Clarification and Filtration

Clarification may be defined as the process that involves the removal or separation of a solid from a liquid, or a fluid from another fluid. The term “fluid” encompasses both liquids and gases. Clarification can be achieved using either filtration or centrifugation techniques. Filtration is mainly required to remove unwanted solid particles from a liquid product or from air and centrifugation is normally used to separate fluid from another fluid or to collect the solid as the product

Filtration is defined as the process in which particles are separated from a liquid by passing the liquid through a permeable material. The permeable medium is a porous material that separates particles from the liquid passing through it and is known as a *filter*.

Thus, filtration is a unit operation in which a mixture of solids and liquid, the *feed, suspension, dispersion, influent* or *slurry*, is forced through a porous medium, in which the solids are deposited or entrapped. The solids retained on a filter are known as the *residue*. The solids form a *cake* on the surface of the medium, and the clarified liquid known as *effluent* or *filtrate* is discharged from the filter. If recovery of solids is desired, the process is called *cake filtration*

.

There are numerous applications of filtration in pharmaceutical processing which mainly include:

(i) clarification of products to improve their appearance, i.e. to give them ‘sparkle’ or ‘brightness’,

(ii) removal of potential irritants e.g. from eye drop preparations or solutions applied to mucous membranes

,

(iii) filtration for recovery of desired solid material from a suspension of slurry, e.g. to obtain a drug or excipient after a crystallization process,

(iv) production of water of appropriate quality for pharmaceutical use,

(v) meeting sterility specification (removal of microorganisms) required for some products using *sterile filtration or aseptic filtration*

,

(vi) Sterilization of solutions and suspensions that are chemically or physically unstable under heating conditions

(vii) detect ion of microorganisms present in liquids by analyzing a suitable filter on which the bacteria are retained and

(viii) assessment of the efficacy of preservatives. Recently, techniques such as nanofiltration, ultrafiltration, and microfiltration have been used to recover colloidal delivery systems from mother liquor

MECHANISMS OF FILTRATION

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

1)Surface Straining

In surface straining, any particle that is larger in size than the pores of the medium deposits on the surface, and stays there until it is removed. Particles that are smaller in size than the pores pass quickly through the medium

2) Depth Straining

Depth straining is also governed by particle size or shape. For filter media that are relatively thick in comparison with their pore diameters, particles will travel along the pore until they reach a point where the pore narrows down to a size too small for the particles to go any further, so that they become trapped

3)Depth Filtration

In depth filtration, the particles becomes entrapped in the depth of the medium, even though they are smaller in diameter, and possibly much smaller, than the pore at that point, They become attached to the pore wall, or to another particle already held by means of van der Waals and other surface forces (*entanglement*)

4)Cake Filtration

Cake filtration (which is a development of surface filtration) begins with the formation of a layer of particles on the surface of the filter medium, with larger pores bridged by a group of smaller particles. On this layer, a cake of particles accumulates to act as the filter medium for subsequent filtration. Cake filtration in which solid recovery is the goal is an important pharmaceutical process

These definitions emphasize that the mechanisms of filtration may result in the trapping of far smaller particles than might be expected from the size of the pores in the medium. The actual mechanism or combination of mechanisms in any specific instance is dependent on the characteristics of both the medium and the suspension being filtered

.

THEORY OF FILTRATION

The flow of liquid through a filter follows the basic rules that govern flow of any liquid through a medium offering resistance. The rate of flow may be expressed as:

$$\text{Rate} = \frac{\text{Driving force}}{\text{Resistance}}$$

The rate may be expressed as volume per unit time and the driving force as a pressure differential. The apparent complexity of the filtration equations arises from the expansion of the resistance term. Resistance is not constant since it increases as solids are deposited on the filter medium. An expression of this changing resistance involves a material balance as well as factors expressing permeability or coefficient of resistance of the continuously expanding cake.

These factors have been taken into account in the formation of the *Darcy's equation:*

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

where, A = Filter area
P= total pressure drop through cake and filter medium
V = volume of filtrate
T = time
η = filtrate viscosity
L = bed thickness in direction of fluid flow
K = permeability coefficient

It is convenient to summarize the theoretic relationship as:

$$\text{Rate of filtration} = \frac{(\text{Area of filter}) \times (\text{Pressure difference})}{(\text{Viscosity}) \times (\text{Resistance of cake and filter})} \quad \ldots (1$$

Interpretation of the basic equations, however, leads to a general set of rules:

1)Pressure increases usually cause a proportionate increase in flow unless the cake is highly compressible. Pressure increases on highly compressible, flocculent, or slimy precipitates may decrease or terminate flow.

2)An increase in area increases flow and life proportional to the square of the area since cake thickness and thus resistance, are also reduced.

3)Cake resistance is a function of cake thickness, therefore, the average flow rate is inversely proportional to the amount of cake deposited.

4) The filtrate flow rate at any instant is inversely proportional to viscosity so, filtration efficiency also may be affected by changes in temperature. The viscosities of most liquids decrease with increase in temperature. Increasing the temperature of heavy pharmaceutical syrups lowers the viscosity and increases filtration rates

5) The permeability coefficient may be examined in terms of its two variables: porosity and surface area

,the cake porosity depends on the way in which particles are deposited and packed. A fast deposition rate, given by concentrated slurries or high flow rates, may give a higher porosity because of the greater possibility of bridging and arching in the cake Surface area

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unlike porosity, is markedly affected by particle size and is inversely proportional to particle diameter. Hence, a coarse precipitate is easier to filter than a fine precipitate even though both may pack with the same porosity.

Most clarification problems can be resolved empirically by varying one or more of these factors

FILTER MEDIA

The surface upon which solids are deposited in a filter is called the filter *medium*. For the pharmacist selecting this important element, the wide range of available materials may be bewildering. The selection is frequently based on past experience, and reliance on technical services of commercial suppliers is often advisable. The ideal filter material should have the following characteristics:

1)A medium for cake filtration must retain the solids without plugging and without excessive bleeding of particles at the start of the filtration. In clarification applications in which no appreciable cake is developed, the medium must remove all particles above a desired size.
2)It should offer minimum resistance and the resistance offered by the medium itself will not vary significantly during the filtration process.
3)It allows easy discharge of cake.
4)It should be chemically and physically inert.
5)It should not swell when it is in contact with filtrate and washing liquid.
6)It should have sufficient mechanical strength to withstand pressure drop and mechanical stress during filtration.

There are a variety of different depth filter and membrane filter materials used in pharmaceutical processes. Depth filters are mainly polymeric fibrous materials. The filter fabrics are commonly woven from natural fibers such as cotton and from synthetic fibers and glass

Filter cloth, a surface type medium, is woven from either natural or synthetic fiber or metal. Cotton fabric is the most common and is widely used as a primary medium, as backing for paper or felts in plate and frame filters, and as fabricated bags for coarse straining. Nylon is often superior for pharmaceutical use, since it is unaffected by molds, fungi, or bacteria, provides an extremely smooth surface for good cake discharge, and has negligible absorption properties. Both cotton and nylon are suitable for coarse straining in aseptic filtrations, since they can be sterilized by autoclaving. Monofilament nylon cloth is extremely strong and is available for openings as small as 10 μm. Teflon is superior for most liquid filtration, as it is almost chemically inert, provides sufficient strength, and can withstand elevated temperatures.

Woven wire cloth, particularly stainless steel, is durable, resistant to plugging, and easily cleaned. Metallic filter media provide good surfaces for cake filtration and are usually used with filter aids. As support elements for disposable media, wire screens are particularly suitable, since they may be cleaned rapidly and returned to service. Wire mesh filters also are installed in filling lines of packaging equipment

Non-woven filter media include felts, bonded fabrics, and kraft papers. A *felt* is a fibrous mass that is free from bonding agents and mechanically interlocked to yield specific pore diameters that have controlled particle retention. High flow rate with low pressure drop is a primary characteristic. Felts of natural or synthetic material function as depth media and are recommended where gelatinous solutions or fine particulate matter are involved.

Porous stainless steel filters are widely used for the removal of small amounts of unwanted solids from liquids (clarification) such as milk, syrup, sulfuric acid, and hot caustic soda. Porous metallic filters can be easily cleaned and repeatedly sterilized

Membrane filter media
are the basic tools for microfiltration, ultrafiltration, nanofiltration and reverse osmosis, Membrane filters, classified as surface or screen filters, are made of various esters of cellulose or from nylon, Teflon, polyvinyl chloride, polyamide, polysulfone, or silver
The filter is a thin membrane, about 150 μm thick, with 400 to 500 million pores per square . centimeter of the filter surface. The pores are extremely uniform in size and occupy about 80% of filter volume

The high porosity permits flow rates at least 40 times higher than those obtained through other media of comparable particle retention capability

Because of surface screening characteristics, prefiltration is often required to avoid rapid clogging of a membrane. The selection of a membrane filter for a particular application is a function of the size of the particle or particles to be removed

Surface-type cartridges of corrugated, resin-treated paper are common in hydraulic lines of processing equipment, but are rarely applied to finished products. Ceramic cartridges have the advantage of being cleanable for reuse by back-flushing. Asbestos and porcelain filter candles are acceptable for some sterile filtrations along with membrane filters

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FILTER AIDS

Usually, the resistance to flow due the filter medium itself is very low, but increases as a layer of solids builds up, blocking the pores of the medium and forming a solid, impervious cake. Poorly flocculated solids offer higher resistance than do flocculated solids or solids providing high porosity to the cake.

In the case of cake filtration, the rate varies with the square of the volume of liquid. When the volume of the filter cake solids per unit volume of filtrate is low, the solids deposited on the filter medium may penetrate the void space, thus making the filter medium more resistant to flow. At a higher concentration of solids in a suspension, the bridging over of openings over the void space, rather than blinding of the openings, seems to predominate

The filter medium becomes plugged or slimy with the accumulation of solids, and the flow of filtrate stops. A filter aid acts by reducing this resistance.

Filter aids are a special type of filter medium. Ideally, the filter aid forms a fine surface deposit that screens out all solids, preventing them from contacting and plugging the supporting filter medium.

Usually, the filter aid acts by forming a highly porous and noncompressible cake that retains solids, as does any depth filter. The duration of a filtration cycle and the clarity attained can be controlled as density, type, particle size, and quantity of the filter aid are varied.

The quantity of the filter aid greatly influences the filtration rate. If too little filter aid is used, the resistance offered by the filter cake is greater than if no filter aid is used, because of the added thickness to the cake. On the other hand, if high amounts of filter aid are added, the filter aid merely adds to the thickness of the cake without providing additional cake porosity

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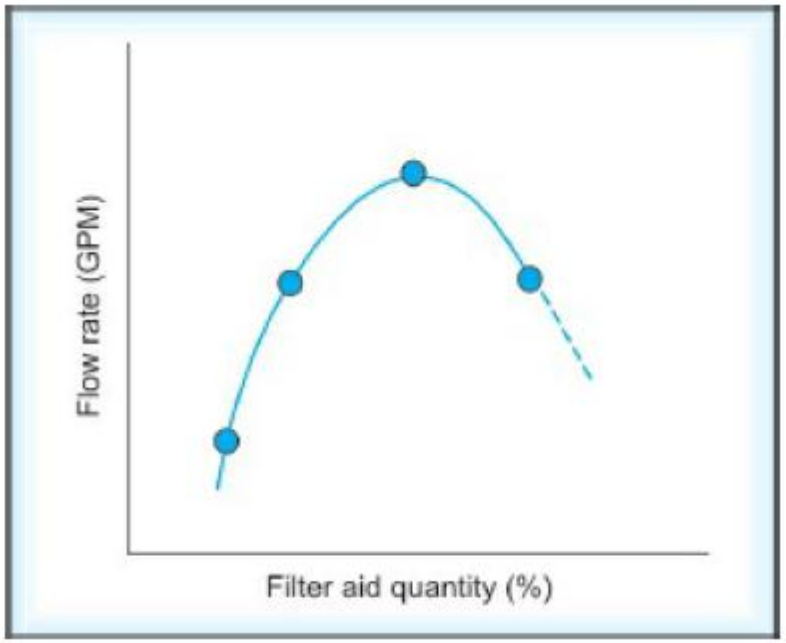


typical plot of filter aid concentration versus permeability. In the figure, flow rate and permeability are directly proportional to each other. At low concentrations of filter aid, the flow rate is low because of low permeability. As the filter aid concentration increases, the flow rate increases and peaks off. Beyond this point, the flow rate decreases as the filter aid concentration is increased
The ideal filter aid performs its functions physically or mechanically and no absorption or chemical action is involved in most cases.
The important characteristics for filter aids are the following:

1)It should have a structure that permits formation of pervious cake.
2)It should have a particle size distribution suitable for the retention of solids, as required.
3)It should be able to remain suspended in the liquid.
4)It should be free of impurities.
5)It should be inert to the liquid being filtered.
6)It should be free from moisture in cases where the addition of moisture would be undesirable
Filter aids are considered to be equivalent in performance when they produce the same flow rate and filtered solution clarity under the same operating conditions when filtering a standard sugar solution

Diatomite (diatomaceous earth) is the most important filter aid. Processed from fossilized diatoms, it has irregularly shaped porous particles that form a rigid incompressible cake. Since diatomite is primarily silica, it is relatively inert and insoluble

Cellulose, asbestos, filter aids are also commercially available. Cellulose is highly compressible and costs two to four times more than diatomite or perlite. It is reserved for applications where the liquids may be incompatible with silica compounds. Cellulose is used as a coarse precoat

Asbestos has good retention on coarse screens, but has limited application because of its high cost, and leaching of fibers into the filterate that might be toxic. Asbestos filters may be used in pharmaceutical industry if their application is followed by membrane filtration

Water-soluble polymers such as flocculating agents are often used as filter aids. The polymers may be derived from vegetable or animal sources, or they may be produced synthetically. Water-soluble polymers may be classified as nonionic, anionic, or cationic, depending on their property to ionize in water

New, high performance filter aids with self flocking (SF) property provide low tortuosity and fine particle filtration with high flow rates. These filter aids are compounded calcined rice hulls that coagulate extremely fine particles into large, rigid, permeable, flocculated particles

Filter aids may be applied by *precoating* or *body-mix* techniques.
Precoating requires suspending the filter aid in a liquid and recirculating the slurry until the filter aid is uniformly deposited on the filter septum

Body mix (direct addition of filter aid to the filter feed) is more common in batch pharmaceutical operations

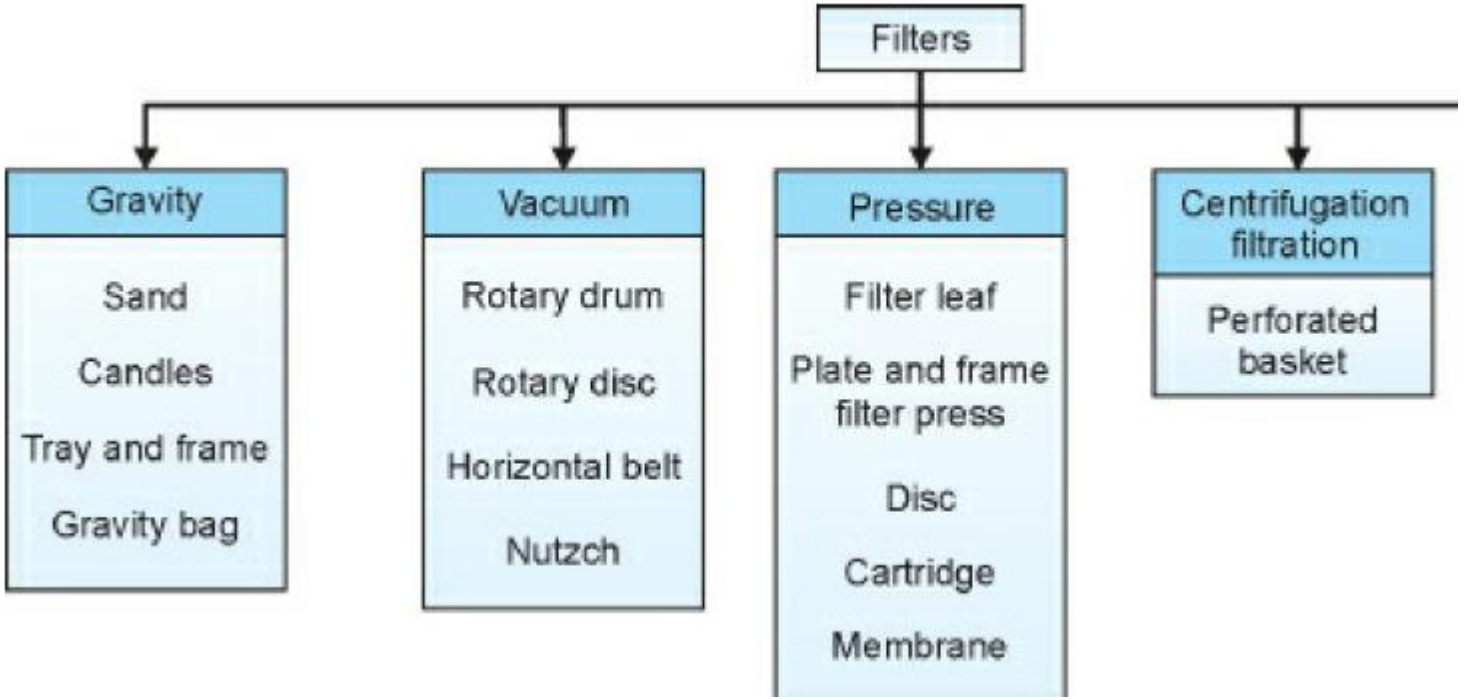
Often, a filter aid performs its function not physically or mechanically, but chemically, by reacting with the solids. These chemicals may cause the solids depositing in a filter bed to adhere more strongly to the filter medium.

Filter aids are chosen by trial and error in either laboratory or plant.
Within the ranges previously indicated, the filter aid is usually selected to give acceptable filtrate at the highest flow rate; however, in pharmaceutical operations in which quality is a primary consideration, the selection usually favours the fine grades, which yield low flow rates.

The most important pharmaceutical factor is inertness. A filter aid may have such extensive absorption properties that desired coloured substances and active principles are frequently removed. The total quantity of any ingredient absorbed may be small, but it may be a considerable portion of the original concentration

FILTRATION EQUIPMENT

Commercial filtration equipment is classified by the end product desired (filtrate of cake solids), by the method of operation (batch or continuous), by type of operation (non-sterile filtration, sterile filtration, centrifugation filtration, centrifugation sedimentation), but most importantly by the type of driving force (gravity, vacuum, pressure and centrifugation)



Gravity Filters

Gravity filters rely on gravity generated low operating pressure (usually less than 1.03×10^4 N/m^2) and give low filtration rates unless very large surfaces areas are used, which limits their use on a large scale

However, these are simple and cheap, and are frequently used in laboratory filtration where volumes are small and low filtration rate is relatively insignificant. Gravity filters employing thick, granular beds are common in water treatment, where clarification of water is done prior to deionization or distillation

Small-scale purification of water may use porous ceramics as a filter medium in the form of hollow "*candles*". The fluid passes from the outside through the porous ceramics into the interior of the hollow candles

Various new gravity filter systems are available commercially such as cylindrical gravity filters, rectangular gravity filters, and hydro-clear gravity filters which utilize granular particles in a basin. Fluid streams pass through the basin and particles are physically and/or chemically captured by the media.

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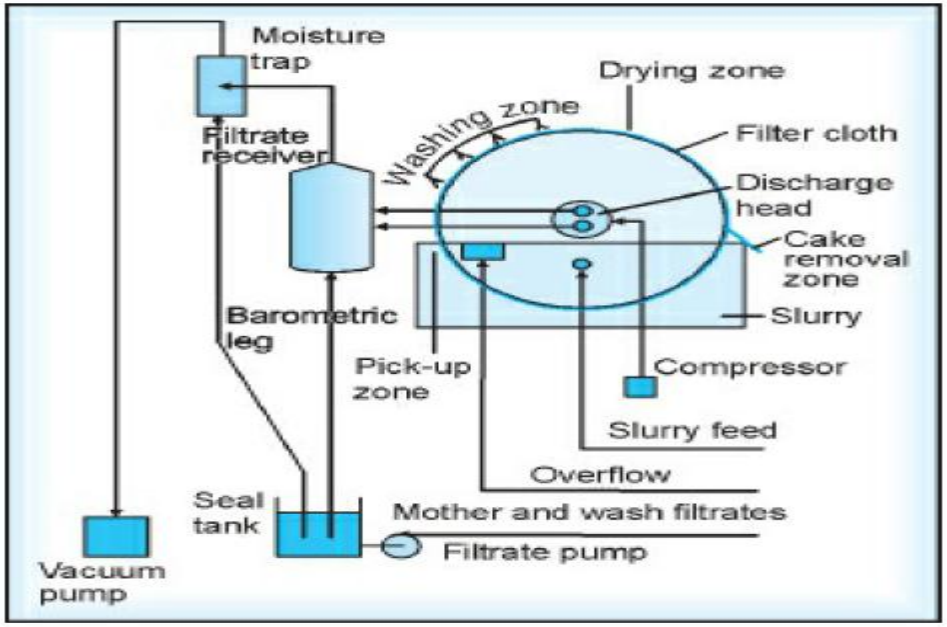
Vacuum Filters

These are employed on a large scale, but are rarely used for the collection of crystalline precipitates or sterile filtration

Vacuum filters are simple and reliable machines, and therefore have gained wide acceptance in the chemical, food and pharmaceutical industries. For large-scale operations, continuous vacuum filters are the most widely used

Rotary Drum Filter

The rotary drum vacuum filter is divided into sections, each connected to a discharge head



Each filter unit is rectangular in shape with a curved profile so that a number can be joined up to form a drum. Each unit has a perforated metal surface and is covered with filter cloth

The slurry is fed to a tank in which solids are held in suspension by an agitator. As the drum rotates, each section passes through the slurry and vacuum draws filtrate through the filter medium at the drum surface (*pick-up zone*).

The suspended solids deposit on the filter drum as a cake, and as rotation continues, vacuum holds the cake at the drum surface. This is followed by washing and further drainage in the drying zone. As the cake moves towards the discharge point, it may be scraped from the drum or it may be supported by strings until it breaks free under gravitational forces (cake removal zone).

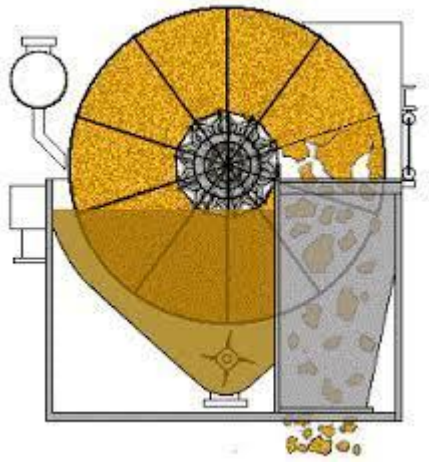
The cake discharge may be done through a scraper, belt, roll or a string. Scraper discharge mechanisms will suit cakes that could be scraped readily and roller discharge mechanism are better for thixotropic cakes

For solids that tend to block the filter cloth, a precoat of filter aids such as diatomaceous earth, perlite and cellulose is deposited on the drum prior to the filtration process

Precoat filters are generally used where a very high degree of clarity is required and solids content is very low (less than 2– 3%) or where solids are sticky and would otherwise clog the filter cloth

Rotary Disc Filter

It consists of several discs, up to 15 in the larger machines, each made up from sectors which are clamped together to form the disc .
Each sector is connected to a vacuum system, compressed air, and appropriate receivers, in the correct sequence, by means of special rotating valve. The operation sequence of a disc filter is similar to a drum filter. The main feature of disc filter is less floor space and the lowest cost of filtration when compared to other vacuum filters.



Pressure Filters

Most of the pressure filters are batch operated but continuous filters are also available. However, owing to the difficulty in removing the cake they are mechanically complex and expensive so mainly used where the added value to the product is high. The filtration rate is influenced, in broad terms, by the properties of the slurry. The trend is that the rate goes up with increased pressure, coarser particles, particle distribution with high uniformity, nonslimy or non-gelatinous solids, noncompressible cakes, lower liquid viscosity and higher temperatures

Plate and Frame Filter Press

The plate and frame filter press is the simplest of all pressure filters and is the most widely used

Filter presses are used for a high degree of clarification of the fluid and for the harvesting of the cake. When clarity is the main objective, a “batch” mode of operation is applied

As the name implies, the plate and frame filter press is an assembly of hollow frames and solid plates that support filter media

One side of the plate is designed for the flow of the feed. After passing the filter media, the filtrate is accommodated on the other side. The solids collect in the frames, and filtrate is removed through place conduits. In cake filtration, the size of the frame space is critical, and wide sludge frames are used

The filter press is the most versatile of filters since the number and type of filter sheets can be varied to suit a particular requirement. It can be used for coarse to fine filtrations, and by special conduit arrangements, for multistage filtration within a single press

The filter press is the most economical filter per unit of filtering surface, and its material of construction can be chosen to suit any process conditions. Labour costs in assembly and cleaning are a primary disadvantage, and leakage between the plates may occur through faulty assembly

Disc Filters

The term disc filter is applied to assemblies of felt or paper discs sealed into a pressure case.

The discs may be preassembled into a self supporting unit, or each disc may rest on an individual screen or plate. Single plate or multiples of single plates may be applied. The flow may be from the inside out wards or outside in wards. The disc filter overcomes some deficiencies of the filter press. Compactness, portability, and cleanliness are obvious advantages for pharmaceutical batch operations

Centrifugation Filtration

In filtering centrifuges, centrifugal force is used to affect the passage of the liquid through the filter medium. This type of filtration is particularly advantageous when very fine particles are involved. Whenever solids recovery is the primary goal, filtering centrifuges must be considered as an alternative to filtration

The advantages of the process are effective washing and drying. Residual moisture after centrifugation is far less than in cakes produced by pressure or vacuum filtration

By this method the moisture content of a cake of coarse crystals can be reduced to as low as 3%., This facilitates the drying operation which normally follows

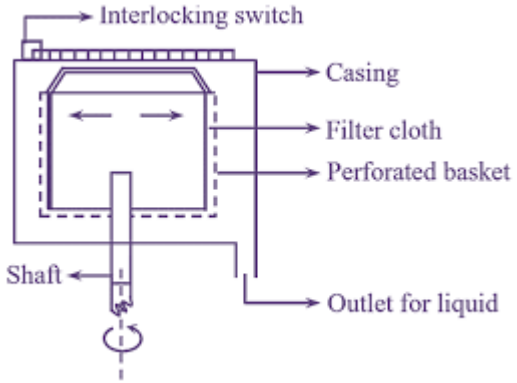
The process is widely used for separating granular products from liquors, but is less effective for concentrated slurries containing smaller particles

Perforated Basket

the device consists of a perforated metal basket mounted on a vertical axis by means of which it can be rotated at a speed of 20 to 25 revolutions per second

The cloth used to retain solids is often supported on a metal screen and the outer casing collects the liquid thrown out from the perforated basket by centrifugal force

Baskets mounted are emptied by shoveling the cake. If, however, top suspension is used, the cake can be more easily withdrawn through traps in the base of the basket



Laboratory Filtration Equipment

Laboratory equipment catalogs offer a wide choice of funnels and flasks adaptable to pharmaceutical filtration studies

For gravity filtration, conventional glass percolators are applicable, in which case the bottom tube is covered with fibrous material. The filtering funnel is the most common of all laboratory filter devices. Filter paper is used with funnels. Sometimes, a plug of fibrous material may be used instead. Filter bags for laboratory use are made of fabric and are mounted for gravity filtration. The uncertainty of adequate clarification with *glass beads* or *sand* has restricted their use as gravity filters for certain operations in the laboratory.

Suction filters are greatly utilized in the laboratory. Usually, a conical funnel and the Buchner funnel are used for suction filtration, as are immersion and suction-leaf filters. Immersion filter tubes, also known as filter sticks, are generally used for small-scale laboratory operations.

Filter paper in circular form is the most common medium for laboratory filtrations. Filter papers are available in a wide variety of textures, purities, and sizes and are available for different uses. They may be circular (1 to 50 cm in diameter), folded, or arranged in sheets or rolls. Some of the special types of laboratory filter papers for pharmaceutical industry are:

1)Filter papers impregnated with activated carbon for the adsorption of colours and odours in pharmaceutical liquids.
2)Filter paper impregnated with diatomaceous earth for the removal of colloidal haze from liquids with low turbidity

Minimum laboratory equipment includes a plate and frame press, a membrane filter holder, and a single-element housing for disposable cartridges.

SPECIALIZED FILTRATION

Sterile/Aseptic Operations

Filtration may be used to clarify and sterilize pharmaceutical solutions that are heat-labile

Membrane filters have become the basic tool in the preparation of sterile solutions

A sterility requirement imposes a severe restraint on filter selection. All sterility tests are presumptive, and one must rely upon total confidence in the basic process, and economics becomes a secondary factor. Membranes with porosity ratings of 0.2 or 0.45 μm are usually specified for sterile filtrations. In this porosity range, membrane filters may clog rapidly, and a prefilter is used to remove some colloidal matter to extend the filtration cycle

The FDA allows the use of 0.45 μm filters only in cases of colloidal solutions in which 0.2 μm filters have been shown to clog very rapidly

High viscosity or abnormal contaminant levels are the primary restraints to the use of membranes, since an extremely large filtration area is needed for practical flow rates

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Simple formulations such as intravenous solutions, ophthalmics, and other aqueous products may be filtered directly through membranes in an economical manner. Heat-labile oils and liquids containing proteins require pretreatment, e.g. centrifugation or conventional filtration, prior to sterilization filtration, The objective is removal of gross contamination that would rapidly plug the finer membranes

The use of filtration to remove bacteria, particulate matter from air, and other gases such as nitrogen and carbon dioxide is widespread in the pharmaceutical industry. The following are some common applications employing initial gas filtration:

1)Vent filtration
2)Compressed air used in sterilizers
3)Air or nitrogen used for product and in process solution transfers and at filling lines
4)Air or nitrogen used in fermentation

Filtration should be the last step in processing, and the filter should be placed as close as possible to the point of use of final packaging. In serial filtrations, only the final unit needs to be sterile, but minimal contamination in prior steps increases the reliability of the total process. Sterile filtration should always be a pressure operation; a vacuum is undesirable since bacteria may be drawn in at leaky joints and contaminate the product

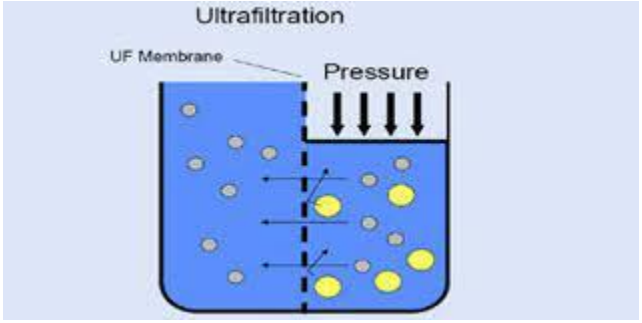
Membrane Ultrafiltration

Unlike conventional filtration, ultrafiltration is a process of selective molecular separation.

It is defined as a process of removing dissolved molecules on the basis of membrane size and configuration by passing a solution under pressure through a very fine filter. Ultrafiltration membrane retains most macromolecules while allowing smaller molecules and solvent to pass through the membrane

The difference between microfiltration and ultrafiltration is significant. The former removes particulates and bacteria; the latter separates molecules

Separation of a solvent and a solute of different molecular size may be achieved by selecting a membrane that allows the solvent, but not the solute, to pass through. Alternatively, two solutes of different molecular sizes may be separated by choosing a membrane that allows the smaller molecule, to pass through but holds back the larger one



The selectivity and retentivity of a membrane are characterized by its molecular weight cut off. It is difficult to characterize the porosity of an ultrafiltration membrane by means of precise molecular weight cut off. The configuration of the molecule and its electrical charge may also affect the separation properties of the membrane

Applications in the pharmaceutical industry are predominantly in the concentration of heatlabile products, such as vaccines, virus preparations, and immunoglobulins. Ultrafiltration also has been used to recover antibiotics, hormones, or vitamins from fermentation broths, to separate cells from fermentation broth, to clarify solutions, and to remove low-molecular-weight contaminants prior to using conventional recovery techniques. The most important application of ultrafiltration is the removal of pyrogens.

Integrity Testing

- An important feature of a filtration system is its ability to be tested for integrity before and after each filtration, which is of high importance especially in sterilization filtration.
- An integrity test is a nondestructive test used to predict functional performance of a filter.
- Each filter has characteristic bubble point and diffusion rate of air through water in a wetted filter as a function of porosity ,
- The common integrity test used to predict the performance of the filter are the bubble point test and the diffusion test.
- The integrity test detect a damage membrane ,system leak, ineffective sealing

Bubble Point Test

- The bubble point is a direct measure of the largest pore in the filter.
- The filter is first wetted and has a liquid above(liquid is held inside the channel by surface tension) and a gas below.
- Since the pores are full of liquids , there will be no passage of gas at zero pressure.(The minimum pressure required to force the liquid outside the capillary should be sufficient to over come the surface tension).
- There is still no passage of gas if pressure is increased slightly.
- When the bubble point pressure is reached, a small bubble forms at the largest opening .
- As the pressure is further increased ,rapid bubbling begins to occur.
- Bubble point pressure for a given membrane is different for different liquids

Bubble Point Test

Failure to hold rated pressure is indicator of inefficient membrane or improper assembly

Diffusion Test

- This test is usually recommended for high volume system like multi-cartridge or other systems with high filtration areas.

- When pressure is applied to a wetted membrane filter, air dissolves in the liquid, diffuses through the film, and is released on the low pressure side

- The diffusion test measure the volume of air that flow through a wet filter membrane from the pressurized site to the atmospheric site

- The air will flow by diffusion process. Pressure is applied using air at 80% of the bubble point pressure for particular membrane.

- Applying pressure at 80% of the bubble point validate filter integrity since there would be a significant increase in air flow at lower pressure indicating damaged membrane ,ineffective seal or system leak.

FILTER SELECTION

In designing or selecting a system for filtration, the specific requirements of the filtration problem must be defined. The following consideration should be addressed before any assistance is requested from the manufacturers of filtration equipment

Once the purpose of the process has been determined, the selection of the filter medium can be made. For example, for a sterilizing filtration, a 0.2 μm pore size is used; for clarification, a plate and frame filter or woven-fiber filter may be used. In general, a pore size smaller than the smallest particle to be removed is selected. The filter medium should be compatible with the liquid or gas to be filtered. It is advisable to check the chemical compatibility charts provided by the vendors for selection of filter type. Filter type, cellulose, poly tetrafluoroethylene (PTFE), fiber, metal, nylon, may be selected based on the chemical resistance to the most aggressive ingredient in the liquid

Filtration surface area is calculated after the filter media, pore size, required flow rate, and pressure differentials are established

For a liquid having a viscosity significantly different from that of water (1 cp), the clean water flow rate is divided by the viscosity of the liquid in centipoises to obtain the approximate initial flow rate for the liquid in question

The broad span of pharmaceutical requirements cannot be met by a single type of filter. The industrial pharmacist must achieve a balance between filter media and equipment capabilities, slurry characteristics, and quality specifications for the final product. The choice is usually a batch pressure filter, which uses either surface or depth filtration principles.

Thank You

DRYING

DEFINITIONS

Drying is the removal of small amount of a liquid from a material by the application of heat which is transferred from a surface into an unsaturated vapor phase. Drying and evaporation are distinguishable merely by the relative quantities of liquid removed from the solid.

Non-thermal methods of drying are:

•**The expression** of a solid to remove liquid by
(the squeezing of a wetted sponge),

•**The extraction** of liquid from a solid by use of a solvent,

•**The adsorption** of water from a solvent by the use of desiccants (such as anhydrous calcium chloride),

•**The absorption** of moisture from gases by passage through a sulfuric acid column,

•**The desiccation** of moisture from a solid by placing it in a sealed container with a moisture-removing material (silica gel in a bottle).

Purpose of drying

•In the preparation of granules in tablets and capsules.

•In the preparation of dried aluminum hydroxide, the spray drying of lactose, and powdered extracts.

•Reduces the bulk and the weight of drying materials (lowering the cost of transportation and storage).

•Aids in the preservation of animal and vegetable drugs by minimizing mold and bacterial growth.

•Removing the moisture facilitates comminution and becomes more friable.

•Dried products are more stable such as effervescent salts, aspirin, hygroscopic powders, ascorbic acid, and penicillin; through reducing the chemical reactivity.

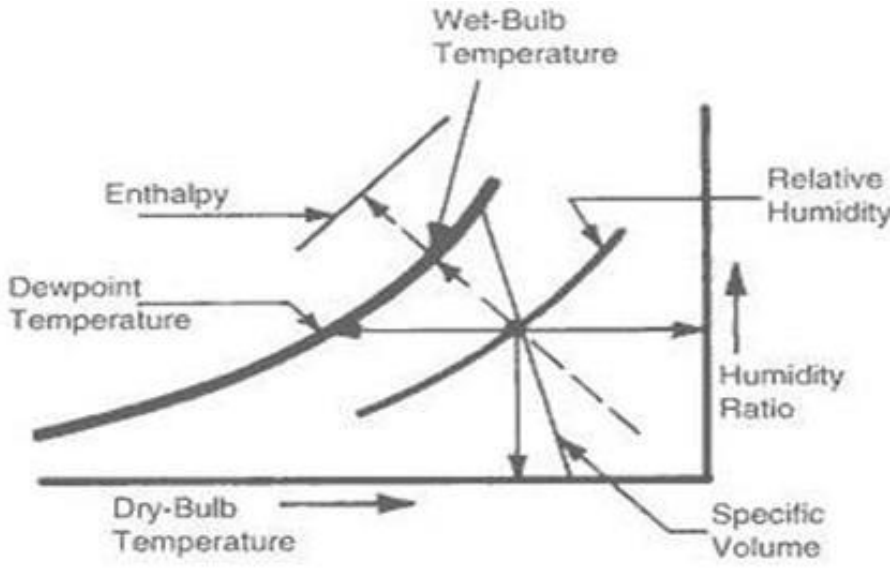
Psychrometry

•**Psychrometry** determines the vapor concentration and carrying capacity of the gas.

•**Vapor-carrying capacity** of the air, nitrogen, or other gas stream passing over the drying material.

•The carrying capacity determines the rate and the extent of drying material (the lowest moisture content).

•**The concentration** of water vapor in a gas is called the humidity of the gas.



The terms of Psychrometry chart

•**Psychrometric or humidity chart** represents the relationship between the temperature and humidity of the air-water vapor system at **constant pressure**.

•The temperature represents the **horizontal axis** and absolute humidity represents the **vertical axis** (the weight of water vapor per unit weight of dry air).

•**CDE curve** is the saturation humidity (absolute humidity) at which the partial pressure of water vapor **in the air** = the vapor pressure of free water at the same temperature. **The air is completely saturated with moisture, and the humidity does not change when it is in contact**

with liquid water at the same temperature that means 100% relative humidity (RH)

•It is boundary of a phase diagram, any point on the curve can determine either by the temperature or the absolute humidity.

•**FCA dotted line** is the absolute humidity (78 grains water/pound dry air); which represents relationship between (T and P).

Dew point C (60°F), the air is saturated with water vapor; dew point is the temperature of (air-water vapor mixture) which is cooled to become saturated (maximum amount of moisture without condensation).

•**Point F (50°F),** when the mixture is cooled below the dew point; the water vapor condenses into a two-phase system of **saturated air (point C**) and **droplets of free water**.

•**Point A (81°F),** the air is not completely saturated at **(A)** which is used for drying purposes **(without changing in FCA)**.

Point (A) = FCA (78)/ CDE at point E(161)= 48%.

•**The relative saturation** (percent relative humidity) is the partial pressure of water vapor in the air to the vapor pressure of free water at the same temperature.

• **GK with 50% relative humidity**

Curves of (T vs H) at a constant **(RH)** of a specific intervals such as **GK curve** with 50% (HR).

•The relative saturation represents the ratio of the absolute humidity**(FCA)** to saturation humidity (**CDE)** at the same temperature.

Note

•If air, at **point A (81°F),** is used to dry a wet material; the difference in vapor pressure between the **surface water** and the **air** leads to evaporate some of the liquid, which may cools the surface below the air temperature

•The heat is transferred from the **Air** to the **liquid** at rate proportional to the temperature difference. This is called **wet –bulb temperature;** define as equilibrium of heat transfer between air-liquid.

•Wet-bulb temperature is measured by thermometer (bulb is covered by wick saturated with water).

•Dry-bulb temperature (actual air temperature) is measured by ordinary thermometer.

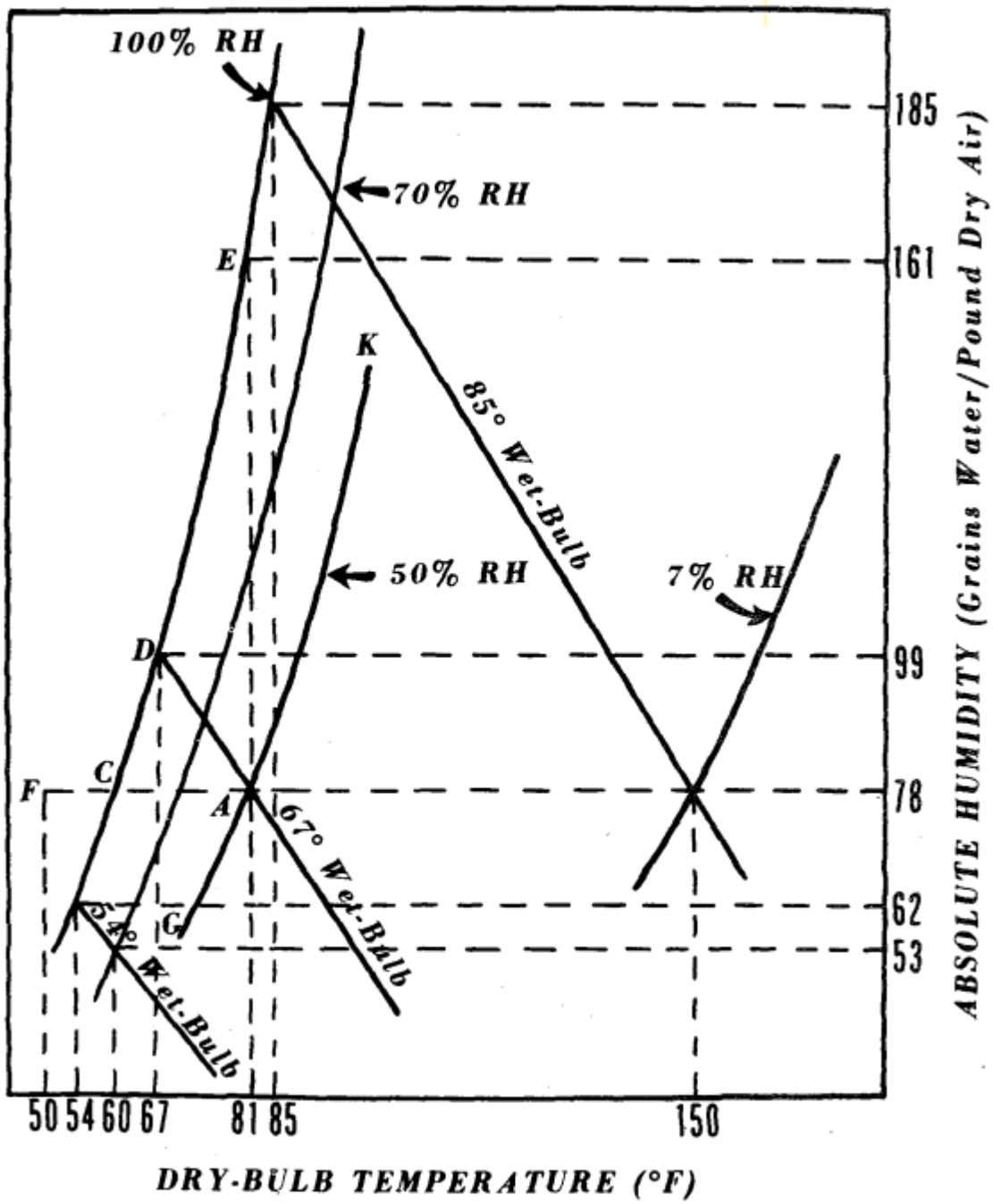


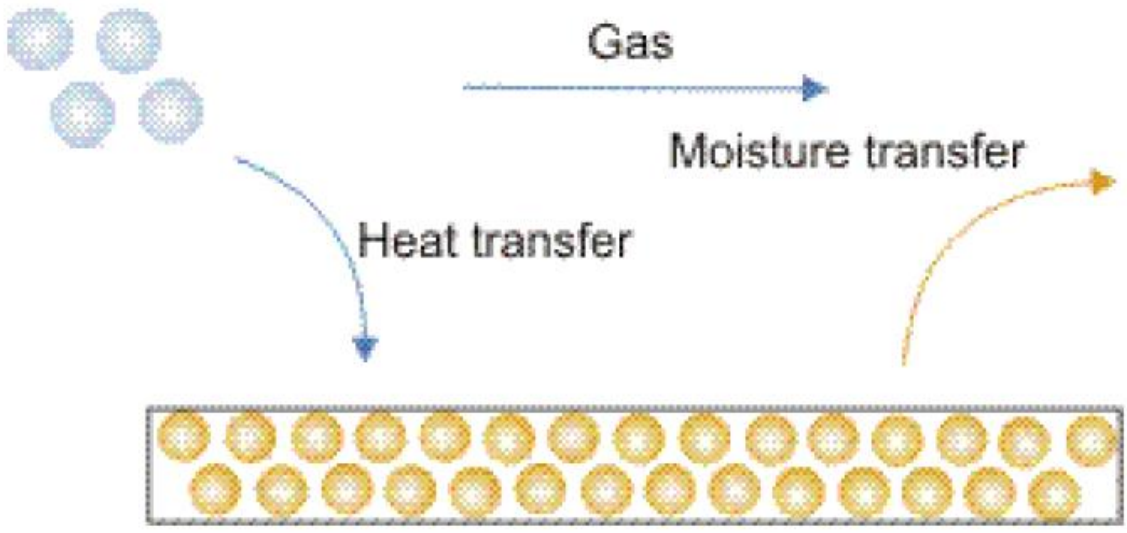
FIG. 3-1. *Diagram of psychrometric chart showing the relationship of air temperature to humidity.*

Theory of Drying

Drying involves heat and mass transfer operations.

•**Heat** is transferred into the material to supply the latent heat required for vaporization of the moisture.

•**Mass transfer** is the diffusion of water through the material to the evaporating surface, then from the surface to the passing air stream.



The rate of evaporation is related to the rate of heat transfer by the equation :

$dW/d\Theta = q/\lambda$

Where ($dW/d\Theta$) is the rate of evaporation, (q)
is the overall rate of heat transfer and (λ) is the latent heat of vaporization.

The driving force for heat transfer is temperature differential.

The rate of diffusion of moisture into the air stream is expressed by the equation:

$dW/d\Theta = k\ A(Hs-Hg)$

Where $dW/d\Theta$ is the rate of diffusion expressed as
pounds of water per hour, k is coefficient of mass
transfer, A is the area of evaporating surface , (Hs Hg) is humidity differential.

The coefficient of mass transfer is not constant but varies with the velocity of the air stream passing over the evaporating surface.

After initial period of adjustment the rate of heat transfer will equal to the rate of mass transfer.

$dW/d\Theta = q/\lambda = k\ A(Hs-Hg)$

The rate of heat transfer include all method of heat transfer which is convection, radiation and conduction From these equations we can conclude that: The rate of drying may be accelerated by
increasing ;(The general principle for efficient drying)

1- The rate of convection of heat transfer which can be achieved by increasing the air flow rate and by raising the inlet air temperature.
2- The rate of radiation heat transfer
3- The rate of conduction can be increased by reducing the thickness of the material to be dried (large surface area)by allowing it to become in close contact with raised temperature surface.
4- Increasing the air velocity also speed up the rate of drying by increasing the coefficient of mass transfer(sufficient turbulence to minimize boundary layer thickness)
5- Dehumidifying the inlet air increase the humidity differential also speed up the rate of drying(low relative humidity)

Drying of Solids

The moisture in a solid is represented as a wet weight or dry-weight.
Wet-weight, the water content is a percentage of the weight of the wet solid.(wt of water in sample / wt of wet sample)
Dry-weight, the water content is a percentage of the weight of the dry solid. (wt of water in sample / wt of dry sample)
Loss on drying (LOD) is calculated by using %LOD=[(wt of water in sample/wt of wet sample)] ×100
Moisture balance is has heat source, the weighted wet sample allowed to dry and obtain %LOD.

Moisture Content

The moisture content in the sample is determined on a dry-weight basis, as shown in

%MC=[(wt of water in sample/wt of dry sample)] ×100

Behavior of Solids during Drying/Rate of Drying

The study of drying rate is crucial to understand the solid behavior during drying.

Rate of drying could be determined by suspending the wet sample on a scale in a drying cabinet and measuring the weight of dry sample as a function of time.

•The data from drying rate is plotted as moisture content versus time.

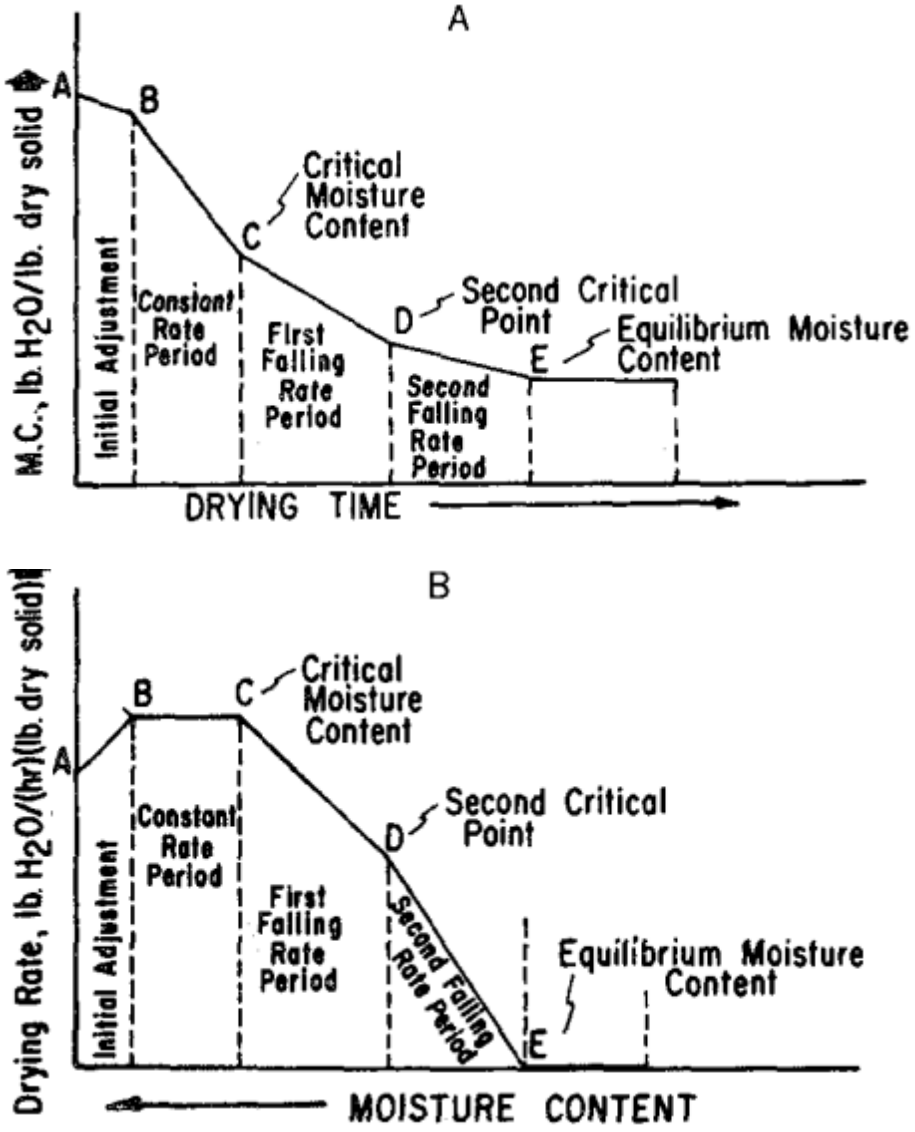
1. Drying rate vs moisture content
2. Moisture content vs drying time

After a period of initial adjustment;

Heating rate=Cooling rate till drying temperature stabilizes. This period of initial adjustment is shown as segment AB in Figures A and B.

B (the temperature stabilized) as long as there is a moisture film at the surface of the drying solid.

BC (constant rate period), the moisture evaporating from the surface is replaced by water diffusing from the interior of the solid (Evaporation rate= Diffusion rate) of evaporation.



C (critical moisture content), no more moisture is replaced and dry spot appears; (Drying rate falls off).

C-D (first falling rate period or the period of unsaturated surface drying), the spots number increases (Drying falls steadily).

D (second critical point), complete evaporation of surface film (Drying rate depends on diffusion rate).

D-E (second falling rate period), drying rate falls rapidly.

E (equilibrium moisture period begins), drying rate=Zero ; the temperature and moisture content remain constant.Continued drying after this point is a waste of time and energy

Classification of Solid Based on Drying Behavior

Solids to be dried may be classified based on their drying behavior into:

1)crystalline solids in which the water is held in
open surface pores and interstitial spaces between particles which are easily accessible to the surface.

2)amorphous solids, the moisture here is integral
part of the molecular structure and entrapped in fine capillaries and pores, accordingly it is difficult to dry than crystalline solids.

Types of Dryers

When considering how to dry a material , certain points should be considered:

1- Heat sensitivity of the material to be dried
2- Physical nature of the material
3- Nature of liquid to be removed
4- The scale of operation

Dryers can be classified based on method of heat transfer or method of sample handling

In the first classification dryer design and energy requirement are important while in the second attention given to the type of the substance to be dried.

In the method of **sample handling** the presence or absence of agitation is the major criterion:

1.Static-bed dryers

2.Moving-bed dryers

3.Fluidized-bed dryers

4.Pneumatic dryers

Static Bed System

• Tray dryer consist of cabinet shelf or compartment in which the material to be dried is spread on trays.

There is no particles movement; only the bulk motion , the exposed surface can be increased by decreasing the thickness of the bed.

Moving-Bed Systems

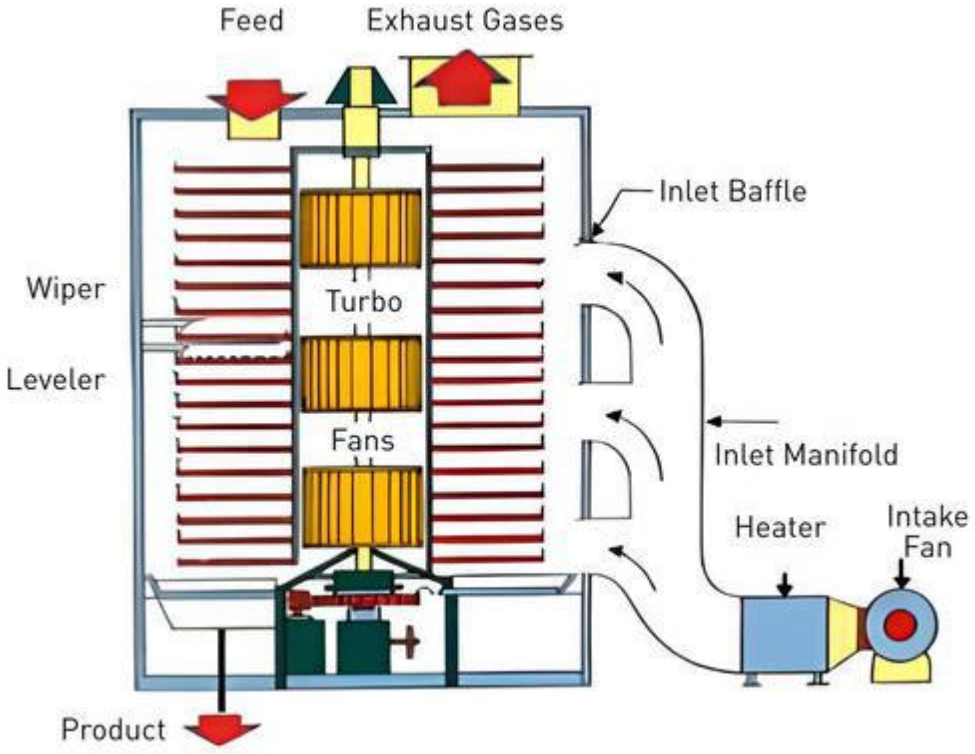
Turbo-Tray Dryers.This type is a continuous shelf, moving-bed dryer; consists of series of rotating annular trays arranged in a vertical stack-Rotating slowly at 0.1 to 1.0 rpm.

-Heated air is circulated by turbo-type fans mounted in the stack center.

-Wet mass fed from the roof of dryer; which leveled by a stationary wiper, then the dried material is pushed through radial slots onto the tray below.

After each cycle the mass transfers to the next shelf until discharge at the bottom.

-Drying rate is faster than tunnel-dryer due to the continuous exposes to the air.



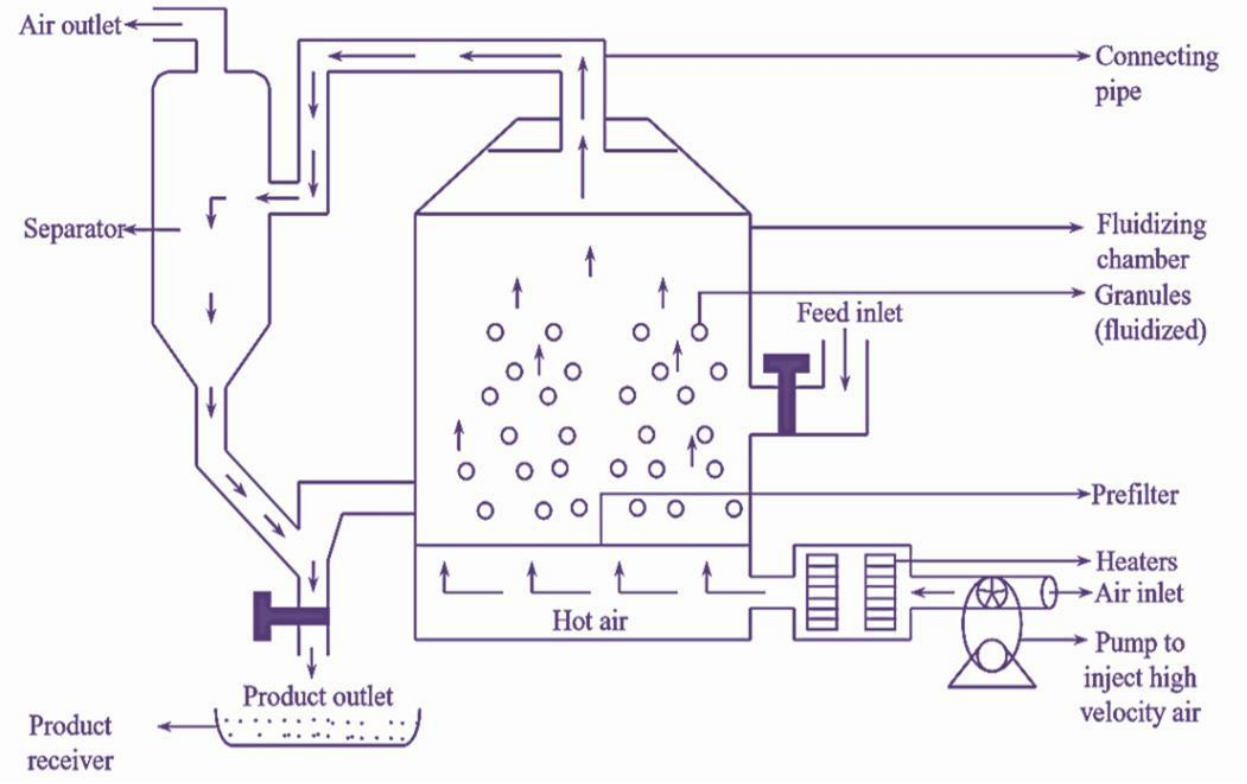
Fluidized-Bed Systems

The solids are partially suspended in the gas stream (the mixture behaves like a liquid) and the solid is fluidized.

The fluidization technique is used for drying granular solids, as each particle is surrounded by the drying gas.

The intense mixing results in uniform conditions of temperature, composition, and particle size distribution throughout the bed.

•The resultant granules are not wet nor completely dried to avoid cracking.



Advantages of Fluidized Bed Dryer

High drying rate due to efficient heat and mass transfer

The drying occur at constant rate because all the surface of particles subjected to heat uniformly

More spherical free- flowing particles can be obtained reduce the problems of aggregation and

migration of color.

Pneumatic Systems

A. Spray Dryers

It can handle only fluid materials such as solutions, slurries, and thin pastes.

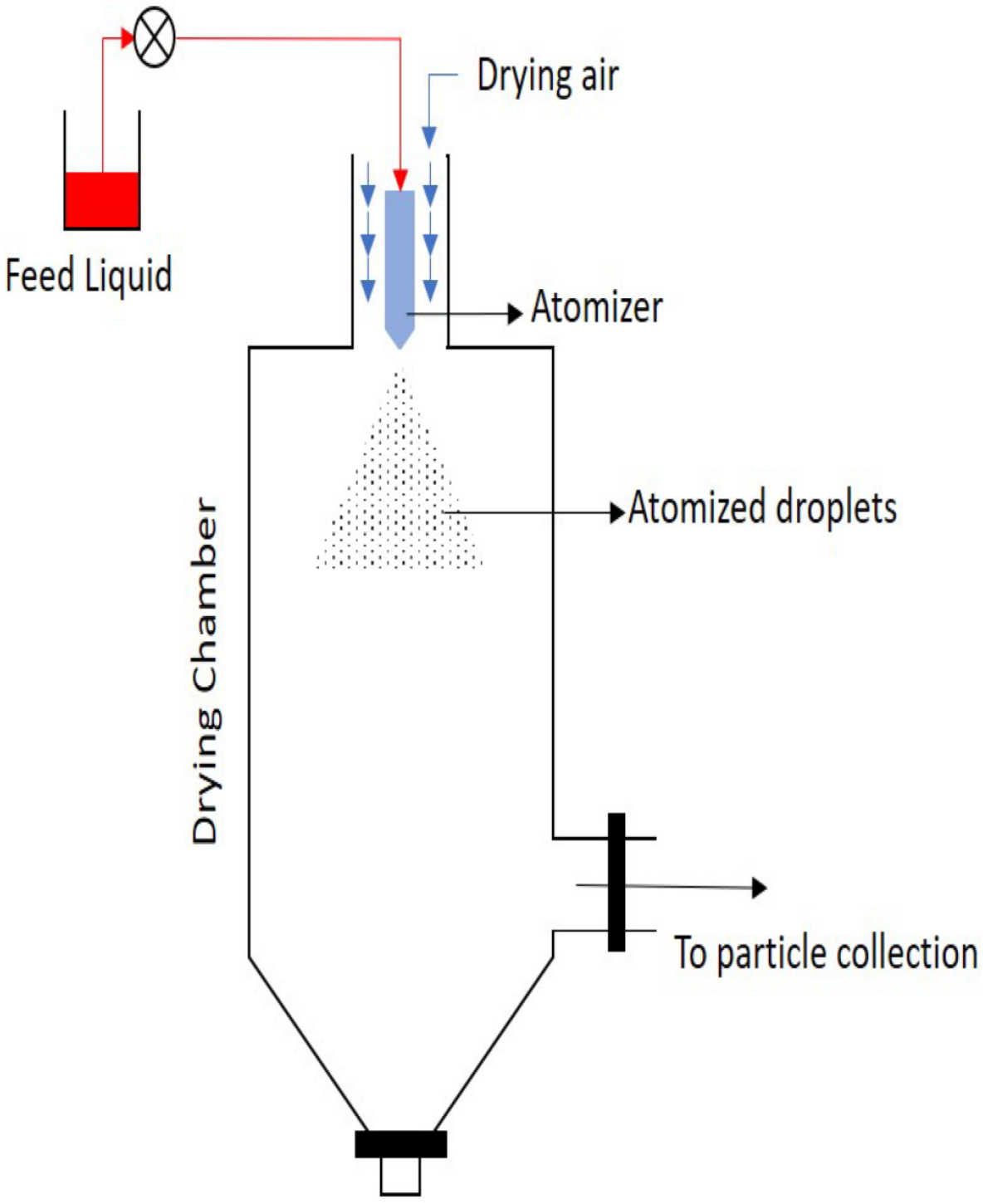
Feeding of fine droplets of fluid is into the hot gas stream. The dried powder is carried by the gas current and gravity flow to the collection system.

When the liquid droplets contact the hot gas,the surface liquid is quickly evaporated, and form a tough shell of solids.

The diffusion rate of the liquid is slower than heat transfer.The internal pressure causes the droplet to swell, and the shell becomes thinner, allowing faster diffusion.

If the shell is nonelastic or impermeable, it ruptures, producing either fragments or budlike forms.

Thus, spray-dried material consists of intact spheres, spheres with buds, ruptured hollow spheres, or sphere fragments


Drying air
Feed Liquid
Atomizer
Atomized droplets
Drying Chamber
To particle collection

B. Spray drying and spray congealing of pharmaceuticals.

Spray drying is rapid drying and the unique form product.

There are three major uses

(1) drying heat-sensitive materials,

(2) changing the physical form of materials (in tablet and capsule manufacture)

(3) encapsulating solid and liquid particles

Spray drying is use in tablet and capsule formulations.

Drying process changes the shape, size, and bulk density of the product.

The spherical particles flow better than the same product dried by conventional method due to size and shape uniformity.

Spray drying is used in the coating and encapsulation of both solids and liquids.

Chilling spray (congealing) consists of suspending the particles in a molten coating material and pumping the slurry into a spray dryer in which cold air is circulated.

Spray congealed coatings are used mainly for taste masking and for sustained-release formulations.

C. Flash Dryers

-The moistened solid is suspended in a finely divided state [velocity (3000-6000 feet/min)] at [temperature (300-1300°F) air stream]

The flash drying is a short-time process.

Specialized Drying Methods

1. Freeze Dryers.

Freeze drying is also referred to lyophilization, or sublimation.

The drying of heat-sensitive materials must be dehydrated to a solid state to maintain the stability through frozen then under a high vacuum to heat(by conduction or radiation) to sublime the frozen liquid leaving only the solid.

•Example; blood serum, plasma, antibiotics, hormones, bacterial cultures, vaccines, and food stuffs.

•The dried product is reconstitution (re-dissolved or re-suspended) by the addition of water before use.

•In freeze drying the water passes directly from solid state (ice) to vapor state without passing through the liquid state. As shown in the schematic pressure-temperature diagram for water.

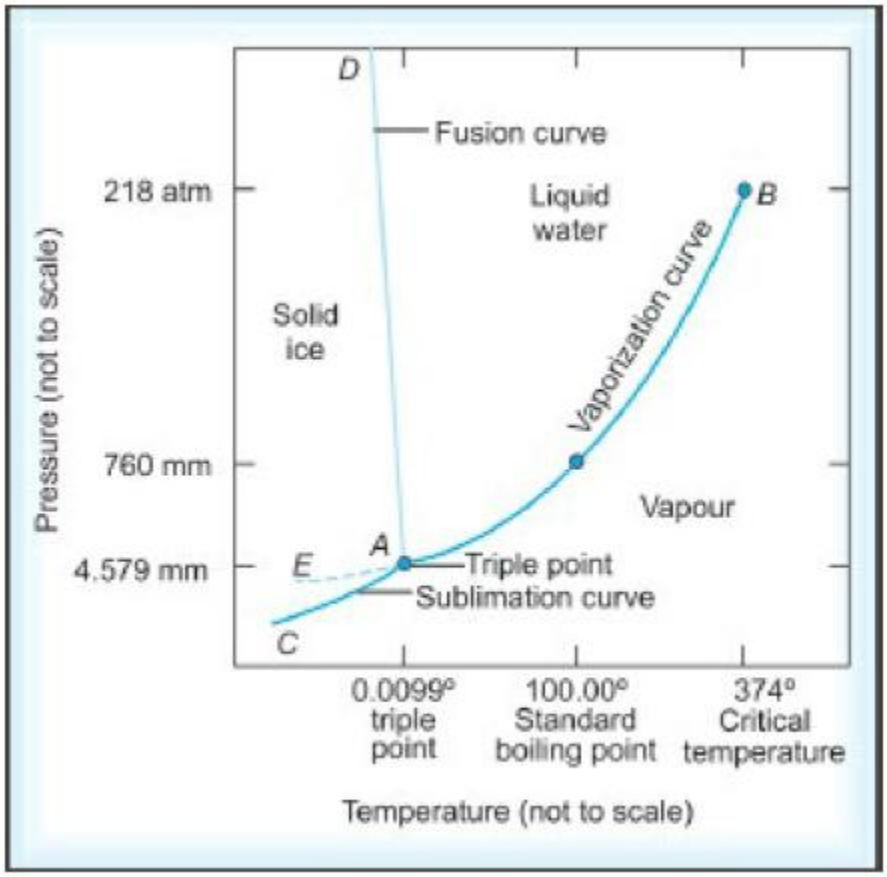
Sublimation occurs at P and T below the triple point, 4.579 mmHg and 0.0099°C.

Stages of Freeze Drying

1- Pre-freezing: Material is frozen by keeping the material below or at −20°C. Pre-freezing the material before application of vacuum avoids foaming.
2- Vacuum: Rotary pumps on small scale, and ejector pumps on large-scale,are used to reduce the pressure sufficiently.

3- Primary drying: During primary drying the latent heat of sublimation must be provided and the vapour removed. Primary drying stage by sublimation can remove the unbound water.

4- Secondary drying: It is used to remove bound water or traces of water left after primary drying. The temperature is raised (up to 50°C) or desiccant is used to carry secondary drying.



B. Microwave Drying

The application of microwave energy to the drying of solids represents a radical departure from conventional means of drying.

Instead of applying heat externally to a material , energy in the form of microwaves is converted into internal heat by interaction with the material itself.

This permits extremely rapid heat transfer throughout the material lead to rapid drying.

the moisture is mobilized as a vapor rather than a liquid, and its movement to the surface can be extremely rapid because it does not depend on mass concentration gradients or on slow liquid diffusion rate

Milling

Milling Concept

Few materials used in pharmaceuticals exist in the optimum size, and most must be comminuted at some stage or the other during the production of a dosage form.

Milling is the mechanical process of reducing the particle size of solids.

Various terms (comminution, crushing, disintegration, dispersion, grinding, and pulverization) have been used synonymously with milling depending on the product, equipment, and the process

Milling equipment is classified as coarse, intermediate and fine according to the size of the final product. Size is conventionally expressed in terms of mesh (number of opening per inch square)

1. Coarse for particles size larger than 20-mesh
2. Intermediate (20-200) mesh (74 -840 micron)
3. Fine for particles size smaller than 200-mesh

A given mill can be used successfully to prepare particles in more than one class. (ex. Hammer mill used for granulation (16-mesh) and for milling crystalline API to a 120-mesh powder)

PHARMACEUTICAL APPLICATIONS

Numerous examples have been quoted to stress the importance of fine particles in pharmacy and milling or grinding offers a method by which these particles can be produced. The surface area per unit weight, which is known as the *specific surface*, is increased by size reduction. In general, a 10-fold increase in surface area has been given by a 10-fold decrease in particle size. This increased surface area affects:

1)Dissolution and therapeutic efficacy: Dissolution and therapeutic efficiency of medicinal compounds that possess low solubility in body fluids are increased due to increase in the area of contact between the solid and the dissolving fluid

2) **Extraction:** Extraction or leaching from animal glands (liver and pancreas) and crude vegetable drugs is facilitated by comminution. The time required for extraction is shortened by the increased area of contact between the solvent and the solid and the reduced distance the solvent has to penetrate into the material.

3)Drying: The drying of wet masses may be facilitated by milling, which increases the surface area and reduces the distance that the moisture must travel within the particle to reach the outer surface. In the manufacture of compressed tablets by wet granulation process, the sieving of the wet mass is done to ensure more rapid and uniform drying

PHARMACEUTICAL APPLICATIONS

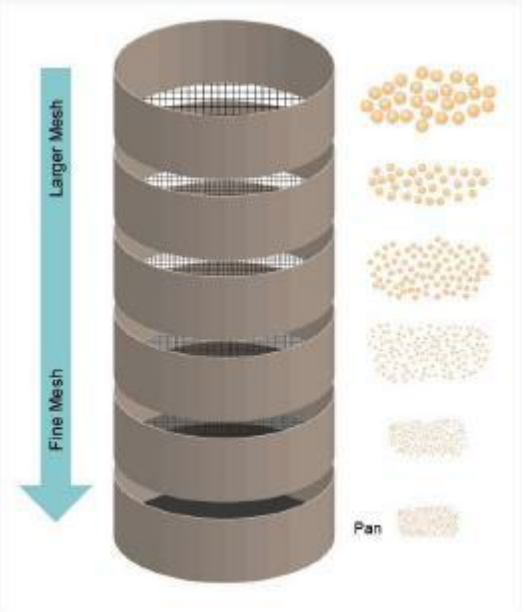
4)Flowability: The flow property of powders and granules is affected by particle size and size distribution. The freely flowing powders and granules in high-speed filling equipment and tablet presses produce a uniform product.

5)Mixing or blending: The mixing or blending of several solid ingredients of a pharmaceutical is easier and more uniform if the ingredients are of approximately the same size. This provides a greater uniformity of dose. Solid pharmaceuticals that are artificially coloured are often milled to distribute the colouring agent to ensure that the mixture is not mottled and uniform from batch-to-batch.

6)Formulation: Lubricants used in compressed tablets and capsules function by virtue of their ability to coat the surface of the granulation or powder. A fine particle size is essential if the lubricant is to function properly. The milling of ointments, creams, and pastes provides a smooth texture and better appearance in addition to improved physical stability. Also, the sedimentation rate of suspensions and emulsions is a function of particle size and is reduced by milling

SIZE DISTRIBUTION AND MEASUREMENTS

1. Microscopy
2. Sieving
3. Sedimentation



THEORY OF COMMINUTION

The mechanical behavior of solids, under stress are strained and deformed, is shown in the stress-strain curve which

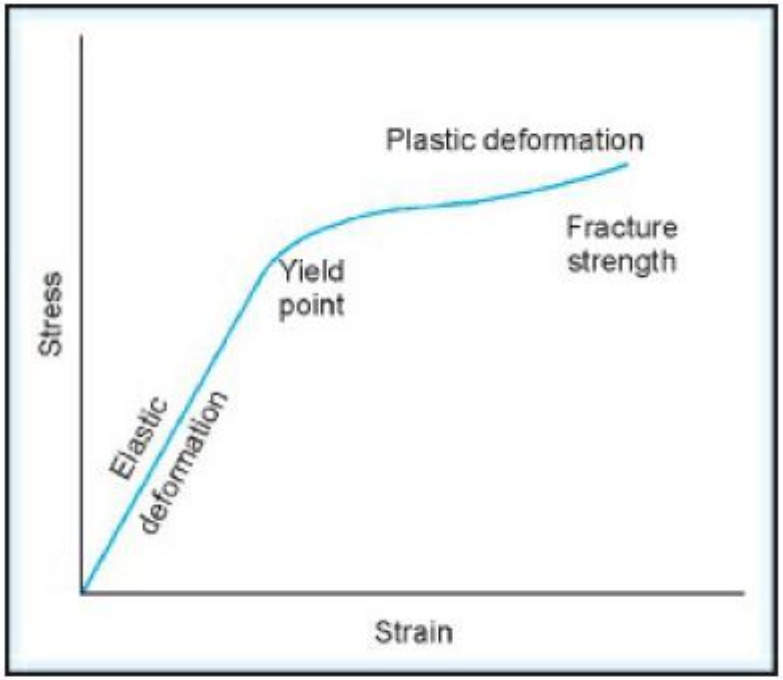


Fig. 2.1: Stress-strain diagram for a solid

The initial linear portion of the curve is defined by Hooke's law(stress is directly proportional to strain), and Young's modulus (slope of the linear portion) expresses the stiffness or softness of a solid in dynes per square centimeter. The stress-strain curve becomes nonlinear at the yield point, which is a measure of the resistance to permanent deformation. With still greater stress, the region of irreversible plastic deformation is reached. The area under the curve represents the energy of fracture and is an approximate measure of the impact strength of the material.

In all milling processes, it is a random matter if and when a given particle will be fractured. If a single particle is subjected to a sudden impact and fractured, it yields a few relatively large particles and a number of fine particles, with relatively few particles of intermediate size. If the energy of the impact is increased, the larger particles are of a smaller size and greater number, and although the number of fine particles is increased appreciably, their size is not greatly changed. It seems that the size of the finer particles is related to the internal structure of the material, and the size of the larger particles is more closely related to the process by which comminution is accomplished.

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If the force of impact does not exceed the elastic limit, the material is reversibly deformed or stressed. When the force is removed, the particle returns to its original form, and the mechanical energy of stress in the deformed particle appears as heat

A force that exceeds the elastic limit fractures the particle, As fracture occurs, the points of application of the force are shifted. The energy for the new surfaces is partially supplied by the release of stress energy

The useful work in milling is proportional to the length of new cracks produced. A particle absorbs strain energy and is deformed under shear or compression until the energy exceeds the weakest flaw and causes fracture or cracking of the particle. The strain energy required for fracture is proportional to the length of the crack formed, since the additional energy required to extend the crack to fracture is supplied by the flow of the surrounding residual strain energy to the crack.

Mechanisms of Comminution

Mills are Equipments designed to impart energy to the material and cause its size reduction. There are four main methods of effecting size reduction, involving different mechanisms:

1)Cutting: It involves application of force over a very narrow area of material using a sharp edge of a cutting device.

2)Compression: In compression, the material is gripped between the two surfaces and crushed by application of pressure.

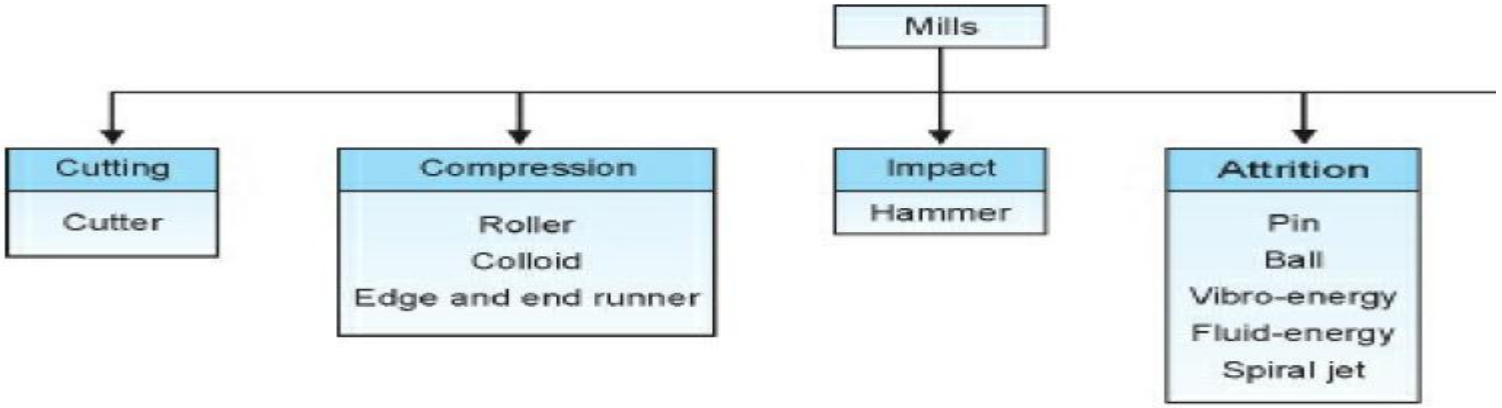
3)Impact: It involves the contact of material with a fast moving part which imparts some of its kinetic energy to the material. This causes creation of internal stresses in the particle, there by breaking it.

4)Attrition: In attrition, the material is subjected to pressure as in compression, but the surfaces are moving relative to each other, resulting in shear forces which break the particles.

EQUIPMENTS

A mill consists of three basic parts: (1) feed chute, which delivers the material, (2) grinding mechanism, usually consisting of a rotor and stator, and (3) a discharge chute.

The principle of operation depends on cutting, compression, impact from a sharp blow, and attrition. In most mills, the grinding effect is a combination of these actions. If the milling operation is carried out so that the material is reduced to the desired size by passing it once through the mill, the process is known as open-circuit milling. A closed circuit mill is the one in which the discharge from the milling chamber is passed through a size-separation device or classifier, and the oversize particles are returned to the grinding chamber for further reduction of size. Closed-circuit operation is most valuable in reduction to fine and ultrafine size. The classification of most commonly used mills in pharmaceutical manufacturing is given in Fig

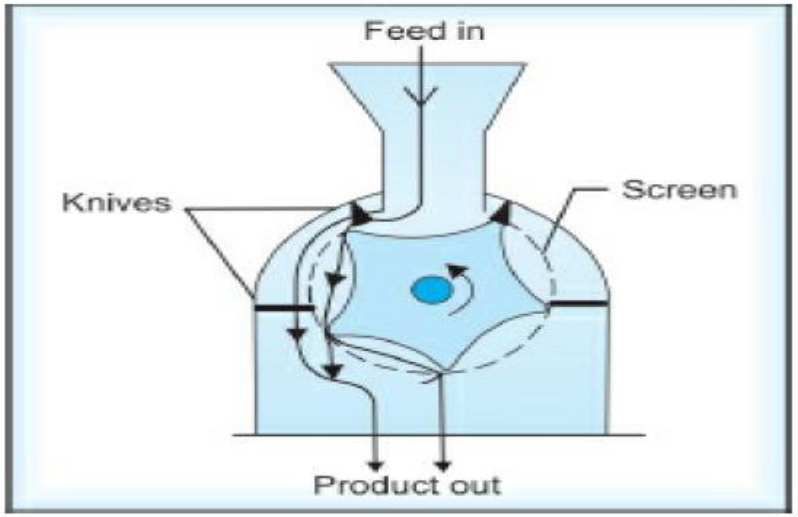


Cutter Mill

The rotary knife cutter has a horizontal rotor with 2 to 12 knives spaced uniformly on its periphery turning from 200 to 900 rpm and a cylindrical casing having several stationary knives

The bottom of the casing holds a screen that controls the size of the material discharged from the milling zone.

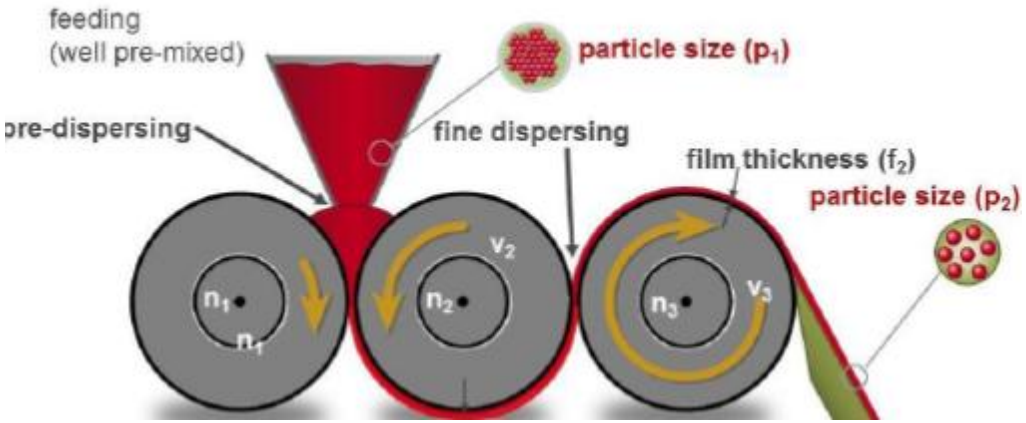
Cutting mills are used for tough, fibrous materials and provide a successive cutting or shearing action rather than attrition or impact.



ROLLER MILL

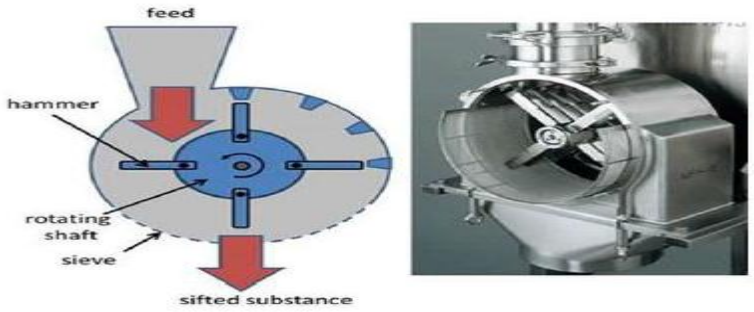
•It consists of two to five smooth roller operating at different speed.
•Mechanism by combination of compression and shearing action.
Two cylindrical rolls mounted horizontally and rotated about their long axes.
one of the rolls is driven directly while the second is rotated by friction as material is drawn through the gap between the rolls.

A form of roller mill used for milling ointments, pastes and suspension where both rolls are driven but at different speeds, so that size reduction occurs by attrition.



Hammer Mill

Construction and working. The hammer mill is an impact mill using a high speed rotor (up to 10,000 rpm) to which a number of swinging hammers are fixed



The material is fed at the top or center, thrown out centrifugally, and ground by impact of the hammers or against the plates around the periphery of the casing. The clearance between the housing and the hammers contributes to size reduction.

The material is retained until it is small enough to fall through the screen that forms the lower portion of the casing. Particles fine enough to pass through the screen are discharged almost as fast as they are formed

The particle size that can be achieved will depend on the type of milling tool selected, rotor speed (calculated as tip speed at the outermost rotating part), and solid density in the mill or solid feed rate

Important processing variables for hammer mills are hammer tip speed and hammer mill screen size.

As can be seen in Figure (a), an increase in hammer tip speed contributes to a higher particle size reduction and thus a relatively fine mash. With an increase in hammer tip speed, the particles will follow a pathway closer to the screen due to the centrifugal force

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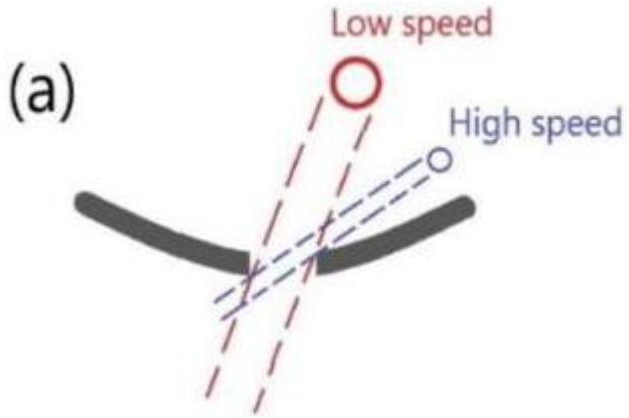
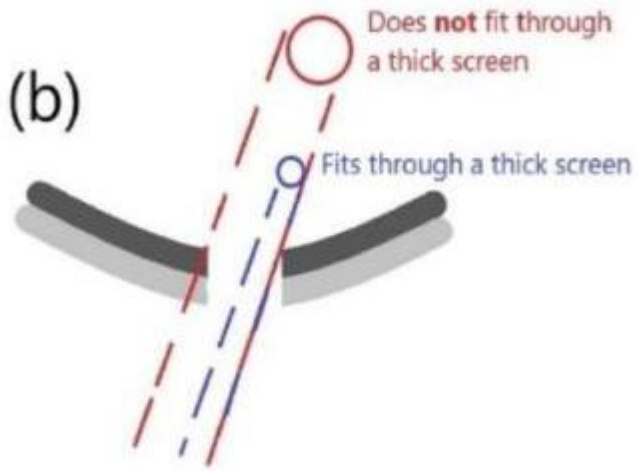


Figure (b) shows that an increase in hammer mill screen thickness will also result in a relatively finer mash, as the coarser particles can only pass through the screen under a relatively narrow range of angles



Applications. The hammer mill can be used for almost any type of size reduction. Its versatility makes it popular in the pharmaceutical industry, where it is used to mill dry materials, wet filter-press cakes, ointments, and Slurries, also a hammer mill can be used for granulation and close control of the particle size of powders

Advantages and disadvantages.

Hammer mills are compact with a high capacity. Size reduction of 20 to 40 μm may be achieved, however, a hammer mill must be operated with internal or external classification to produce ultrafine particles. Because the inertial forces vary with mass as the inverse cube of the diameter, small particles with a constant velocity impact with much less kinetic energy than larger ones, and the probability that particles less than a certain size will fracture decreases rapidly

In addition, small particles pass through the screen almost as fast as they are formed. Thus, a hammer mill tends to yield a relatively narrow size distribution. Hammer mills are simple to install and operate. The speed and screen can be rapidly changed. They are easy to clean and may be operated as a closed system to reduce dust and explosion hazards

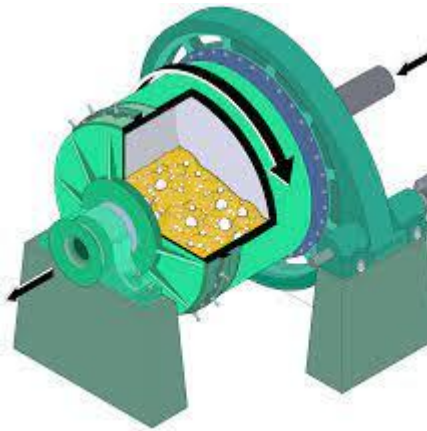
.

Ball Mill

Construction and working., the ball mill consists of a horizontally rotating hollow vessel of cylindrical shape with the length slightly greater than its diameter. The mill is partially filled with balls of steel or pebbles, which act as the grinding medium

Most ball mills utilized in pharmacy are batch-operated, however, continuous ball mills are available, which are fed through a hollow trunnion at one end, with the product discharged through a similar trunnion at the opposite end. The outlet is covered with a coarse screen to prevent the loss of the balls.

In a ball mill rotating at a slow speed, the balls roll and cascade over one another, providing an attrition action. As the speed is increased, the balls are carried up the sides of the mill and fall freely onto the material with an impact action, which is responsible for most size reduction



The factor of greatest importance in the operation of the ball mill is the speed of rotation.

1-At low angular velocities (Fig. a) the balls move with the drum until the force due to gravity exceeds the frictional force of the bed on the drum, and the balls then slide back to the base of the drum. This sequence is repeated, producing very little relative movement of balls so that size reduction is minimal.

2- At high angular velocities (Fig. b) the balls are thrown out on to the mill wall by centrifugal force and no size reduction occurs.

3-At about two-thirds of the critical angular velocity where centrifuging occurs (Fig. c), a cascading action is produced

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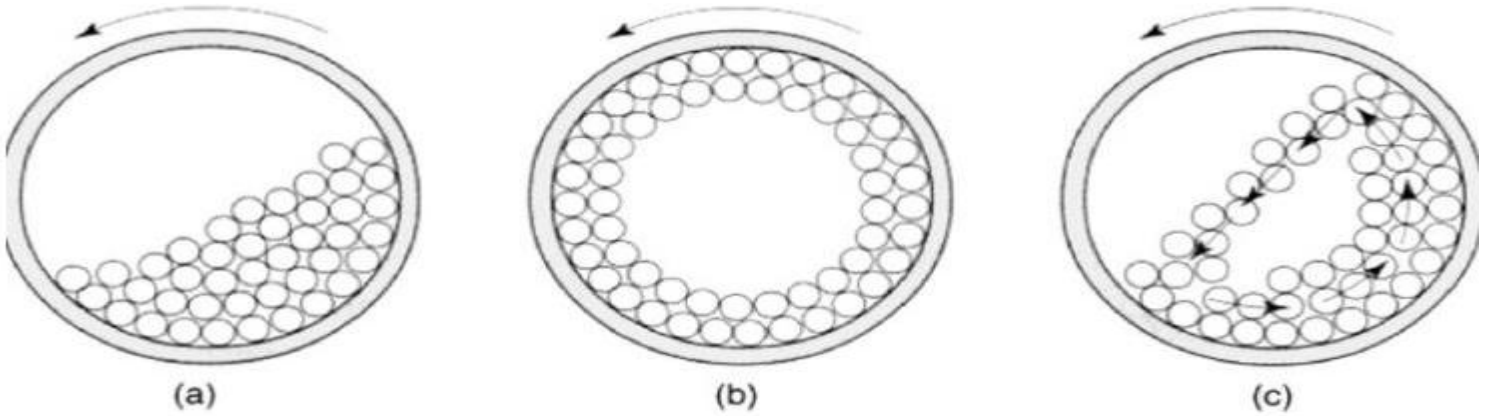


Advantages and disadvantages.

In addition to being used for either wet or dry milling, the ball mill has the advantage of being used for batch or continuous operation

In a batch operation, unstable or explosive materials may be sealed within an inert atmosphere and satisfactorily ground. Ball mills may be sterilized and sealed for sterile milling in the production of ophthalmic and parenteral products.

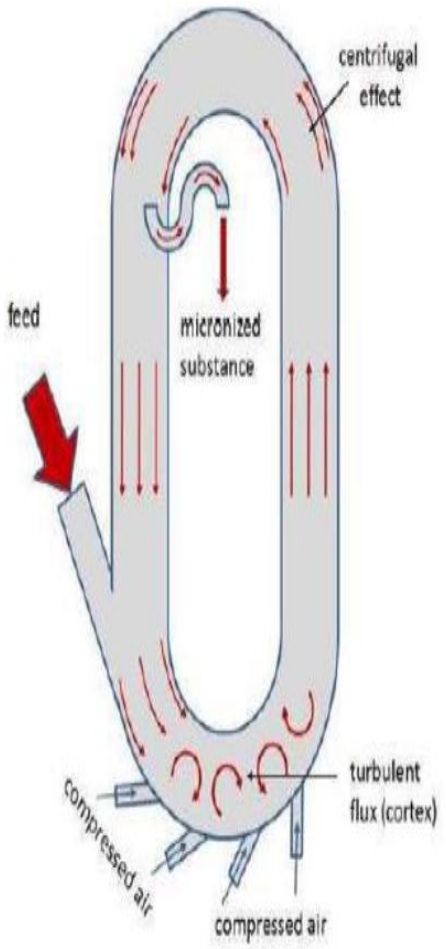
The installation, operation, and labor costs involved in ball milling are low. Finally, the ball mill is unsurpassed for fine grinding of hard and abrasive materials.

Fluid-energy Mill

Construction and working.

In the fluid-energy mill or micronizer, the material is suspended and conveyed at high velocity by air or steam, which is passed through nozzles at pressures of 100 to 150 pounds per square inch (psi).

The violent turbulence of the air and steam reduces the particle size
chiefly by inter particular attrition.
Air is usually used because most pharmaceuticals have a low melting point or are thermo labile. As the compressed air expands at the orifice, the cooling effect counteracts the heat generated by milling



.

The most important machine-related factors are the grinding chamber geometry and the number and angle of the nozzles. In selecting fluid-energy mills for production, the cost of a fluid-energy source and dust collection equipment must be considered in addition to the cost of the mill

Advantages and disadvantages.

Powders with all particles below a few micrometers may be quickly produced by this method. The disadvantage of high capital and running costs may not be so serious in the pharmaceutical industry because of the high value of the materials which are often processed.

One drawback of this type of mill is the potential for build-up of compressed product in the mill. This can affect milled particle size by changing the open volume in the mill or open area in the classifier, especially if classifier vanes or gas nozzles become plugged or blocked

FACTORS INFLUENCING MILLING

The properties of a solid determine its ability to resist size reduction and influence the choice of equipment used for milling. The specifications of the product also influence the choice of a mill.

1) Nature of Material

The physical nature of the material determines the process of comminution. Fibrous materials (*Glycyrrhiza, Rauwolfia*) cannot be crushed by pressure or impact and must be cut. Friable materials (dried filter cake, sucrose) tend to fracture along well-defined planes and may be milled by attrition, impact, or compression

2)Moisture Content

The presence of more than 5% water hinders comminution and often produces a sticky mass upon milling. This effect is more pronounced with fine materials than with larger particles. At concentrations of water greater than 50%, the mass becomes a slurry, or fluid suspension. The process is then a wet milling process, which often aids in size reduction. An increase in moisture can decrease the rate of milling to a specified product size

3)Temperature

The heat during milling softens and melts materials with a low melting point. Synthetic gums, waxes, and resins become soft and plastic. Heat-sensitive drugs may be degraded or even charred. Pigments (ocher and sienna) may change their shade of color if the milling temperature is excessive. Unstable compounds and almost any finely-powdered material may ignite and explode if the temperature is high.

4)Particle Shape

An impact mill produces sharp, irregular particles, which may not flow readily. When specifications demand a milled product that will flow freely, it would be better to use an attrition mill, which produces free-flowing spheroidal particles.

5)Polymorphism

Milling may alter the crystalline structure and cause chemical changes in some materials. Wet milling may be useful in producing a suspension that contains a metastable form of material causing crystal growth and caking. For example, when cortisone acetate crystals are allowed to equilibrate with an aqueous vehicle, subsequent wet milling provides a satisfactory suspension.

TECHNIQUES OF MILLING

In addition to the standard adjustments of the milling process (i.e., speed, screen size, design of rotor and load), special techniques of milling may be Useful.

1) Special Atmosphere

Hygroscopic materials can be milled in a closed system supplied with dehumidified air. Thermolabile, easily oxidizable, and combustible materials should be milled in a closed system with an inert atmosphere of carbon dioxide or nitrogen. Almost any fine dust (dextrin, starch, sulfur) is a potential explosive mixture under certain conditions and especially if static electrical charges result from the processing.

2)Temperature Control

As only a small percentage of the energy of milling is used to form new surface, the bulk of the energy is converted to heat. This heat may raise the temperature of the material by many degrees, and unless the heat is removed, the solid will melt, decompose, or explode. To prevent these changes in the material and avoid stalling of the mill, the milling chamber should be cooled by means of a cooling jacket or a heat exchanger

3)Pretreatment

For a mill to operate satisfactorily, the feed should be of the proper size and enter at a fairly uniform rate. If granules or intermediate sized particles are desired with a . minimum of fines, pre-sizing is vital. Pretreatment of fibrous materials with high-pressure rolls or cutters facilitates comminution

4)Subsequent Treatment

If extreme control of size is required, it may be necessary to recycle the larger particles, either by simply screening the discharge and returning the oversized particles for a second milling

5) Wet and Dry Milling

The choice of wet or dry milling depends on the use of the product and its subsequent processing. If the product undergoes physical or chemical change in water, dry milling is recommended, Wet grinding is beneficial in further reducing the size, but flocculation restricts the lower limit to approximately 10 μm. Wet grinding eliminates dust hazards, and is usually done in low-speed mills, which consume less power

.

SELECTION OF A MILL

In general, the materials used in pharmaceuticals may be reduced to a particle size less than 40-mesh by means of ball, roller, hammer, and fluid-energy mills.

The choice of a mill is based on :

(1) Product specifications (size range, particle size distribution, shape, moisture content and physical and chemical properties of the material),

(2) capacity of the mill and production rate requirements

,

(3) versatility of operation (wet and dry milling, rapid change of speed and screen, safety features),

(4) dust control (loss of costly drugs, health hazards and contamination of plant),

(5) sanitation (ease of cleaning and sterilization),

(6) auxiliary equipment (cooling system, dust collectors, forced feeding and stage reduction)

,

(7) batch or continuous operation

(8) economical factors (cost, power consumption, space occupied and labor cost).

Mixing

Almost every pharmaceutical product contains more than one component, and this necessitates mixing or blending stages in their manufacturing process

mixing as a process “in which two or more ingredients in separate or roughly mixed condition are treated so that each particle of any one ingredient is as nearly as possible adjacent to a particle of each of the other ingredients

The term *blending* is synonymous with mixing, and *segregation* is the opposite

Mixing tends to result in a randomization of dissimilar particles within a system . This is to be distinguished from an ordered system in which the particles are arranged according to some iterative rule and thus follow a repetitive pattern

Mixing is a fundamental step in most process sequences, and is normally carried out:

1-To control heat and mass transfer
2-To secure uniformity of composition so that small samples withdrawn from a bulk material represent the overall composition of the mixture
3-To improve single phase and multi-phase systems
4-To promote physical and chemical reactions, such as dissolution, in which natural diffusion is supplemented by agitation

Mixing can be classified as positive, negative, or neutral

Positive mixing applies to the systems where spontaneous, irreversible and complete mixing would take place, by diffusion, without the expenditure of energy, provided time is unlimited , In general, positive mixtures, such as a mixture of two gases or two miscible liquids do not present any problems during mixing.

Negative mixing are generally more difficult to form and maintain, and require a higher degree of mixing ,any two-phase systems such as suspensions of solids in liquids, emulsions and creams tend to separate out quickly, unless energy is continually expended on them

Neutral mixing occurs when neither mixing nor de-mixing takes place unless the system is acted upon by an external energy input. Neutral mixtures are static in behavior, have no tendency to mix spontaneously or segregate spontaneously and include mixture of powders, pastes and ointments

Fluid MIXING

Flow Characteristics

Fluids may be generally classifies as Newtonian and non Newtonian, depending on the relationship between their shear rates and the applied stress.

Forces of shear are generated by interactions between moving fluids and the surfaces over which they flow during mixing.

The rate of shear may be defined as the derivative of velocity with respect to distance measured normal to the direction of flow

The viscosity is the ratio of shear stress to the shear rate

For Newtonian fluids, the rate of shear is proportional to the applied stress, and such fluids have a dynamic viscosity that is independent of flow rate.

While for non-Newtonian fluids apparent dynamic viscosity is a function of the shear stress

Fluid MIXING

Mixing Mechanisms

Mixing mechanisms for fluids fall essentially into four categories: bulk transport, turbulent flow, laminar flow, and molecular diffusion. Usually, more than one of these mechanisms is operative in practical mixing situations.

1-**Bulk Transport** The movement of a relatively large portion of the material being mixed from one location in a system to another location in a given system ,rotating blades and paddles are usually used

2-**Turbulent Mixing** The phenomenon of turbulent mixing is the direct result of turbulent fluid flow, which is characterized by a random fluctuation of the fluid velocity at any given point within the system

3-**Laminar Mixing** When two dissimilar liquids are mixed through laminar flow, the shear that is generated stretches the interface between them

4-**Molecular Diffusion** The primary mechanism responsible for mixing at the molecular level is diffusion, resulting from the thermal motion of the molecules

Equipments

A system for liquid mixing commonly consists of two primary components:
(1) a tank or other container suitable for holding the material being mixed,
and (2) a means of supplying energy to the system so as to bring about
reasonably rapid mixing.

Power may be supplied to the fluid mass by means of an impeller, air stream, or liquid jet
Besides supplying power, these also serve to direct the flow of material within the vessel. Baffles, vanes, and ducts are also used to direct the bulk movement of material in such mixers, thereby increasing their efficiency.

When the material to be mixed is limited in volume so that it may be conveniently contained in a suitable mixer, *batch mixing* is usually more feasible, however, for larger volumes *continuous mixing* is preferred

Batch mixing

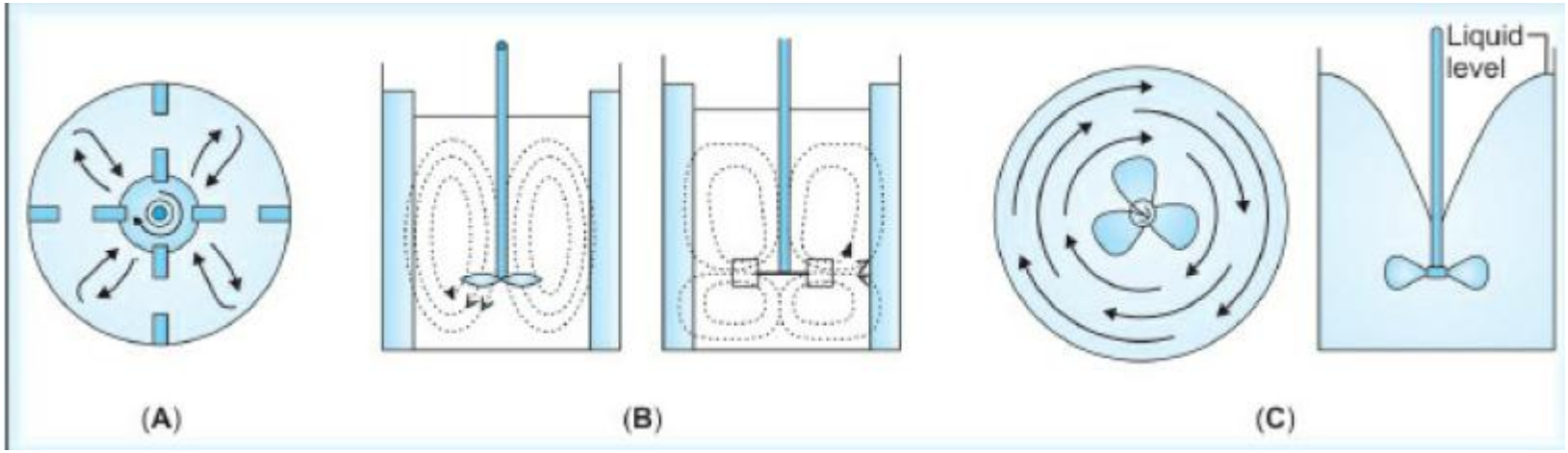
1-Impellers

Liquids are most commonly mixed by impellers rotating in tanks. These impellers are classified as (i) propellers, (ii) turbines and (iii) paddles. The distinction between impeller types is often made on the basis of the type of flow pattern they produce, or on the basis of the shape and pitch of the blades.

The flow pattern may be analyzed in terms of three components:

1) radial (perpendicular to the impeller shaft),
2) Axial or longitudinal (parallel to the impeller shaft),
3) tangential (tangential to the circle of rotation around the impeller shaft)

. These may occur singly or in various combinations.



Propellers

Propellers of various types and forms are used, but all are essentially a segment of a multithreaded screw, that is, a screw with as many threads as the propeller blades Also, like the machine screws, propellers may be either right- or left-handed depending on the direction of slant of their blades

Although any number of blades may be used, the three-blade design is most commonly used with fluids

The blades may be set at any angle or pitch, but for most applications, the pitch is approximately equal to the propeller diameter

Propellers are most efficient when they run at high speeds in liquids of relatively low viscosity

Although some tangential flow does occur, the primary effect of a propeller is due to axial flow. Also, intense turbulence usually occurs in the immediate vicinity of the propeller

Turbines

They are usually distinguished from propellers in that the blades of the latter do not have a constant pitch throughout their length

When radial-tangential flow is desired, turbines with blades set at a 90-degree angle to their shaft are employed

With these type of impellers, a radial flow is induced by the centrifugal action of the revolving blades

.

Turbines having tilted blades produce an axial discharge quite similar to that of propellers

Because they lend themselves to a simple and rugged design, these turbines can be operated satisfactorily in fluids 1000 times more viscous than fluids in which a propeller of comparable size can be used

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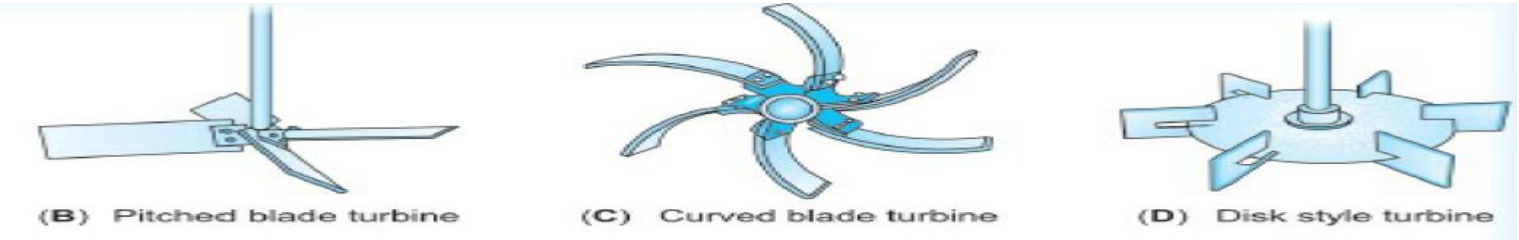


(B) Pitched blade turbine (C) Curved blade turbine (D) Disk style turbine

Paddles

Paddles are also employed as impellers and are normally operated at low speeds of 50 rpm or less

Their blades have a large surface area as compared to the tank in which they are employed, a feature that permits them to pass close to the tank walls and effectively mix viscous liquids and semisolids which tend to cling to these surfaces

Circulation is primarily tangential, and consequently, concentration gradients in the axial and radial directions may persist in this type of mixer even after prolonged operation.

Operating procedures should take these characteristics into account ,With such mixers, for example, ingredients should not be layered when they are added to the mixing tank

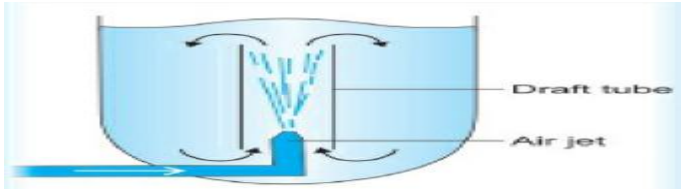
2-Air Jets

Air jet devices involve sub-surface jets of air, or less commonly of some other gas, for effective mixing of certain liquids.
Of necessity and for obvious reasons, the liquids must be of low viscosity, non foaming, nonreactive with the gas employed, and reasonably nonvolatile.

The jets are usually arranged so that the buoyancy of the bubbles lifts liquids from the bottom to the top of the mixing vessel.

This is often accomplished with the aid of draft tubes ,These serve to confine the expanding bubbles and entrained liquids, resulting in a more efficient lifting action by the bubbles, and inducing an upward fluid flow in the tube. This flow tends to circulate fluid in the tank, bringing it into the turbulent region in the vicinity of the jet.

The overall circulation in the mixing vessel brings fluid from all parts of the tank to the region of the jet itself. Here, the intense turbulence generated by the jet produces intimate mixing



3-Fluid Jets

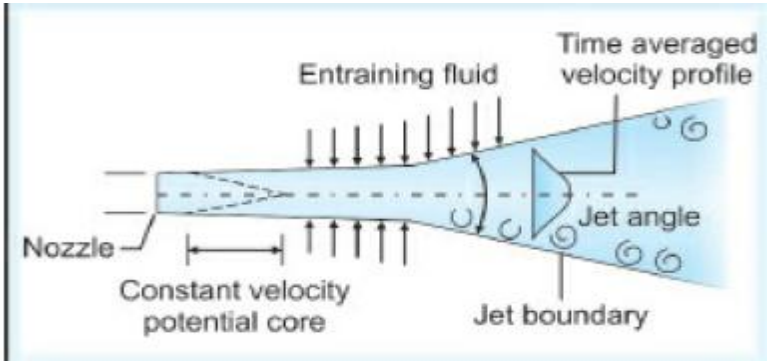
They utilize liquids pumped at high pressure into a tank for mixing.

The power required for pumping can often be used to accomplish the mixing operation, either partially or completely.

In such a case, the fluids are pumped through nozzles arranged to permit a good circulation of material throughout the tank

In operation, fluid jets behave somewhat like propellers and they generate turbulent flow axially.

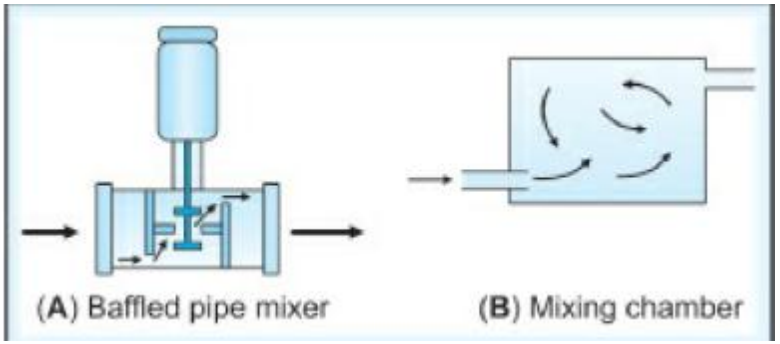
However, they do not themselves generate tangential flow, like propellers. Jets also may be operated simply by pumping liquid from the tank through the jet back into the tank



Continuous or In-line Mixers

The process of continuous mixing produces an uninterrupted supply of freshly mixed material, and is often desirable when very large volumes of materials are to be handled.
It can be accomplished essentially in two ways:
1-in a *tube or pipe* through which the material flows and in which there is very little back flow or recirculation,
2-or in a *mixing chamber* in which a considerable amount of holdup and recirculation occur

To ensure good mixing efficiency, devices such as vanes, baffles, screws, grids, or combinations of these are placed in the mixing tube.



Continuous or In-line Mixers

Mixing in such systems requires careful control of the feed rate of raw materials if a mixture of uniform composition is to be
obtained.

The requirement of an exact metering in such a device results from the lack of recirculation, which would otherwise tend to average out concentration gradients along the pipe.

Where suitable metering devices are available, this method of mixing is very efficient. Little additional power input over that required for simple transfer through a pipe is necessary to accomplish mixing.

Practical Considerations
Vortexing

A vortex develops at the center of the vessel when liquids are mixed by a centrally-mounted vertical-shaft impeller. This particularly is characteristic of turbine with blades arranged perpendicular to the impeller shaft. These impellers tend to induce tangen-tial flow, which does not itself produce any mixing, except possibly near the tank walls where shear forces exist, instead, swirl and the vortex formation. This is true except at very low impeller speeds or at very high liquid viscosities (>20,000 cps), neither of which is normally encountered in practice in the pharmaceutical industry. When a vortex is formed, air is drawn into the impeller and is dispersed into the liquid, which is undesirable, as it may lead to foaming, especially if surfactants are present, and also because the full power of the impeller is not imparted to the liquid. The entrapped air also causes oxidation of the substances in certain cases and reduces the mixing intensity by reducing the velocity of the impeller relative to the surrounding fluid.

Vortixes may be avoided by

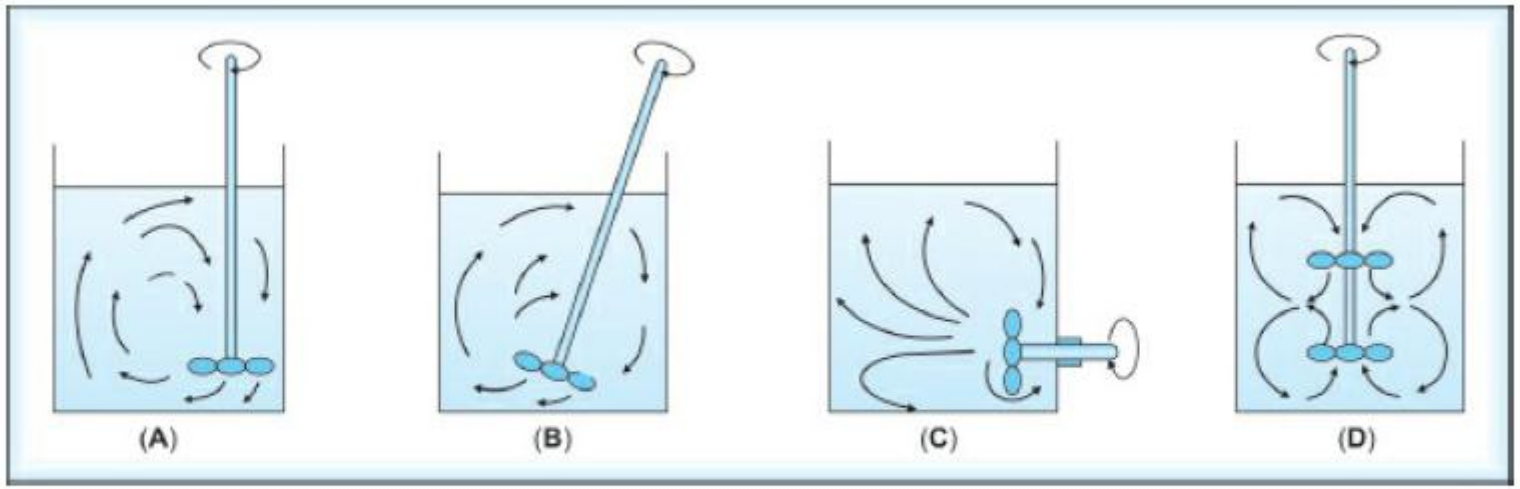
(i) changing arrangement of the impeller,

(ii) changing the tank geometry,

(iii) using a push-pull propeller,

(iv) using baffles and

(v) using diffuser ring.



Figs 1.10A to D: Different arrangements of impellers in a vessel with flow pattern to prevent vortex: (A) Off-centre; (B) Inclined; (C) Side-entering; (D) Push-pull propeller

Kneaders

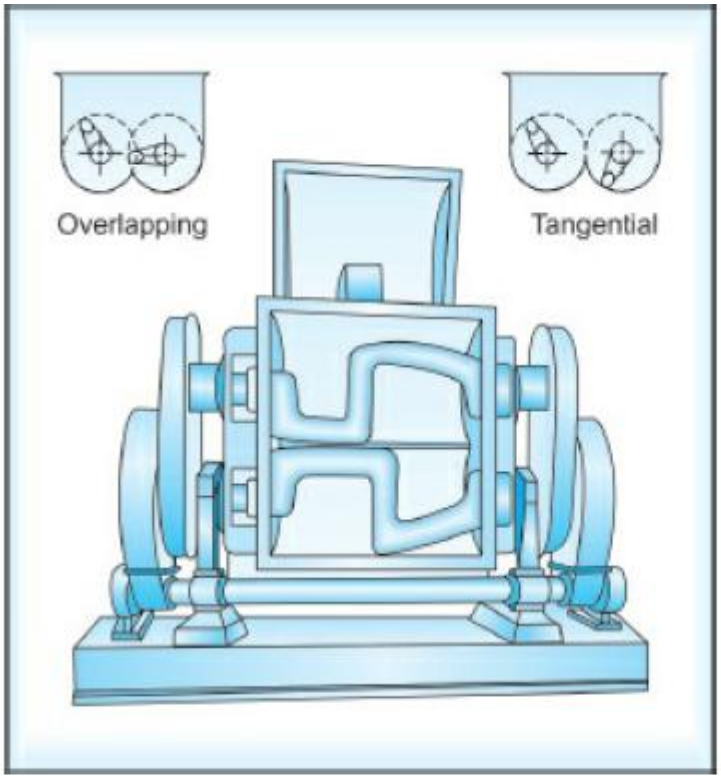
Sigma-Blade Mixer

Sigma-blade mixer has counter-rotating blades or heavy arms that work the plastic mass. The blades rotate tangentially with a speed ratio of about 2:1.

The shape and difference in rotational speed of the blades facilitate lateral pulling of the material and impart kneading and rolling action on the material

.Shear forces are also generated by the high viscosity of the mass and are thus effective in deaggregation as well as distribution of solids in the

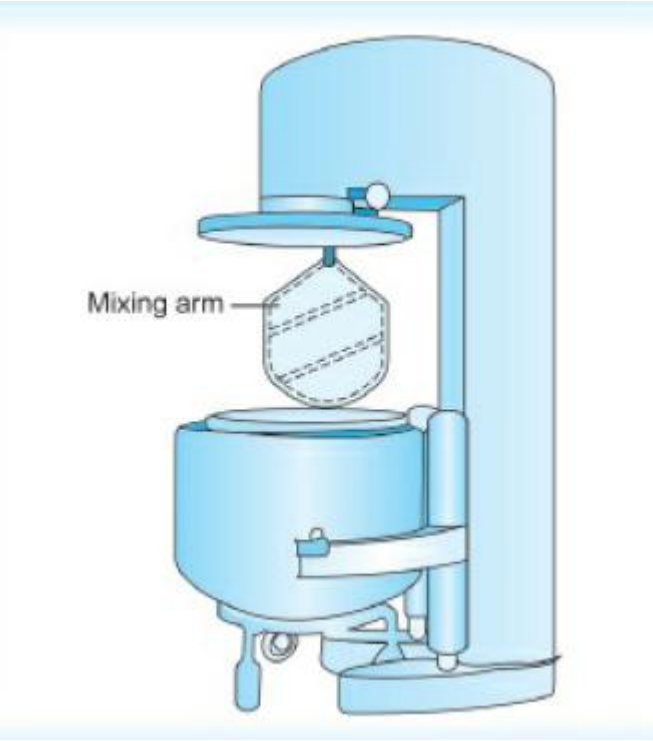
fluid vehicle.



: Schematic representation of a top-loading sigma-blade mixer with overlapping blades

Planetary Mixer

It imparts planetary mixing action, whereby the mixing element rotates round the circumference of the mixer's container, while simultaneously rotating about its own axis. The double rotation of the mixing element and its offset position reduces the dead zones and avoids vortex formation.

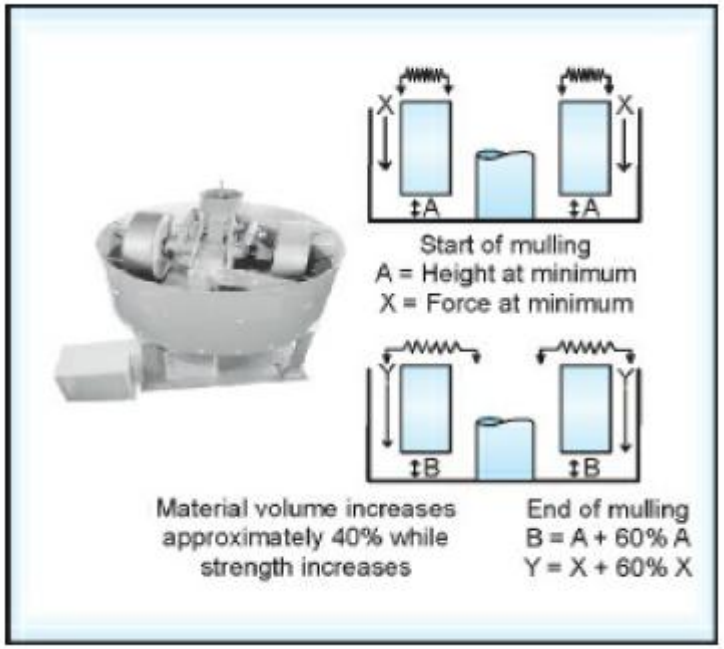


Mulling Mixers

Mulling mixers provide forces that incorporate kneading, shearing, smearing, and blending of materials for a total uniform consistency. This process produces just enough pressure to move, intermingle and push particles into place without crushing, grinding, or distorting the ingredients. The result is a final mixture of truly uniform consistency in both physical and chemical structure.

Mulling

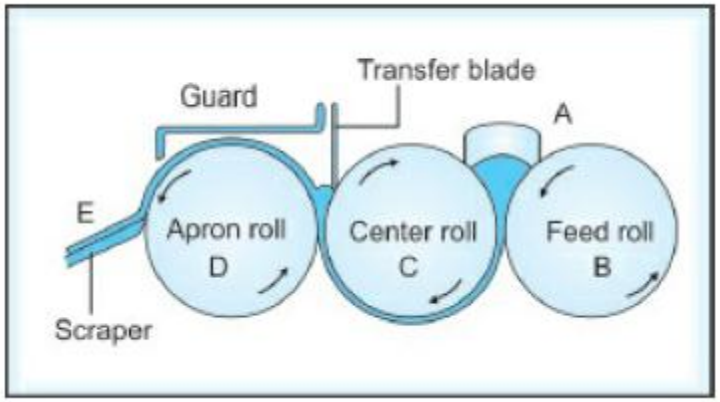
mixers are efficient in deaggregation of solids, but are typically inefficient in distributing the particles uniformly throughout the entire mass. These devices are suitable for mixing previously mixed material of uniform composition, but containing aggregates of solid particles. In the event of segregation during mulling, a final remixing may be necessary.



Schematic representation of the mulling mixer

Roller Mills

Roller mills consist of one or more rollers and are commonly used. Of these, the three-roller types are preferred (Fig. 1.15). In operation, rollers composed of a hard, abrasion-resistant material, and arranged to come into close proximity to each other are rotated at different rates. Depending on the gap, the material that comes between the rollers is crushed, and also sheared by the difference in rates of movement of the two surfaces.


Transfer blade
Guard
A
E
Apron roll
D
Center roll
C
Feed roll
B
Scraper

In extreme cases of solid-liquid mixing, a small volume of liquid is to be mixed with a large quantity of solids. This process is essentially one of coating the solid particles with liquid and subsequent transfer of liquid from one particle to another. In this type of mixing, the liquid is added slowly to reduce the tendency of the particles to form a lump. However, the process is not for fluids mixing, but for solids mixing. When the particles tend to stick together because of the surface tension of the coating liquid, the equipment used is the same as that for pastes. If the solids remain essentially free flowing, the equipment is the same as that used for solids mixing.

Mixer Selection

One of the first and often most important considerations in any mixing problem is equipment selection

Factors that must be taken into consideration for appropriate mixer selection include :
(1) the physical properties of the materials to be mixed, such as density, viscosity, and miscibility,

(2) economic considerations regarding processing, for example, the time required for mixing and power expenditure necessary

(3) cost and maintenance of the equipment
.
however, the selection of equipment depends primarily upon the viscosity of the liquids, and is made according to the mechanism by which intense shearing forces can best be generated.

Low Viscosity Systems

Monophasic systems of low viscosity are classified as positive mixtures, and if given time, mix completely without external agitation. Agitation reduces the time required for mixing, allowing a fast decay in the intensity of segregation. In general, for low viscosity liquids no great problems are encountered unless the operational scale is very large. The viscous character and density of the fluid(s) to be mixed determine, to a large extent, the type of flow that can be produced, and therefore, also the nature of the mixing mechanisms involved. Fluids of relatively low viscosity are best mixed by methods that generate a high degree of turbulence, and at the same time circulate the entire mass of material. These requirements are satisfied by air jets, fluid jets, and the high-speed propellers discussed earlier. A viscosity of approximately 10 poises may be considered as a practical upper limit for the application of these devices.

Intermediate Viscosity Systems

The mixing of systems composed of immiscible liquids (emulsions) or finely divided solids with a liquid of low viscosity (suspensions) depends on the subdivision or deaggregation of one or more of these phases, with subsequent dispersal throughout the mass of the material to be mixed. These processes are often carried out in a single mixing operation, provided that shear forces of sufficient intensity to disrupt aggregates can be generated. At low soliddisperse phase concentrations the flow properties are Newtonian and mixing by propellers is satisfactory as long as the dispersed components oppose settling.

Under such conditions it may be desirable to increase the impeller size and decrease its speed. Emulsions and suspensions are of such viscosity that it is difficult, if not impossible to generate turbulence within their bulk, and laminar mixing, and molecular diffusion must be relied upon. Mixing of such fluids may be accomplished with a turbine of flat blade design. A characteristic feature of such impellers is the relative insensitivity of their power consumption to the density and/or viscosity of the material.

High Viscosity Systems

Viscous ointments are efficiently mixed by the shearing action of two surfaces in close proximity, and moving at different velocities with respect to each other. This is achieved in paddle mixers, in which the blades clear the container walls by a small tolerance. Such mixers are relatively efficient, since they not only generate sufficient shear to reduce globule size, but if properly constructed, also induce sufficient circulation of the material to ensure a uniform dispersion throughout the complete mixture.

As the percentage of solids is increased, or if highly viscous fluids are employed, the solid-liquid system takes on the consistency of a paste or dough. For thicker pastes and plastic masses, a kneading, stretching and folding action is employed. The forces required to induce shear are considerable, and the equipment used is of heavy design. In such cases, sigma-blade mixer and muller mixer are the commonly used mixers.

Mixing of solids

• In the manufacture of tablets or granules normally a number of additives are added. Therefore, mixing of powder becomes essential part of the process.
• Mixing is considered as a critical factor, especially in case of potent drugs and low dose drugs where high amounts of adjuvants are added.
• The diverse characteristics of particles such as size, shape, volume, surface area, density, porosity, and flow charge contribute to the solid mixing.

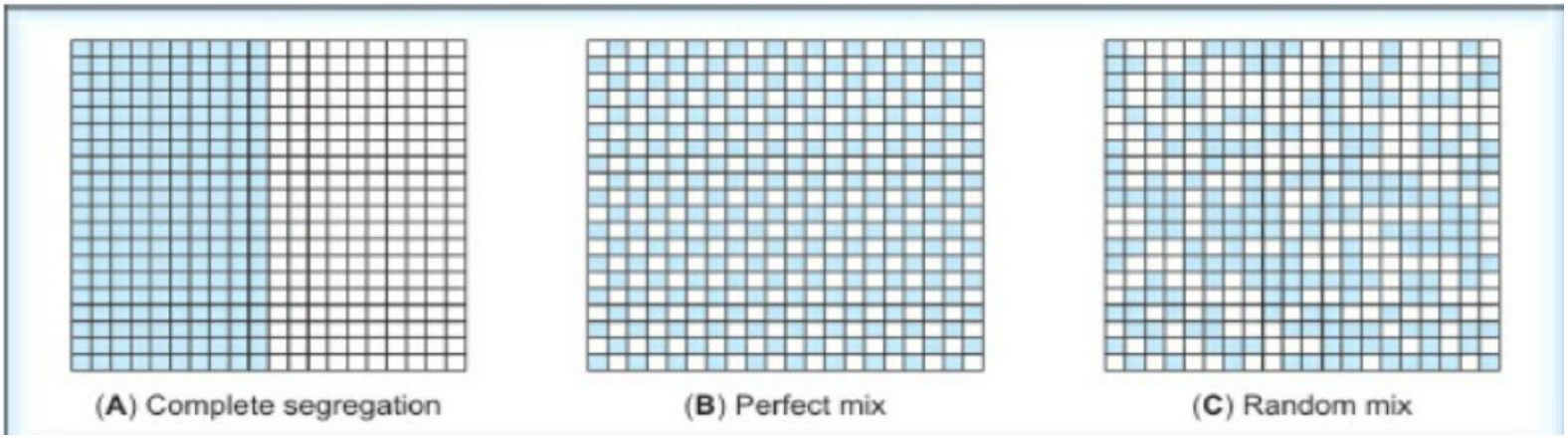
From the definition of mixing, the ideal situation or “perfect mix” in this case would be produced when each particle lies as closely as possible in contact with a particle of the other component. Although a perfect mixture would offer a point uniformity, such arrangement is virtually impossible to get in practice by any mixing equipment.

Powder mixing, however, is a “chance” process and in practice the best type of mix likely to be obtained is a “random mix” where the probability of finding one type of particle at any point in the mixture is equal to its proportion in the mixture.

Segregation is the central problem associated with the mixing and handling of the solid particles, such segregation of particulate solids can occur during mixing as well following the mixing operation

Solids tend to segregate by virtue of differences in the size, density, shape, and other properties of the particles of which they are composed.

The second requirement for segregation can be met by the Earth's gravitational field, or by a centrifugal, electrical, magnetic field generated in the course of processing



Factors Affecting Demixing

1)Particle Size and Size Distribution

a difference in the particle sizes of components of a formulations the main cause of segregation in powder mixes. Smaller particles tend to fall through the voids between larger particles, and thus move to the bottom of the mass

Segregation problem due to particle size difference can be reduced by:

a) Selection of a particular sized fractions (e.g. by sieving to remove fines or lumps) to achieve drug and excipients of the same narrow particle size range.

b) Milling of components to either reduce the particle size range or to ensure all that particles are below approximately 30 μm, at which size segregation does not tend to cause serious problems

.

c) Granulation of the powder mix (size enlargement) so that large numbers of different particles are evenly distributed in each segregating unit/granule.

Factors Affecting Demixing
2) Particle shape

Particle shape is important because as the shape of a particle deviates more significantly from a spherical form, the free movement it experiences along its major axis also decreases.

Spherical particles exhibit the greatest flowability, and are therefore more easily mixed, but they also segregate more easily than non-spherical particles. Irregular or needle-shaped particles may become interlocked, decreasing the tendency to segregate once mixing has occurred

Controlled crystallization during production of the drug/excipients to give components of a particular crystal shape or size range reduces the tendency to segregate.

3) Particle Charge

The mixing of particles whose surfaces are non-conducting (electrically) often results in the generation of surface charges, as evidenced by a tendency of the powder to clump following a period of agitation. Surface charging of particles during mixing is undesirable, for it tends to decrease the process of inter-particulate “diffusion.”

Mechanism of mixing of solids

1. Convective mixing/Macro mixing:

• Inversion of the powder bed using blades or paddles or screw element, in which large mass of material moves from one place to another.

• 2. Shear mixing:

• In this type, forces of attraction are broken down so that each particle moves on its own between regions of different components and parallel to their surface.

• 3. Diffusion mixing/Micro mixing:

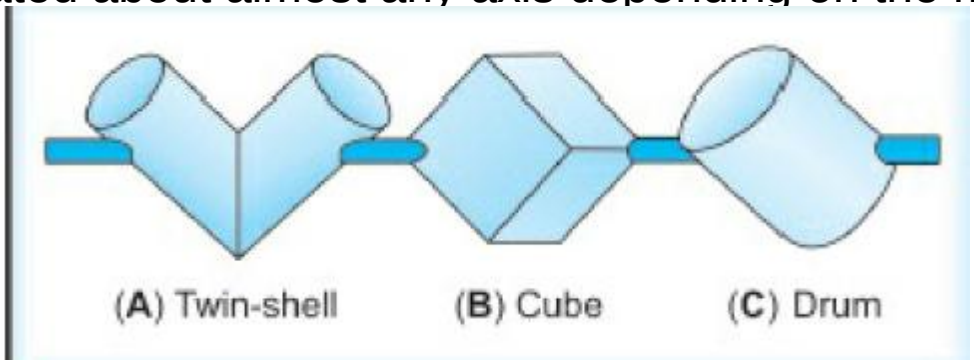
• Involves the random motion of particle within the powder bed, thereby particles change their position relative to one another.

Equipments/Batch
Tumblers/Blenders

A tumbling mixer consists of a container of the one of several geometric forms, which is mounted so that it can be rotated about an axis to cause movement of the material in all planes, which is necessary for rapid overall mixing.

The resulting tumbling motion is accentuated by means of baffles, lifter blades or simply by virtue of the shape of the container

Various types of tumblers with different geometric shapes such as twin-shell, double-cone, drum, cube and tetrahedral blenders are commercially available ,which may be rotated about almost any axis depending on the manufacturer.



The popular twin-shell blender is of this type and takes the form of a cylinder that has been cut in half at approximately a 45-degree angle with its long axis, and then rejoined to form a "*V*" shape. This is rotated so that the material is alternately collected at the bottom of the "*V*" and then split into two portions when the "*V*" is inverted. This is quite effective because the bulk transport and shear, which occur in tumbling mixers, generally, are accentuated by this design

The efficiency of tumbling mixers is highly dependent on the speed of rotation. Rotation that is too slow neither produces the desired intense tumbling or cascading motion, nor does it generate rapid shear rates.

On the other hand, rotation that is too rapid tends to produce centrifugal force sufficient to hold the powder to the sides of the mixer, and thereby, reduces efficiency

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Agitator Mixers

Agitator mixers employ a stationary container to hold the material and bring about mixing by means of moving screws, paddles, or blades. Since these mixers do not depend entirely on gravity as do the tumblers, they are useful in mixing solids that have been wetted, and are therefore in a sticky or plastic state. The high shear forces that are set up are effective in breaking up lumps or aggregates. Well-known mixers of this type include the following:

Ribbon Mixer/Blender

It consists of a horizontal cylindrical tank usually opening at the top and fitted with helical blades or ribbons The blades are mounted on the horizontal axle by struts, and are rotated to circulate the material to be mixed

The helical blades are wound (in most cases) in the opposite directions to provide for the movement of material in both directions along the axis of the tank. Although little axial mixing in the vicinity of the shaft occurs, mixtures with high homogeneity can be produced by prolonged mixing even when the components differ in particle size, shape, or density, or there is some tendency to aggregate

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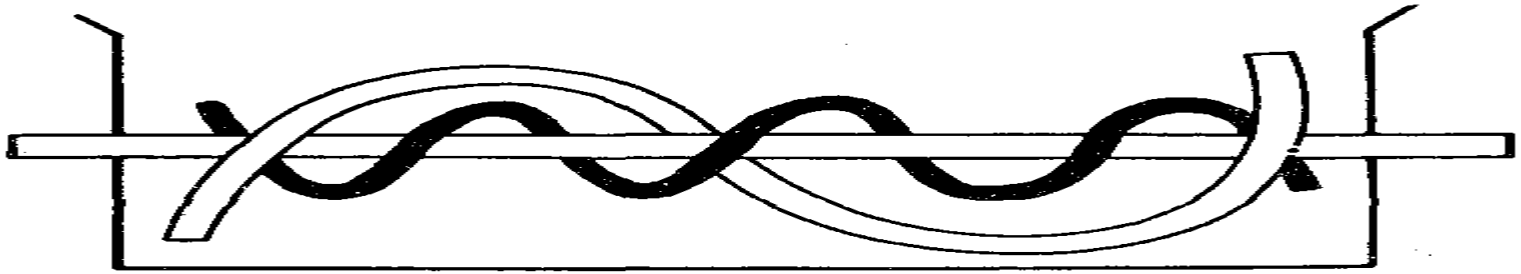


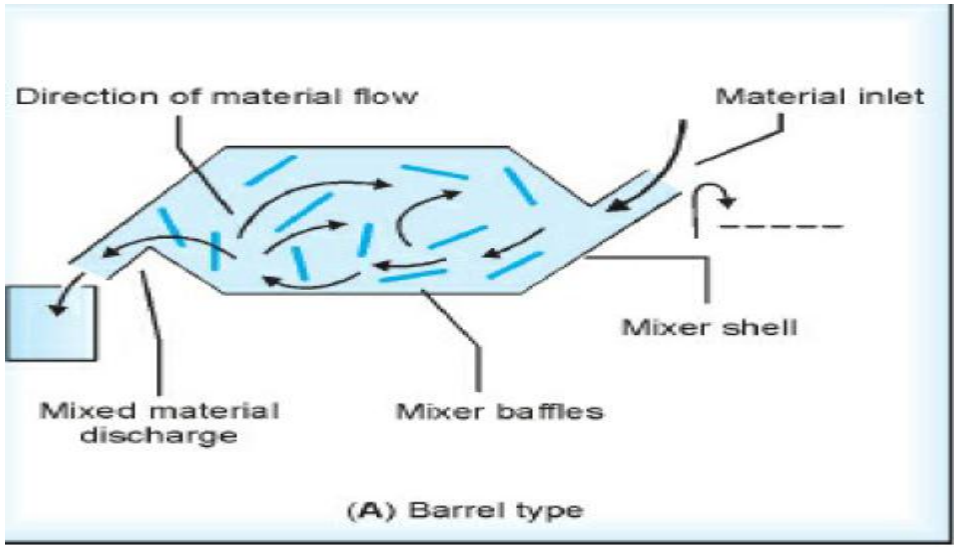
Continuous Mixers

A characteristic of solids mixing equipment is that all else being equal, mixtures produced by large mixers have greater variations in composition than those produced by small mixers. This is an important consideration when relatively small portions of the mixture are required to fall consistently within a narrow composition range.

Continuous mixing processes are somewhat analogous to those discussed under fluid mixing. Metered quantities of the powders or granules are passed through a device that reduces both the scale and intensity of segregation, usually by impact or shearing action.

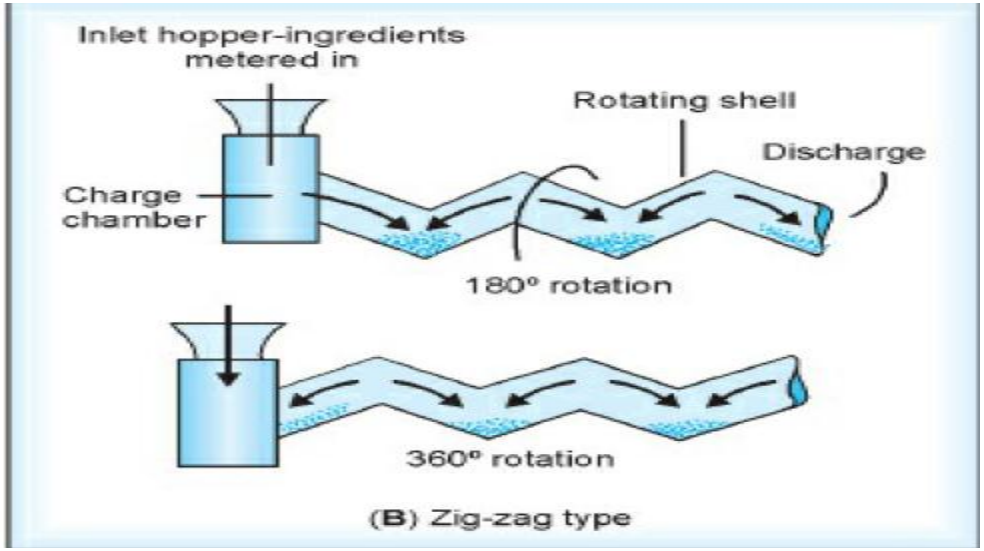
Barrel Type Continuous Mixer

In this mixer, the material is mixed under tumbling motion .The presence of baffles further enhances the mixing. When the material approaches the midpoint of the shell, a set of baffles causes a part of the material to move backwards. Such a mechanism provides intense mixing of ingredients



Zig-zag Continuous Blender

It consists of several “V”-shaped blenders connected in series ,when the blender is inverted, the material splits into two portions, one-half of the material moves backwards, while the other moves forward. In each rotation, a part of the material moves towards the discharge end



Mixer Selection

Mixer Property

An ideal mixer should produce a complete blend rapidly with as gentle mixing action as possible to avoid product damage. It should be dust-tight, cleaned and discharged easily, and require low maintenance and low power consumption.

Rotating shell mixers suffer from poor cross-flow along the axis. The addition of baffles or inclining the drum on the axis increases cross-flow and improves the mixing action. In cubical and polyhedron-shaped blenders, due to their flat surfaces, the powder is subjected more to a sliding than a rolling action, a motion that is not conductive to efficient mixing. In double cone blenders the mixing pattern provides a good cross-flow with a rolling rather than sliding motion. The uneven length of each shell in twin-shell blender provides additional mixing action when the powder bed recombines during each revolution of the blender. Twin-shell and double-cone blenders are recommended for precision blending.

The shearing action that develops between moving blades and trough in agitator mixers serves to breakdown powder agglomerates. Ribbon mixers are not precision blenders and also suffer from the disadvantage of being more difficult to clean than the tumblers and having a higher power requirement.

The mechanical heat build-up and the relatively higher power requirement are the drawbacks also associated with sigma blade and planetary mixers. However, the shorter time interval necessary to achieve a satisfactory blend may offset these factors. Blendex provides efficient batch and continuous mixing for a wide variety of solids without particle size reduction and heat generation.

Material Property

Powders that are not free-flowing or that exhibit high forces of cohesion or adhesion between particles of similar or dissimilar composition are often difficult to mix owing to agglomeration.

The clumps of particles can be broken down in such cases by the use of mixers that generate high shear forces or that subject the powder to impact. The use of agitators preferably planetary and sigma

blade are recommended for such powders.

For strongly cohesive materials, it is typically necessary to fragment agglomerates through the introduction of high shear, “intensification,” devices such as agitators or mills that energetically deform grains on the finest scale.

THANK YOU

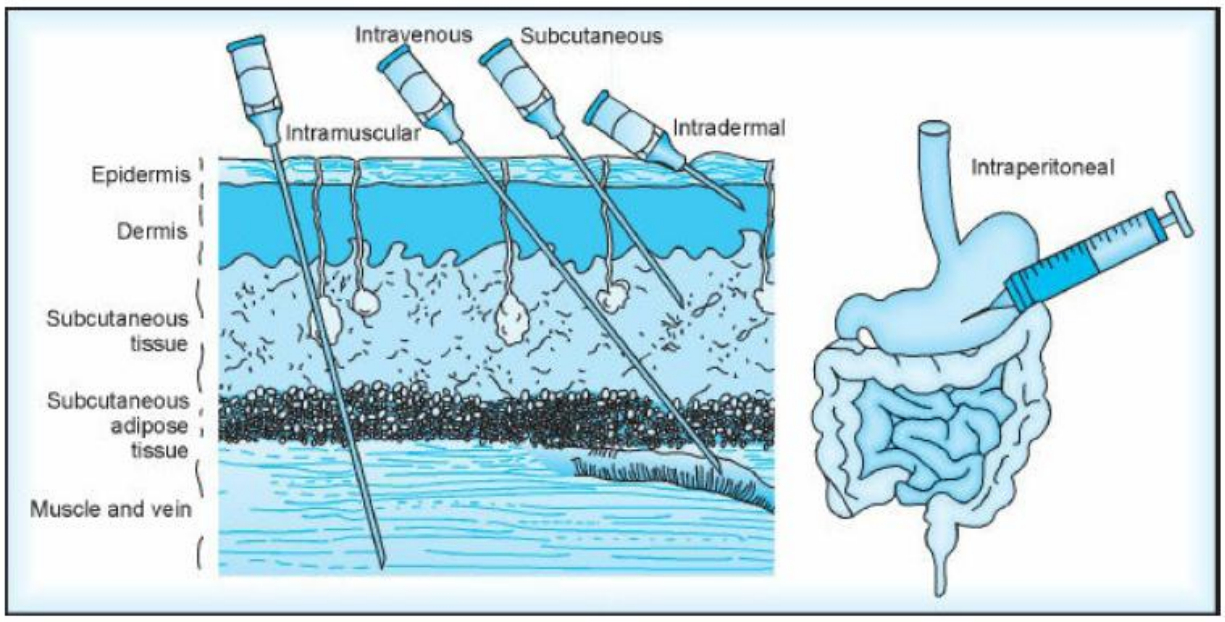
Sterile Products

Sterile products are dosage forms of therapeutic agents that are free of viable microorganisms. Principally, these include parenteral, ophthalmic, and irrigating preparations. Of these, parenteral products are unique among dosage forms of drugs because they are injected through the skin or mucous membranes into internal body compartments. Thus, because they have circumvented the highly efficient first line of body defense, i.e. the skin and mucous membranes, they must be free from microbial contamination and toxic components, as well as possess an exceptionally high level of purity.

All components and processes involved in the preparation of these products must be selected and designed to eliminate, as much as possible, contamination of all types, whether of physical, chemical, or microbiologic origin.

Parenteral preparations may be given by various routes: intravenous,

intramuscular, subcutaneous, intradermal and intraperitoneal.



When injection occurs via an intravascular route, complete drug availability occurs immediately; no absorption is necessary. For all other

routes, at least a blood vessel wall, and usually one or more tissue cell walls,

must be permeated before the drug can enter the circulation. Most often, this

occurs by passive diffusion and is most favourable when the drug has both

lipophilic and hydrophilic properties, with the former being predominant.

With non-vascular injections, absorption is also affected by such factors as the size and number of blood vessels supplying the tissue, the movement (exercise) of the tissue following injection, the physical and chemical properties of the drug and such characteristics of the dosage form as whether it is a solution, suspension, or emulsion, the nature of the vehicle, and its pH. Once in the circulating blood, the physiologic effect of a therapeutic agent is affected by the extent to which it distributes throughout the body, by the degree of binding to plasma proteins and by its rate of elimination by hepatic metabolism and/or renal excretion.

Intravenous and intraspinal preparations are rarely given in a form other than aqueous solutions. The danger of blockage of fine capillaries, particularly in the brain, precludes the use of forms other than solutions for IV administration, although emulsions have been given in which the particle size of the dispersed phase is carefully controlled. The sensitivity of the nerve tissues generally precludes the use of anything but the purest of solutions for intraspinal medication. Preparations given intramuscularly, subcutaneously, or intradermally can be administered as solutions, suspensions, or emulsions.

Even solid pellets may be implanted subcutaneously or intramuscularly. The vehicles can range from Water for Injection, to glycols, to fixed oils. Although care must be exercised to avoid undue tissue irritation, mild local irritation is permissible at these injection sites.

The nature of a preparation can influence significantly the rapidity of onset of a therapeutic effect from a drug, the duration of the effect, and the form of the absorption pattern achieved. Therefore, the development of the formulation for a parenteral product must be integrated carefully with its intended administration in a patient.

The chemical and physical properties of a drug must be determined, its interaction with any desired excipients must be studied, and the effect of each step of the process on its stability must be studied and understood.

Preparations for the eye, though not introduced into internal bodycavities, are placed in contact with tissues that are very sensitive to contamination. Therefore, similar standards are required for ophthalmic preparations.

Irrigating solutions are now also required to meet the same standards as parenteral solutions because during an irrigation

procedure, substantial amounts of these solutions can enter the bloodstream directly through open blood vessels of wounds or abraded mucous membranes.

EFFECT OF ROUTE OF ADMINISTRATION

The intended route of administration has a marked effect on the formulation of a parenteral product. The volume in which a dose of the drug must be encompassed is one factor to consider. For intracutaneous injections a volume of more than 0.2 ml rarely is used because tissue volume is small and compact; also, absorption is quite slow owing to the lack of blood vessels. Volumes of 1 ml or less may be injected subcutaneously and only occasionally are volumes of more than 2 ml given intramuscularly. Volumes of 10 ml or less may be given intraspinally, but only by the IV route may large volumes be given safely, provided careful control of the rate of administration is undertaken. It is not convenient to administer a volume of more than 20 ml by a syringe, and usually it is not practical to set up an infusion unit for less than 250 ml. Isotonicity is a characteristic that is probably of greatest importance for intraspinal injections because the circulation of the cerebrospinal fluid is slow, and disturbances of osmotic

pressure quickly cause headache and vomiting. Since intracutaneous injections are given mostly for diagnostic purposes, nonisotonic solutions may cause false signs of irritation. Isotonicity is preferable for the comfort of the patient, but is not essential for SC and IM injections. For the rapid absorption of drugs given intramuscularly, a slightly hypertonic solution may increase the rate by causing local effusion of tissue fluids. Usually, IV fluids should be isotonic, although slow administration of a paratonic solution may be performed safely if rapid dilution with the blood occurs.

In general, only solutions of drugs in water may be given intravenously. Suspensions may not be given because of the danger of blockage of the small blood vessels. Aqueous or oleaginous suspensions and oleaginous solutions cannot normally be given subcutaneously because of the pain and irritation caused. Muscle tissue tolerates oils and suspended particles fairly well and is therefore the only route normally suitable for their administration.

The administration of a drug deep into the muscle tissue results in a pool of the product at the site of injection. From this depot,

the drug is released at a rate determined to a large extent by the characteristics of the formulation.

Whether the solvent is aqueous or oleaginous affects the rate of absorption; oleaginous solutions are usually more slowly absorbed. Increasing the viscosity of solutions slows the absorption, just as gelatin or polyvinylpyrrolidone in water and aluminum monostearate in oils. Utilizing modifications of the drug molecule to render it less soluble (for instance, the formation of various esters or salts) permits the production of stable suspensions, causing a marked reduction in the rate of absorption of the drug from the depot. Thus, utilizing various modifications in formulation of the product makes it possible to retard the rate at which a drug is released from a depot.

Ophthalmic preparations are formulated in much the same way as parenteral solutions. The eye is particularly sensitive to irritation; therefore, formulation should be directed towards minimizing irritation. Normally, clean aqueous solutions are preferable for ophthalmic use. Suspensions of solids have been used in the eye when the therapeutic need superseded the need to avoid irritating effects, as for the suspensions of corticosteroids used occasionally. It has been found that a

foreign body sensation increases as the concentration of suspended particles, regardless of size, approaches 5%.

Sterile products are most frequently solutions or suspensions, but may even be solid pellets for tissue implantation. The control of a process to minimize contamination for a small quantity of such a product can be achieved with relative ease. As the quantity of product increases, the problems of controlling the process to prevent contamination multiply. Therefore, the preparation of sterile products has become a highly specialized area in pharmaceutical processing. The standards established, the attitude of personnel and the process control must be of a superior level.

FORMULATIONS

Ophthalmic Preparations

Products to be instilled into the eye, while not parenterals by definition, have many similar, and often identical, characteristics. The formulation of stable, therapeutically-active ophthalmic preparations requires high purity of ingredients as well as freedom from chemical, physical (particles), and microbial contaminants. These preparations usually require buffers to stabilize the pH of the product, additives to render it

isotonic or nearly so, and stabilizers such as antioxidants when appropriate for the particular ingredients. Those ophthalmics used in larger quantities, such as eye irrigants, or in the case of devices such as contact lenses, are usually relatively uncomplicated solutions similar to large-volume parenterals. One characteristic not as critical for ophthalmics is freedom from pyrogens since pyrogens are not absorbed systemically from the eye; however, insofar as pyrogens are indicative of a microbiologically clean process, they should not be present.

Freeze-dried Products

Solutions intended to be freeze-dried must be aqueous, for the drying process involves the removal of water by sublimation. Since the solution is in existence for only a brief period during processing, stability problems related to the aqueous system are practically nonexistent. However, the formulation must reflect the characteristics to be imparted to the solid residue (cake) after drying, and those required of the solution after reconstitution at the time of use. Often, the drug alone does not give sufficient solid residue or the characteristics appropriate for the product; therefore, substances often must be added to provide the characteristics desired.

Among the characteristics required of a good cake are (1) a uniform colour and texture, (2) a supporting matrix of solids sufficient to maintain essentially the original volume after drying and (3) sufficient strength to prevent crumbling during storage. In addition, the nature and amount of solids in the solution largely determine (1)the eutectic temperature of the frozen solution, the subzero temperature at which the frozen material will melt, which determines the temperature below which the product must be held during freeze-drying, (2) the rate of thermal and vapour transfer through the product during the process of drying and (3) the rate of solution of the product during reconstitution.

The percentage of solids in the frozen plug should be between approximately 2 and 25%.Among the best salts for providing uniform crystal size, uniform colour and texture, physical strength, and rapid reconstitution are the monobasic and dibasic sodium phosphates. Sodium chloride is often used, but when used alone, the cake tends to shrink markedly in volume and to appear crusty and crumbly. When organic substances, such as mannitol, sorbitol, sucrose, and gelatin are used to provide solids for the cake, care must be taken during the heating, particularly

during the terminal stages of drying, to avoid discolouration of the cake by charring. Added substances required in the formulation must not be volatile under the conditions of drying; therefore, antibacterial agents such as phenol, chlorobutanol, and benzyl alcohol should not be used.

Long-acting Formulations

Long-acting parenteral drug formulations are designed, ideally, to provide slow, constant, and sustained release of a drug over a prolonged period of time, essentially to simulate and replace the more hazardous, continuous i.v. infusion of a drug.

In one type of depot formulation, which is referred to as "dissolution controlled," the rate of drug absorption is controlled by the slow dissolution of drug particles, with subsequent release to tissue fluid surrounding the bolus of product in the tissue. The formation of drug salts with very low aqueous solubility is one of the most common approaches to this type of formulation. Control of the particle size also can contribute to slow dissolution in that larger particles or crystals dissolve more slowly than small crystals with proportionately more surface area. Further, the suspension of the drug particles in vegetable

oils, and especially if gelled with substances such as aluminum monostearate, produces prolonged absorption rates.

Another type of depot formulation is produced by the binding of drug molecules to adsorbents. Only the free portion, in equilibrium with that which is bound, can be absorbed. As drug is absorbed, a shift in equilibrium is established, and the drug is slowly released from the bound state to the free state. This is particularly exemplified by the binding of vaccines to aluminum hydroxide gel to provide a sustained release. A third type of depot preparation is the encapsulation type, in which biodegradable or bioabsorbable macromolecules such as gelatin, phospholipids, and long-chain fatty acids become a diffusion matrix for the drug. The drug is encapsulated within the matrix, and release of drug molecules is controlled by the rate of permeation out of the diffusion barrier and by the rate of biodegradation of the barrier macromolecules. A fourth type is the esterification type depot preparation, in which esters of a drug that are bioerodible are synthesized.

The esterified drug is deposited in tissue at the site of injection to form a reservoir of drug. The rate of drug absorption is controlled by the partitioning of the drug esters from the

reservoir to tissue fluid and by the rate at which the drug ester regenerates the active drug molecule. Often, these esters are dissolved or suspended in oleaginous vehicles, which further slow the release.

Suspensions: The solids content of parenteral suspensions usually ranges between 0.5 and 5%, but may go as high as 30% in some antibiotic preparations. The amount of solids and the nature of the vehicle determine the viscosity of the product, an important factor because of syringeability, the facility with which the product is passed in and out of a syringe. The property of thixotropy is sometimes utilized, particularly with oleaginous suspensions, to provide the sedimentation stability of a gelled preparation during storage and the syringeability of a fluid at the time of administration.

Probably the most important requirement for parenteral suspensions is a small and uniform particle size.

The stabilization of a suspension for the period between manufacture and use presents a number of problems. As indicated, solids gradually settle and may cake, causing difficulty in redispersion prior to use. Surface active agents may aid in the preparation and stabilization of a suspension by

reducing the interfacial tension between the particles and the vehicle. Polysorbate 80, lecithin, Emulphor EL-620 and Pluronic F-68 are among thesurface active agents that have been used in parenteral suspensions. The concurrent addition of a hydrocolloid, such as sodium carboxymethylcellulose, may enhance the effect of the surfactant and cause loss of surface charge of the dispersed particles, water repellency, and the tendency to agglomerate. The following is an example of such a formulation:

Cortisone acetate, microfine	25 mg
Polysorbate 80 (surface active agent)	4 mg
Sodium CMC (protective colloid)	5 mg
Sodium chloride (for tonicity effect)	9 mg
Benzyl alcohol (antibacterial)	9 mg
Water for Injection, to make	1 ml

Emulsions:

The principal problem in the formulation of parenteral emulsions is the attainment and maintenance of uniform oil droplets of 1 to 5 μm in size as the internal phase. With emulsions, separation of the phase does not occur as readily as with suspensions because the difference in density between the oil and water is relatively small. One such product, an emulsion

of a natural vitamin K1, has been stabilized with lecithin.

The preparation of a parenteral emulsion is troublesome. It is made more difficult by the rigid requirement for particle size control to prevent emboli in blood vessels, by the limited choice of emulsifiers and stabilizers of low toxicity, and by the preservation of the oil phase against the development of rancidity.

FORMULATION DEVELOPMENT

The formulation of a sterile product involves the combination of one or more ingredients with a medicinal agent to enhance the convenience, acceptability, or effectiveness of the product. Rarely is it preferable to dispense a drug singly as a sterile dry powder unless the formulation of a stable liquid preparation is not possible.

Therapeutic Agent

A therapeutic agent is a chemical compound subject to the physical and chemical reactions characteristic of the class of compounds to which it belongs. Therefore, a careful evaluation must be made of every combination of two or more ingredients to ascertain whether or not adverse interactions occur, and if they do, of ways to modify the formulation so that the reactions

are eliminated or minimized. The formulation of sterile products is challenging, with respect to the knowledge and ingenuity of the persons responsible.

The amount of information available to the formulator concerning the physical and chemical properties of a therapeutic agent, particularly if it is a new compound, is often quite meager. Information concerning basic properties must be obtained, including molecular weight, solubility, purity, colligative properties, and chemical reactivity, before an intelligent approach to formulation can begin. Improvements in formulation are a continuing process, since important properties of a drug or of the total formulation may not become evident until the product has been stored or used for a prolonged time. However, because of the extensive test documentation required by the US Food and Drug Administration (FDA), only outstanding formulations can be justified for continuance to the state of a marketed product.

Vehicles or Solvent System

Aqueous Systems: the most frequently employed vehicle for sterile products is water, since it is the vehicle for all natural body fluids.

One of the most inclusive tests for the quality of water is the total solids content, a gravimetric evaluation of the dissociated and un-dissociated organic and inorganic substances present in water. the 10 ppm total solids officially permitted for Water for Injection may be much too high when used as the vehicle for many products. Water shall contain a minimal amount of organic compounds. Such compounds are undesirable for two main reasons: they may be toxic, and/or they may serve as sources of nutrition for microorganisms. In practice, Water for Injection normally should not have a conductivity of more than 1micromho (1 megohm, approximately 0.1 ppm NaCl) and total organic carbon (TOC) not more than 500 ppm.

Non-aqueous and Mixed Solvents:

In the formulation of sterile pharmaceutical products, it is sometimes necessary to eliminate water entirely or in part from the vehicle, primarily because of solubility factors or hydrolytic reactions.

Water-immiscible solvents include fixed oils, ediyl oleate, isopropyl myristate, and benzyl benzoate. The most frequently used non-aqueous solvents are polyediylene glycol, propylene glycol, and fixed oils.

Solvent selection: A parenteral therapeutic agent is given by preference as a solution. If aqueous, the solution is physiologically compatible with body tissues, and the biologic response elicited should be reasonably predictable.

The high dielectric constant of water makes it possible to dissolve ionizable electrolytes, and its hydrogen bonding potential brings about the solution of such organic substances as alcohols, aldehydes, ketones, and amines. Conversely, water is a poor solvent for nonpolar compounds, such as alkaloidal bases, which require non-polar solvents. Since therapeutically active compounds given by injection range in property from highly polar to non-polar, solvents having complementary properties must be employed if a solution is to be achieved. Adding to the complexity of solvent selection, is the requirement that solvents to be injected must be of low toxicity to body tissues. Ether is a solvent for testosterone, but is highly irritating to body tissues and cannot be used alone as a solvent for an injectable preparation. Frequently, the desired solubility can be achieved with mixed solvents, e.g. the use of approximately 40% ethanol in water to solubilize the digitalis glycosides.

Compounds that are dissolved in water are often subject to degradativereactions, such as hydrolysis, oxidation, decarboxylation, and racemization.Formulation must be designed, in such cases, to minimize the degradative effects. Often, these reactions are markedly affected by the pH of the solution. Epinephrine in solution undergoes racemization and oxidation, but if the pH is maintained at 3.0 or less, little reaction occurs. The oxidation reaction can be further reduced by displacing atmospheric oxygen with an inert head space gas and adding 0.1% (w/v) sodium metabisulfite as an antioxidant. Atropine sulfate rapidly hydrolyzes in solution, but if the pH is maintained with a buffer system at about 3.5 to 4.0, hydrolysis does not occur at a significant rate.

The use of a mixed solvent system often reduces degradative reactions.Barbituric acid derivatives hydrolyze readily in water, particularly at a lowpH. It has been shown, however, that pentobarbital sodium is soluble and stable in a vehicle containing 60% polyethylene glycol 400 and 10% ethanol in water at a pH of 8.

The aforementioned reactions do not occur in an anhydrous, non-polar vehicle, such as fixed oil, although the presence of a

small amount of water may permit slight reactions. Oleaginous injections are subjected, however, to the disadvantages of being viscous (thus difficult to administer, particularly in cold weather) and of involving frequent incidence of pain upon injection.

Solutes

The physical and chemical purity of solutes used for sterile preparations must also be exceptional. Obviously, the contaminants entering a product with a solute have the same effect as if they entered via the vehicle. Even small traces of contaminants may be detrimental to products, necessitating purification of the solute. For a few substances (for example, ascorbic acid and calcium gluconate), special parenteral grades are commercially available.

In addition, solutes should be free from microbial and pyrogenic contamination. This entails not only proper quality of the chemical as procured, but also storage conditions designed to prevent contamination, particularly after a container has been opened. Preferably, production lots should be designed to use the entire contents of packages of chemicals whenever possible.

Added Substances

Substances added to a product to enhance its stability are essential for almost every product. Such substances include solubilizers, antioxidants, chelating agents, buffers, tonicity contributors, antibacterial agents, antifungal agents, hydrolysis inhibitors, antifoaming agents, and numerous other substances for specialized purposes. At the same time, these agents must be prevented from adversely affecting the product. In general, added substances must be nontoxic in the quantity administered to the patient. They should not interfere with the therapeutic efficacy or with the assay of the active therapeutic compound. They must also be present and active when needed throughout the useful life of the product. Therefore, these agents must be selected with great care, and must be evaluated as to their effect upon the entire formulation.

Antibacterial agents: Antibacterial agents in bacteriostatic concentration must be included in the formulation of products packaged in multiple-dose vials, and are often included in formulations to be sterilized by marginal processes or made by aseptic manipulation.

Antioxidants: Antioxidants, included in many formulations to protect a therapeutic agent susceptible to oxidation, particularly under the accelerated conditions of thermal sterilization, may function in at least two ways., i.e. (1) by being preferentially oxidized (reducing agents), and thereby gradually used up, or (2) by blocking an oxidative chain reaction in which they are not usually consumed. In addition, certain compounds have been found to act as synergists, increasing the effectiveness of antioxidants, particularly those blocking oxidative reactions. A fourth group of compounds are useful in this connection in that they complex with catalysts that otherwise would accelerate the oxidative reaction. Because of the differences in action, combinations of these agents are sometimes used.

Antioxidants (reducing agents)

Ascorbic acid Sodium bisulfite

Antioxidants (blocking agents)

Ascorbic acid esters Butylated hydroxytoluene (BHT)

Synergists

Ascorbic acid Citric acid

Chelating agents

Ethylenediaminetetraacetic acid salts

It should also be mentioned that for those products in which oxygen enters into a degradative reaction, an antioxidant effect can be achieved by displacing oxygen (air) from contact with the product. Usually, this is accomplished by saturating the liquid with either nitrogen or carbon dioxideand sealing the final container after displacing the air above the product with the gas.

Buffers:

Buffers are added to maintain the required pH for many products, as change in pH may cause significant alterations in the rate of degradative reactions. Changes in pH may occur during storage as a result of the dissolution of glass constituents in the product, release of constituents from rubber closures or plastic components in contact with the product,dissolution of gases and vapours from the airspace in the container and diffusion through the rubber or plastic component, or reactions within the product. Buffers must have the capacity to maintain the pH of the productagainst these influences, but not enough to prevent the body fluids from over whelming the buffer ollowing administration. In most cases, the biologic effectiveness of the drug is maximum at or near the biologic fluid pH rather than at the stabilizing pH of the injected product.

Acetates, citrates and phosphates are the principal buffer systems used, but buffer systems making use of other ingredients in the formulation are often used to reduce the total number of ingredients in the product.

Tonicity contributors:

Compounds contributing to the isotonicity of a product reduce the pain of injection in areas with nerve endings. Various agents are used in sterile products to adjust tonicity. Simple electrolytes such as sodium chloride or other sodium salts and non-electrolytes such as glycerin and lactose are most commonly used for this purpose.

Chelating agents:

Chelating agents may be added to bind, in nonionizable form, trace amounts of heavy metals, which if free, would catalyze degradative changes. The chelating agent most commonly used is the trisodium or calcium disodium salt of ethylenediamine tetra-acetic acid in a concentration of about 0.05% (w/v).

Inert gases:

These have been used to displace oxygen from a solution and reduce the possibility of oxidative changes in the formulation. Inert gases may be used to stabilize solutions in other ways. For

example, sodium bicarbonate injection decomposes, particularly during autoclaving, to produce sodium carbonate, carbon dioxide, and water. Saturation of the solution with carbon dioxide inhibits this reaction and stabilizes the solution.

Protein stabilizers:

A number of ingredients have been shown to stabilize proteins, both in the dry and solution state. Serum albumin competes with therapeutic proteins for binding sites in glass and other surfaces and minimizes the loss of the protein caused by surface binding. A number of different types of substances are used as **cryoprotectants** and **lyoprotectants** to minimize protein denaturation during freeze-drying. Antioxidants, buffers and chelating agents are also used to stabilize proteins in solution when necessary.

CONTAINERS

Glass containers traditionally have been used for sterile products, many of which are closed with rubber stoppers. Interest in plastic containers for parenterals is increasing, and such containers are being used for commercial ophthalmic preparations and IV solutions.

Plastic Containers:

The principal ingredient of the various plastic materials used for containers is the thermoplastic polymer. Although most of the plastic materials used in the medical field have a relatively low amount of added ingredients, some contain a substantial amount of plasticizers, fillers, antistatic agents, antioxidants, and other ingredients added for special purposes. These ingredients are not usually chemically bound in the formulation and, therefore, may migrate out of the plastic and into the product under the conditions of production and storage. Considerable variability also has been encountered in the purity of the commercially available polymers. Plastic containers are used mainly because they are light in weight, are non-breakable, and, when low in additives, have low toxicity and low reactivity with products. Tissue toxicity can occur from certain polymers, but additives are a more common cause. Reactivity due to sorption(absorption and/or adsorption) has been found to occur most frequently with the polyamide polymers, but additives leached from any of the plastic materialsmay interact with ingredients of the product.

Glass Containers

Glass is still the preferred material for containers for injectable products. The two general types of glass are soda-lime and borosilicate. The glass that is most resistant chemically is composed almost entirely of silicon dioxide, but it is relatively brittle and can only be melted and molded at high temperatures. The USP provides the Powdered Glass and the Water Attack tests for evaluating chemical resistance of glass. The test results are measures of the amount of alkaline constituents leached from the glass by purified water under controlled elevated temperature conditions; the Powdered Glass test is performed on ground, sized glass particles, and the Water Attack test is performed on whole containers. On the basis of the results from the official tests, glass compounds are classified into four types. The greatest chemical resistance is provided by Type I, and the least by NP (non-parenteral) glass. It should be noted, however, that within these types, as well as Types II and III.

Type I glass is preferred for most sterile products, but Types II and III may be used when the product has a non-aqueous vehicle or the period of contact with the aqueous vehicle is brief, as with

dry powders reconstituted just prior to use, or if the non-reactivity between the glass and product has been established.

Physical Characteristics

The protection of light-sensitive products from the degradative effect of ultraviolet rays may be one of the important physical characteristics of a glass container. Ultraviolet rays can be completely filtered out by the use of amber glass.

Container use Considerations

Single-dose containers are intended to provide sufficient drug for just one dose, the integrity of the container being destroyed when opened so that it cannot be reclosed and used again. Single-dose containers may range from liter bottles of IV solutions to 1 ml, or smaller, cartridges. The desire for further reduction in the risk of contamination, both bacterial and viral, and an increased control over the administration of drugs, particularly in a hospital, have led to the recent development of single-dose, disposable administration units. For most of these units, the product container is a glass cartridge with plastic and metal fitments separated from immediate contact with the product.

Rubber Closures

Rubber closures are used to seal the openings of cartridges, vials, and bottles, providing a material soft and elastic enough to permit entry and withdrawal of a hypodermic needle without loss of the integrity of the sealed container.

Ideally, closures should be completely nonreactive with the product with which they are in contact. No such ideal compound exists; therefore, each rubber compound should be tested for compatibility with each preparation with which it is to be used. Two general compatibility problems exist, namely, the leaching of ingredients from the rubber compound with subsequent reaction with ingredients of the product, and the removal of ingredients from the product by sorption by the rubber compound or by vapour transfer through the closure.

Several properties of rubber closures are significant, particularly elasticity, hardness, and porosity. Rubber closures must be sufficiently elastic to provide a snug fit between the closure and the neck and lip of the glass container.

Devices

Devices associated with sterile products include the following:

Administration sets for large volume parenterals (LVPs)

Filter needles

Hypodermic needles

Hypodermic syringes

In-line filters

Plastic irrigating solution bottles

Plastic LVPs containers

Plastic ophthalmic dropping bottles

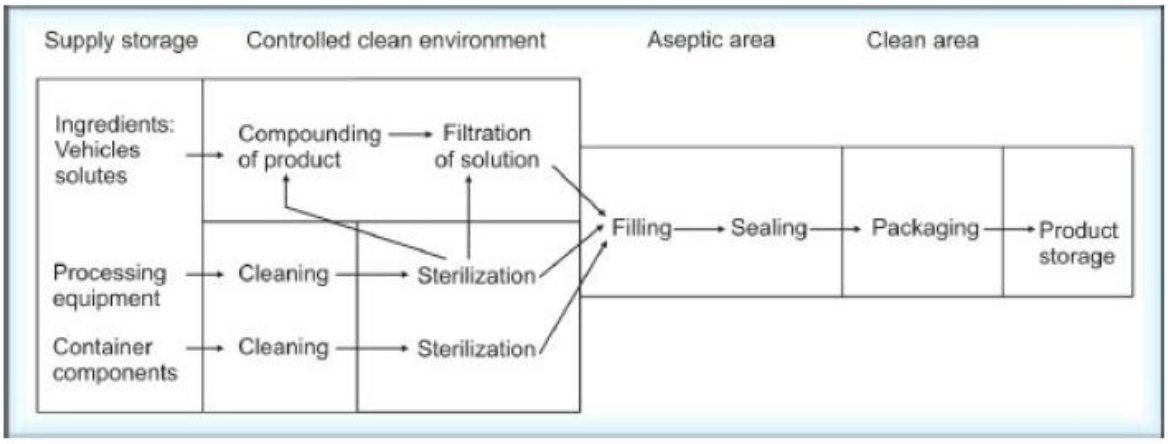
Transfer needles

Transfer sets

Although the contact time of the product with the device is usually brief, it is intimate; therefore, compatibility between the device and the product must be evaluated. For example, it has been shown that insulin can be adsorbed by PVC tubing during the time of contact for administrative of an IV solution, approximately 6 h.

PRODUCTION

The production process includes all of the steps from the accumulation and combining of the ingredients of the formula to the enclosing of the product in the individual container for distribution. Intimately associated with these processes are the personnel who carry them out and the facilities in which they are performed. The most ideally planned processes can be rendered ineffective by personnel who do not have the right attitude or training, or by facilities that do not provide an efficiently-controlled environment. To enhance the assurance of successful manufacturing operations, all process steps must be carefully reduced to writing after being shown to be effective.



Quality Control

The three general areas of quality control are incoming stock,

manufacturing (processing), and the finished product. For sterile products, incoming stock control encompasses routine tests on all ingredients as well as special evaluations such as pyrogen tests on WFI, glass tests on containers, and identity tests on rubber closures. It also may be necessary to perform microbial load (bioburden) tests to determine the number and types of microorganisms present. Process control in the manufacture of sterile products involves all of the innumerable tests, readings, and observations made throughout the manufacturing process of a product, including conductivity measurements during the distillation of WFI, confirmation of volume of fill in product containers, recording of cycle time and temperature for thermal sterilization of the product, and confirming the count and identity of labels for the product. The production control includes all of the final assays and tests to which the product is subjected. In addition to the usual chemical and biologic tests, a sterile product is subjected to a leak test (when applicable), a clarity test, a pyrogen test (when applicable), and a sterility test.

Leak Test

Ampoules are intended to provide a hermetically sealed container for a single dose of a product, thereby completely

barring any interchange between the contents of the sealed ampoule and its environment.

The leak test is intended to detect incompletely-sealed ampoules so that they may be discarded. Tip-sealed ampoules are more likely to be incompletely sealed than are those that have been pull-sealed. In addition, small cracks may occur around the seal or at the base of the ampoule as a result of improper handling. Vials and bottles are not subjected to such a leak test because the rubber closure is not rigid; however, bottles are often sealed while a vacuum is being pulled so that the bottle remains evacuated during its shelf-life.

Clarity Test

Clarity is a relative term, the meaning of which is markedly affected by the subjective evaluation of the observer. Unquestionably, a clean solution having a high polish conveys to the observer that the product is of exceptional quality and purity. It is practically impossible, however, to prepare a lot of a sterile product so that every unit of that lot is perfectly free from visible particulate matter, i.e. is, from particles that are 30 to 40 μm and larger in size.

Although particulate matter is of primary concern in products given intravenously, all parenteral products should be free from insoluble particles.

Suspensions, emulsions, or dry solids, in addition to solutions, should be compounded and processed under clean conditions to minimize the presence of foreign particles.

The visual inspection of a product container is usually done by individual human inspection of each externally clean container under good light, baffled against reflection into the eyes, and viewed against a black and white background, with the contents set in motion with a swirling action, since a moving particle is much easier to see than one that is stationary.

Pyrogens and Pyrogen Test

Water used in parenteral and irrigating solutions should be free of pyrogens. To achieve this, proper controls must be maintained in the preparation and storage of water. Pyrogens are products of metabolism of microorganisms. Most bacteria and many molds and viruses have been reported as producing pyrogens. The gram-negative bacteria produce the most potent pyrogenic substances as endotoxins. Chemically, pyrogens are

lipid substances associated with a carrier molecule, which is usually a polysaccharide but may be a peptide.

About 1 h after injection into man, pyrogens roduce a marked rise in body temperature, chills, body aches, cutaneous vasoconstriction, and a rise in arterial blood pressure.

Antipyretics eliminate the fever, but not the other systemic effects of pyrogens.

The fever response to pyrogens in rabbits is the basis for the official pyrogen test.

Sterility Test

All products labeled “sterile” must pass the sterility test, having been subjected to an effective process of sterilization. The test for sterility is intended for detecting the presence of viable form of microbes in pharmacopoeial preparations.

Method A: Membrane Filtration

A suitable unit consists of a closed reservoir and a receptacle between which a properly supported membrane of appropriate porosity is placed. A membrane suitable for sterility test has a nominal pore size not greater than 0.45 μm, diameter of approximately 47 mm and whose effectiveness to retain

microorganisms has been established. Cellulose nitrate filters, for example, are used for aqueous, oily, and weakly alcoholic solutions; and cellulose acetate filters, are used for strongly alcoholic solutions. Specially adapted filters may be needed for certain products such as antibiotics.

Method B: Direct Inoculation

Apart from testing oily solutions, creams, ointments and solid products, direct inoculation method is utilized particularly for surgical devices, sterile devices, surgical dressings and sutures, in case where membrane filtration method appears difficult. In this test, the quantity of the preparation to be examined is transferred directly into the culture medium so that the volume of the product is not more than 10% of the volume of the medium, unless otherwise prescribed.

Sterilization

Sterilization is the process designed to produce a sterile state. The traditional concept of the sterile state is the absolute condition of total destruction or elimination of all living microorganisms.

With terminal methods of sterilization of a parenteral product, particularly steam under pressure, a probability of no more than one nonsterile unit in a million (10^{-6}) is readily achievable.

The term *aseptic* indicates a controlled process or condition in which the level of microbial contamination is reduced to the degree that microorganisms can be excluded from a product during processing. It describes an "apparently" sterile state.

Microorganisms exhibit varying resistance to sterilization procedures. The degree of resistance varies with the specific organism. In addition, spores, the form that preserves certain organisms during adverse conditions, are more resistant than vegetative forms of the organism.

a sterilization process must be planned to be lethal to the most resistant spores of microorganisms normally encountered, with additional treatment designed to provide a margin of safety against a sterilization failure.

Validation of sterilization process

All sterilization processes (thermal, chemical, radiation, and filtration) are designed to destroy or eliminate microbiologic contaminants present in a product. The official test for sterility of the product is a destructive test on a selected sam-

ple; thus, the task of proving that all units of a product are sterile must involve the employment of probability statistics.

Microbial Death Kinetic Terms

An important term in expressing microbial death kinetics for heat, chemical, and radiation sterilization is the *D value*. The D value is the time (for heat or chemical exposure) or the dose (for radiation exposure) required for the microbial population to decline by one decimal point (a 90%, or one logarithmic unit, reduction). The D value may be estimated graphically, as shown in Figure 21-1, or mathematically, as shown by equation (1):

$$D = \frac{U}{\log N_0 - \log N_u} \qquad (1)$$

where U is the exposure time or exposure dose, under specific conditions, N_0 is the initial microbial population (product bioburden) and N_u is the microbial population after receiving U time

or dose units of sterilant exposure. For example, after 5 min of product exposure to a temperature of 121°C, the microbial population was reduced from 2×10^5 to 6×10^3. Then, the D value at 121°C is:

$$D_{121} = \frac{5 \text{ min}}{\log(2 \times 10^5) - \log(6 \times 10^3)} = 3.28 \text{ min}$$

Thus, at 121°C, the microbial population is decreased by 90% every 3.28 min.

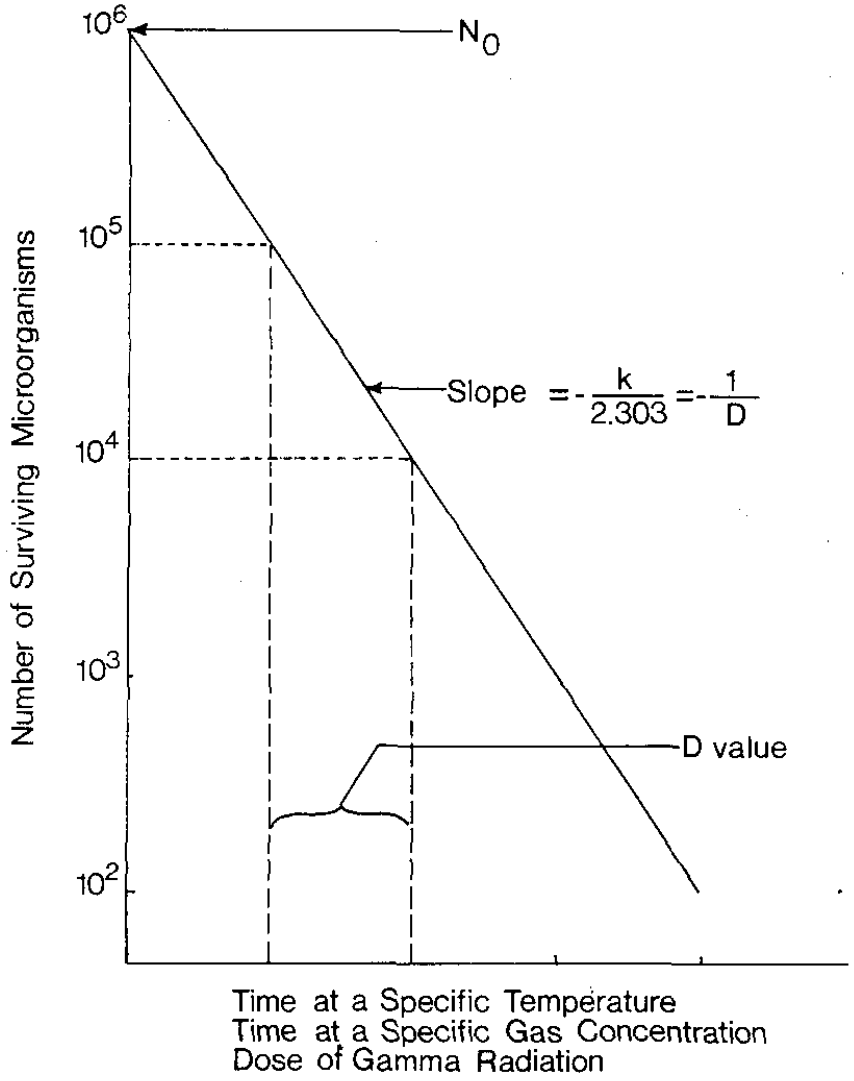


FIG. 21-1. *Graphic representation of the semilogarithmic microbial death rate.*

Other key terms used in the determination of microbial death rates include *microbial load,* or *bioburden;* the *Z value;* the *F value;* the F_0 value; and the probability of nonsterility. These terms are defined in Table 21-2, and Z value plots are shown in Figure 21-2.

TABLE 21-2. *Definition of Key Terms Employed in Microbial Death Kinetics*

Symbol	*Term*	*Definition*
N_0	Bioburden	The population or number of living microorganisms per defined unit, surface, or system.
Z	Resistance value	The number of degrees (C or F) required for a 1 log reduction in the D value. $Z = -\frac{T_1 - T_2}{\log D_2 - \log D_1}$
F (T,z) or F_T^z	Sterilization process equivalent time	The equivalent time at temperature T delivered to a unit of product calculated using a specified value of z.
F_0	Sterilization process equivalent time	The equivalent time at a temperature of 121°C delivered to a unit of product calculated using a z value of 10°C.
N_u	Probability of nonsterility	The number of nonsterile units per batch or the theoretic or extrapolated number of living microorganisms per defined unit after a given equivalent heating time U at a specific temperature T.
$N_u = \text{antilog}\left(\log N_0 - \frac{U_T}{D}\right)$		

Aseptic processing also requires validation to assure batch to batch consistency in producing a given probability of product sterility. While D and F_0 values cannot be applied, a probability of nonsterility levels can be obtained by process simulation testing using microbiologic growth medium, a suitable type and number of challenge microorganisms, and a relevant number of containers. The percent contamination level (% C) is calculated as follows:

$$\% \, C = \frac{N_G}{N_T - N_D} \times 100 \qquad (5)$$

where N_G is the number of undamaged containers with microbial growth, N_T is the total number of containers filled, and N_D is the number of damaged contaminated containers. Procedures for validation of aseptic fill for solution drug products have been presented in a recent publication by the Parenteral Drug Association.[10]

Physical Processes of Sterilization

Thermal Methods

The lethal effectiveness of heat on microorganisms depends upon the degree of heat, the exposure period, and the moisture present. Within the range of sterilizing temperatures, the time required to produce a lethal effect is inversely proportional to the temperature employed. For example, sterilization may be accomplished in 1 hour with dry heat at a temperature of 170°C, but may require as much as 3 hours at a temperature of 140°C.

mechanism by which microorganisms are killed by heat is thought to be the coagulation of the protein of the living cell.

Dry Heat. Substances that resist degradation at temperatures above approximately 140°C (284°F) may be rendered sterile by means of dry heat. Two hours exposure to a temperature of 180°C (356°F) or 45 min at 260°C (500°F) normally can be expected to kill spores as well as vegetative forms of all microorganisms. This total sterilizing cycle time normally includes a reasonable *lag time* for the substance to reach the sterilizing temperature of the oven chamber, an appropriate hold period to achieve sterilization, and a cooling period for the material to return to room temperature.

Factors in Determining Cycle Time. The cycle time is composed of three parts: (1) the thermal increment time of both the chamber and the load of material to be sterilized, assuming both start at room temperature, (2) the hold period at the maximum temperature, and (3) the cooling time.

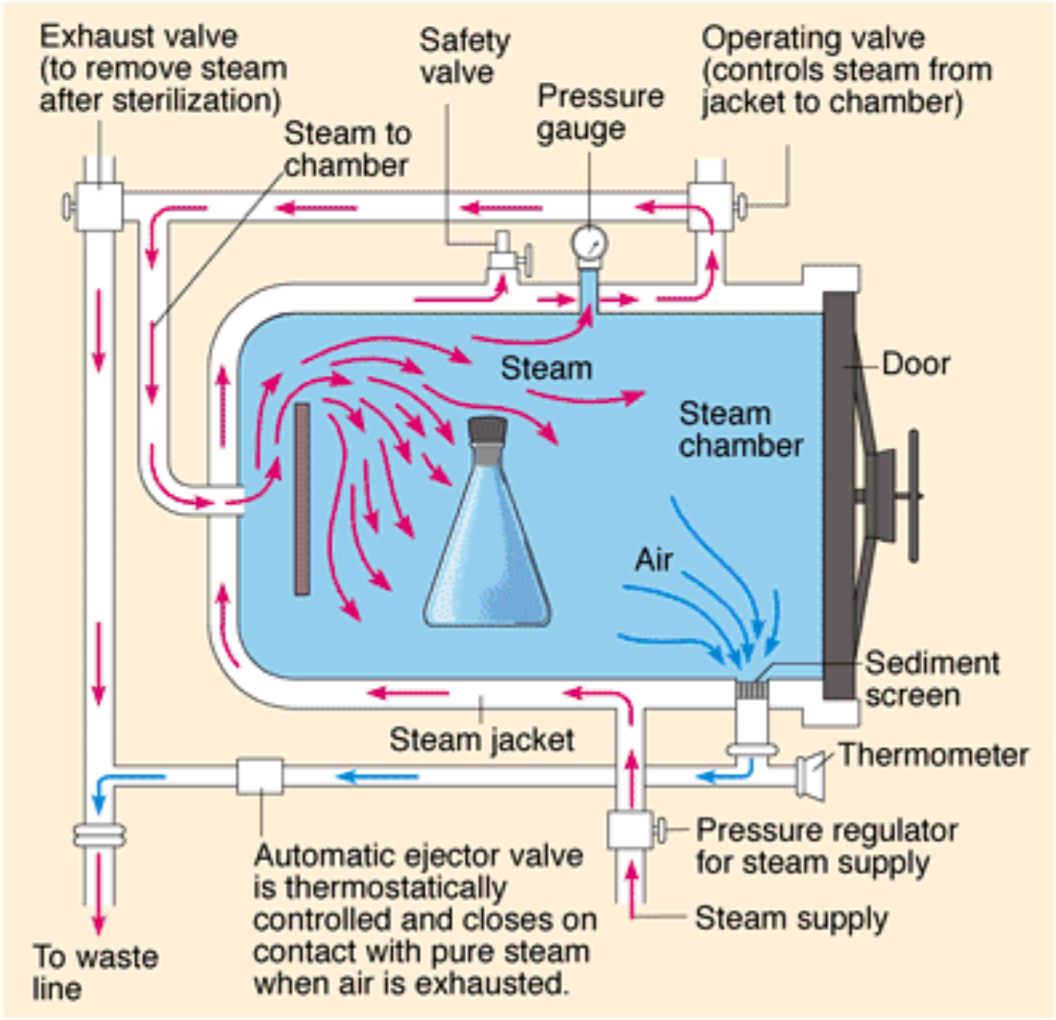
Sterilizer Types. The ovens used to achieve hot air sterilization are of two types, natural convection and forced convection.

Effect on Materials. The elevated temperatures required for effective hot air sterilization in a reasonable length of time have an adverse effect on many substances. Cellulose materials, such as paper and cloth, begin to char at a temperature of about 160°C (320°F). At these temperatures, many chemicals are decomposed, rubber is rapidly oxidized, and thermoplastic materials melt. Therefore, this method of sterilization is reserved largely for glassware, metalware, and anhydrous oils and chemicals that can

Moist Heat. Moist heat is more effective than dry heat for thermal sterilization. It should be remembered, however, that normal moist heat cycles do not destroy pyrogens.

As previously noted, moist heat causes the coagulation of cell protein at a much lower temperature than dry heat. In addition, the thermal capacity of steam is much greater than that of hot air. At the point of condensation (*dew point*), steam liberates thermal energy equal to its heat of vaporization.

Factors Determining Cycle Time. Spores and vegetative forms of bacteria may be effectively destroyed in an autoclave employing steam under pressure during an exposure time of 20 min at 15 pounds pressure (121°C [250°F]) or as little as 3 min at 27 pounds pressure (132°C [270°F]).



Indicators for Evaluating the Sterilization Process.

Among the indicators available, the most widely used is the thermocouple. These indicators are often connected to recorders so that a continuous record of the actual temperature at the location of the thermocouple can be obtained.

For autoclave sterilization, a variety of other indicators also are used. These include wax or chemical pellets that melt at 121°C and paper strips that are impregnated with chemicals that change color under the influence of moisture and heat. All of these have limited reliability for indicating the length of time that a temperature of 121°C has been maintained.

Resistant bacterial spores in sealed ampuls or impregnated in dry paper strips are used as biologic indicators. Their destruction is evidence of the intended effect of a sterilization process.

Application of Thermal Methods of Sterilization. It is generally accepted that the most reliable thermal method of sterilization is the use of moist heat under pressure. Therefore, this method of sterilization should be employed whenever possible. Aqueous pharmaceutical preparations in hermetically sealed containers that can withstand the temperature of autoclaving can be rendered sterile and remain so indefinitely unless tampering with the seal occurs. Nonaqueous preparations in sealed containers cannot be sterilized in this manner during a normal cycle because no water is present within the container to generate steam and thereby effect sterilization.

Nonthermal Methods

Ultraviolet Light. Ultraviolet light is commonly employed to aid in the reduction of contamination in the air and on surfaces within the processing environment. The germicidal light produced by mercury vapor lamps is emitted almost exclusively at a wave length of 2537 Angstrom units (253.7 millimicrons). It is subject to the laws for visible light, i.e., it travels in a straight line, its intensity is reduced in proportion to the square of the relative distance it travels, and it penetrates materials poorly or selectively. Ultraviolet light penetrates clean air and pure water well, but an increase in the salt content and/or the suspended matter in water or air causes a rapid decrease in the degree of penetration. For most other applications, penetration is negligible, and any germicidal action is confined to the exposed surface.

Lethal Action. When ultraviolet light passes through matter, energy is liberated to the orbital electrons within constituent atoms. This absorbed energy causes a highly energized state of the atoms and alters their reactivity. When such excitation and alteration of activity of essential atoms occurs within the molecules of microorganisms or of their essential metabolites, the organism dies or is unable to reproduce. The principal effect may be on cellular nucleic acids, which have been shown to exhibit strong absorption bands within the ultraviolet wavelength range.

Maintenance and Use. To maintain maximum effectiveness, ultraviolet lamps must be kept free from dust, grease, and scratches because of the large reduction in emission intensity that will occur. Also, they must be replaced when emission levels decrease substantially (about 30 to 50%) owing to energy-induced changes in the glass that inhibits the emission.

Ionizing Radiations. Ionizing radiations are high-energy radiations emitted from radioactive isotopes such as cobalt-60 (*gamma rays*) or produced by mechanical acceleration of electrons to very high velocities and energies (*cathode rays, beta rays*). Gamma rays have the advantage of being absolutely reliable, for there can be no mechanical breakdown; however, they have the disadvantages that their source (radioactive material) is relatively expensive and the emission cannot be shut off as it can from the mechanical source of accelerated electrons. Accelerated electrons also have the advantage of providing a higher and more uniform dose rate output.

Electron Accelerators. Electron accelerators are of two general types, the linear and the Van de Graaff accelerators. The principle of the linear accelerator may be followed from Figure 21-5. Very high-frequency microwaves (radar) collect electrons from a cathode and accelerate them as they travel through the vacuum tube, reaching almost the speed of light. The electrons are emitted and directed to the target at an energy range of 3 to 15 million electron volts (meV). Since energy potentials of 10 meV or higher may produce radioactive materials, linear accelerators of more than 9 meV are not normally used for sterilizing.

The Van de Graaff accelerators are capable of energy potentials up to 3 meV. They utilize the force exerted on a charged particle by a high voltage potential in an electric field as a means of direct particle acceleration.

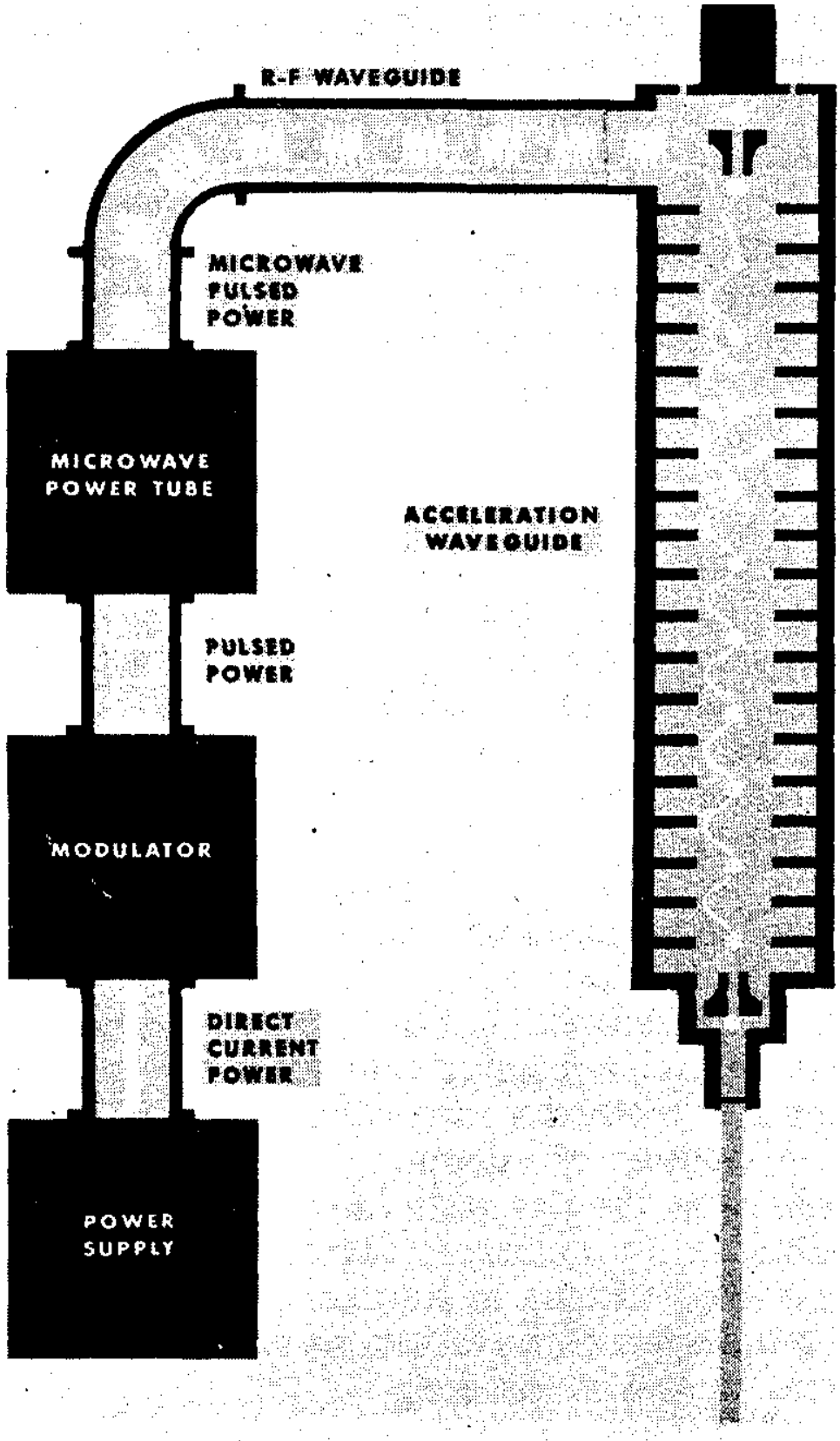


FIG. 21-5. *Operating principle of a linear electron accelerator. (Courtesy of High Voltage Engineering Corp.)*

Lethal Action and Dosage. Ionizing radiations destroy microorganisms by stopping reproduction as a result of lethal mutations.

Applications for Sterilization. Accelerated electrons or gamma rays may be used to sterilize select products by a continuous process.

The use of radiation is increasing in frequency and extent as experience is gained with this method, particularly for the sterilization of medical plastic devices. It has been given new impetus by the question raised by the Occupational Safety and Health Administration (OSHA) on the safety of ethylene oxide and the low environmental level now being permitted. Availability of facilities for this method, using both energy sources, is increasing. An individual medical device or pharmaceutical manufacturer may not justify the high cost of a facility for radiation sterilization, but the increasing availability of centers performing contract services is making this method a more viable option.

A number of vitamins, antibiotics, and hormones in the dry state have been successfully sterilized by radiation. Liquid pharmaceuticals are more difficult to sterilize because of the potential effect of the radiations on the vehicle system as well as the drug.

Filtration. Filtration may be used for the removal of particles, including microorganisms, from solutions and gases without the application of heat. Ideally, filters should not alter the solution or gas in any way, neither removing desired constituents nor imparting undesired components. This requirement essentially limits the types of filters currently employed to the polymeric types listed in Table 21-5A, B. Furthermore, almost all of those currently in use with parenteral solutions and gases are of the membrane type, that is, tissue-thin material removing particles primarily by sieving. When a filter does remove constituents from a solution such removal is usually due to the phenomenon of adsorption, which being a surface phenomenon, occurs during only the first portion of the filtration, that is, until the surface of the filter is saturated with the adsorbed molecule or ion. The most common attack on the filter itself is due to the solvent properties of the vehicle of certain parenteral products. Since the most common solvent for parenteral solutions is water, and the use of other types of solvents is limited, this usually is not a problem. Moreover, the development

of membrane filters composed of materials having high resistance to most pharmaceutical solvents has further reduced this problem.

Function of Filters. Membrane filters function primarily by sieving, or by screening particles from a solution or gas, thus retaining them on the filter surface. Because of the nature of membrane filters and their limited thickness, there is little entrapment within the filter medium, this being a mechanism applicable to the function of depth filters, such as those made of glass and paper. Membrane filters also function in some instances by electrostatic attraction. This would apply particularly to the filtration of dry gases, in which electrostatic charges tend to increase because of the frictional effect of the flowing gas.

0.22 and 0.45um Pores: Used to filter most bacteria. Don't retain spirochetes, mycoplasmas and viruses.

0.01 um Pores: Retain all viruses and some large proteins.

Types of Filters. Since the filter membranes are designed to be used once and then discarded, they are disposable; further, filter housings composed of plastic polymers, which are also intended to be disposable, are becoming increasingly available. Thus, all after-use cleaning is eliminated. In addition, the membrane filter is sealed into the housing by the manufacturer, so that the risk of leakage is minimal.

Aseptic Processing. Sterilization of a solution by filtration provides an extremely clean solution, removing dirt particles as well as microorganisms in the micron size range.

Aseptic processing is technically not a sterilization process, but is mentioned here because of its close involvement with sterilization by filtra-

Chemical Processes of Sterilization

Gas Sterilization

Gas sterilization is not new. Such gases as formaldehyde and sulfur dioxide have been used for sterilization for many years. These gases are highly reactive chemicals, however, and are difficult to remove from many materials after exposure. Therefore, their usefulness is limited. Two newer gases, ethylene oxide and beta-propiolactone, have fewer disadvantages than the older agents and therefore have assumed importance in sterilization.[23] Undoubtedly, the advent of plastic materials and the need for a practical method of sterilizing them have spurred the

development of the newer gaseous sterilizing agents, particularly ethylene oxide.

Ethylene Oxide. Ethylene oxide (EtO) is a cyclic ether ($[CH_2]_2O$) and is a gas at room temperature. Alone, it is highly flammable, and when mixed with air, explosive. Admixed with inert gases such as carbon dioxide or one or more of the fluorinated hydrocarbons (Freons) in certain proportions, ethylene oxide is rendered nonflammable and safe to handle. As a gas, it penetrates readily such materials as plastic, paperboard, and powder. Ethylene oxide dissipates from the materials simply by exposure to the air. It is chemically inert toward most solid materials. On the other hand, in the liquid state, as compressed in cylinders, ethylene oxide dissolves certain plastic and rubber materials and requires particular care in handling.

Mechanism of Action. Ethylene oxide is believed to exert its lethal effect upon microorganisms by alkylating essential metabolites, affecting particularly the reproductive process.[23] The alkylation probably occurs by replacing an active hydrogen on sulfhydryl, amino, carboxyl, or hydroxyl groups with a hydroxyethyl radical. The altered metabolites are not available to the microorganism, and so it dies without reproducing.

Application. Alkylation may also occur with drug molecules in pharmaceutical preparations, particularly in the liquid state. Therefore, ethylene oxide sterilization of pharmaceuticals is limited essentially to dry powders of substances shown to be unaffected. It has extensive application, however, to plastic materials, rubber goods, and delicate optical instruments. It has also been found that stainless steel equipment has a longer useful life when sterilized with ethylene oxide instead of steam. The effective penetrability of ethylene oxide makes it possible to sterilize parenteral administration sets, hypodermic needles, plastic syringes, and numerous other related materials enclosed in distribution packages of paperboard or plastic.

Although the cycle time for sterilization with ethylene oxide is quite long and certain problems contributing to sterilization failures have yet to be elucidated, this method of sterilization has made it possible to sterilize many materials that would be virtually impossible to sterilize with other known methods.

Beta-propiolactone. Beta-propiolactone ($[CH_2]_2OCO$) is a cyclic lactone and is a nonflammable liquid at room temperature. It has a low vapor pressure, but since it is bactericidal against a wide variety of microorganisms at relatively low concentrations, no difficulty is experienced in obtaining bactericidal concentrations of the vapor. It is an alkylating agent and therefore has a mode of action against microorganisms similar to that of ethylene oxide. Studies have indicated that vapor concentrations of approximately 2 to 4 mg per liter of space are effective at a temperature not below 24°C (75°F) and a relative humidity of at least 70%, with an exposure period of at least 2 hours.[27]

The penetrability of beta-propiolactone vapor has been found to be poor. Therefore, its principal use appears to be the sterilization of surfaces in large spaces, such as entire rooms.

Surface Disinfection

The use of chemical disinfectants in the pharmaceutical industry is designed primarily to reduce the microbial population so that asepsis can be maintained in a limited, controlled environment. Most disinfectants do not destroy spores during any reasonable contact period; therefore, they do not sterilize a surface. However, as adjuncts to thorough cleaning of surfaces, disinfectants properly used may be expected to provide an aseptic condition of the surfaces involved.

The effectiveness of a disinfectant depends on the nature of the surface, the nature and degree of contamination, and the microbicidal activity of the agent employed. Hard smooth surfaces are much easier to disinfect than rough porous ones. Since most disinfectants are not effective against spores, only vegetative forms of microorganisms can be expected to be killed. The effectiveness of the agent will depend on the number of organisms present and their sensitivity to the agent. Therefore, it is essential to select an agent that has been proven effective against the common contaminants.