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Pharmaceutical Technology

Aims: Pharmaceutical technology teaches the different dosage forms with respect to their raw materials, composition, and method of preparation, stability, storage and uses.

References:

- Ansel, H., Allen, L. and Popovich, N., "Pharmaceutical dosage forms and drug delivery system",10th ed., Lippincott Williams and Wilkins, (2014).
- James Swarbrick, "Encyclopedia of Pharmaceutical Technology" 3rd ed., Informa Health Care, (2007).

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No	Lecture title	hours
1.	Dispersed systems: their classification; comparisons between different systems.	2
2.	Solutions and types of solutions.	2
3.	Solubility: Factors affecting solubility; expression of dissolution; dissolution rate versus solubility; preparation of solutions containing non-volatile materials.	4
4.	Official solutions; classification of official solutions; preparation and uses.	4
5.	Aqueous solutions containing aromatic principles; aromatic waters; methods of preparations; stability.	4
6.	Syrups: sugar based syrups; artificial and sorbitol based syrups; stability of syrups.	4
7.	Definition and methods of clarification; filter aids in clarification.	3
8.	Preparation of solutions using mixed solvent systems; spirits, and elixirs.	3
9.	Extraction; maceration and percolation.	3
10.	Tinctures; fluid extracts; extracts of resins and oleoresins.	4
11.	Colloidal dispersions; lyophilic; lyophobic.	6
12.	Coarse dispersion; suspensions.	6

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Definition and methods of clarification; filter aids in clarification.

By
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2016/2017

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Outlines

- Definitions and terminology
- Clarification methods
- Factors affecting rate of filtration
- Filter media
- Filter aid

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Definitions

- **Filtration**: The process of separation of solid from a fluid by means of a porous medium that retains the solid though allows the fluid to pass.

- **Clarification**: This term is applied when solid do not exceed 1.0% w/v, and filtrate is the primary product.

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- **Ultra-Filtration**: Ultrafiltration is a separation process using membranes with pore sizes in the range of 0.1 to 0.001 micron. Typically, ultrafiltration will remove high molecular-weight substances, colloidal materials, and organic and inorganic polymeric molecules.

- **Cake Filtration**: If recovery of solid is desired, the process is called cake filtration.

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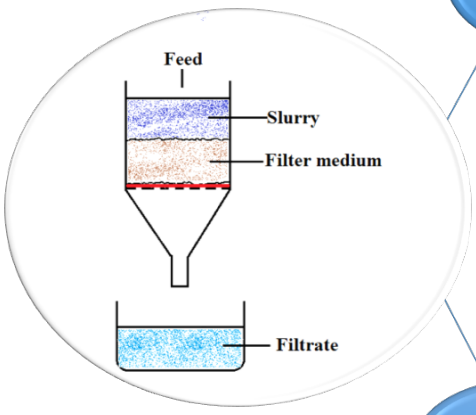
Terms



- **Slurry** • Suspension to be filtered
- **Filter medium** • Porous medium used to retain solid
- **Filter cake** • Accumulated solids on the filter
- **Filtrate** • Clear liquid passing through the filter

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Size

- Depending on the pore size, filter membranes can remove particles defined in the range :

1. microfiltration (0.1 to 2 μm, e.g., bacteria),
2. ultrafiltration (0.01 to 0.1 μm, e.g., virus),
3. nanofiltration (0.001 to 0.01 μm, e.g., organic compounds in the molecular weight range of 300 to 1,000), and
4. reverse osmosis (particles <0.001 μm).

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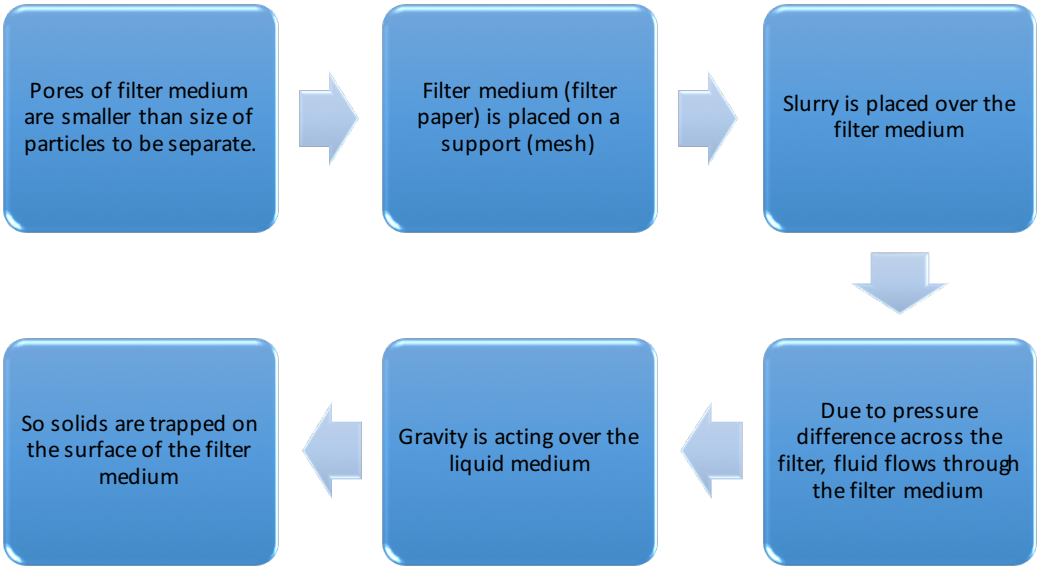
Process of filtration



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Clarification

- It is a term used to describe processes that involve the removal or separation of a solid from a fluid, or a fluid from another fluid.

- **Objectives:**
  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).

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Homework

Give examples "applications" for each type of filtration mentioned previously? (Pharmaceutics The Science of Dosage Form Design Aulton, Chapter 22 Clarification).

- Production of sterile products:
  - ✓HEPA filters or laminar air bench
  - ✓Membrane filters.
- Production of bulk drugs
- Production of liquid dosage
- Effluents and waste water treatment

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Mechanism of filtration

- The mechanism whereby particles are retained by a filter is significant only in initial stages of filtration.

Straining	• Similar to sieving, i.e., particles of larger size can't pass through smaller pore size of filter medium.
Impingement	• Solids having the momentum move along the path of streaming flow and strike (impinge) the filter medium. Thus the solids are retained on the filter medium.
Entanglement	• Particles become entwined (entangled) in the masses of fibres (of cloths with fine hairy surface or porous felt) due to smaller size of particles than the pore size. Thus solids are retained within filter medium.
Attractive forces	• Solids are retained on the filter medium as a result of attractive force between particles and filter medium, as in case of electrostatic filtration.

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Factors influencing the choice of filtration techniques

Properties of solid	Properties of liquids	Properties of solid in slurry	Objectives	Temperature
• Particle shape • Particle size • Particle charge • Density • Particle size distribution • Rigidity or compressibility of solid under pressure • Tendency of particle to flocculate or adhere together	• Density • Viscosity • corrosiveness	• Rate of formation of filter cake especially in early stage of filtration. • Concentration	• Whether the solid or liquid or both are to be collected. • Speed of operation	• Temperature of suspension

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Clarification can be achieved by three methods or techniques:

1) Settling,
2) Filtration,
3) Absorption and adsorption.

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Settling

- It is the simplest method of clarification.
- It is done by allowing the liquid to stand in a suitable container until the suspended matter is settled down or risen to the top of the liquid.
- Acceleration of settling can be done by centrifugation.
  - In this process the liquid is rotated in a special container at high speed. The device used for centrifugation is called centrifuge.
  - The centrifugal forces developed inside the centrifuge drive the suspended particles to the bottom and sides of the device.

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Note

- The effective force "centrifugational effect" is proportional to the square of speed of rotation and may be several thousand times as the gravitational force involved in natural settling.

$$C=2.01*dn^2$$

Where:

- C: Centrifugal effect
- d: Diameter of rotation
- n: Speed of rotation.

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Filtration

- Filtration is the process by which the suspended matter is removed from fluid by passing the mixture through porous, fibrous or granular substances.
- Filtration can be classified into the following categories depending on the physical state of the suspended matter and medium:

  - **Solid-liquid filtration**
  - **Solid-gas filtration**
  - **Liquid-liquid filtration**
  - **Liquid-gas filtration**

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Factors affecting the rate of filtration

- The laboratory Buchner funnel and flask is a convenient filter that can be used to illustrate the factors that influence the rate at which a product can be filtered.

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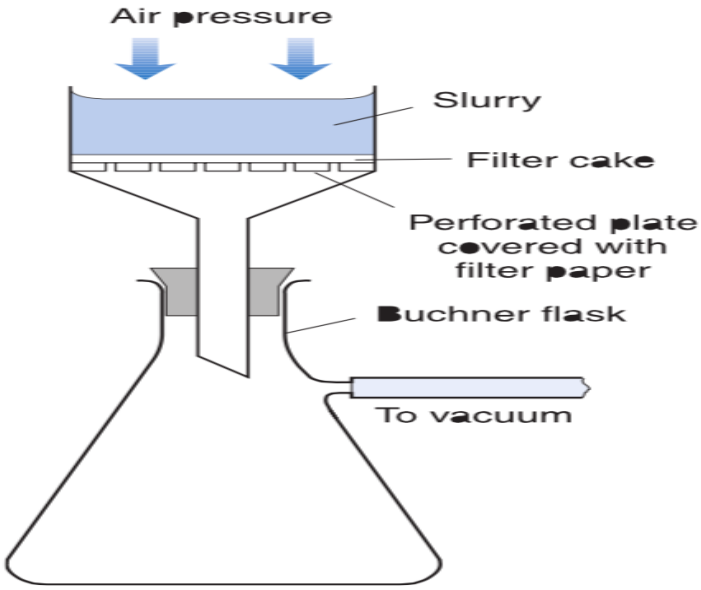

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The factors are combined in the Darcy equation:

The rate of filtration (volume of filtered material (**V**) obtained in unit time (**t**) depends on the following factors:

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

- The area available for filtration (**A**), which in this case is the cross-sectional area of the funnel;
- The pressure difference (**ΔP**) across the filter bed (filter medium and any cake formed).
- The viscosity of the fluid passing through the filter, i.e. the filtrate (**μ**).
- The thickness of the filter medium and any deposited cake (**L**).

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- The proportionality constant K (m^2) expresses the ***permeability*** of the filter medium and cake and will increase as the porosity of the bed increases.

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

Where:

k : the permeability of the filter medium and cake,

e : the porosity of the cake, and

s : specific surface area of the particles comprising the cake.

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Filter Media

- The filter medium used for clarification must have the following properties:

➢ Capable of delivering a clear filtrate at suitable production rate.

➢ It must withstand the mechanical stress which may be imposed on it without rupturing or being compressed significantly.

➢ No chemical or physical interactions with the components of the filtrate should occur.

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Types of Filter Media

There are two different types of filters:

1. Depth filters, and
2. Membrane filters.

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Depth filters

- Depth filters retain suspended matter within the depth of the filter matrix.
- In this case, suspended particles have to move through the tortuous path of the fiber matrix and eventually will collide with a fiber and separate from the medium.
- Due to the depth retention, such filters have a very high load capacity and are able to separate a high load of suspended matter of different sizes.

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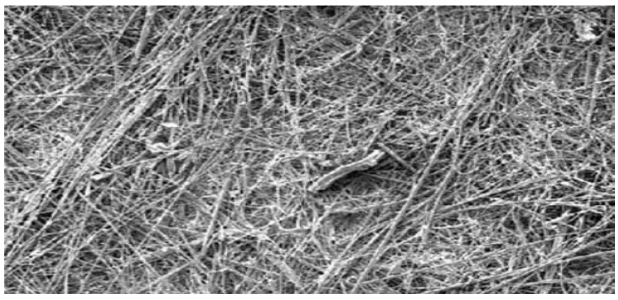
- Depth filter are fibrous materials: for example, polypropylene, borosilicate, or glassfibre materials.
- Borosilicate and glassfibre materials are highly adsorptive and commonly used to remove colloidal substances, like iron oxide from water or colloidal particles from sugar solutions.



SEM of the random fiber matrix of a depth filter.

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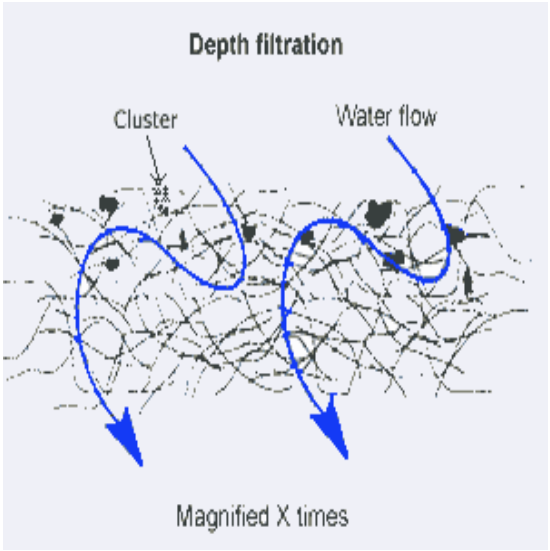

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Membrane Filters

- Membrane filters are surface retentive filters and, therefore, have the distinct disadvantage to clog faster.
- In comparison to depth filters, membrane filters have a narrow pore size distribution, which results in a sharper retention rate.
- Another advantage of membrane filters is the fact that these are integrity testable. Therefore, flaws or defects can be detected, which is critical, due to the function of membrane filters, mainly in separating microorganisms from pharmaceutical solutions.

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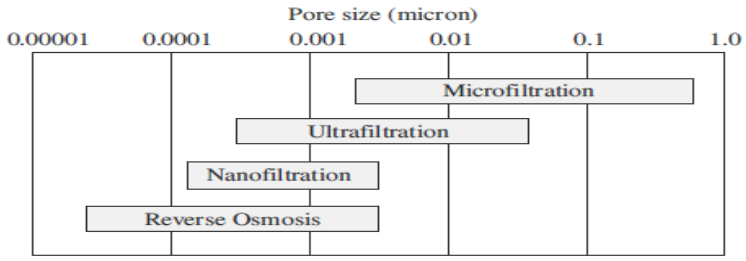
- Membrane filters are made in a wide variety of pore sizes.
- The effective pore size for membranes vary, and membranes can be used in reverse osmosis (RO), nanofiltration (NF), ultrafiltration (UF), and microfiltration (MF).



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

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Examples of Membrane Filters

Filter fabrics: They are commonly woven from natural fibers such as cotton and from synthetic fibers and glass.

Examples:

- Cotton fabric which is most common and widely used as a primary medium.
- Nylon is often superior for pharmaceutical use, since it is unaffected by molds, fungi, or bacteria; provides extremely smooth surface for good cake discharge; and has negligible absorption properties.
- Teflon is superior for most liquid filtrations because it is almost chemically inert, provides sufficient strength and can withstand elevated temperature.

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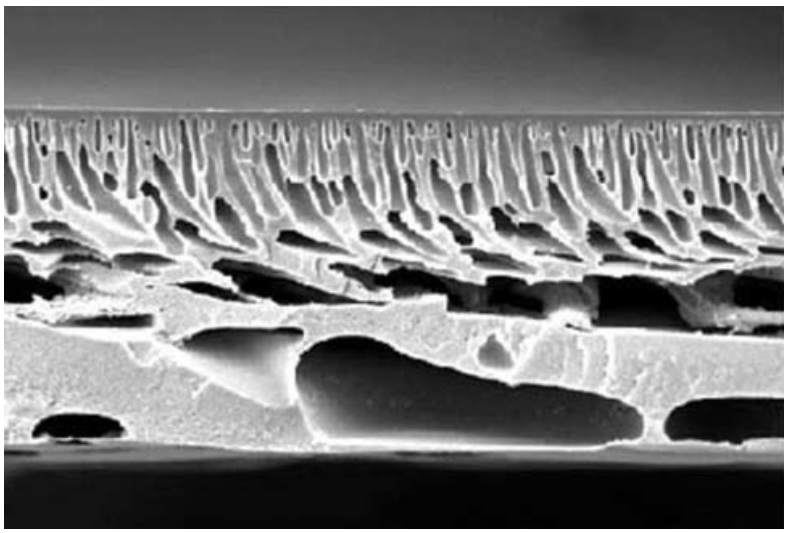

Skin layer structure of a UF membrane.

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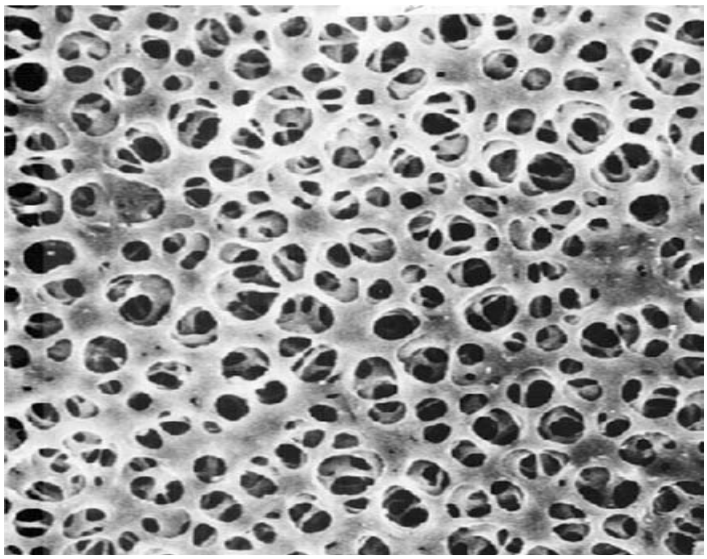

Porous structure of cellulose acetate.

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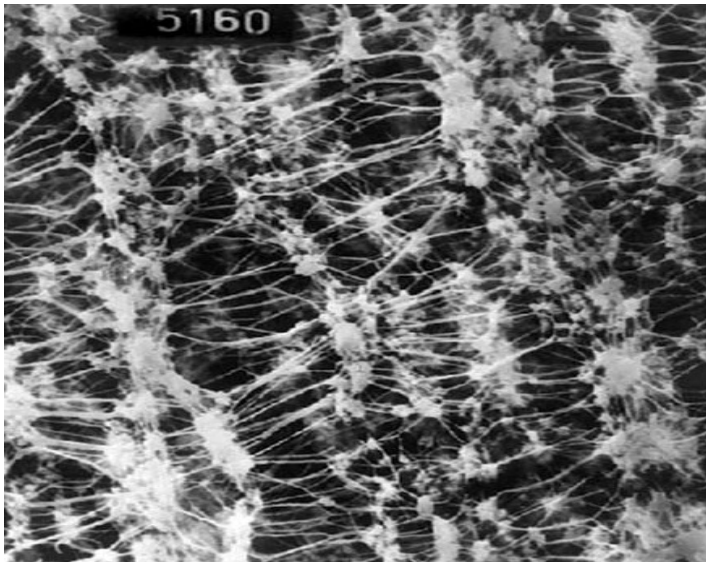

PTFE membrane structure.

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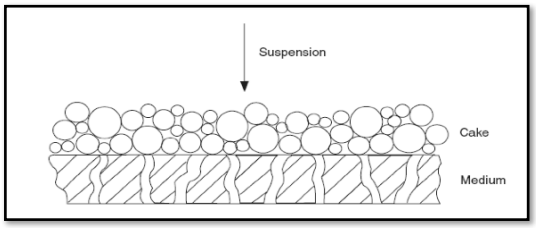
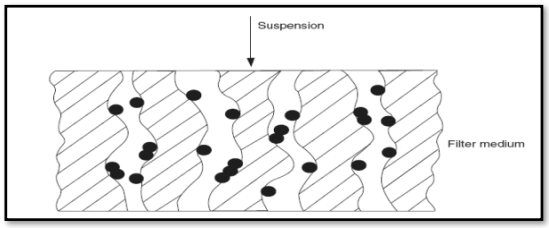
Difference between surface and depth filtration

- **Surface/ screen filtration**
  - ➢ It is a screening action by which pores or holes of medium prevent the passage of solids.
  - ➢ Mechanism involved : straining and impingement
  - ➢ For this, plates with holes or woven sieves are used.
  - ➢ Efficacy is defined in terms of mean or maximum pore size.



- **Depth filtration**
  - ➢ In this slurry penetrates to a point where the diameter of solid particles is greater than that of the tortuous void or channel.
  - ➢ Mechanism : Entanglement
  - ➢ The solids are retained with a gradient density structure by physical restriction or by adsorption properties of medium.



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Surface filtration

- The size of particles retained is slightly higher than the mean pore size of medium.
- Mechanical strength of filter medium is less, unless it is made of stainless steel.
- It has low capacity.
- The size of particles retained is more predictable.
- Equipment is expensive because ancillary equipment such as edge clamps is required.
- Ex. Cellulose membrane filter.

Depth filtration

- The size of particles retained is much smaller than the mean pore size of medium.
- Mechanical strength of filter medium is high.
- It has high capacity.
- The size of particles retained is less predictable.
- Equipment is cheaper because ancillary equipment is not required.
- Ex. Ceramic filters and sintered filters.

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Filter Aids

- They are special type of filter media that form a fine surface deposit that screens out all solids and preventing them from contacting and plugging the supporting filter medium.
- Usually, the filter aid acts by forming a highly porous, and non compressible cake that retains solids as does any depth filter.
- Filter aids are insoluble adsorbent materials that may be added to liquid prior to its filtration to increase the efficiency of filtration.

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These filter aids can be used in two different ways.

1. They can be used as a precoat before the slurry is filtered. This will prevent gelatinous-type solids from plugging the filter medium and also give a clearer filtrate.
2. They can also be added to the slurry before filtration. This increases the porosity of the cake and reduces resistance of the cake during filtration.

- The use of filter aids is usually limited to cases where the cake is discarded or where the precipitate can be separated chemically from the filter.

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The Characteristics of Filter Aid

- It should have a structure that permits the formation of porous and noncompresable cake (not dense),
- It should have a particle size distribution suitable for the retention of solids as required,
- It should be able to remain suspended in the liquid to be filtered (low sp gr),
- It should be free of impurities,
- It should have high adsorption capacity,
- It should be inert to the liquid being filtered,
- It should be free of moisture in cases where the addition of moisture to the liquid is undesirable.

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Examples of Filter Aids

- **Purified talc:** Non absorbent, chemically inert, reasonable particle size.

- **Diatomite:** is the naturally occurring fossilized remains of diatoms. The most important use relative of high-quality diatomite is as a filtering media. The naturally occurring fossilized remains of diatoms have innate filtering characteristics due to their unique honeycomb structure.

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- **Charcoal**: Good absorbent but not used for coloured preparations, alkaloids or glycosides.
- **Perlite**: It is aluminum silicate of light weight, inert, impart no taste or odor to liquids being filtered, and are virtually insoluble in mineral and organic acids at all temperatures. A perlite filter aid makes a filtering layer (cake) that transfers the actual filtering from the septum to the whole mass of filter aid.
- **Chalk**: Reacts with acids, not for general use.

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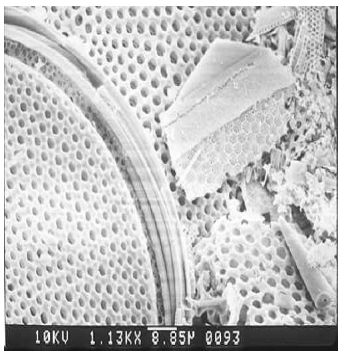
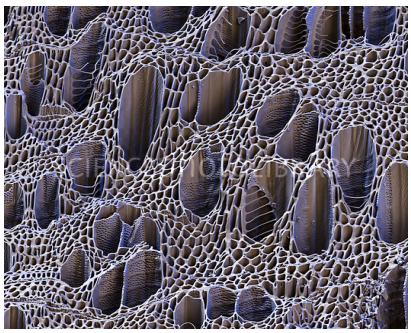
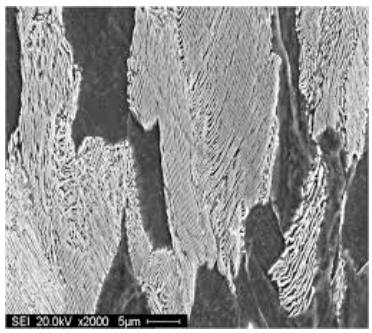
Diatomite



Charcoal



Perlite



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Absorption and Adsorption

- Filter media can affect clarification through absorption and adsorption processes in addition to their sieving effect.
- In absorption, the foreign particles are trapped within the medium, while in adsorption, the foreign substances adhere to the surface of the media.
- Frequently, filter aids provide the absorption and adsorption functions.

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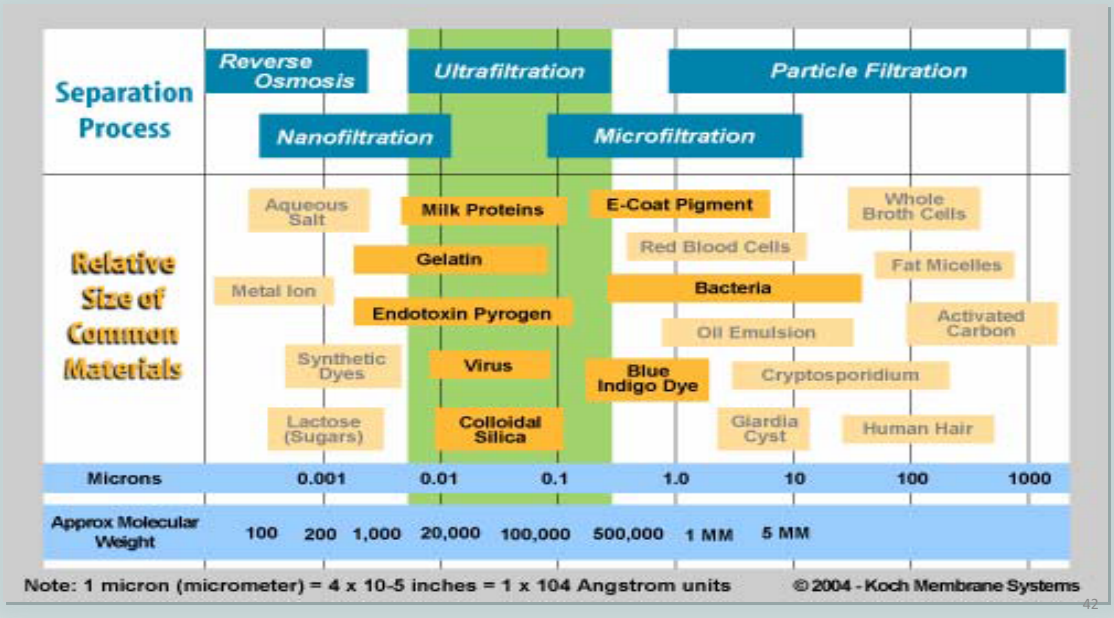

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Thanks for your attention