel of Water.
- Removal of the cake is facilitated by the use of reverse air flow.

2. Plate and Frame Filter Press

- The **simplest** and most widely used of all pressure filters.
- Filter press are used for **high degree of clarification** of the **fluid** and for the **harvesting of the cake**.
- This is designed for a certain batch size and NOT for continuous operation.
- This press is made up of two units, known respectively as plates and frames, with a filter medium, usually filter cloth, between the two.

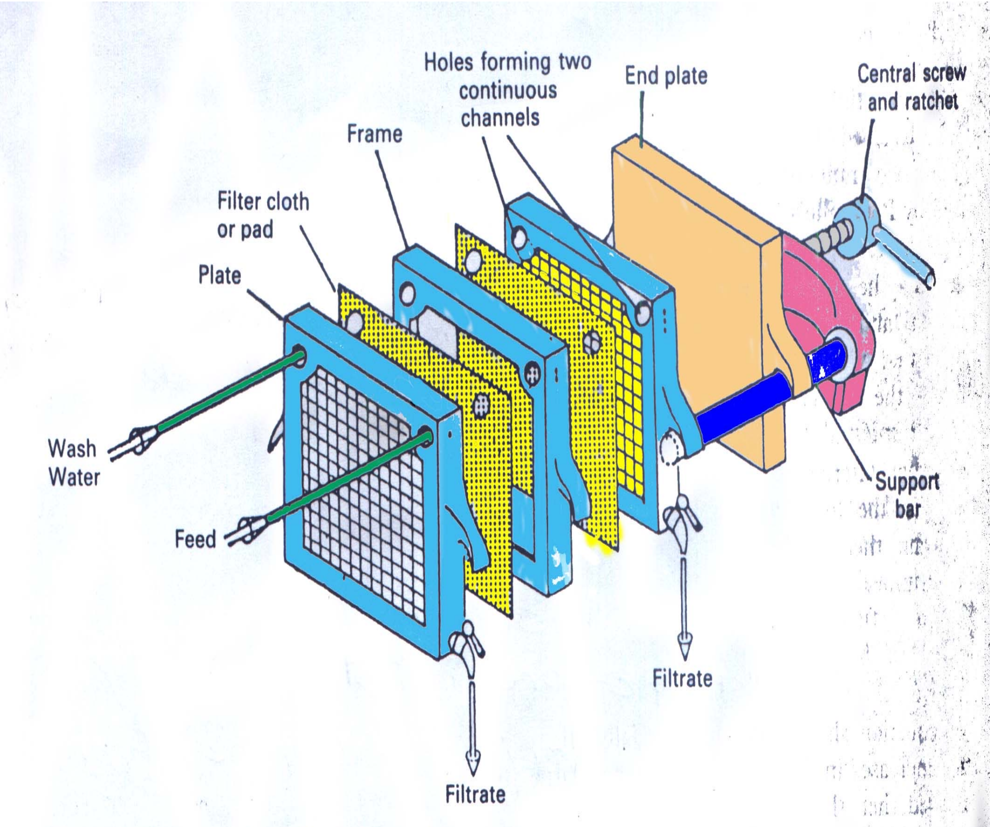


Fig. 31.5 Filter press. Assembly of plates and frames

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Plate and Frame Filter Press

- The slurry enters the frame from the feed channel.
- The filtrate passes through the filter medium on to the surface of the plate while the solids form a filter cake in the frame.
- The filtrate then drained down the surface of the plate , between the projections on the surface and escapes from the outlet.

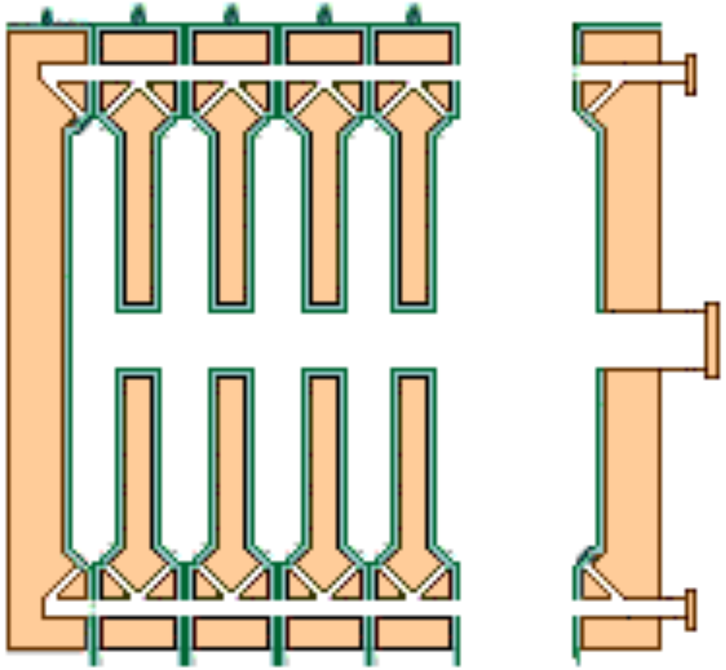
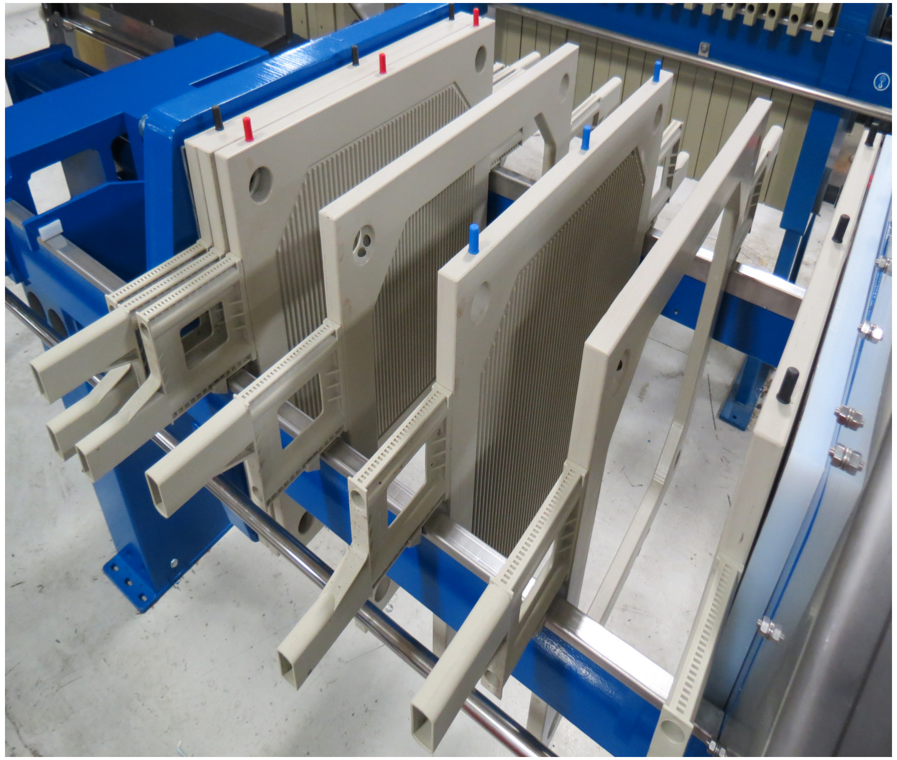


Plate and Frame Filter Press

- **Advantage:**
- This type is the **most versatile** of filters since the number and type of filer sheets can be varied to suit a particular requirement.
- Can be **used for coarse and fine** filtration or both on the same time.
- The most economical filter per unit of filtering surface.
- **Disadvantage**:
- **Labor** cost in assembly and cleaning is high.
- **Leakage** between plates may occur.
- It is a **batch filter**, so it is a time consuming.



Centrifugation Filtration

- Centrifugal force can be used either to provide the **driving force (ΔP)** for the filtration process (perforated basket type).
- And/or to **replace the gravitational** force in sedimentation processes (for non perforated basket).
- This type of filtration is particularly advantageous **when very fine particles are involved**.
- This is mostly used on laboratory or small scale processing and can be consider as an **alternative to filtration.**
- Centrifugation can be **used for washing** of solids in which the remaining solid is redispersed and centrifuged again for several times.

Centrifugation Filtration

- **Perforated basket**:
- Consist of perforated metal basket which rotates on its axis.
- Filter cloth <u>can be added</u> which will be supported by the metal basket.
- **Imperforated basket**:
- the liquid is removed through a skimming tube , while the solid particles, **sediment to the wall.**

Centrifugation Filtration

- **Advantages of a centrifuge**:

1. It is **very compact**, occupying very little floor space.
2. It is capable of handling slurries with **high proportions of solids** .
3. The amount of **moisture in solid** after centrifugation is **far less** than in cakes produced by pressure or vacuum filtration. This will facilitate drying process.

- **Disadvantages**:

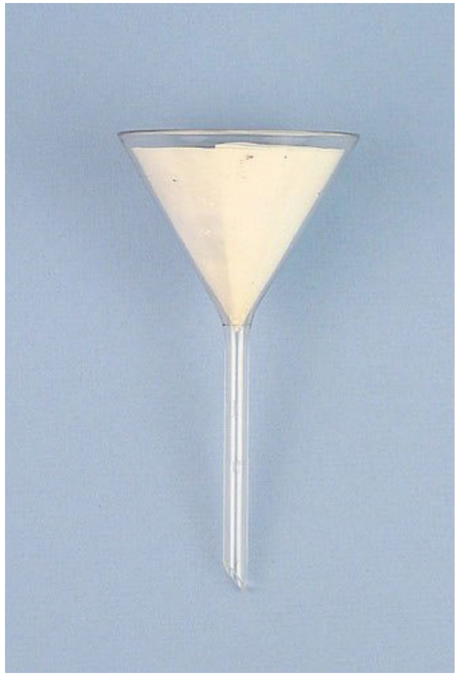
1. **Batch process** (not continuous process).
2. It involves a **considerable labor cost**, making the process expensive.

Centrifugation Filtration

- A type of **perforated basket** is filtration tube which is used for laboratory scale filtration.
- It is a tube that contain filter inside them which will be in the shape of smaller tube inside the larger tube.
- The fluid is added to the internal tube and after centrifuge, the solid will be held inside the filter tube leaving the liquid in the bigger tube.
- Filter can be in any pore size.

Laboratory Filtration Equipment

- **Filter paper and funnel** are the most common laboratory tools for filtration such as Buchner and conical funnel.
- Sometimes, a plug of fibrous material may be used instead.
- **Suction funnel set** can be used using with Buchner and plug filtration types.
- **Filter paper in circular form** is the most common medium for laboratory filtration.
- Filter paper are available in wide variety of textures, purities and sized and are available for different uses.



Specialized Filtration

- **Sterile/Aseptic operations**:
- Filtration may be used to **clarify and sterilize** pharmaceutical solutions that are **heat-labile**.
- **Membrane filter** have become the basic tool in the preparation of sterile solution and have been officially accepted by the United State Pharmacopeia (USP) and FDA.
- Membrane with porosity rating of 0.22 um are usually specified for sterile filtration.
- However, in this size range, membrane filters may clog rapidly and a **prefilter is used** to remove some colloidal matter to extend the filtration cycle.