SEPERATION: CLARIFICATION AND FILTERATION

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CLARIFICATION

- **Any process concerned with the removal of material not in solution so that a liquid is rendered sparkling clear.**
- **A very high standard of clarification is required in pharmaceutical solutions to:**

– **Produce an elegant product.**

– **Avoid the danger to the patient from serious side effects following the use of contaminated parenteral or ophthalmic products e.g. glass particles, pyrogens.**

CLARIFICATION

- **Clarification may involve filtration and non-filtration processes.**
- **Non-filtration processes may be essential preliminaries to clarification.**
  - **e.g. PRECIPITATION of material to be removed by filtration or**
  - **AGGLOMERATION of finely divided particles to assist removal.**

SUBSTANCES REQUIRING SEPARATION FROM LIQUIDS

1. Cell debris (extraction from crude drugs, contaminants)
2. Proteins (extraction from crude drugs, contaminants)
3. Resins, fats, waxes & insoluble fraction of volatile oils (aromatic waters)
5. Foreign particles from the apparatus introduced during the course of preparation.
6. Precipitates formed by reaction with atmospheric gases
7. Products of fermentation, enzyme, bacterial and fungal action (biological)
8. The undesired products of chemical interaction during the course of preparation or after preparation

SUBSTANCES REQUIRING SEPARATION FROM LIQUIDS

- **From the above we can see that the substances to be removes may:**
  - **Never have been in solution**
  - **Be formed or precipitated DURING preparation**
  - **Be formed or precipitated AFTER preparation.**

1. NEVER BEEN IN SOLUTION

- **Very fine particles of vegetable matter carried through from the crude drug.**
- **Some are sufficiently fine to pass through a filter paper; allow to settle then decant off the clear liquid.**

SUBSTANCES REQUIRING SEPARATION FROM LIQUIDS

2. FORMED OR PRECIPTATED DURING PREPARATION.

A. Alteration in Solvent

- **precipitation of matter insoluble in dilute alcohol**

  i. Dilution of concentrated liquid extract.

  ii. Dilution of concentrated aromatic water (1-40)

  iii. Precipitation of proteins and resins.

Allow for adequate time from complete precipitation prior to filtration, following dilution of ethanolic vehicle.

SUBSTANCES REQUIRING SEPARATION FROM LIQUIDS

B. Precipitation of Albuminous Matter

- **Precipitate is formed by coagulation through boiling, then is filtered off. e.g. Liquorice liquid extract**
- **the protein is heat slowly and after full stirring the precipitate is skimmed off. Subsidence is allowed and then filtered after the change in solvent.**

C. Defatting

- **Suspended fat and oil removed (otherwise product is cloudy) by adding hard paraffin, shaken and cooled.**
- **The paraffin dissolves the suspended fat and sets to form a solid layer on the surface.**
- **The layer is perforated and the defatted liquid is decanted. e.g. Nux Vomica Liquid Extract**

SUBSTANCES REQUIRING SEPARATION FROM LIQUIDS

3. PRECIPITATION AFTER PREPARATION

Calcium Hydroxide Solution BP (Lime Water) •

Interact with CO_2 $\longrightarrow$ precipitation of $CaCO_3$ and secondly a settling of excess $Ca(OH)_2$ occurs.

- **This solution is always decanted and NEVER SHAKEN before use.**

SEPARATION METHODS

1. Lotion
2. Decantation
3. Percolation
4. Filtration
   - Preliminary
   - Polish
5. Centrifugation
6. Miscellaneous methods of Clarification
   - Agglomeration by heating
   - Separation oil/water by filtration

SEPARATION METHODS

SUPERNATANT LIQUID The liquid which separates from the precipitate.

1. LOTION

- **Process whereby the soluble impurities are removed from insoluble material by the addition of a suitable washing solvent.**

e.g. $CaCl_2 + Na_2CO_3 \longrightarrow 2NaCl + CaCO_3\downarrow$

Washing agent is water, decant the salt solution, keep the precipitate ($CaCO_3$).

SEPARATION METHODS

2. DECANTATION

- Technique used to remove the supernatant liquid above an insoluble compound/s.
- Can be used when supernatant is to be either retained or discarded

A. Retain Supernatant

– The insoluble matter is allowed to settle to the bottom and the supernatant is carefully decanted (poured off) without

disturbing the insoluble matter.

– Further clarification can be done by filtration if there is fine material left in the supernatant.

SEPARATION METHODS

SEPARATION METHODS

B. Discard Supernatant

- **Decantation can be a subsequent step to the lotion process, efficient purification process.**
- **Procedure follows:**

i. Solid washed by agitating with solvent.

ii. Solid is allowed to settle and is retained.

iii. Supernatant is decanted.

- **The effectiveness of the washing and separation process.**

Example of preparing mercuric iodide:

$$HgCl_2 + KI_2 \longrightarrow K^+ + 2Cl^- + HgI_2 \downarrow$$

- **100mg of mercuric chloride is dissolved in 50mL of water. The solution is mixed with 220mg of potassium iodide dissolved in 50ml of water produces 100mg of KCl which is an impurity remains dissolved in water (100mL)**

SEPARATION METHODS

- To free the mercuric iodide from contamination the supernatant is decanted:

i. 90mL = 90mg (10mg of KCL left)

ii. + 90ml water – 90mL = 9mg (1mg left)

iii. + 90ml water – 90mL = 0.9mg (0.1mg left)

- 2 washings have removed 99.9mg of KCl.
- Supernatant liquid may also be syphoned, removes the supernatant without disturbing the solid.

SEPARATION METHODS

3. PERCOLATION or COLATION

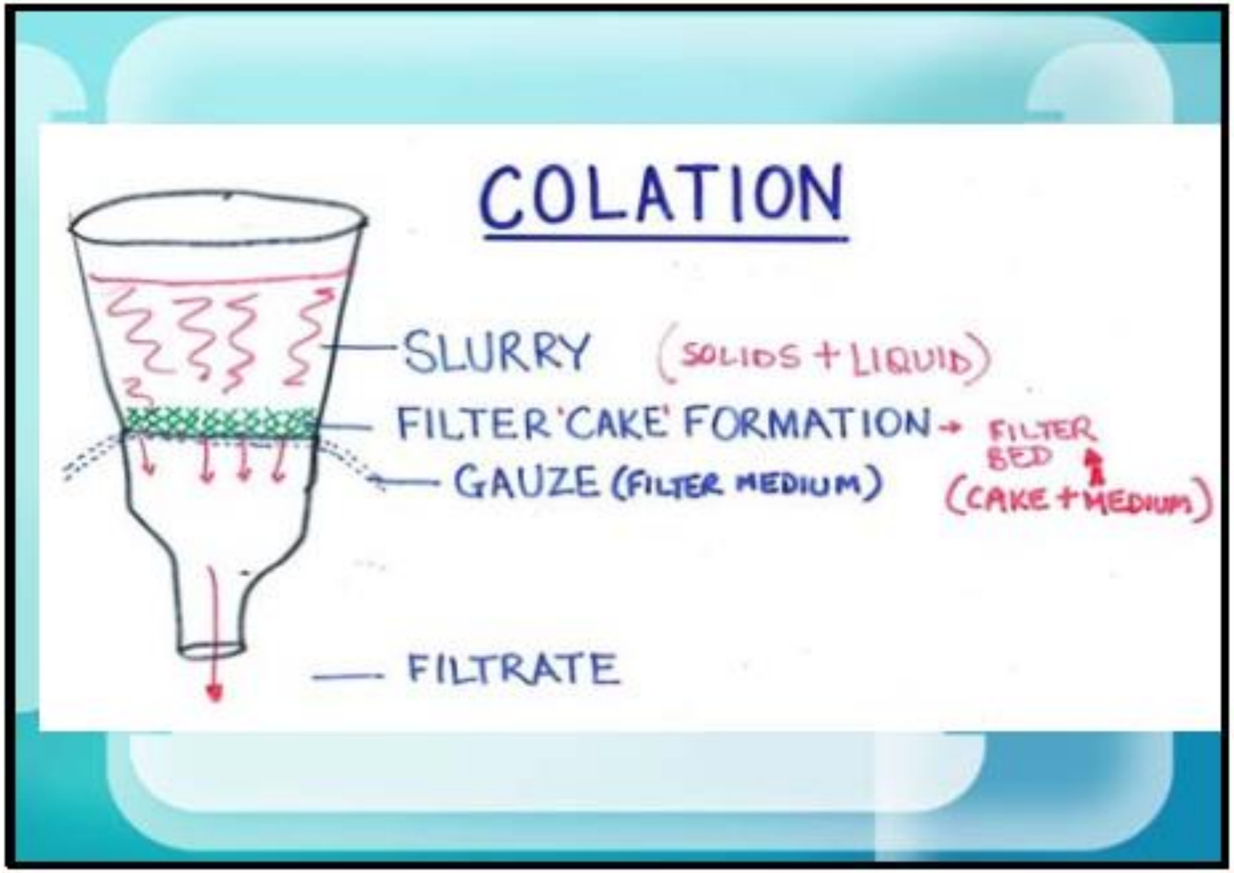
- Can be the first step to filtration.
- Pour mixture of solid/liquid through cloth or porous substance which retains the solid.

– Gauze, muslin etc (non corrosive), glass wool, asbestos (corrosive liquids).

- Treat the cotton material first to prevent contamination from “size” (gelatin, albumin precipitation of alkaloids).
- With large scale operations a “filter bed” is formed by the solids.
- With small scale operations gauze is used to remove large foreign materials.

– Heterogeneous systems i.e. different phases e.g. emulsions, suspensions.

SEPARATION METHODS



SEPARATION METHODS

4. <u>FILTRATION</u>

A. Preliminary Filtration

- **Using medium and large pore size filters, preliminary filtration is used to remove coarse particles and probably will not produce a solution clear solution.**
- **Decantation, colation or centrifugation can be used.**

B. Polish Filtration

- **Process renders the solution SPARKLING CLEAR and involves the use of fine filtering medium (small pore size)**

SEPARATION METHODS

5. <u>MISCELLANEOUS METHODS</u>

A. Agglomeration by Heating

- Removal of fats, waxes and similar substances which are solid at room temperature but melt at higher temperature.
- Fats, waxes melt, rise to the surface and coalesce there, at room temperature and them removed (scum) e.g. Honey BPC

B. Separation of Oil & Water by Filtration

- Fixed oils or fats (melted) will not pass through a filter paper wet with water.
- The aqueous portion will pass through the wet filter paper and the oily portion will be retained.
- Impurities from the oil may be removed by passing the oily portion through a dry filter.

FILTRATION

DEFINITION:

- **Separation of a solid form a liquid (slurry), by the means of a porous medium that retains the solid, but allows the fluid to pass.**
- **In pharmaceutics, usually aiming to obtain a liquid in a transparent condition i.e. a solution that is clear, be able to see through but not necessarily colourless**

FACTORS AFFECTING FILTRATION

Filtration may be affected by the characteristics of the slurry:

1. Liquid Properties – density, viscosity.

- **This can influence the choice of filter medium.**

2. Solid Properties – particle shape, particle size distribution.

3. Proportions of solids in the slurry

- **This will affect the filter cake thickness, porosity and compressibility of the solids.**

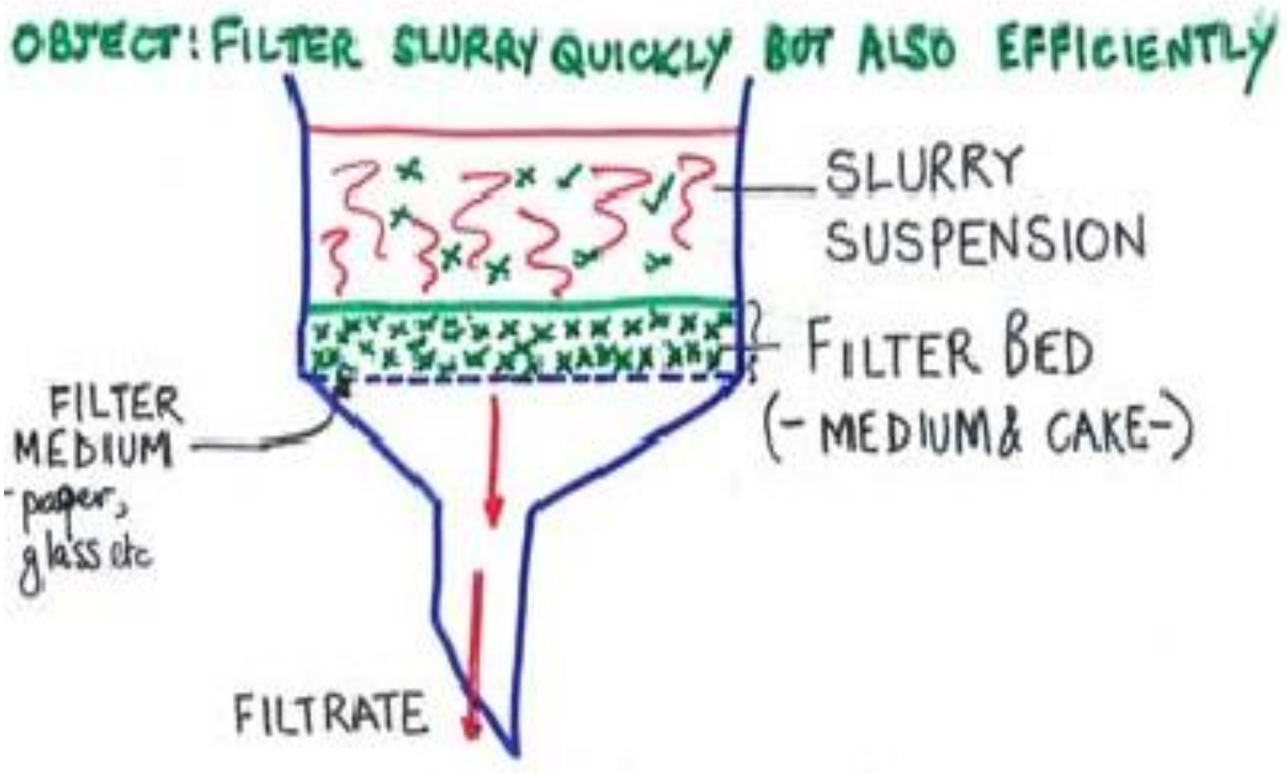
4. Whether the objective is to collect the solid, the liquid or both.

5. Whether the solids have to washed free from the liquid or a solute.

FACTORS AFFECTING FILTRATION

- Speed of operation is a major factor to be considered in any filtration process.
- The Objective of the operation is to filter the slurry as quickly as possible but efficiently i.e. the process must be economical.
- The resistance to the flow of the liquid in this system thus increases progressively throughout the operation as the cake increases in thickness.

FACTORS AFFECTING FILTRATION



FACTORS AFFECTING FILTRATION RATE: DARCY'S LAW

1. Volume of filtrate/time dV/dt cm^3/s
2. Area of filtrate medium A cm^2
3. Pressure drop across filter medium and filter cake ΔP pa
4. Viscosity of the filtrate μ (η) pa/ s
5. Thickness of filter cake $\mathcal{L}$ *cm*

- Relationship described by DARCY'S LAW

$$\frac{dV}{dt} = \frac{K.A.\Delta P}{\eta\,\mathcal{L}}$$

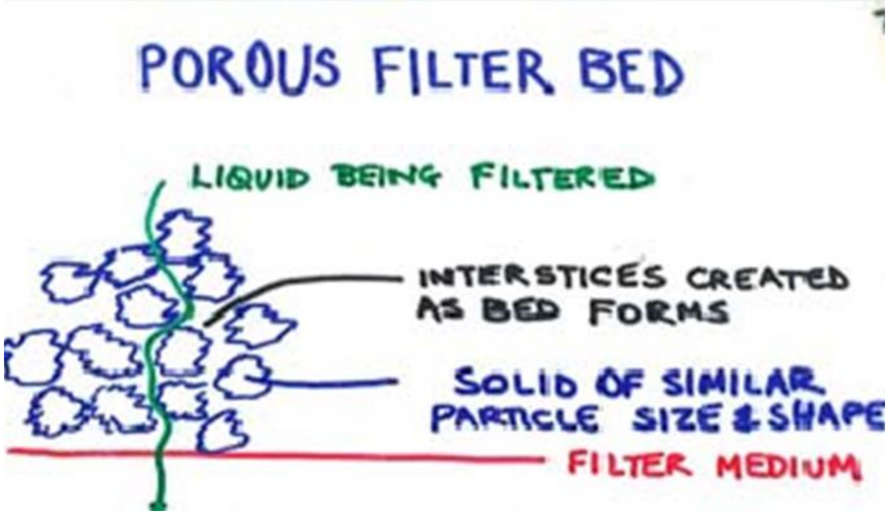
FACTORS AFFECTING FILTRATION RATE: DARCY'S LAW

- Darcy's Law represents the rate of flow through the capillaries of the filter medium and filter cake; it is similar to the equation for the flow through a single tube.
- Darcy's Law is further developed to the KOZENY-CARMEN equation.

FACTORS AFFECTING FILTRATION RATE: DARCY'S LAW

<u>**Wide-ranging Particle Size Distribution**</u>

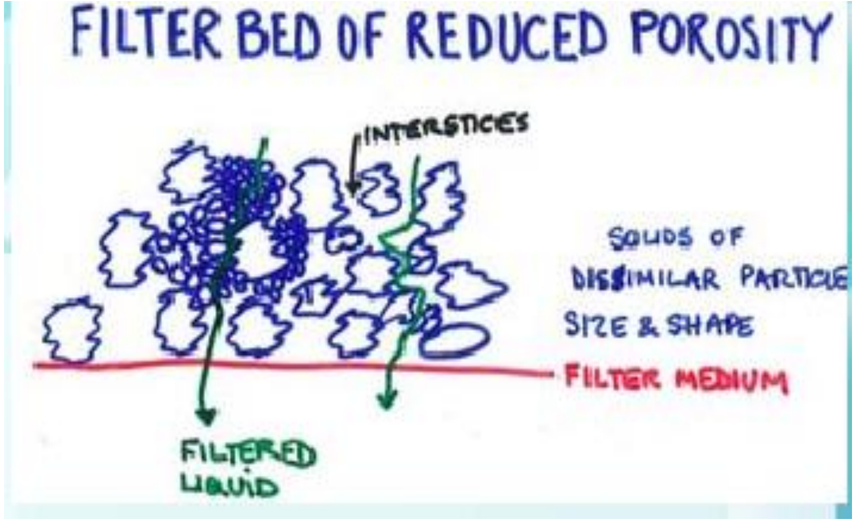
- **Allows for formation of large pores throughout the filter bed as it is laid down.**
- **Results in quicker filtration initially but the rate is decreased as the smaller particles fill up the spaces reducing porosity but increasing the efficiency of the process over time**



FACTORS AFFECTING FILTRATION RATE: DARCY'S LAW

<u>Narrow Particle Size Distribution of Small Size</u>

- **Smaller particles may tend to block off the pores in the filter paper reducing the rate and resulting in the need to frequently change the filter paper.**
- **Efficiency is increased but the rate is decreased.**



FACTORS AFFECTING FILTRATION RATE: DARCY'S LAW

Narrow Particle Size Distribution of Large Size

- **Allows for the formation of larger pores or capillaries throughout the filter bed as it is laid down.**
- **Rapid rate of filtration and efficiency.**
- **This is suitable if the pore size of the paper is sufficient to exclude solids present.**
- **Paper needs to be strong enough NOT to break under weight if the large proportion of solids is present in slurry.**

FACTORS AFFECTING FILTRATION RATE

In Darcy's Law K is = proportionality constant and expresses the permeability of the filter medium and cake and will increase as the porosity of the bed increases. Therefore K should be as large as possible to maximize filtration rate.

- **If K is taken to represent the permeability of the cake and the cake forms an impermeable cake the filtration rate can be improved with a filter aid which aids in the formation of open porous cakes.**

FACTORS AFFECTING FILTRATION RATE

- **Methods used to increase filtration rate (Darcy's Law etc):**

1. <u>↑ Area available for filtration</u>

– Distributes cake over a larger area ↓ $\mathcal{L}$ (thickness of cake).

2. <u>↑ Pressure difference across the filter cake.</u>

– Pressure may be a driving force for filtration.

– May cause "cake compression" ⟶ ↓ porosity

FACTORS AFFECTING FILTRATION RATE

3. ↓ Filtrate viscosity

– Heat ⟶ ↓ viscosity

4. ↓Thickness of filter cake

– May need to remove the cake periodically e.g. change filter papers.

– May ↓ thickness by ↑ filtering area.

5. ↑ Permeability of the cake

– use a filter aid ⟹ formation of a cake with greater porosity (↑K).

– May also ↓ compressibility of the cake and prevent blockage.

FACTORS AFFECTING FILTRATION RATE: KOZENY-CARMEN EQUATION

KOZENY-CARMEN EQUATION

- **Development from Darcy's Law**
- **Accounts for the;**

1. **Porosity (Ɛ) of the filter bed**
2. **Specific surface (S) of the bed**
3. **Irregularities in capillary size within the bed.**

$$Q = \frac{A\,\Delta P\,\varepsilon^{3}}{\eta S^{2}\,K\,\mathcal{L}\,(1-\varepsilon)^{2}}$$

Factors Affecting Filtration Rate

Q = Rate of flow

– Flow rate is proportional to area (A) i.e. an increase in area will lead to an increase in flow rate.

A = Cross sectional area of the bed

– Filter aids increase area when slurry contains solids of small particle size.

ΔP = Pressure drop across the bed

– Vacuum can be applied to create a negative pressure (gravity is positive pressure)

ε = Porosity of bed

– Increasing porosity will lead to an increase the rate of flow.

Factors Affecting Filtration Rate

$\mathcal{L}$ = Depth of bed

– As the depth of the bed increase there is an decrease in the rate of flow.

S = Specific surface of bed

– Specific surface (S) bed is NOT the same as surface area i.e. surface area relates to the particle size.

K = Kozeny Constant (Usually 5)

– Allows for a good filtration rate.

η = Viscosity of liquid

– Increasing viscosity (η) of the liquid will lead to a decrease in rate of flow.

Factors Affecting Filtration Rate

Therefore rate of flow will depend on:

1. Area of filter surface

– Larger the area   faster rate.

2. Porosity of filtering medium

– Smaller pores   slower rate but efficiency is greater.

3. Depth of medium

– ↑ depth of filter bed ↑ efficiency but ↓ rate.

4. Porosity

– May have a ↓ porosity as bed ↑ (if solids compress & channels block).

FILTER AIDS IN CLARIFICATION

- **Tend to counteract unfavourable characteristics of badly filtering material e.g. colloidal (slimy), these solutions clog easily.**

• Objective is to prevent the medium becoming clogged and to create and open porous cake used with a slurry

with solids of smaller particle size.

Desirable characteristics of filtering aids are:

– Insoluble

– Light

– Porous

– Inert

– Recoverable

FILTER AIDS IN CLARIFICATION

Methods of Use:

1. Pre-coat filter medium to prevent blocking of the filter bed by fine particles in slurry this leads to a decrease in porosity.

2. Adding the filtering aid to the slurry (conc. 0.1- 0.5%w/v) to produce a porous medium and trap fine particles of the slurry.

- **Examples of filter aids:**

1. Talc

– Non absorbent, chemically inert, reasonable particle size.

2. Siliceous Earth e.g. Fullers Earth, Kaolin

– Used to aid filtration of fixed oils

– Absorbs colour and alkaloids which will cause a change in the quality of the preparation.

FILTER AIDS

3. Charcoal

– Good absorbent but not used for coloured preparations, alkaloids or glycosides

4. Chalk, magnesium carbonate

– Reacts with acids, not for general use.

5. Protein e.g. white of eggs, gelatin

– Form insoluble compounds with tannins, phenols and heavy metals.

- These filter aids prevent medium becoming clogged and create an open, porous cake.

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FILTRATION MEDIUM

- Examples of filter medium include paper, paper pulp, sand, siliceous earth, asbestos, ground glass and charcoal.
- Increasing porosity of filter medium will increase the rate of filtration

The choice of filter media used will depend on;

1. Purpose of filtration
2. Quantity to be filtered
3. Operating pressure required i.e. if increase strength if there is increasing pressure.
4. Viscosity and filtration temperature

FILTRATION MEDIUM

1. FILTER PAPERS

i. White Paper

– High quality treated to remove contaminating acids.

ii. PVC Plastic Papers

– Incompatible with alcohols, volatile oils or phenols.

– Range of sizes available (different pore sizes and diameters)

2. SINTERED GLASS FILTERS

suitable for general purpose, therefore very useful grade to use.

– Expensive and fragile e.g. Buchner

– May be used with corrosives

– May be cleaned and sterilised

FILTRATION MEDIUM

3. SINTERED STEEL

– Strong, so can apply with high ΔP for high Q.

– For large scale filtration

4. ASBESTOS FILTERS

– Used where collected solid is ignited (gravimetric analysis).

– Bacterial filters in sterility testing

5. POROUS PORCELAIN

– Used in industry

6. MEMBRANE FILTERS

– Micro porous plastic

– Uniform pore size

– used as a process of selective molecular separation or colloid separation.

CENTRIFUGATION

Centrifugation is used for the separation of

– a solid from a liquid

– two immiscible liquids.

- **Centrifuge – a bowl or basket capable of being rotated at high speed.**
- **Used when ordinary filtration is difficult e.g. slimy compressible substances, syrups etc.**
- **Centrifuges are often used in the lab to separate solid material from a liquid, the solid typically forming a ‘plug’ at the bottom of the test-tube at the end of the process**

CENTRIFUGATION

There are three basic types of centrifuges:

- **Filtration**
- **Sedimentation**
- **Ultra-centrifuges**

1- Filteration

- **Compact (cf capacity).**
- **Can handle a high proportion of solids in slurry.**
- **Final product has low moisture content (cf filter cake).**
- **Process removes dissolve solids (cf evaporation).**
- **Rapid**

CENTRIFUGATION

Disadvantages:

– **Complicated cycle – high labour cost.**

– **Batch lots – intermittent process.**

- **Uses:**

– **Removes unwanted solids e.g. ppt protein in insulin.**

– **Separation and drying of solids.**

CENTRIFUGATION

2. SEDIMENTATION TYPE

- **Separate solids of small particle size from liquids.**
- **Solids are deposited on walls and removes at intervals.**
- **Separates immiscible liquids which form 2 layers – heavier moves to wall.**
- **Efficiency depends on velocity of rotation.**

- **Uses:**

– **Remove dirt and water from oils e.g. olive oil.**

– **Remove/separate liquid/liquid phases in extraction phase of antibiotic manufacture.**

– **Separate blood plasma/whole blood.**

CENTRIFUGATION

3- ULTRACENTIFUGE

- **Used for separation of extremely fine solid material.**
- **Can cause sedimentation of protein molecules.**