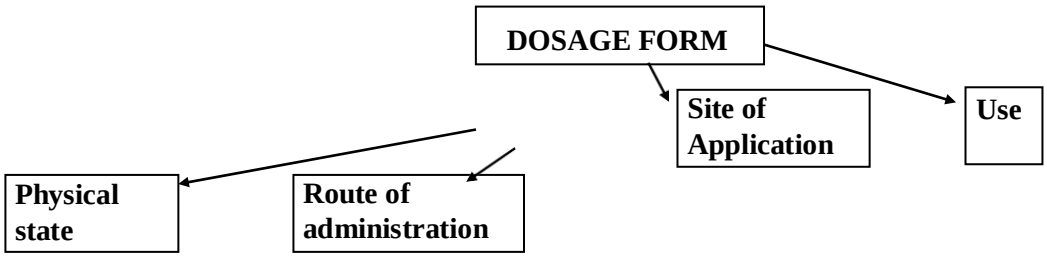
PHARMACEUTICAL
CHAPTER=1
DOSAGE FORMS

DRUG: "A drug may be defined as an agent, intended for use in the diagnosis, mitigation, treatment, cure or prevention of disease in man or in animals".

DOSAGE FORM: Drugs are rarely administered in their original pure state. They are converted into suitable formulation which are called dosage forms. Every dosage form is a combination of the drug and other non-drug components.

CLASSIFICATION OF DOSAGE FORMS



(i) Solid	(i) Oral	(i) Skin	(i) Internal
(ii) Semisolid	(ii) Parenteral	(ii) Eye	(ii) External
(iii) Liquid	(iii) Rectal	(iii) Tooth	
(iv) Gaseous	(iv) Nasal	(iv) Hand	
		(v) Foot	
		(vi) Hair	
		(vii) Nose	

Route of administration	Dosage forms
Oral	Powders, tablets, capsules, solutions, emulsions, syrups, elixirs, magmas, gels, cachets, pills.
Parenteral	Solutions, suspensions, emulsions.
Transdermal	Ointments, creams, powders, pastes, lotions, plaster
Rectal	Suppositories, tablets, ointments, creams, douches, foams.

Urethral	Suppositories
Sublingual	Lozenges, tablets
Intranasal	Solutions, sprays, inhalations.
Conjunctival	Ointments
Intra-ocular	Solutions
Intra-respiratory	Aerosols

CACHETS

Cachets consists of a dry powder enclosed in a shell. The shell is prepared from a mixture of rice flour and water by moulding into suitable shape and then dried.

Two types of cachets are there:

(i) Wet seal cachets:

Lower half of the cachet is filled with powdered drug. Then the flange of the empty upper half of the cachet is moistened with water, and pressed over the lower half. The cachet is dried for 15 minutes.

(ii)Dry seal cachets:

Drug powder is filled in the lower half and the upper half is pressed over it just like a capsule.

Use:

They are used for administering the drug with unpleasant taste and a large dose. Before administration, a cachet should be immersed in water for few seconds and then placed on the tongue and swallowed with water.

e.g. - Sodium aminosalicylate cachets, Sodium aminosalicylate and isoniazid cachets.

CAPSULES

Capsule are the solid unit dosage form of medicament in which the drug or drugs are enclosed in a practically tasteless, hard or soft soluble container of shell made up of gelatin.

Hard gelatin capsules are made up of two cylindrical halves, one slightly larger in diameter but shorter in length known as cap and the other slightly shorter in diameter but longer in length known as base.

Soft gelatin capsules are flexible in nature. They may be spherical, ovoid cylindrical or tubes. The small spherical capsules are also known as ‘pearls’. Soft gelatin capsules are used to enclose solids, semisolids or liquids for oral administration the capsule is placed on the tongue and

swallowed with a drink of water. Examples of hard gelatin capsules: Ampicillin capsules, multivitamin capsules.
Examples of soft gelatin capsules: chloramphenicol soft gelatin capsules.

DUSTING POWDER

These are meant for external application on to the skin and are generally applied in a very fine state of subdivision to avoid local irritation.
Dusting powders are of two types:
(i) Medical
(ii) Surgical
Medical dusting powders are mainly used for superficial skin conditions and for antiseptics, anti- pruritic, astringent, anti-perspirant, absorbent, protective and lubricant purposes.
E.g. dicophane dusting powder, zinc and salicylic acid dusting powder

Surgical dusting powders are used in body cavities, and also on major wounds as a result of burns and umbilical cords of infants. Surgical dusting powders must be sterilised before their use.
Dusting powders are generally prepared by mixing two or more ingredients on of which must be either starch, kaolin or talc as one of the ingredients of the formulations. Talc and kaolin are commonly used because they are chemically inert. however, since these materials are usually contaminated with pathogenic bacteria, these must be sterilised.
e.g. Neosporin powder

LOZENGES

Lozenges are solid dosage form of medicaments which are meant for slow dissolution in the mouth. Along with medicament they contain a sweetening agent, flavoring agent and a strong binding agent. They may be prepared either by moulding or by compression.
Examples are compound bismuth lozenges, liquor ice lozenges.

PESSARIES

Pessaries are solid unit dosage form of medicament meant for introduction into vagina. The bases used for the manufacture of pessaries are such that at room temperature they retain the original shape but when inserted into the body cavity either it melts or dissolve in the cavity fluids

to release the medicament.

POWDERS

Powders are solid dosage form of medicament meant for internal and external use. The powders meant for internal use are known as oral powders whereas those meant for external use are known as dusting powders.

TABLETS

Tablets are unit solid dosage form of medicament or medicament with or without suitable diluents. They are prepared usually by compression. Tablets are generally meant for oral administration but may be used by other routes of administration.

E.g.-paracetamol tablets.

SUPPOSITORIES

Suppositories are special shaped solid dosage form of medicament for insertion into body cavities other than mouth. These products are so formulated that after insertion, they will either melt of dissolve in the cavity fluids to release the medicament.

Suppositories vary in shapes, sizes and weights. General suppositories from 1 to 2 gm are prepared with either cocoa-butter or glycerol- gelatin base.

E.g. aminophylline.

SEMISOLID DOSAGE FORMS

CREAMS

Creams are viscous liquid or semisolid emulsions intended for application to the skin i.e. for external use.

Creams are of two types, aqueous creams and oily creams. In case of aqueous creams the emulsions are oil-in-water type and in case of oily creams emulsions are of water-in-oil type.

e.g. cetomacrogol cream, cetrimide cream.

Advantages of creams:

1. Creams are more acceptable to the patients because they are less greasy

and are easier to apply.
2. They interfere less with skin functions.
3. O/w type of creams can be rub onto the skin more readily and are easily removed by washing. W/o can be spread more evenly.
4. O/w type of cream are less likely to soil clothes.
5. Evaporation of water from o/w type of cream causes cooling sensation.
6. O/w creams absorbs the discharges from the wound very quickly.

Disadvantages:

1. Since it is a semisolid preparation and containing oil in large amount, some of which are inedible, hence creams are not used for internal use. Basically creams are meant for application onto the skin.
2. The aqueous phase is prone to the growth of molds and bacteria hence preservatives should be used.
3. Sometimes acidification of oils take place.

They are used for lubricating catheters, surgical gloves and rectal thermometers.
The gelling agents may be gelatin, or a carbohydrate such as starch, tragacanth, sodium alginate or cellulose derivative.

OINTMENTS

Ointments are the soft semisolid, greasy preparations meant for external application onto the skin or mucous membrane (rectum and nasal mucosa).They usually contain a medicament dissolved, suspended or emulsified in the base. Ointments are used for their emollient and protective action to the skin. E.g.-compound benzoic acid ointment, certified emulsifying ointment

PASTES

Pastes are semisolid preparations meant for external application to the skin. They generally contain large amount of finely powdered solids such as starch, zinc oxide, calcium carbonate etc. They provide a protective coating over the areas to which they are applied. The base may be anhydrous (liquid or soft paraffin) or water-soluble (glycerol or a mucilage). Their stiffness make them useful as protective coatings. E.g.-magnesium sulfate paste.

OPHTHALMIC OINTMENTS

Ophthalmic ointments are meant for application to the eye. They should be sterile and free from irritation. They should be packed in sterile containers which should keep the preparation sterile until whole of it is used up. E.g.-atropine eye ointment Chloromycetin eye ointments

LIQUIDS

AROMATIC WATERS: Aromatic waters are also known as medicated waters. They are dilute, usually saturated, aqueous solutions of volatile oils (e.g. peppermint oil, cinnamon oil) or volatile substances (e.g. camphor).

Uses:

(i) Some of them have a mild therapeutic action but

(ii) Mainly they are used as flavoring agents in preparations meant for internal use.

SYRUPS: Syrups are liquid oral preparations in which the vehicle is a concentrated aqueous solution of sucrose or other sugar.

Advantages of syrups

1. Syrups retards oxidation because it is partly hydrolyzed into reducing sugar such as dextrose and laevulose.
2. It prevents decomposition of many vegetable substances. Syrups have high osmotic pressure which prevents the growth of bacteria, fungi and molds which are the chief causes of decomposition in solutions of vegetable matter.
3. They are palatable. Due to the sweetness of sugar it is a valuable vehicle for the administration of unpalatable substances.

ELIXIRS: Elixirs are clear, liquid, oral preparations of potent or nauseous drugs. They are pleasantly flavored and usually attractively colored and are very stable. They are used for the production of clear solution. Essential oils from flavoring agents may produce faint opalescence, hence alcohol 10 □ 20% is useful for keeping oils in solution.

LINCTUSES: Linctus's are viscous, liquid, oral preparations that are usually prescribed for the relief of cough.

- They contain medicaments which have demulcent (which soothes the

inflamed mucous membrane preventing contact with air in the surroundings), sedative or expectorant action. The viscous vehicle soothes the *sore* membrane of the throat.

- The usual dose is 5 ml. Linctus's should be taken in small doses, sipped and swallowed slowly without diluting it with water in order to have the maximum and prolonged effect of medicaments.
- Simple Syrup is generally used as a vehicle. For diabetic patients Sorbitol solution is used instead of Simple Syrup.

CHAPTER=2
Metrology

Metrology is the branch of science dedicated to measurement, which is defined as the process of comparing an unknown quantity.

There are two type of weight and measurement system used in pharmacy.

1. Imperial system
2. Metric system

Imperial system: It is an old system based on arbitrary units. This system are used to required dispensing the prescriptions.

Imperial system is divided into two parts:

a. Avoirdupois system
b. Apothecaries system

a. **Avoirdupois system:** In this system Pound is the standard unit for the measurement of mass and weight.
b. **Apothecaries system:** The standard weight in this system is grain and all are weight are derived from it.

Metric system: This system of weight and measurement is a new system. It is also known as international system of weight and measurement

Isotonic Solution

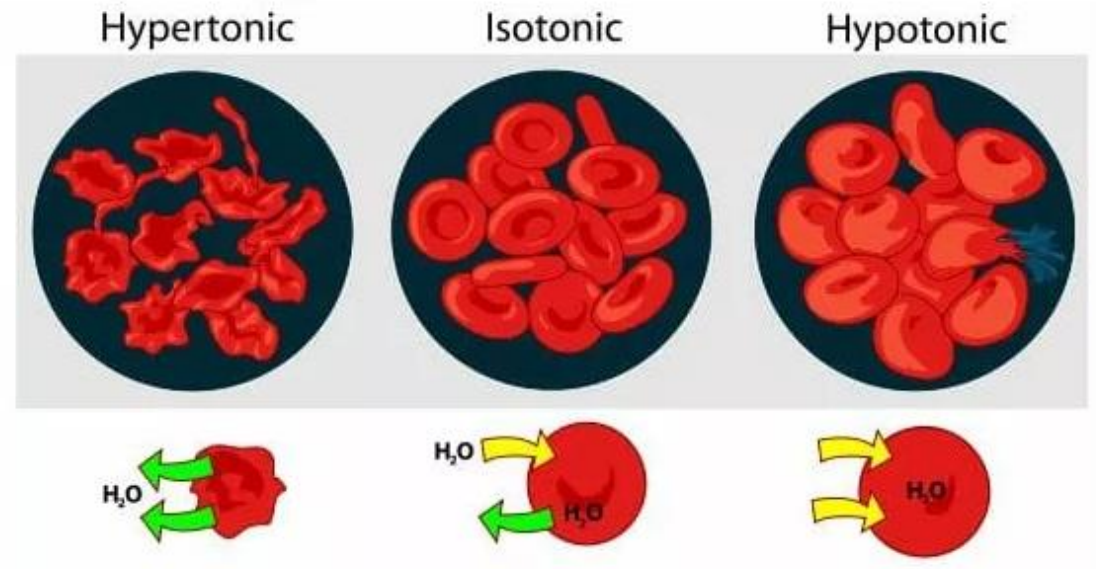
An isotonic solution is one that has the same *osmolarity*, or solute concentration, as another solution. If these two solutions are separated by

a semipermeable_membrane, water will flow in equal parts out of each solution and into the other. The effect is zero water flow between the two solutions, although water is moving both ways. In biology, some cells must be maintained in an isotonic solution to support cellular functions. Many animal cells, which lack a cell_wall to provide support against the effects of water pressure, rely on the stability of the external environment to maintain their shape. Most animals maintain the pH and osmolarity of the fluids inside of their bodies to create isotonic solutions to bathe their cells in. This solution can carry nutrients and water, but only in proportions equal to that inside the cell.

A depiction of a cell in an isotonic solution can be seen above. Note that because there is the same concentration of solute molecules inside and outside of the cell that water molecules are simply exchanged through the cell membrane. This can be contrasted to the effects of a *hypertonic solution*, in which water molecules leave the cell, or a *hypotonic solution* in which water enters the cell.

Examples of Isotonic Solution: Blood Cells

When the plasma surrounding blood cells is an isotonic solution, compared to the solution inside the blood cells, the cells function normally. The isotonic solution allow the cells to move water and nutrients in and out of the cells. This is necessary for blood cells to perform their function of delivering oxygen and other nutrients to other parts of the body. If the cells are in a hypertonic environment, they will become plasmolyzed and will not contain enough water to perform cellular functions. If the cells exist in a hypotonic environment, they will lyse, spilling their contents into the bloodstream. This can cause dangerous side effects, as well as the loss of many blood cells.



Indian Pharmacopoeia:

The Indian Pharmacopoeia Commission (IPC) is an Autonomous Body under Ministry of Health & Family Welfare, Govt, of India primarily with the objectives of regularly updating the Indian Pharmacopoeia by publishing new edition and its addenda, National Formulary of India and other related tasks such as preparing, certification and distribution of reference substances & functions as National Coordination Centre (NCC) for Pharmacovigilance Programme of India (PvPI).

CHAPTER=3
Packaging of Pharmaceuticals

A Pharmaceutical Package container is an article or device which contains the Pharmaceutical Product and the container may or may not in direct contact with the product. The container which is designed for pharmaceutical purpose must be stable.

Ideal Qualities of a Pharmaceutical Package.

1. It should have sufficient mechanical strength so as to withstand handling, filling, closing and transportation.
2. It should not react with the contents stored in it.
3. It should be of such shape that can be elegant and also the contents can be easily drawn from it.
4. It should not leach alkali in the contents.
5. The container should not support mould growth.
6. The container must bear the heat when it is to be sterilized.
7. The contents of container should not be absorbed by the container.
8. The material used for making the container should be neutral or inert.
9. Any part of the container or closure should not react with each other.
10. Closure should be of non toxic nature and chemically stable with container contents.

Types of Package

1. Primary Packaging: Primary packaging are those package which are in direct contact with the Pharmaceutical formulation. The main aim of primary package is to protect the formulation from environmental, chemical, mechanical and/or other hazards.

2. Secondary Packaging: The package external to Primary package is known as secondary package. This package provide additional protection during warehousing and also provide information about drug product for e.g Leaflets.

Functions:

- Protect the flexible containers.
- Protection from tough handling during transportation.

3. Tertiary packaging Examples: Barrel, crate, container, pallets, slip sheet.

It is outer package of secondary packaging & prevents damage to the products. It is used for bulk handling & shipping.

Components of packaging

1. Container: The containers refer in which the product/ medicine is placed & enclosed. It is direct contact with drug.
2. Closure: It is tightly packs the container to exclude oxygen, carbon dioxide, moisture & prevents the loss of water and volatile substances from the products.
3. Carton/outer: Which gives secondary protecion against mechanical and other environmental hazards. It is outer covering. Cartoons are made up of cardboard, wood pulp etc.
4. Box: In this multiples of products are packed. It provides primary defense against external hazards. The boxes are made up of thick cardboard and wood.

The materials selected for packaging must have the following characteristics:

- Mechanical properties.
- Physico-chemical properties
- Biological properties.
- Economical aspects.

Types of packaging materials: The following materials are used for the consruction of containers and closures.

1. Glass a. Type-1 borocilicate glass.
2. Type -2 treated sodalime glass.
3. Type-3 regular sodalime glass.
4. Type-4 NP general purpose sodalime glass.

METALS

Advantages

a. Metal containers are strong, relatively unbreakable opaque.
b. Resistance to chemical attack.
c. Impervious to water vapor, bacteria
d. Readily coats a number of metals

Disadvantages

a. This is the most expensive metal among tin, lead, aluminium, & iron.
b. Currently some eye ointments still package in pure tin ointment tubes.

Aluminum
Advantages
1. Aluminium is a light metal hence the shipment cost of the product is less.
2. They provide attractiveness of tin at somewhat lower cost.

Disadvantages
a. As a result of corrosion process H2 may evolve
b. Any substance that react with the oxide coating can cause corrosion.

Uses: Aluminum ointment tubes, Screw capes.

Plastics
General properties of plastics:
- Robust, strong, light, aesthetic.
- Plastics are synthetic polymers of high molecular weight.
- Easy to handle.
- They are poor conductor of heat.

Types of plastics: Plastics are classified in to 2 groups according to their behavior when heated.
- Thermoplastic type: On heating, they soften to a viscous fluids which hardens again on cooling. Eg: Polyetyline, Polypropylene, PVC, Polystyrene, Nylon etc.
- Thermosetting type: When heated, they may become flexible but they do not become liquid, usually hard and brittle at room temperature. Eg: Phenol, Formaldehyde, Urea etc.

Rubber: Natural rubber consists of long chain polymers of isoprene units linked together in the cis portion. Its most important source is the tree Hevea braziliensis from which latex, containing 30 to 40% of rubber in colloidal suspension, exudes when shallow cuts are made in the bark. A. Butyl rubber: These are co polymer of isobutylene with 1-3% of butadiene.
Advantages
- Permeability to water vapor and air is very low.
- Water absorption is very low.

CHAPTER= 4
Size Separation

Size separation is a unit operation that involves the separation of a mixture of various size particles into two or more portions by means of screening surfaces. Size separation is also known as sieving, sifting, screening. This technique is based on physical differences b/w the particles such as size, shape and density.

Factors affecting size reduction

- Material structure.
- Some substances are homogeneous in character.
- Mineral substances may have lines of weakness.
- The materials splits to form flake-like particles.
- Vegetable drugs have a cellular structure often leading to long fibrous particles.

Size Separation Methods:

a. Sieving
b. Cyclone separator
c. Air separator Elutriation.

Sieving:

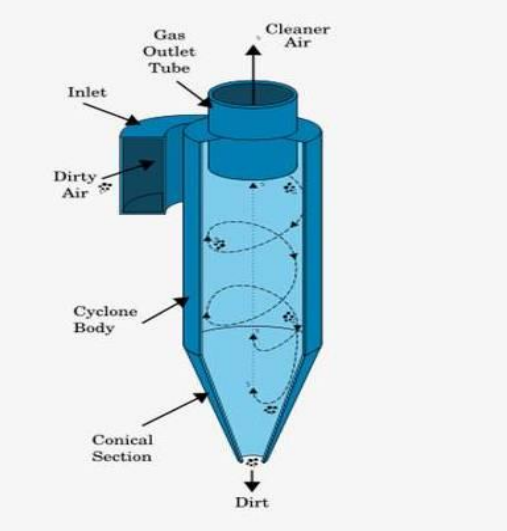
Sieving Working of mechanical sieves A. Agitation Oscillation: Back and froth Vibration: Rapid vibration Gyration: Rotatory B. Brushing: C. Centrifugal: Principle: Sieving

a. Sieves:

Sieves Sieves for pharmacopeial testing are constructed from wire cloth with sqare meshes, woven from wires of brass, bronze, stainless steel etc., Number of sieve: No of meshes in a length of 2.54 cm in each transfer direction parallel to the wires. Nominal size of aperture: Distance between the wires. Length of the side of the square aperture. (in mm or µm). Nominal diameter of the wire: Made of suitable diameter in order to give a suitable aperture and sufficient length. Approximate % sieving area: The area of the meshes as a percentage of the total area of the sieve. Generally the sieving area is kept within the range of 35-40% in order to give suitable strength to the sieve. Tolerance average aperture size: Fine sieves cannot be woven with same accuracy.

b. Cyclone Separator:

Principle: Centrifugal force used to separate the solids from fluids Depends not only on particle size but particle density Hence, coarse particles will settle down and fine particles will be carried out with fluid .



Working: The suspension of particles is introduced tangentially at a very high velocity. The rotatory flow

causes the particles to be acted on by centrifugal force. The solids (Coarse) are thrown out the walls, thereafter it falls in to a conical base and discharged through solid outlet Cylindrical Vessel with a conical base

Uses: It is used to separate the suspension of solids from liquids or gases

c. Air Separator:

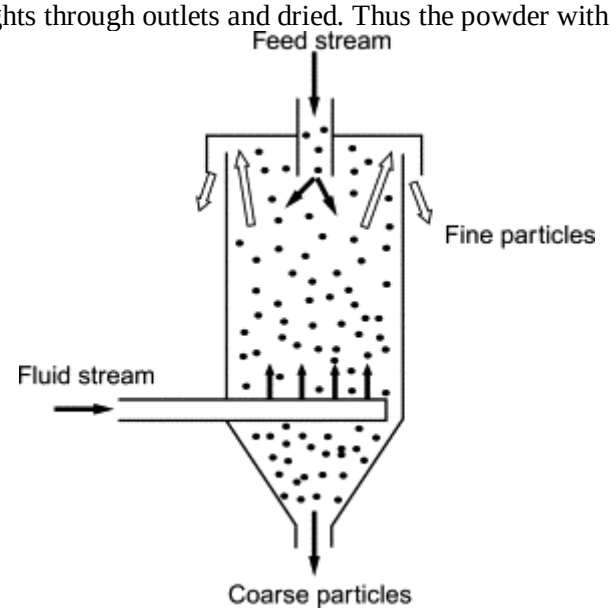
Principle: It works on the same principal as that of cyclone separator, but in this case the air movement is obtained by means of rotating disc and blades

Working: The powder is passed to fall on rotating discs and blades. Rotating discs will produce air flow and rotating blades will reduce the size of the particles Cylindrical Vessel with a conical base

Uses: It is attached to ball mill or hammer mill to separate and return oversized particles for further size reduction.

Elutriation Methods:

Elutriation Methods the size separation of powders is based on the low density of fine particles and high density of coarse particles. Elutriation tank is used to separate the coarse and fine particles after levigation . The dry powder or paste made from levigation process is mixed with large quantity of water and made suspend in the tank. Depending on density of particles they will settle down or suspended in water. The sample is drawn from different heights through outlets and dried. Thus the powder with various size fractions are obtained.



Advantages: The process is continuous The separation is quick as compare to that other methods of separation. Depending on the number of fractions required, the same number of tubes of different area of cross section can be connected nowadays in elutriation process, the particles are suspended in a moving fluid. The apparatus consists of vertical columns. One column will give single separation in two fractions. For further fractions the number of tubes of increasing area of cross section is connected in series. The fractions are separated and dried.

Application of size separation:

Application/uses of size separation Determination of particle size & size distribution used for production of tablet and capsule. It is a quality control tool for analysis of raw material. To optimize the process condition such as method of agitation, time of screening, feed rate etc. To measure the efficiency of size reduction equipments.

CHAPTER=5
Mixing

Mixing may be defined as the process in which two or more than two components in a separate or roughly mixed condition are treated in such a way so that each particle of any one ingredient lies as nearly as possible to the adjacent particles of other ingredients or components. This process may involve the mixing of gases, liquids or solids in any possible combination and in any possible ratio of two or more components. Mixing of a gas with another gas, mixing of miscible low viscosity liquids and mixing of a highly soluble solid with a low viscosity liquid to effect dissolution are relatively simple as compared to the mixing of gases with liquids, mixing of liquids of high viscosity though miscible, mixing of two immiscible liquids such as aqueous and oily solutions to form emulsions, mixing of solids with liquids when the proportion of solids is high and mixing of solids with solids, specialized equipments are required for these operations.
Some of the examples of large scale mixing practiced in pharmacy are:

- Mixing of powders in varying proportions prior to granulation or tableting.
- Dry mixing of the materials for direct compression in tablets.
- Dry blending of powders in capsules and compound powders (insufflations).
- Blending of powders in cosmetics in the preparation of face powders, tooth powders
- Dissolution of soluble solids in viscous liquids for dispensing in soft capsules and in the preparation of syrups
- Mixing of two immiscible liquids for preparation of emulsions.

Objectives of mixing

- To ensure that there is uniformity of composition between the mixed ingredients which may be determined by taking samples from the bulk material and analyzing them, which should represent overall composition of the mixture.
- To initiate or to enhance the physical or chemical reactions e.g. diffusion, dissolution etc.
- When two or more than two miscible liquids are mixed together, this results in to a solution known as true solution.
- When two immiscible liquids are mixed in the presence of an emulsifying agent, an emulsion is produced.
- When a solid is dissolved in a vehicle, a solution is obtained.
- When an insoluble solid is mixed with a vehicle, a suspension is obtained.
- When a solid or liquid is mixed with a semisolid base, an ointment or a suppository is produced.
- When two or more than two solid substances are mixed together, a powder is obtained which when filled into capsule shell is known as capsules and when compressed under heavy pressure is called tablet.

Types of Mixtures: Mixtures may be classified as follows:
1. Positive mixtures
2. Negative mixtures
3. Neutral mixtures

I. Positive Mixtures – These types of mixtures are formed when two or more than two gases or miscible liquids are mixed together by means of diffusion process. In this case no energy is required provided the time allowed for solution formation is sufficient. These types of materials do not create any problem in mixing.
II. Negative Mixtures – These types of mixtures are formed when insoluble solids are mixed with a vehicle to form a suspension or when two immiscible liquids are mixed to form an emulsion. These mixtures are more difficult to prepare and require a higher degree of mixing with external force as there is tendency of the components of these mixtures separate out unless they are continuously stirred.
III. Neutral Mixtures – Many pharmaceutical products such as pastes, ointments and mixed powders are the examples of neutral mixtures. They are static in their behavior. The components of such products do not have any tendency to mix spontaneously but once mixed, they do not separate out easily.

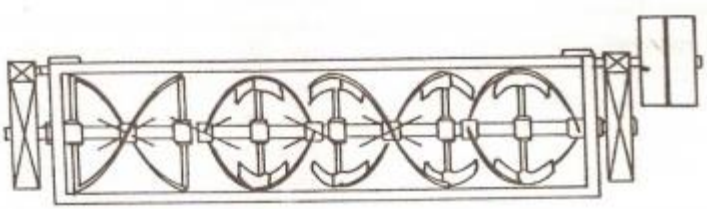
Factors influencing mixing

™ Nature of the product – Rough surface of one of the components does not induce proper mixing. The reason for this is that the active substance may enter into the pores of the other ingredient. A substance that can adsorb

on the surface can decrease aggregation, for e.g. addition of colloidal silica to a strongly aggregating zinc oxide can make it a fine dusting powder which can be easily mixed.
™ Particle size – Variation in particle size leads to separation as the small particles move downward through the spaces between the bigger particles. As the particle size increases, flow properties also increases due to the influence of gravitational force on the size. It is easier to mix two powders having approximately the same particle size.
™ Particle shape – For uniform mixing, the particles should be spherical in shape. The irregular shapes can become inter-locked and there are less chances of separation of particles once these are mixed together.
™ Particle charge – Some particles exert attractive forces due to electrostatic charges on them. This results to separation or segregation.

Mechanism of Mixing In all type of mixers, mixing is achieved by applying one or more of the following mechanisms:
Convective mixing – During convective mixing transfer of groups of particles in bulk take place from one part of powder bed to another. Convective mixing is referred to as macromixing.
Shear mixing – During shear mixing, shear forces are created within the mass of the material by using agitator arm or a blast of air.
Diffusive mixing – During this mixing, the materials are tilted so that the gravitational forces cause the upper layers to slip and diffusion of individual particles take place over newly developed surfaces. Diffusion is also sometimes referred to as micromixing.

Powder mixers Dry mixer (stationary container):
For batch work the dry mixer which is the stationary shell type is often used. This consists of a semi-cylindrical trough, usually covered and provided with two or more ribbon spirals. One spiral is right-handed and the other left-handed. So that the material is worked back and forth in the trough. Ribbon cross section and pitch and number of spirals on the ribbon are varied for different materials varying from low density, finely divided materials to fibrous or sticky materials. It may be centre discharge or end discharge. Another variation is the mounting of cutting blades on the central shaft.



A broad ribbon lifts and conveys the materials while a narrow one will cut through the materials while conveying. Ribbon blenders are often used on the large scale and may be adapted for continuous mixing.

Dry Mixer: The paddle mixer has a stationary outer vessel and the powders are agitated by paddles rotating within. The equipment is suitable to heating, by jacketing the vessel, and also permits a kneading effect by the use of appropriately shaped paddles or beaters. In the bowl mixer the paddle is mounted vertically and in the trough mixer (e.g., dry mixer) a number of vanes are mounted horizontally. Vertical screw mixer: In these types of mixers, the screw rotates about its own axis while orbiting around the centre axis of the conical tank. In another variation, the screw does not orbit but remains in the centre of the conical tank and is tapered so that the swept area steadily increases with increasing height. This type of mixer is mainly used for free flowing solids.

CHAPTER=6
Evaporation

Evaporation means simply vaporization from the surface of the liquid. Evaporation is an unit operation by which a solvent is evaporated from a solution by boiling the liquor in a suitable vessel and withdrawing the vapor, leaving a concentrated liquid residue.

Objective of evaporation:

To make a solution more concentrated. Generally extracts are concentrated in this way.

Factors affecting evaporation:

(i) Temperature:

Heat is necessary to provide the latent heat of vaporization, and in general, the rate of evaporation is controlled by the rate of heat transfer. Rate of heat transfer depends on the temperature gradient.

Many pharmaceutical agents are thermolabile. So the temperature that will cause the least possible decomposition should be used.

E.g. many glycosides and alkaloids are decomposed at temperature below 100^0C.

E.g. Hormones, enzymes and antibiotics are extremely heat sensitive substances. E.g. Malt extract (containing enzyme) is prepared by evaporation under reduced pressure to avoid loss of enzymes.

Some antibiotics are concentrated by freeze-drying.

(ii) Temperature and time of evaporation

Exposure to a relatively high temperature for a short period of time may be less destructive of active principles than a lower temperature with exposure for a longer period.

Film evaporators used a fairly high temperature but the time of exposure is very short. An evaporating pan involve prolonged heating.

(iii) Temperature and moisture content

Some drug constituents decompose more rapidly in the presence of moisture, especially at a raised temperature (by hydrolysis). Hence, evaporation should be carried out at a low controlled temperature, although the final drying can be performed at higher temperature when little moisture remains.

E.g. Belladonna Dry Extract is an example of this type.

(iv) Type of product required

Evaporating pans or stills will produce liquid or dry products, but film evaporators will yield only liquid products. So a dilute extract can be first concentrated in a film evaporator and then the concentrated extract may be died in an evaporating pan.

(v) Effect of concentration

As the liquor becomes concentrated, the increasing proportion of solids results in elevation of the boiling point of the solution. This leads to a greater risk of damage to thermo labile constituents and reduction of the temperature gradient.

In general concentrated solutions will have increased viscosity, causing thicker boundary layers, and may deposit solids that may build up on the heating surface that reduce heat transfer.

All these problems may be minimized by turbulent flow condition.

EVAPORATORS

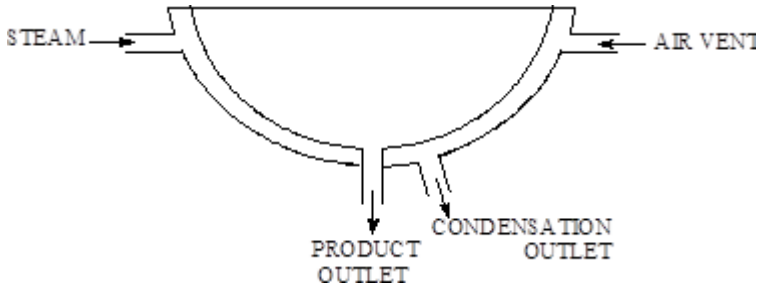
Evaporators are classified according to the form of the movement,

(i) Natural circulation evaporators.
(ii) Forced circulation evaporation
(iii) Film evaporators

(I)Natural Circulation Evaporator

Construction

The apparatus consists of a hemispherical, or shallow pan, constructed from a suitable material such as copper or stainless steel and surrounded by a steam jacket. The hemispherical shape gives the best surface/ volume ratio for heating, and the largest area for separation of vapor. The pan may have a mounting, permitting it to be tilted to remove the product, but the shallow form makes this arrangement somewhat unstable, and an outlet at the bottom, is common.



EVAPORATING PAN

Working

The dilute solution is taken in the pan. Steam is introduced through the steam inlet into the jacket to heat the pan. In these evaporators the movement of the liquid results from convection currents set up by the heating process. The concentrated liquid is collected through the outlet placed at the bottom of the pan.

Advantages:

(a) It is simple and cheap to construct.
(b) It is easy to use, clean and maintain.

Disadvantages:

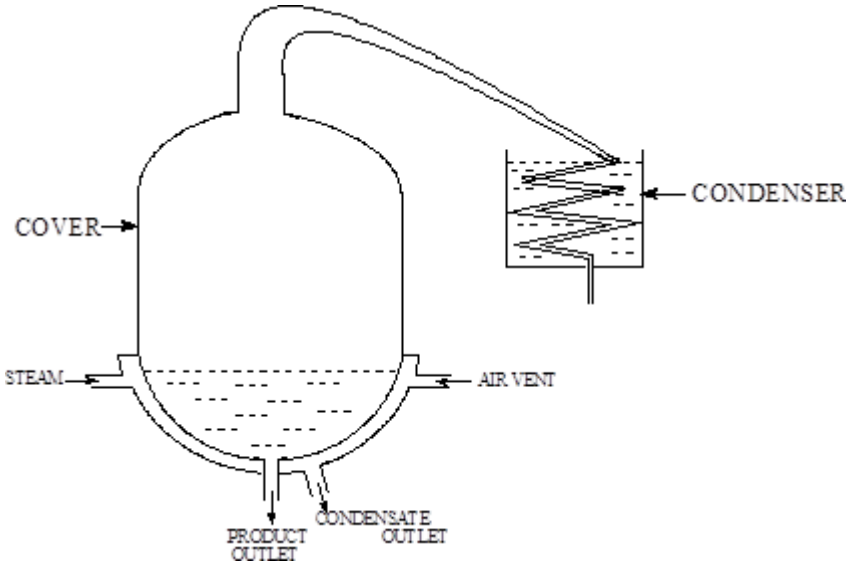
(a) Having only natural circulation, the overall coefficient of heat transfer will be poor and solids are likely to deposit on the surface, leading to decomposition of the product and a further deterioration in heat transfer.
(b) Also many products give rise to foaming.
(c) The total liquor is heated over all the time, which may be unsatisfactory with thermo labile materials.
(d) The heating surface is limited and decreases proportionally as the size of the pan increases.
(e) The pan is open, so the vapor passes to the atmosphere, which can lead to saturation of the atmosphere.
(f) Only aqueous liquids can be evaporated in these pans.
(g) Pan evaporation cannot be done under reduced pressure.
(h) Can only be used for thermo labile products.

EVAPORATING STILLS

Construction

It consists of a jacketed-evaporating pan with a cylindrical *cover* that connects it to a condenser. The overall assembly is called *still*. The cover is clamped with the evaporating pan. *Working*

The dilute liquid is fed into the still, the cover is clamped. Steam is introduced into the jacket. The liquid is evaporated and condensed in the condenser and collected. The product (i.e. concentrated liquid) is collected through the product outlet.



Advantages:

(a) Simple construction and easy to clean and maintain.
(b) The vapor is removed by condensation which
  (i) speeds evaporation
  (ii) reduces inconvenience and
  (iii) Allows the equipment to be used for solvents other than water e.g. ethanol.

(c) A receiver and vacuum pump can be fitted to the condenser, permitting operation under reduced pressure and, hence, at lower temperature.

Disadvantages:

(a) Natural convection only
(b) All the liquor is heated all the time
(c) The heating surface is limited.

SHORT TUBE EVAPORATOR (Basket type vertical short tube evaporator)

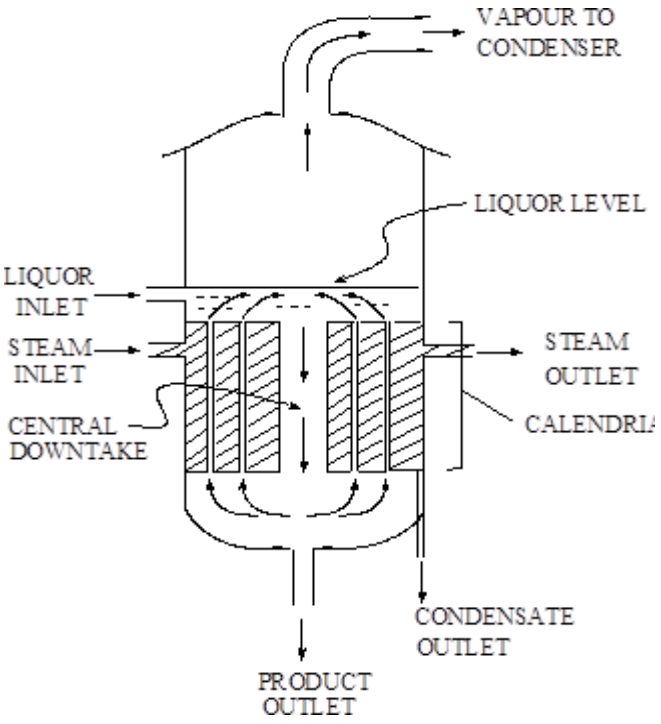
Construction and Principle

Construction

The evaporator is a cylindrical vessel. The lower portion of the vessel consists of a nest of tubes with the liquor inside and steam outside– this assembly is called *calendar*. The specifications of calendric are as follows:

Tube length: 1 – 2 m
Tube diameter: 40 – 80 mm Diameter of evaporator:2.5 m
Number of tubes: 1000

The feed inlet is at the top of the calendar. The product outlet is placed at the bottom of the evaporator. Steam inlet and outlet is placed from the side of the calendric. *Working*



- The feed is introduced through the feed inlet and the liquor is maintained at a level slightly above the top of the tubes (of calendar), the space above this is left for the disengagement of vapor from the boiling liquor.
- The liquor in the tubes is heated by the steam and begins to boil, when the mixture of liquid and vapor will shoot up the tubes (in a similar manner to that of a liquid that is allowed to boil to vigorously in a test-tube).
- This sets up a circulation, with boiling liquor rising up the smaller tubes of the calendric and returning down the larger central down take.
- The product is collected through the product outlet.

Advantages

1. Use of tubular calendric increases the heating area, Possibly by a factor of 10 to 15 compared to that of an external jacket.
2. The vigorous circulation reduces boundary layers and keeps solids in suspension, so increasing the rate of heat transfer.
3. Condenser and receiver can be attached to run the evaporation under vacuum with no aqueous solvents.

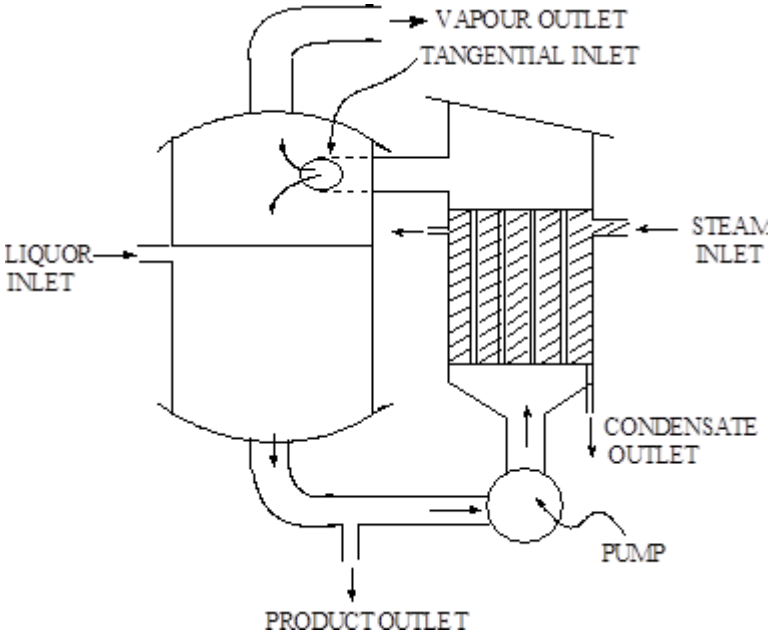
Disadvantages

1. Since the evaporator is filled to a point above the level of the calendric, a considerable amount of liquid is heated for a long time. The effect of this continual heating can be reduced to some extent by removing concentrated liquor slowly from the outlet at the bottom of the vessel.
2. Complicated design, difficult for cleaning and maintenance.
3. The head (pressure) of the liquor increases pressure at the bottom of the vessel and, in large evaporators where the liquor depth may be of the order of 2 m; this may give rise to a pressure of about 0.25 bar, leading to elevation of the boiling point by 5 to 6^0C.

FORCED CIRCULATION EVAPORATORS

Forced circulation evaporators are natural circulation evaporators with some added form of mechanical agitation. Different forms of forced circulation evaporators can be designed.

- An evaporating pan, in which the contents are agitated by a stirring rod or pole could be described as a forced circulation evaporator.
- A mechanically operated propeller or paddle agitator can be introduced into an evaporating pan or still.
- Propeller or paddle agitator can be introduced into the down take of a short-tube evaporator.
- A typical forced circulation evaporator can be shown as follows:



Construction

The evaporator consists of a short tube calendric and a large cylindrical vessel (body of the evaporator) for separation of vapor and

Liquid takes place. The liquor inlet is provided at the side of the cylindrical vessel. A pump is fitted in between the calendric and the body of the evaporator. A tangential inlet for liquid under high pressure is placed at neck of the body of the evaporator. The vapor outlet is placed at the top of the body and it may be passed through a condenser to collect the condensed liquid.

Working Principle

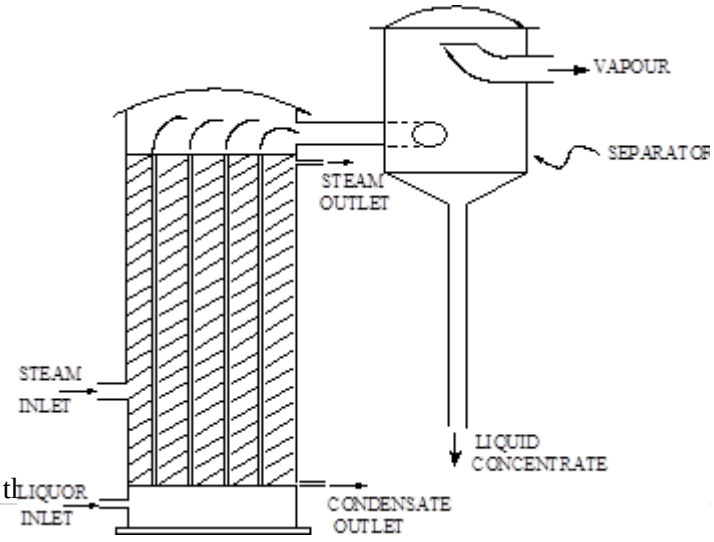
Feed is introduced through the liquor inlet. Pump will force the liquid through the calendric. Steam heats the liquid inside the calendric. As it is under pressure in the tubes the boiling point is elevated and no boiling takes place. As the liquor leaves the tubes and enters the body of the evaporator through the tangential inlet there is a drop in pressure and vapor flashes off from the superheated liquor. The concentrated liquid is pumped out through the product outlet and the vapor is collected through the vapor outlet.

Advantages

- Rapid liquid movement improves heat transfer, especially with viscous liquids or materials that deposit solids or foam readily.
- The forced circulation overcomes the effect of greater viscosity of liquids when evaporated under reduced pressure.
- Rapid evaporation rate makes this method suitable for thermo labile materials, e.g. it is used in practice for the concentration of insulin and liver extracts.

FILM EVAPORATORS

Film evaporators spread the material as a film over the heated surface, and the vapor escapes the film.



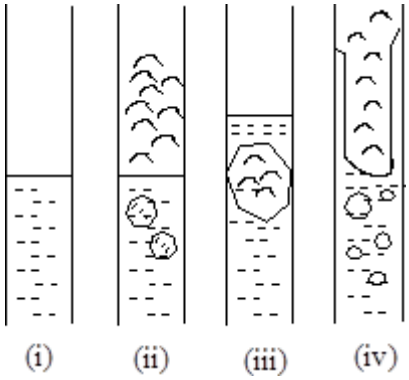
Long tube evaporators (Climbing film evaporators)

Construction and working principle

The heating unit consists of steam-jacketed tubes, having a length to diameter ratio of about 140 to 1, so that a large evaporator may have tubes 50 mm in diameter and about 7 m in length.

The liquor to be evaporated is introduced into th

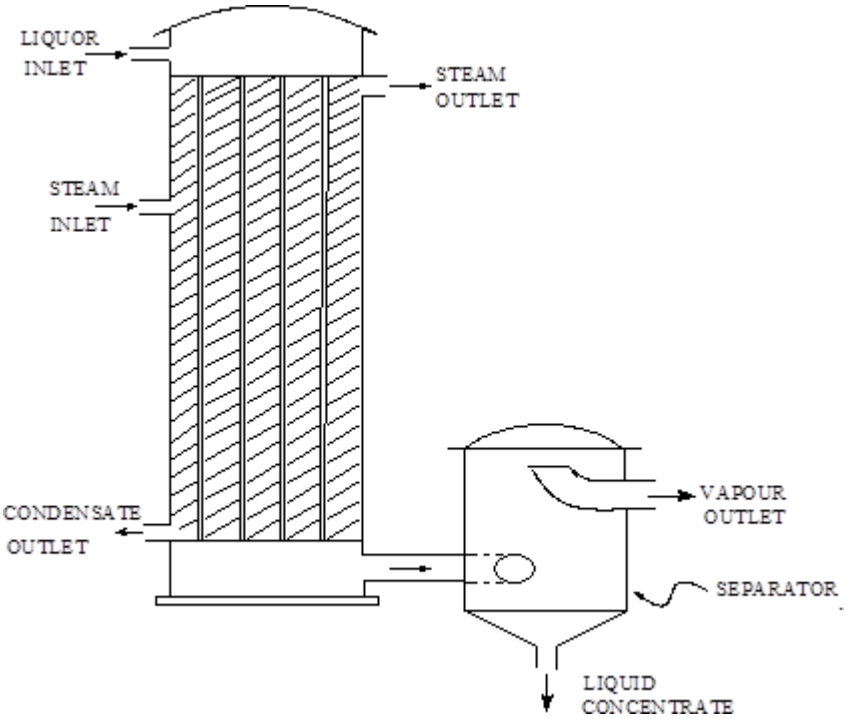
and rises up the tubes, hence it is called climbing film evaporator. At the upper end, the mixture of vapor and concentrated liquor enters a separator, the vapor passes to a condenser, and the concentrated liquid to



a receiver.Cold or pre heated liquor is introduced into the tube. Heat is transferred to the liquor from the walls and boiling begins, increasing in vigor. Ultimately sufficient vapor has been formed for the smaller bubbles to unite to a large bubble, filling the width of the tube and trapping a 'slug' of liquid above the bubble .
As more vapor is formed, the slug of liquid is blown up the tube, the tube is filled with vapor, while the liquid continues to vaporize rapidly, the vapor escaping up the tube and, because of friction between the vapors and liquid, the film also is dragged up the tube up to a distance of 5 to 6 meters.

Long tube evaporators (Falling film evaporators)

Construction and working principle the heating unit consists of steam- jacketed tubes, having a length to diameter ratio of about 140 to 1, so that a large evaporator may have tubes 50 mm in diameter and about 7 m in length.
The liquor to be evaporated is introduced at the top of the evaporator tubes and the liquor comes down due to gravity.
The concentrate and vapor leaves the bottom. They are separated in a chamber where the concentrate is taken out through product outlet and vapor from vapor outlet.



Advantages of long tube evaporator(s) since the movement of the film is assisted by gravity, more viscous liquid can be handled by falling film evaporator.

(i) Very high film velocity reduces boundary layers to a minimum giving improved heat transfer.
(ii) The use of long narrow tubes provides large surface area for heat transfer.
(iii) Because of increased heat transfer efficiency, a small temperature gradient is necessary with less risk of damage to thermo labile materials.
(iv) Although the tubes are long, they are not submerged, as in the short-tube evaporator; so that there is no elevation of boiling point due to hydrostatic head.

Disadvantages

(i) Expense to manufacture and install the instrument is high.
(ii) Difficult to clean and maintain.
(iii) From the operational point of view the feed rate is critical. If too high, the liquor may be concentrated insufficiently, whereas, if the feed rate is to low, the film cannot be maintained and dry patches may form on the tube wall.

Factors affecting evaporation:

(vi) Temperature:

Heat is necessary to provide the latent heat of vaporization, and in general, the rate of evaporation is controlled by the rate of heat transfer. Rate of heat transfer depends on the temperature gradient.

Many pharmaceutical agents are thermo labile. So the temperature that will cause the least possible decomposition should be used.

E.g. many glycosides and alkaloids are decomposed at temperature below 100^0C.

E.g. Hormones, enzymes and antibiotics are extremely heat sensitive substances. E.g. Malt extract (containing enzyme) is prepared by evaporation under reduced pressure to avoid loss of enzymes.

Some antibiotics are concentrated by freeze-drying.

(vii) Temperature and time of evaporation

Exposure to a relatively high temperature for a short period of time may be less destructive of active principles than a lower temperature with exposure for a longer period.

Film evaporators used a fairly high temperature but the time of exposure is very short. An evaporating pan involve prolonged heating.

(viii) Temperature and moisture content

Some drug constituents decompose more rapidly in the presence of moisture, especially at a raised temperature (by hydrolysis). Hence, evaporation should be carried out at a low controlled temperature, although the final drying can be performed at higher temperature when little moisture remains.

E.g. Belladonna Dry Extract is an example of this type.

(ix) Type of product required

Evaporating pans or stills will produce liquid or dry products, but film evaporators will yield only liquid products. So a dilute extract can be first concentrated in a film evaporator and then the concentrated extract may be died in an evaporating pan.

(x) Effect of concentration

As the liquor becomes concentrated, the increasing proportion of solids results in elevation of the boiling point of the solution. This leads to a greater risk of damage to thermo labile constituents and reduction of the temperature gradient.

In general concentrated solutions will have increased viscosity, causing thicker boundary layers, and may deposit solids that may build up on the heating surface that reduce heat transfer.

All these problems may be minimized by turbulent flow condition.

CHAPTER=7
Distillation

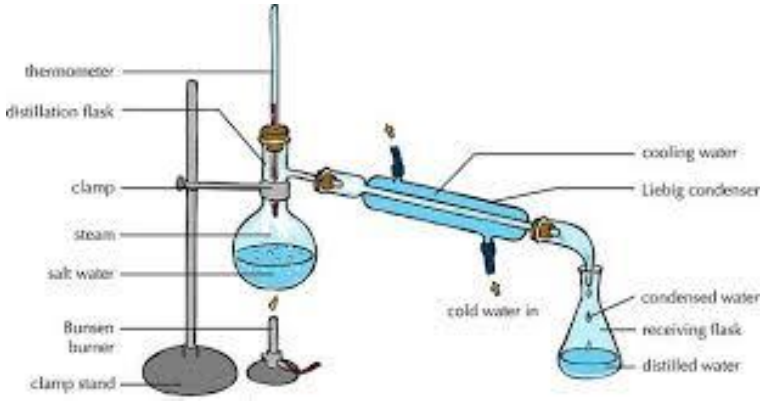
Distillation is the process of converting liquid into its vapours by heating and recovering it again into liquid by condensing the vapour.

Difference between Evaporation and Distillation:

	Distillation	Evaporation
i)	Distillation occurs at the boiling point of liquid.	Evaporation occurs below the boiling point.
ii)	Collection and condensation of vapour is done.	Collection and condensation of vapour is not done.
iii)	Vapour is formed throughout the liquid	Vapour is formed at the surface of liquid, evaporation is surface phenomenon.
iv)	Distillation is carried out when condensed vapour is required.	Evaporation is carried out when concentrated residue is required.

❖ Simple distillation:

Simple distillation is a process of converting a liquid into its vapour in a distillation still, transferring the vapour to another place and condensing it again into liquid. The liquid to be purified is taken in the distillation flask fitted with a thermometer and a water condenser. The flask is heated on water, oil or a sand bath depending upon the boiling point of the substance being distilled. The vapour of the liquid get condensed when pass through the condenser and are collected in the receiver. The impurities remain in the distillation flask.



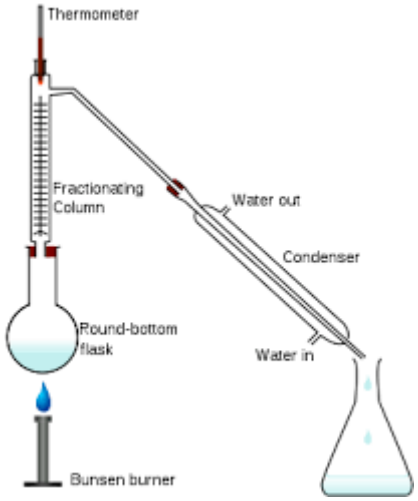
Applications:

- Organic solvents are purified by distillation.

- To separate non-volatile solid from volatile liquids such as alcohol, ether, benzene etc.
- It is also used to recover alcohol from the extract during the separation of dry extract.

❖ Fractional distillation

Fractional distillation is used for separating a mixture of two or more miscible liquid mixed with each other and having different boiling points. During the process of fractional distillation, the boiling point of the mixture is increased gradually as more and more components having low boiling point is distilled first. The mixture can be separated into pure components by fractional distillation.



In the process, the mixture of miscible liquid to be separated is placed in the distillation falsk. On heating, the mixture gets converted into vapours which enters into the fractionating column. The purpose pf fractionating column is to increase the cooling surface and to provide obstructions to the passage of asending vapour and decending liquid. The result of this vapour liquid contract is the the more volatile components tend to be transferred to the liquid. The condensed vapour of the liquid having low boiling point enter into condenser. The condensed liquid is falls into the receiver.

Applications:

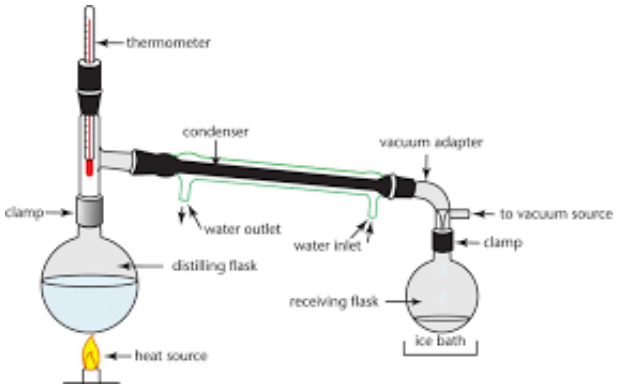
- It is used for the manufacturing of ethyl alcohol.
- It is used for separation of miscible liquid such as alcohol and water, acetone.

- It is used for the preparation of volatile oils like lemon and orange oils.

❖ **Vacuum distillation**:

This method is applicable for thermolabile substance or for substance which decompose on boiling at atmospheric pressure. When vapour pressure equal to the atmospheric pressure. So boiling point of the liquid may be lowered to the desired temperature by reducing pressure on its surface.

In this process of distillation chances of superheating and bumping are greatly increased due to the reduced pressure. This difficulty may be Overcome by the use of a special type of distillation flask, one arm of which carries a capillary tube, which is partially closed at the upper end and by a pressure tubing screw clip arrangement to regulate air. The pressure inside the apparatus is reduced by a vacuum pump. A manometer is also used to regulate the pressure. The Claisen flask is connected to a receiver through condenser. Heating of Claisen flask is not started until the desired vacuum has beenattained.

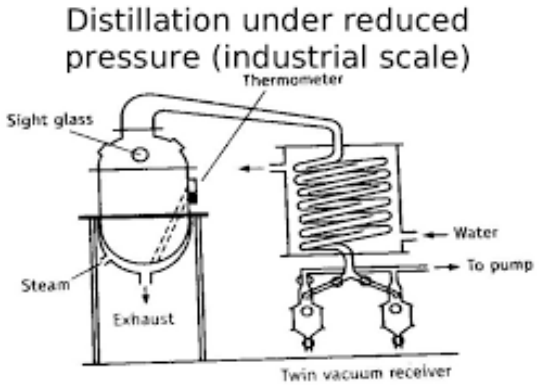


Applications (i) It is used for separating or purification of liquids which undergo decomposition at their boiling point.
(ii) It is used for concentrating and drying of extracts which undergo decomposition of active constituents when heated under normal atmospheric
pressure.
(iii) It is also used for preparation of light porous product

Vacuum stills:

Vacuum stills are used for large scale distillation under reduced

pressure. It is used for those substances which have high boiling point at atmospheric pressure and get destroyed at high temperature Vacuum stills are made up of metals such as copper or stainless steel. which can withstand a high vacuum. A glass observation window is provided for the operator to see the progress of the distillation. A tap is provided near the hood of the still for filling the still. Two receivers are used to collect the distillate without stopping the distillation. A vacuum pump is used for reducing the pressure in the vacuum still.



Application:

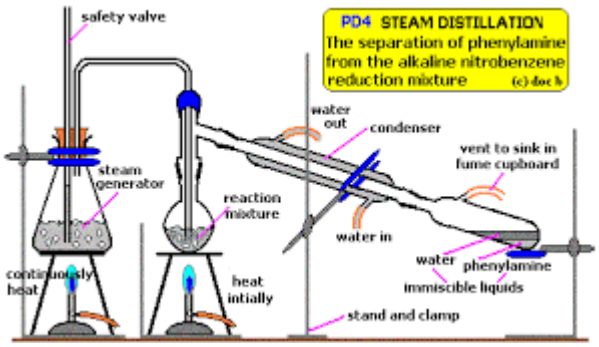
(i) It is used for concentrating and drying of extract which undergo docomposition of active constituents when heated under normal atmospheric pressure.

(ii) It is also used for the distillation of thermolabile substances.

Ques: What is steam distillation? What are its applications?

Steam distillation involves the distillation of substances in a current of steam. The technique is applied to those substances which are steam volatile, insoluble in water, have a fairly high vapour pressure at 100°C and contain non-volatile impurities.

The substance to be distilled is placed in the flask. Flask is heated just to boil the contents and steam from the generator is passed through it. The vapours of the pure compound mixed with steam pass over and are condensed while passing through the water condenser. The pure compound along with water is collected in a receiver.



The distillate forms two layers and the florentine receiver helps to separate these layers. The main advantage of this method is that the chances of decomposition of active constituents is less because the process is carried out at a temperature less than 100°C

(i) It is used for the preparation of aromatic waters.
(ii) It is also used for purification of glycerin, fatty acids and other volatile oils like terpentine oil.
(iii) It is also used for distillation of liquids which are immiscible with water.

Water in pharmaceutical practice as per 1.P.

(i) Purified water
(ii) Water for injection
(iii) Sterile water for injection.

(i) **Purified Water**: Water which is free from volatile and non-Water for injection volatile impurities is called purified water. It is prepared from drinking water by distillation or by use of ion-exchange resins or by reverse osmosis. Such water must comply with limit tests for chlorides, sulphates, calcium, copper, lead, iron, oxidizable matter, total solids and ammonia. It is liable to get contaminated by micro-organisms, hence purified water should not be used for preparation meant for parenteral administration. It is a colourless, odourless, tasteless, clear liquid. The pH ranges from 4.5 to 7.0. It is also free from dissolved carbon dioxide. It should be stored in tightly closed containers. It is a practice that whenever distill water is prescribed, purified water is to be dispensed.

(ii) **Water for Injection**: Water which is free from volatile and non- volatile impurities, pyrogens and micro-organisms is called water for injection. It is obtained by distillation of petable water, purified water or distilled water. It contains no added substances. The purity specification limits, the quantities of chloride, sulphate, calcium, heavy metal ions, carbon dioxide, ammonia, oxidizable substances and total solids. IP. Describes water for injection as colourless, odourless, tasteless, clear liquid. The pH ranges from 5.0 to 7.0. It should be stored in tightly closed glass containers and must be used within 24 hours for the preparation of parenteral products. The heating and storing of water for injection at 80°C will prevent bacterial growth. It is used for the preparations of parenteral dosage form.

(iii) **Sterile water for Injection** : I.P. describes sterile water for Injection as a colourless, odourless, tasteless clear liquid which is sterilized and suitably packed. It is free from pyrogens and micro-organisms. The pH range is between 4.5 to 7.5. It must comply with the tests for sterility. It should also comply with the tests for CO_2, Cl^-, So_4^{--}, NO_3^-,, NO_2^-, NH_4^+,ca^{2+} and heavy metal 1ons. It should be stored in single dose containers not larger than one litre in size. The solid contents should not be more than 0.004% (w/v) for sterile water tor injection in glass container. Higher total solid content is permitted in sterile water for injection to allow for the material leached from the glass container during sterilization process.

Distilled water

Distilled water and water for injection can be prepared continuously without the impurities of gases, hydrolysis of salts, etc. by using distillation stills. A distillation still used for the manufacturing of distilled water. It consists of a boiler which is made of cast iron. It is connected to condenser through the baffles. The condensed tubes and baffles which come in contact with vapours and purified water are of stainless steel. For heating. it has heating elements or coils. The cooled water enters at the bottom of condenser and is heated by condensing

vapours. The flow rate is adjusted in such a way that water gets heated at 90-95°C betfore it enters the boiler. The top of the condenser jacket is open for removal of gases. A constant level device is fitted in such a way that only the heated water free from gases enters the boiler. The stills containing the bafiles are used for the manufacturing of purified water free from pyrogens and other impurities (i.e.,water for injection). The purified water free from pyrogen is filled into ampoules and after sealing they are sterilized in an autoclave at a temperature of 115°C for 30 minutes. When water for injection free from carbon dioxide is required, the distillate should be boiled for 10 minutes with minimum exposure to air which can be done by covering the mouth of the flask, Distilled water may be prepared from drinking water by distillation, by use of ion exchange resins. Ion exchange process are also used for the preparation of purified water which can be used for all pharmaceutical purpose except where water for injection is required. This is due to the fact that during ion exchange processes, the pyrogens are not effectively removed.

CHAPTER=8

DRYING

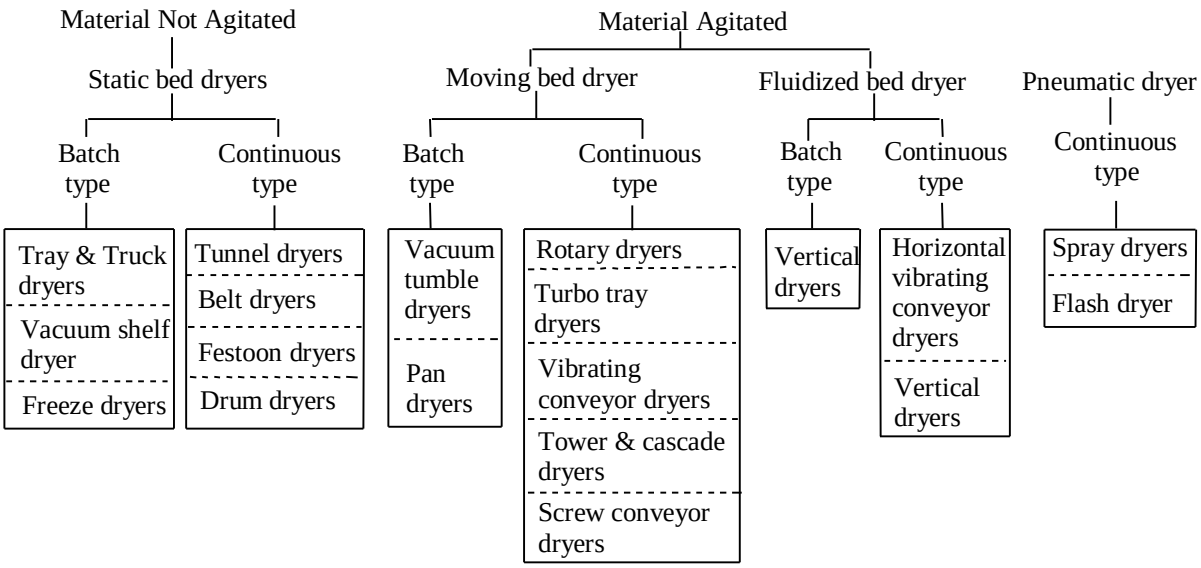
Drying is defined as the removal of liquid from a solid by thermal method. When large amount of liquid is evaporated from a solution or slurry the process is called ‘evaporation’. When very small amount of liquid is evaporated from solids the process is called ‘drying’. The final product is a ‘dried solid’.

Purpose of drying in pharmaceutical industries

1. Drying is most commonly used in pharmaceutical industries in the preparation of granules, which can be packed in bulk or compressed into tablets or filled in capsules.
2. Drying is required for processing of materials like, drying of aluminium hydroxide, spray drying of lactose and preparation of powdered extracts.
3. Drying is used to reduce the bulk weight that lowers the transportation and storage costs of that material.
4. Drugs obtained from plant and animal sources, when dried, becomes more friable. Thus drying helps in size reduction of natural drugs.
5. Animal and vegetable drugs are preserved against mold growth in dried condition.
6. Dried products often are less many stable than moist ones as in the case of effervescent salts, aspirin, hygroscopic powders, ascorbic acids and penicillin.

CLASSIFICATION OF DRYERS

Classification based on solid handling



Classification of dryers, based on methods of solids handling

Classification based on heat transfer mechanism

1. Convection dryers
   (a) Tray or shelf dryers
   (b) Tunnel dryers
   (c) Rotary dryers
   (d) Fluidized bed dryers
2. Conduction dryers
   (a) Vacuum oven (b) Freeze dryers
3. Radiant heat dryers
   (a) Infra-red dryers

TRAY DRYER or Truck Dryer

Construction: It consists of a small cabinet or a large compartment in which trays containing wet materials are placed. The compartment wall is insulated to reduce heat loss.

1. In tray dryers the trays are directly placed inside the cabinet.
2. The truck dryer the trays are loaded on to the trucks (shelves on wheel) and then the trucks are introduced inside the heating cabinet.

The bottom of the trays are either perforated or having wire-mesh bottom.

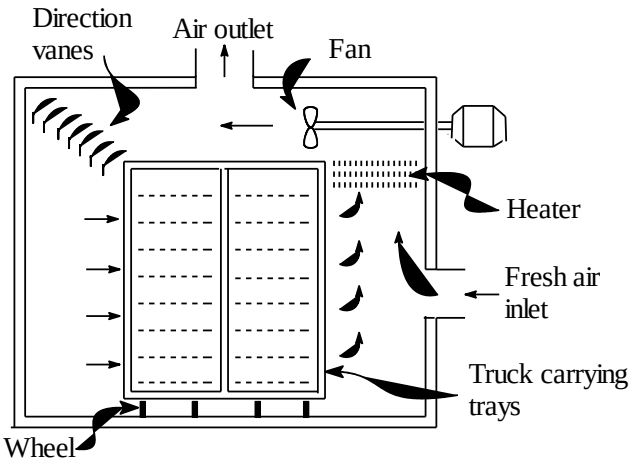


Fig. Truck dryer

1. The material is heated by hot air circulated by means of fans that removes the humid air from the cabinet.

The trays containing the load remain in the dryer until drying is complete, after which they are withdrawn, emptied and recharged for drying the next batch.

Energy sources: Dry air can be heated either by electricity or steam.

Applications

1. Drying of crude drugs, chemicals, powders, tablet granules etc.
2. It is a batch process and materials can be handled separately.

ROTARY DRYERS

Construction

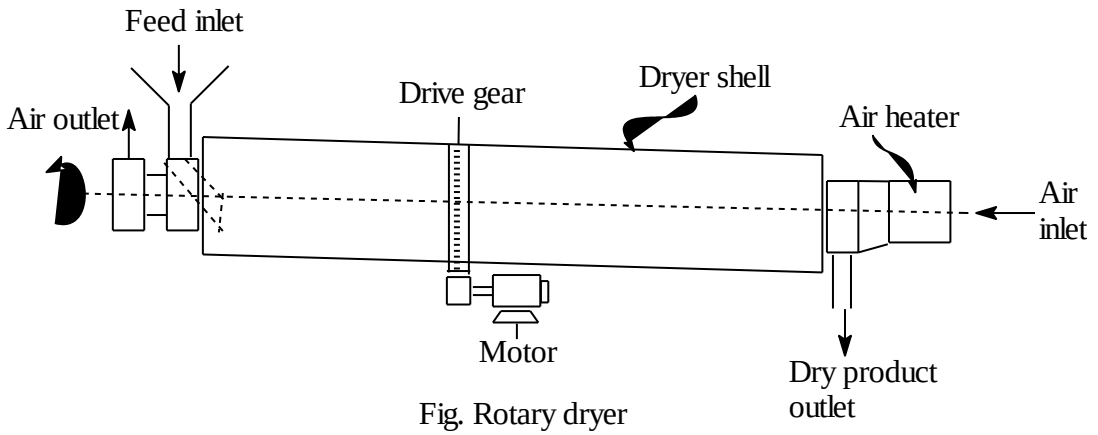


Fig. Rotary dryer

It is a cylindrical shell (10 m length) mounted with a slight slope so that the material will move through the shell as it is slowly rotated at about 10 rpm. To improve contact the shell contains baffles or flights, which lift the solids and spill the particles through the air stream.

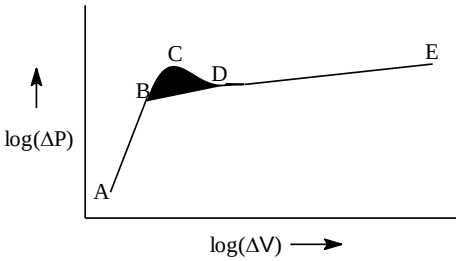
The hot air flows counter current to the flow off material.

Application

It is used for continuous drying on a large scale of any powdered or granular solid.

FLUIDIZED BED DRYER

Principle



Let us consider a situation where a bed of granules is placed over a perforated bottom container and hot air is flown from bottom through the bed. The pressure drop (ΔP) across the bed and the air velocity (V) are measured. If the air velocity is gradually increased and ΔP is plotted against V then the following curve is observed.

1. *Point A*: When the air velocity is very low flow takes place between the particles without causing any disturbance.
2. *Point B*: When the velocity is increased to a certain value the frictional drag on the particles become equal the force of gravity of the particle.
3. *Point C*: Rearrangement of the particles occurs to offer least resistance.

4. *Point D*: Eventually the particles are suspended in the air and can move, ΔP decreases slightly because of greater porosity.
5. Further increase in the air velocity causes the particles to separate and move freely, and the bed is fully *fluidized*. Any additional increase in velocity separate the particles further, i.e. the bed expands, without appreciable change in ΔP until E.
6. In the D-E region the air flows through the bed in the form of bubbles – the term *boiling bed* is generally used for this stage.
7. Above point E the solid particles entrain into the gaseous phase and the particles float in the gas.

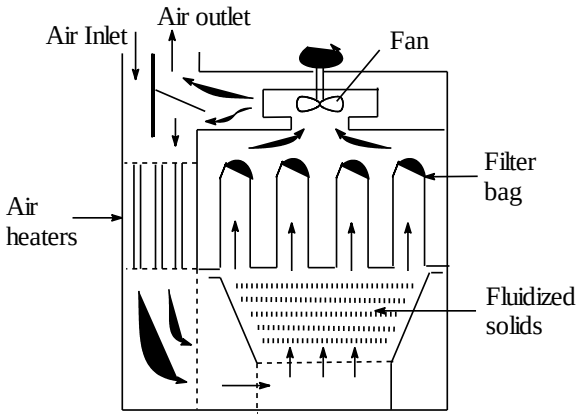


Fig. Fluidized bed dryer

Construction

Two types of fluidized bed dryers are there

1. vertical fluidized bed dryer – for batch process
2. horizontal fluidized dryer – for continuous process

The dryer consists of:

1. Air handler: This is a source of dry and hot air. It is also attached by means of heating and dehumidifying air, if necessary.
2. Plenum: It consists of a screen or plate to distribute the incoming air as it enters the dryer.
3. Product container: This container holds the product that is to be dried.
4. Expansion chamber: This chamber is situated above the product container and holds the suspended material.
5. Filter: The upper part of the expansion chamber has bag filters. It prevents fines from escaping into the atmosphere or collecting on the blades that pulls the air through the dryer.

Applications

1. Wet granulation:

1. Fluidized bed dryers are used to dry the previously prepared wet granules.

2. Powders are agglomerated in the drying chamber by spraying liquid binder over it, while the hot air dries the agglomerates to form dry granules.

2. Coating of tablets

The fluidized bed dryer can be used for coating granules also. This technique is called Wurster technique.

In fluidized condition the powder is coated by coating solution sprayed from the nozzles. As the particles are coated they become heavier. When the mass developed becomes higher than the drag force given by the fixed air velocity the particles no longer floats. They fall back, which is then collected as product.

Advantages

1. Efficient heat and mass transfer facilitate high drying rates. Heating time of thermolabile materials is minimized.
2. Individual particles of the bed get dried in the fluidized state. So, most of the drying will be at constant rate and the falling rate period is very short.
3. Temperature can be controlled uniformly.
4. A free-flowing product is obtained.
5. Since the bed is not static, free movement of individual particles eliminates the risk of soluble materials migrating.
6. Short time yields a high output from a small floor space.

Disadvantages

1. Turbulence of fluidized state may produce fine particles due to attrition.
2. Fine particles lead to segregation, so they must be collected by bag filters.
3. Static charges may be produced due to vigorous movement of particles in hot dry air.

VACUUM DRYER

Conduction is used as the principle method of heat transfer in dryers that are operated under vacuum.

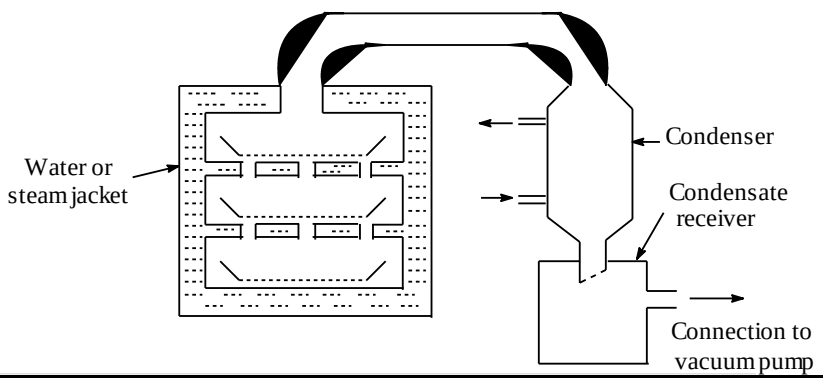


Fig. Vacuum dryer

Convection cannot take place when air is nearly absent.

Construction

It is a jacketed vessel through which steam or hot water is passed. The vessel can be closed airtight. The oven is connected through a condenser and receiver to a vacuum pump. The supports of the shelves form part of the jacket, giving a larger area for heat conduction. Materials to be dried are kept in a tray and placed on the shelves. Hot water or steam is passed through the jacket, a vacuum pump is connected to the chamber.

Advantages:

1. Drying takes place at low temperature, so thermolabile materials can be dried.
2. It reduces the risk of oxidation during drying.
3. It produces porous and friable granules. [N.B. Because under vacuum the vapor forms bubbles and in this condition the material is dried.]
4. The solvent can be recovered from the condenser.

Disadvantages

1. Heat coefficients are low. Most of the heating takes place by conduction, some is from radiation from the wall of the jacket around. So the drying rate is slow.
2. Labor and running costs are high.

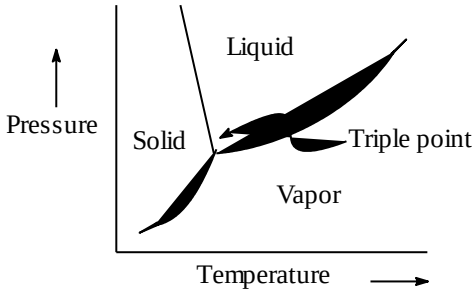
Applications:

1. To dry a thermolabile material like Penicillin.
2. To produce porous form such as dry extract.
3. To recover the solvent, for example to recover ethanol from ethanol extractives.

FREEZE DRYER

Principle

The temperature and pressure of the material is reduced below the triple point of solvent to be dried. Under these conditions, any heat transferred is used as latent heat and the ice sublimes directly to vapor state (without formation of liquid state).



Triple point of pure water is 4579 μm of Hg and 0.0099^0C. Pharmaceutical products remain in solution. In this case the pressure and temperature below which water evaporates directly from ice to vapor state is called *eutectic point*. In freeze dryer the pressure and temperature is maintained well below the *eutectic point*. Generally it is carried out at -10^0C to -40^0C, and at pressure of 2000 to 100 μm Hg.

Construction

Freeze dryer consists of

1. *a chamber for vacuum drying*:
   Two types of chambers are there, one for batch type and another for continuous type operation.
2. *a vacuum source*:
   Vacuum is achieved either by vacuum pump or by steam ejector or a combination of two.
3. *a heat source*:
   Heat is provided by conduction or radiation.
4. *a vapor removal system*:
   For removal of water vapor condensers, desiccants, pumps or scrapper blades are employed.

Stages of freeze drying process

(a) Preparation and pretreatment:

Protein solutions take 8 to 10 times longer period than pure water. Therefore, in such cases, it is desirable to concentrate the solution under normal vacuum tray dryer.

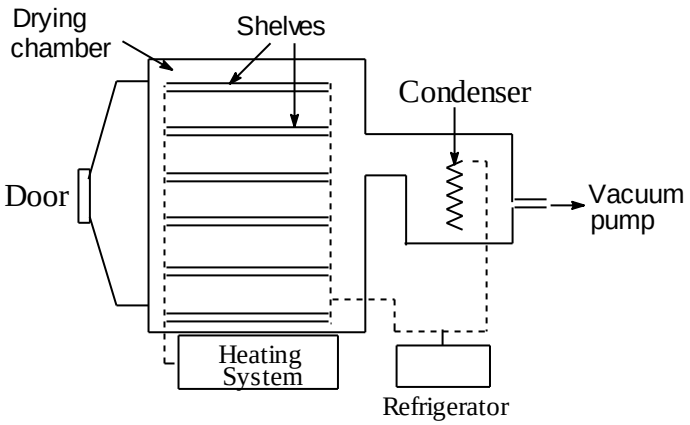


Fig. Industrial freeze dryer

(b) Pre-freezing

The aqueous solutions to be dried are packed in vials, ampoules or bottles. They are then cooled to solidify the water. Cooling can be done by using cold-shelves (-50^0C), alcohol baths (-50^0C) or liquid nitrogen bath (-195^0C).

1. Thinner the layer of frozen material higher is the drying rate. The usual thickness is kept at 0.5 to 0.75 inches.
2. Low freezing rates produces larger crystals of ice. Sublimation of water from this material leaves large pores. So freezing rate is generally maintained at 3 to 25^0C/min resulted in a product having pore size of 1 to 45 μm.

(c) Primary drying (Sublimation of ice under vacuum)

A vacuum of 0.5 bar is applied on the frozen materials. The temperature is increased to 30^0C within 2 hours. Then the temperature is kept constant. During this stage around 98 to 99% water is removed from the materials.

(d) Secondary drying (Removal of residual moisture under high vacuum)

Temperature is maintained at 30^0C continuously and vacuum is lowered to a pressure of 0.07 bar. The rate of drying is very low it takes 10 to 20 hours to dry 1% moisture.

(e) Packing

Inert gas is introduced inside the dryer to break the vacuum. Then the vials and ampoules are sealed within the dryer to reduce the contact of atmospheric gases.

Advantages

1. Drying takes place at a very low temperature, so that the enzyme action is inhibited, and decomposition (e.g. hydrolysis) is minimized.

2. The solution is frozen, so that the final dry product is a network of solid occupying the same volume as the original solution. Thus there is no case-hardening and the product is light and porous.
3. The dried products are readily re-dissolved or re-suspended by the addition of water prior to use (this procedure is termed as *reconstitution*).
4. The solutions do not concentrate during drying (like in other drying methods). Hence salts do not concentrate and denature the proteins present in the same solution.
5. Under high vacuum there is no contact with air, and oxidation is minimized.

Disadvantage

1. It produces a very hygroscopic product, hence should be sealed in the final package within the dryer.
2. The process is very slow.
3. The instruments are very costly.

Applications:

1. Maintenance and preservation of microbial culture.
2. Solution of penicillin can be stored at $0 - 2^0$C and used within two-three days, but if freeze dried then it is stable for several months.
3. To produce fibrin foam [N.B. Fibrinogen is dissolved in sodium chloride injection and whipped into a foam that is then clotted by addition of human thrombin. The foam is then freeze dried].
4. To prepare gelatin sponge [N.B. A solution of gelatin containing traces of formaldehyde is foamed, freeze dried, sterilized and used as surgical dressing.]
5. Used to dry sera, blood products, certain enzymes, plant extracts, diagnostics, mammalian tissues useful in skin and bone graft surgery.

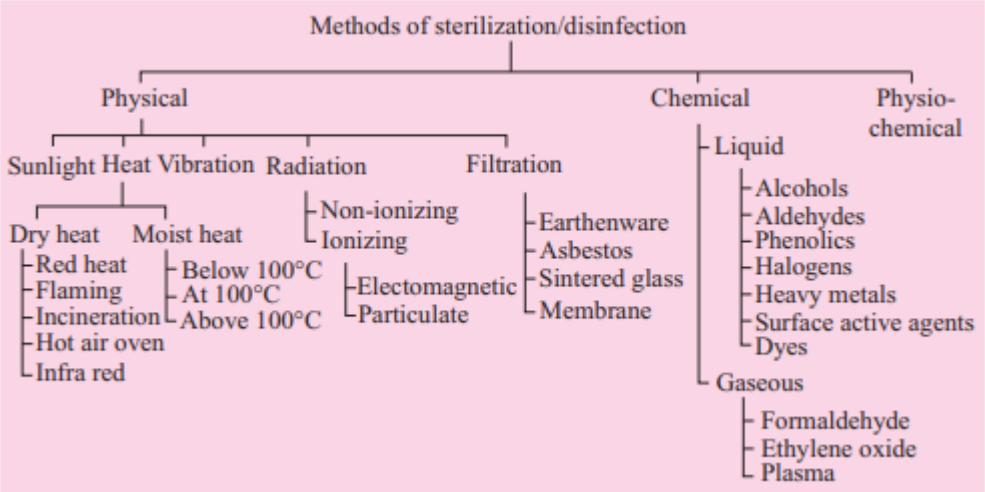
CHAPTER=9
Sterilization

Sterilization are essential for ensuring that medical and surgical instruments do not transmit infectious pathogens to patients. Because sterilization of all patient-care items is not necessary, health-care policies must identify, primarily on the basis of the items' intended use, whether cleaning, disinfection, or sterilization is indicated.

Methods of sterilization

The various methods of sterilization are:

1. Physical Method: (a) Thermal (Heat) methods (b) Radiation method (c) Filtration method
2. Chemical Method
3. Gaseous method



Heat Sterilization:

Heat sterilization is the most widely used and reliable method of sterilization, involving destruction of enzymes and other essential cell constituents. The process is more effective in hydrated state where under conditions of high humidity, hydrolysis and denaturation occur, thus lower heat input is required. Under dry state, oxidative changes take place, and higher heat input is required. This method of sterilization can be applied only to the thermostable products, but it can be used for moisture-sensitive materials for which dry heat (160- 180°C) sterilization, and for moisture-resistant materials for which moist heat (121-134°C) sterilization is used. The efficiency with which heat is able

to inactivate microorganisms is dependent upon the degree of heat, the exposure time and the presence of water. The action of heat will be due to induction of lethal chemical events mediated through the action of water and oxygen. In the presence of water much lower temperature time exposures are required to kill microbe than in the absence of water. In this processes both dry and moist heat are used for sterilization.

Dry Heat Sterilization: Examples of Dry heat sterilization are:
1. Incineration
2. Red heat
3. Flaming
4. Hot air oven

It employs higher temperatures in the range of 160-180°C and requires exposures time up to 2 hours, depending upon the temperature employed. The benefit of dry heat includes good penetrability and non-corrosive nature which makes it applicable for sterilizing glass-wares and metal surgical instruments. It is also used for sterilizing non-aqueous thermo-stable liquids and thermostable powders. Dry heat destroys bacterial endotoxins (or pyrogens) which are difficult to eliminate by other means and this property makes it applicable for sterilizing glass bottles which are to be filled aseptically.

Hot-air oven:

Dry heat sterilization is usually carried out in a hot air oven, which consists of the following:

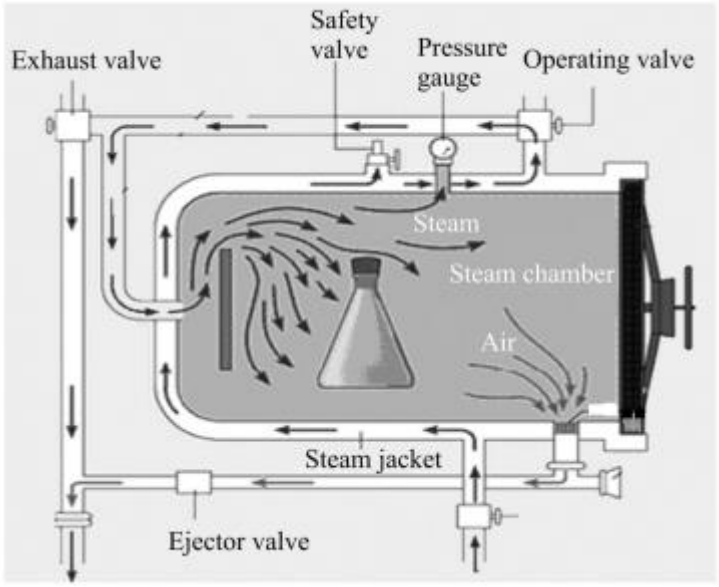
(i) An insulated chamber surrounded by an outer case containing electric heaters.
(ii) A fan
(iii) Shelves
(iv) Thermocouples
(v) Temperature sensor
(vi) Door locking controls.

Operation:

(i) Articles to be sterilized are first wrapped or enclosed in containers of cardboard, paper or aluminium.

(ii) Then, the materials are arranged to ensure uninterrupted air flow.
(iii) Oven may be pre-heated for materials with poor heat conductivity.
(iv) The temperature is allowed to fall to 40°C, prior to removal of sterilized material. Moist Heat Sterilization: Moist heat may be used in three forms to achieve microbial inactivation.

Autoclaving:
Moist heat sterilization involves the use of steam in the range of 121-134°C. Steam under pressure is used to generate high temperature needed for sterilization. Saturated steam acts as an effective sterilizing agent. Steam for sterilization can be either wet saturated steam (containing entrained water droplets) or dry saturated steam (no entrained water droplets).



An Autoclave Autoclaves use pressurized steam to destroy microorganisms, and are the most dependable systems available for the decontamination of laboratory waste and the sterilization of laboratory glassware, media, and reagents. For efficient heat transfer, steam must flush the air out of the autoclave chamber. Before using the autoclave, check the drain screen at the bottom of the chamber and clean if blocked. If the sieve is blocked with debris, a layer of air may form at the bottom of the autoclave, preventing efficient operation. Autoclaves should be

tested periodically with biological indicators like spores of Bacillus stearothermophilus to ensure proper function. This method of sterilization works well for many metal and glass items but is not acceptable for rubber, plastics, and equipment that would be damaged by high temperatures. Autoclaves, or steam sterilizers essentially consist of following:

1. A cylindrical or rectangular chamber, with capacities ranging from 400 to 800 litres.
2. Water heating system or steam generating system
3. Steam outlet and inlet valves
4. Single or double doors with locking mechanism.
5. Thermometer or temperature gauge
6. Pressure gauges Operation For porous loads (dressings) sterilizers are generally operated at a minimum temperature of 134°C for one hour, and for bottled fluid, sterilizers employing a minimum temperature of 121°C are used. Ensure that there should be sufficient water in the autoclave to produce the steam. The stages of operation of autoclaves include air removal, steam admission and sterilization cycle.

RADIATION STERILIZATION

Many types of radiation are used for sterilization like electromagnetic radiation (e.g. gamma rays and UV light), particulate radiation (e.g. accelerated electrons).The major target for these radiation is microbial DNA. Gamma rays and electrons cause ionization and free radical production while UV light causes excitation. Radiation sterilization with high energy gamma rays or accelerated electrons has proven to be a useful method for the industrial sterilization of heat sensitive products. But some undesirable changes occur in irradiated products, an example is aqueous solution where radiolysis of water occurs.

Radiation sterilization is generally applied to articles in the dry state; including surgical instruments, sutures, prostheses, unit dose ointments, plastic syringes and dry pharmaceutical products. UV light, with its much lower energy, and poor penetrability finds uses in the sterilization of air, for surface sterilization of aseptic work areas, for treatment of manufacturing grade water, but is not suitable for sterilization of pharmaceutical dosage forms. Gamma ray Sterilizer: Gamma rays for

sterilization are usually derived from cobalt-60 source.
This source is housed within a reinforced concrete building with 2 m thick walls. Articles being sterilized are passed through the irradiation chamber on a conveyor belt and move around the raised source. Ultraviolet Irradiation: The optimum wavelength for UV sterilization is 260 nm. A mercury lamp giving peak emission at 254 nm is the suitable source of UV light in this region. Electron Accelerator There are two types of electron accelerator machines, the electrostatic accelerator which produces electrons with maximum energies of 5 MeV, and the microwave linear accelerator which produces electrons with maximum energies of 10 MeV. Higher energies cause better penetration into the product but there is a risk of induced radiation. A high energy electron beam is generated by accelerating electrons from a hot filament down an evacuated tube under high potential difference, and then additional energy is imparted to this beam in a pulsed manner by a synchronized traveling microwave. Articles to be sterilized are arranged on a horizontal conveyor belt and are irradiated from one or both sides.

CHAPTER=10

Aseptic Technique

Aseptic technique means using practices and procedures to prevent contamination from pathogens. It involves applying the strictest rules to minimize the risk of infection. Healthcare workers use aseptic technique in surgery rooms, clinics, outpatient care centers.

Surgical technique:

Surgical skill does not negate the need for aseptic technique but the competence with which the tissues are handled is closely tied to the degree of contamination a wound can overcome. To assure maximum blood supply to the healing tissue, it must be handled gently with either a skin hook or toothed tissue forceps, and unnecessary tension on the wound edges during closure avoided. Hemostasis should be achieved in a manner that does not compromise blood supply, implant excessive amounts of suture, or induce unnecessary thermal damage. Electro cautery is an indispensable tool but it must be used judiciously. Excessive thermal destruction of tissue is associated with an increased risk for infection.[43] Consider bipolar cautery, which directs current between the tips of the forceps, and produces significantly less tissue necrosis than monopolar cautery at comparable energy settings.[58] Avoid extensive thermal damage by tying off large-diameter vessels or muscular arteries. When possible, use the smallest effective monofilament suture and limit unnecessary suture, particularly braided silk, which enhances the virulence of staphylococci 10 000-fold.

Aseptic technique demands the use of sterile gloves. Although their effectiveness in the control of infection in regard to minimally invasive spinal injections has never been demonstrated, some have advocated the use of masks, hats, and gowns.

A sterile cover for the C-arm image intensifier allows the physician to control and direct the image during the periprocedural period. In addition, this prevents contaminating detritus from falling onto the sterile field from the equipment. A sterile, long, 6- to 12-inch, radio-opaque pointer, combined with a skin marking pen enables the injectionist to mark the proposed skin entry site in a radiation safe manner.

Aseptic techniques are those that do some or all of the following:

- Remove or kill microorganisms from hands and objects
- Employ sterile instruments and other items
- Reduce a patients risk of exposure to microorganisms

Aseptic technique refers to the practices performed immediately before and during a clinical procedure. They include:

- Handwashing
- Surgical scrub
- Using barriers (personal protective equipment)
- Patient prep
- Maintaining the sterile field
- Using safe operative technique (making small incisions, avoiding trauma to tissue and surrounding structures, and controlling bleeding)
- Maintaining a safer environment in the surgical/procedure area

Nurses in all practice settings need to have a good understanding of the importance of hand asepsis and the proper technique for achieving skin preparation of the surgical or procedural site, Denholm adds. They also need to understand the basics of caring for and cleaning surgical instruments including the decontamination process and how to evaluate packaging systems to ensure conditions have been met for sterilization, storage, and handling of sterile instruments and supplies.

Glove use is important and gloves must be used appropriately. In a study measuring how the improper use of gloves limits compliance to hand hygiene and exposes patients to infection

CHAPTER=11

Tablets

Tablets are solid dose pharmaceutical preparation containing drug substances usually prepared with the aid of suitable pharmaceutical excipients. They may vary in size, shape, weight, hardness, thickness, disintegration and dissolution characteristics and in other aspects, depending on their intended use and method of manufacture. It used to provide systemic administration of therapeutic agents. Tablets are prepared primarily by compression of granules or powder blends, with a limited number prepared by moulding. Most tablets are used in the oral administration of drugs. Many of these are prepared with colourants and coatings of various types. Other tablets, such as sublingual, buccal, or vaginal tablets, are prepared to have features most applicable to their particular route of administration.

Advantages of Tablets

- Tablets are elegant in appearance and convenient to use.
- They are superior to other dosage forms with respect to chemical, physical and microbiological stability.
- Tablets provide stable and an accurately measured dosage of drug substance to patients.
- Tablets can be formulated to protect unstable drug substances or disguise unpalatable excipients.
- Tablets are generally inexpensive to manufacture.
- It is easier to mask the unpleasant taste of some APIs in tablets thus improving patient acceptability.
- Tablets may be formulated to contain two or more drug substances (even if they are physically or chemically incompatible), thus reducing multiple tablet use.
- Tablets may be easily manufactured to show product identification using coloured coatings, embossed markings, and printing.
- Tablets may be designed to release their active substance at a particular site within the gastrointestinal tract to reduce side effects,

promote absorption at that site or provide a local effect (e.g. ulcerative colitis).

- With the exception of proteins which are denatured in the gastrointestinal tract, all classes of therapeutic agents may be administered orally in the form of tablets

Disadvantages of Tablets

- The manufacture of tablets requires a series of unit operations (weighing, milling, drying, mixing etc.) thus there is an increased level of product loss at each stage in the formulation process.
- The absorption of medicament from tablets is dependent on physiological factors, such as gastric resident/emptying time, and thus, vary from one .patient to another.
- The compression properties of certain drug substance are poor and may present problems in their subsequent formulation and manufacture as tablets.

General Properties of Tablets

- A tablet must be strong and hard to withstand mechanical shock during manufacturing, packing, shipping, dispensing and use.
- The drug content of the tablet must be bioavailable that is, the tablet must be able to release its content in a predictable and reproducible manner.
- The tablet must be chemically and physically stable to maintain its chemical and physical attributes during manufacture, storage, and use.
- The tablet should have elegant product identity which is free from any tablet defect.
- Tablets must be uniform in weight and in drug content.

Types of tablets

The various tablet types are described as follows:

1. Compressed tablets represent a significant proportion of tablets that are clinically used to provide systemic administration of therapeutic agents either in an uncoated state or in a coated state. These tablets are

designed to provide rapid disintegration in the gastric fluid following ingestion hence, allowing rapid release of the drug and, ultimately, systemic absorption of the dosage form.

Compressed tablets are formed by compression of powdered, crystalline, or granular materials into the required geometry by the application of high pressures, utilizing steel punches and die. In addition to the Active Pharmaceutical Ingredients, compressed tablets usually contain a number of pharmaceutical excipients e.g., bulking agents, disintegrants, binders, lubricants, controlled-release polymers and other miscellaneous adjuncts such as colourants and flavourants which serve different and specialized purpose during tablet manufacture, storage, and use. Examples of compressed tablets include tablets for oral, buccal, sublingual, or vaginal administration.

2. Film-coated tablets are conventional tablets coated with a thin layer of polymer (e.g., hydroxypropyl methylcellulose, hydroxypropyl cellulose) or a mixture of polymers (e.g., Eudragit E100) capable of forming a skin-like film. The film is usually coloured and also impacts the same general characteristics as sugar coating with the added advantage of being more durable, less bulky, and less time-consuming to apply. By its composition, the coating is designed to break and expose the core tablet at the desired location in the gastrointestinal tract.

3. Enteric-coated tablets are compressed tablets that have delayed-release properties. They are coated with polymeric substances (such as cellulose acetate phthalate/cellulose acetate butyrate; hydroxypropylmethylcellulose succinate; and methacrylic acid copolymers) that resist solution in gastric fluid but disintegrate and allow drug dissolution and absorption in the intestine.

Tablet Excipients:

In tablet formulation, many materials are usually combined at various quantities to produce a tablet that is of good standard. These materials serve different and specialized functions in the tablet. The type and

quantity of each raw material used is dependent on the intended tablet type and formulation technique. Tablet Excipients include:

- **Binders /granulating fluid:** E.g. acacia gum, tragacanth, corn starch, methylcellulose, gelatin, panwar gum, ghatti gum, mucilage of isapol husks, carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone and sugars, such as sucrose, glucose, dextrose, molasses, and lactose etc.
- **Bulking agents/ diluents/fillers –** g., anhydrous lactose, spray dry lactose, microcrystalline cellulose, corn starch, dicalcium phosphate, calcium sulfate, lactose, cellulose, kaolin, mannitol, sodium chloride, etc.
- **Disintegrating agents –** e.g., starch, clays, celluloses, algins, gums, and cross-linked polymers (croscarmellose, crospovidone, and sodium starch glycolate) etc.
- **Lubricants – e.**g., metallic stearate, magnesium stearate, calcium stearate, stearic acid, hydrogenated vegetable oil, corn starch, boric acids, sodium chloride, sodium lauryl sulphate etc.
- **Glidants** – e.g., colloidal silicon dioxide Cab-o-sil, Talc etc.
- **Colouring agents**
- **Flavoring agents**– e.g., Aspartame.
- **Adsorbent** – e.g., silicon dioxide, magnesium oxide, starch, magnesium silicate etc.

Manufactured of tablets:

Tablets are commonly manufactured by one of the following manufacturing processes:

Wet granulation

1. Milling of drugs and excipients.
2. Mixing of drugs and excipients.
3. Preparation of binder dispersion.
4. Mixing of binder solution with powder to form a coarse mass.
5. Coarse sieving
6. Drying of moist granules.

7. Sieving of the dried granules and mixing with disintegrant and lubricant.
8. Compression into tablets.

Dry granulation Process:

1. Milling of drugs and excipients.
2. Mixing of milled powders.
3. Compression of mixed powders into slugs (big tablets).
4. Milling and sieving of the slugs.
5. Mixing with disintegrant and lubricant.
6. Compression into tablets.

Direct compression

1. Milling of drugs and excipients.
2. Mixing of powders, disintegrant and lubricant.
3. Compression into tablet

Defects of tablets are:

Lamination: Lamination is the separation of a tablet into two or more distinct horizontal layers.

Sticking: Sticking refers to the tablet material adhering to the die wall. Filming is a slow form of sticking and is largely due to excess moisture in the granulation.

Cracking: Small fine cracks observed on the upper and lower center surface of the tablets, or very rarely on the side wall are referred to as cracks.

Chipping: Chipping is defined as the breaking of tablet edges, while the tablet leaves the press or during subsequent handling and coating operation.

Mottling: Mottling is the term used to describe an unequal distribution of colour on a tablet.

Double Impression: Double impression involves only those punches, which have a monogram or other engraving on them.

CHAPTER=12
Capsules

Capsules are solid dosage forms in which one or more medicinal and or inert substances are enclosed within a small shell or container generally prepared from a suitable form of gelatin. Capsules are usually intended to be administered orally by swallowing them whole. Occasionally, capsules may be administered rectally or vaginally.

Advantages:

1. Neat and elegant in appearance.
2. Tasteless shell to mask the unpleasant taste/odor of the drug.
3. The contents may be removed from the gelatin shell and employed as a pre measured medicinal powder, the capsule shell being use to contain a dose of the medicinal substance.
4. Commonly embossed or imprinted on their surface the manufacturer's name and product code readily identified.
5. The ready solubility of gelatin at gastric pH provides rapid release of medication in the stomach.
6. Packaged and shipped by manufacturers at lower cost less breakage than liquid forms.
7. More stable and longer shelf life.

Disadvantages:

1. Capsules are not suitable for liquids that dissolve gelatin, such as aqueous or hydro alcoholic solutions.
2. The concentrated solutions which require previous dilution are unsuitable for capsules because if administered as such lead to irritation into stomach.
3. Not useful for efflorescent or deliquescent materials. Efflorescent cause capsules to soften & Deliquescent may dry the capsule shell to brittleness.

GELATIN

Gelatin is heterogeneous product derived by hydrolytic extraction of animal's collagen. The sources of gelatins including animal bones, hide portions and frozen pork skin.

TYPES OF GELATIN
Type A
Type B

TYPE A - Derived from acid treated precursor that exhibits an ISO electric point at pH-9. It is manufactured mainly from pork skin.

TYPE B - Derived from alkali treated precursor that exhibits an ISO electric point at pH-4.7. It is manufactured mainly from animal bones.

MANUFACTURE OF EMPTY GELATIN CAPSULES:
Steps involved in making empty gelatin capsules...
• Dipping
• Spinning
• Drying
• Stripping
• Trimming
• Joining
• Polishing

• Once raw materials have been received and released by Quality Control, the gelatin and hot demineralized water are mixed under vacuum in Stainless Steel Gelatin Melting System.

• From receiving tanks, the gelatin solution is transferred to stainless steel feed tanks.

• Dyes, opacifants, and any needed water are added to the gelatin in the feed tanks to complete the gelatin preparation procedure.

• From the feed tank, the gelatin is gravity fed to Dipper section.

Dipping : Pairs of the stainless steel pins are dipped into the dipping solution to simultaneously form the caps and bodies for 12sec. The dipping solution is maintained at a temperature of about 50o C in a heated, jacketed dipping pan & pins are at 22oc.

Spinning : The pins are rotated to distribute the gelatin over the pins uniformly and to avoid the formation of a bead at the capsule ends it is rotated 2½ times by moving upward.

Drying : The gelatin is dried by a blast of cool air to form a hard shells. The pins are moved through a series of air drying kilns, Here gently moving air which is precisely controlled for volume, temperature, and humidity, removes the exact amount of moisture from the capsule halves.

Stripping : A series of bronze jaws strip the cap and body portions of the capsules from the pins. Trimming and joining: The stripped cap and body portions are trimmed to the required length by stationary knives. The cap and body lengths are precisely trimmed to a ±0.15 mm tolerance. After trimming to the right length, the cap and body portion are joined.

• Finished capsules are pushed onto a conveyer belt which carries them out to a container.
• Capsule quality is monitored throughout the production process including size, moisture content, single wall thickness, and color.
• Capsules are sorted and visually inspected on specially designed Inspection Stations.
• Perfect capsules are imprinted with the client logo on high- speed

Capsule size:
For human use, empty capsules ranging in size from 000 the largest to 5 the smallest. Generally, hard gelatin capsule are used to encapsulate between 65 mg to 1 gram.

Types of Capsules
Hard gelatin capsules
Soft gelatin capsules

Hard Gelatin Capsules

These are used for administration of solid medicaments. The capsule shell is prepared from gelatin. It consists of two parts i.e. body and cap. The powdered material is filled into the cylindrical body of the capsules and then the cap is placed over it.

Principles of capsule Filling:
Auger Fill principle:
Rectifier descends the capsules such that caps are turned up and bodies down. From rectifying unit these are placed one by one in filling ring kept on rotating mode. The lower ring is rotated with a suitable speed and the hopper containing powdered drug is held over this ring. The auger drives the drug into bodies.

Vibratory Fill Principle:
The feed is placed in the feed hopper and the capsule bodies are passed under it. A perforated resin plate is placed in the feed hopper. Due the vibrations of the resin plate, the powder flows freely through the pores into bodies.

Piston – Tamp principle:
These piston tamps alter the shape of powder by compressing the powder to form slugs. These plugs are transferred into the empty capsule bodies with the application of slight pressure. Finally the bodies are ejected from the machine. Compression force 50-200N

Vacuum Fill principle:
It consists of an open ended cylinder. The upper end of this is fitted with a piston. The open end is placed in bulk powder. Vacuum is applied & the piston is moved upward by sucking the predetermined amount of powder which results in filling of the cylinder.

FILLING OF HARD GELATIN CAPSULES:
- Punch Method or Manual Filling.
- Hand Filling or Semi Automatic Capsules Devices.
- Automatic filling machine.
- Eli-lily
- Farmatic

• Hofliger and Karg
• Zanasi Nigris
• Parke-Davis
• Osaka
• Macofar SAS

These machine differ in there design and output Punch Method:

- Powder is placed on a sheet of a clean paper or porcelain plate using spatula which is formed into a cake having a depth of approximately one-fourth to one-third the length of the capsule body.

- Then empty capsule body is held between the thumb and forefinger and punched vertically into the powder cake repeatedly until filled.
Soft Gelatin Capsules

Soft Gelatin capsules are one piece, hermetically sealed, soft gelatin shells containing a liquid, a suspension, or a semisolid.

MANUFACTURE OF SOFT GELATIN CAPSULES:
Plate process

Rotary die process
Accogel machine
Bubble Method

Plate process:
• Place the gelatin sheet over a die plate containing numerous die pockets.
• Application of vacuum to draw the sheet in to the die pockets.
• Fill the pockets with liquid or paste.
• Place another gelatin sheet over the filled pockets, and Sandwich under a die press where the capsules are formed and cut out.

Rotary die press:
 In this process, the die cavities are machined into the outer surface of the two rollers.

 Gelatin is properly weighed & dispensed in melting tank under vacuum.
 Two plasticized gelatin ribbons are continuously and simultaneously fed
with the liquid or paste fill between the rollers of the rotary die mechanism.
 As the die rolls rotate, the convergence of the matching die pockets seals and cuts out the filled capsules.

EVALUTION OF CAPSULES:

(1) Content uniformity
(2) Disintegration test.
(3) Weight variation test
(4)Dissolution test.
(5)Moisture permeation test.
(6)Content uniformity:

The amount of active ingredient should be within the range of 85% to 115% of the label amount for 9 of 10 capsules, with no unit outside the range of 70% to 125% of label amount.

Disintegration test for capsules:

 Place 1 capsule in each of the 6tubes of the basket & suspend the assembly in water at 37°C ± 2oC,which is repeatedly immersed 30 times per minute.

 The capsules pass the test if no residue of drug or other than fragments of shell remains on No. 10 mesh screen of the tubes.

Weight variation test: 20 capsules are taken at random and weighed. Their average weight is calculated, then each capsule is weighed individually and their weight is noted. The capsule passes the test if the weight of individual capsule falls with in 90-110% of the average weight.

Moisture permeation test:

Acc. to U.S.P the unit dose container is packed along with dehydrated pellets, which have the property of changing color in the presence of moisture. The weight of test capsule is compared with the under test capsules. Diff. in weights gives the amount of moisture absorbed.

Dissolution test for capsules:

 Place 1000ml of water having a temp. of 36.5o to 37.5o into the vessel. Place specified number of capsules in basket 7 adjust the speed to 100 rpm.

Withdraw req. volume for every 10min time interval. Filter and determine the amount of active ingredient.

The sample passes the test if the amount of active ingredients in the solution is not less than 70% of the stated amount.

PACKING & STORAGE OF CAPSULES:

Capsules should be packed well closed glass & plastic container & stored at temp. not exceeding 30oc. Capsules are individually protected by enclosing in strip & blister packaging.

 In strip packing the capsule is hermetically sealed within the strips of an aluminum or plastic film.

 In blister packs, a press on the blister forces the capsule through the backing strip.

Capsules have a larger shelf life in unopened glass bottles than in strip pack & but this is reversed.

CHAPTER =13
Immunological Products

Artificial immunity is induced by immunisation. This is achieved by giving a vaccine (active immunisation) or immunoglobulin (passive immunisation).

Active immunity

This is the stimulation of the immune mechanism to produce antibodies by giving an antigen as a vaccine. Such vaccines may be:

- Live attenuated viruses (rubella, measles, oral polio, mumps) or bacteria - bacillus Calmette-Guérin (BCG).
- Inactivated viruses (parenteral polio, hepatitis A) or parts of the bacterium or virus (pneumococcal vaccine, influenza).
- Inactivated bacterial toxins (diphtheria and tetanus).
- Genetically engineered (hepatitis B vaccine).

Live attenuated vaccines

Produce longer-lasting immunity, similar but less than that produced by natural infection. Often one dose confers long-lasting immunity; however, they are inherently less stable than killed vaccines, with the possibility of reversion to wild strain, as in polio. Some may spread, enhancing herd immunity but putting at risk the immunocompromised.

Inactivated vaccines

Usually require a series of primary vaccinations followed by boosters. Some of these vaccines have adjuvants (for example, aluminum hydroxide, aluminum phosphate) to enhance the antibody response. There is no risk of person-to-person spread, and the vaccines are more stable.

Humoral immunity

Activation of B lymphocytes by an antigen produces millions of antibodies (immunoglobulins IgG, IgM, IgA, IgD, IgE), which bind to

and neutralise the antigen. After recognising their particular antigen, they multiply and differentiate into plasma cells. Plasma cells produce large amounts of antibody in the form of large glycoproteins (immunoglobulins). Initially IgM is produced - the primary response. This is a slow response and two injections may be needed. Further injections of antigen will produce, after a few months, an accelerated or secondary response producing IgG. IgG antibodies are longer-lasting. When levels of IgG fall, a further dose of vaccine or booster will increase IgG levels again.

Cell-mediated immunity

The cell-mediated immune response does not involve major antibody production but does rely on antigen recognition (in association with self major histocompatibility complex (MHC) molecules) and lymphocyte responses to destroy infected cells and prevent organisms replicating within cells. Lymphocytes differentiating in the thymus and called T lymphocytes are mainly of two types (expressing two major forms of MHC):

- **CD4 or T-helper cells** - interact with class II MHC molecules, leading to stimulation of various immunological molecules - eg, B lymphocytes - to produce antibody. They also produce cytokines which activate macrophages. They are further classified according to the cytokines produced as T-helper 1 (activate macrophages - involved in cytotoxic and delayed hypersensitivity responses) and T-helper 2 (make interleukin-4 and -5 and stimulate B lymphocytes to support antibody production).
- **CD8 or T-suppressor/cytotoxic cells** - interact with class I MHC molecules, leading to a chain of events that destroys host cells infected by a virus.

Passive immunity

This is achieved by giving immunoglobulins and the protection is immediate but lasts only a few weeks. There are two types:

- Human normal immunoglobulin (HNIG) from pooled plasma. This contains antibodies to infections prevalent in the donor population.

Some of these, such as that for hepatitis A, may be falling, ultimately affording less protection.

- Specific immunoglobulin for tetanus, varicella-zoster virus, rabies and hepatitis B. These are derived from pooled serum of convalescent patients.

Vaccine

A vaccine is a biological preparation that provides active acquired immunity to a particular infectious disease. A vaccine typically contains an agent that resembles a disease-causing microorganism and is often made from weakened or killed forms of the microbe, its toxins, or one of its surface proteins. The agent stimulates the body's immune system to recognize the agent as a threat.

Vaccination given during childhood is generally safe. Adverse effects, if any, are generally mild. The rate of side effects depends on the vaccine in question. Some common side effects include fever, pain around the injection site, and muscle aches. Additionally, some individuals may be allergic to ingredients in the vaccine.

Types

Vaccines contain dead or inactivated organisms or purified products derived from them.

There are several types of vaccines in use.[33] These represent different strategies used to try to reduce the risk of illness while retaining the ability to induce a beneficial immune response.

Inactivated vaccine

Some vaccines contain inactivated, but previously virulent, micro-organisms that have been destroyed with chemicals, heat, or radiation. Examples include the polio vaccine, hepatitis A vaccine, rabies vaccine and some influenza vaccines.

Attenuated vaccine

Some vaccines contain live, attenuated microorganisms. Many of these are active viruses that have been cultivated under conditions that disable

their virulent properties, or that use closely related but less dangerous organisms to produce a broad immune response. Although most attenuated vaccines are viral, some are bacterial in nature. Examples include the viral diseases yellow fever, measles, mumps, and rubella, and the bacterial disease typhoid.

The live *Mycobacterium tuberculosis* vaccine developed by Calmette and Guérin is not made of a contagious strain but contains a virulently modified strain called "BCG" used to elicit an immune response to the vaccine. The live attenuated vaccine containing strain *Yersinia pestis* EV is used for plague immunization. Attenuated vaccines have some advantages and disadvantages. They typically provoke more durable immunological responses and are the preferred type for healthy adults. But they may not be safe for use in immunocompromised individuals, and on rare occasions mutate to a virulent form and cause disease.