INDUSTRIAL PROCESSING AND BASIC PRINCIPLES INCLUDING CRYSTALLIZATION AND LYOPHILIZATION

[1]Yashoda Mariappa Hegde, [2]Rajesh Kumar N, [1]Geetha Srinivas

[1] Research Scholar, Department of Pharmaceutics, Swamy Vivekanandha College of Pharmacy,Elayampalayam, Namakkal, Tamilnadu 637205, India

[2] Associate Professor, Department of Pharmaceutics, Senghundhar College of Pharmacy, Tiruchengode, Namakkal, Tamilnadu 637205, India

Correspondance:

Ms. Yashoda Mariappa Hegde,

Research Scholar,

Department of Pharmaceutics,

Swamy Vivekanandha College of Pharmacy,

Elayampalayam, Namakkal, Tamilnadu 637205, India

Mobile: +91 6382805079

E-mail: yashoda276h@gmail.com

INDUSTRIAL PROCESSING AND BASIC PRINCIPLES

Pharmaceutical engineering is the study of industrial processes that transform or separates raw material into pharmaceutically acceptable products like drugs and excipients. The study of chemical engineering concepts with a focus on pharmacy is known as pharmaceutical engineering. The goal is to provide a chemical engineering methodology for processing pharmaceuticals and manufacturing bulk drugs. Following are a few examples of pharmaceutical engineering applications:

1. **Production of dosage forms:** Conversion of drugs into dosage forms which are suitable for use by the patients. For example, Conversion of Diclofenac sodium into tablets, capsule, gel, solution.
2. **Production of bulk drugs:** Chemicals are converted into drugs. For example, Salicylic acid is acetylated to obtain acetylsalicylic acid (aspirin).
3. **Production of antibiotics:** Involves fermentation technology i.e., manufacturing of drugs using microbes with the aid of precursors. For example, Penicillin G is produced using *Penicillium Chrysogenum* along with aid of precursor phenyl acetic acid.
4. **Production of biologicals:** Extraction of drugs from animal, plants, minerals and native raw materials into purified products. Examples are Vaccines, DNA recombinant technology product, and insulin.

UNIT OPERATIONS AND UNIT PROCESSES

Unit operations

The small numbers of distinct individual phases that make up a physical or chemical process are sometimes referred to as unit operations, and each step is part of the process. Every unit operation adheres to a certain scientific principle. Several unit operations and their underlying concepts include:

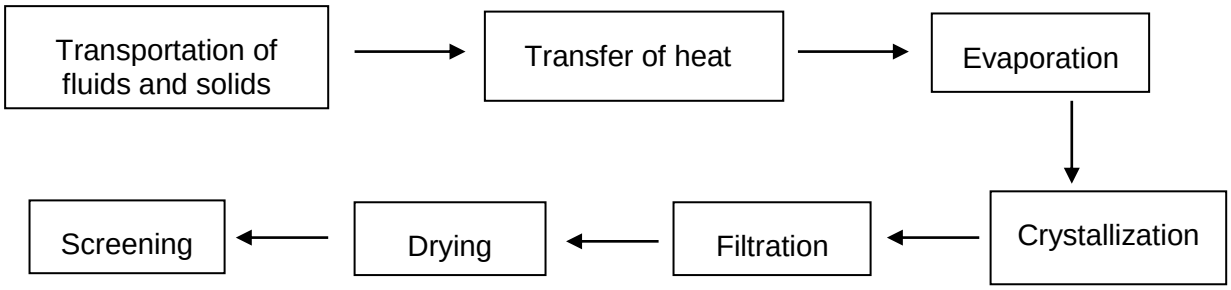
- *Drying:* It is a unit operation to remove liquid or moisture from solids by evaporation with the aid of heat. Example is removal of excess moisture from the wet granules for production of tablets

- *Filtration:* It is a unit operation in which solid particles in a liquid or gaseous fluid is removed by the use of a filter medium that permits the fluid to pass through but retains the solid particles.
- *Size reduction:* this is the unit operation in which drugs are reduced to smaller pieces or coarse particles or fine powder.
- *Distillation:* This unit operation involves conversion of liquid into vapour by heating and reconverting vapour again into liquid by condensing the vapour. Example is extraction of eucalyptus oil from its leaves by distillation.
- *Size separation:* It is a unit operation that involves the separation of a mixture of various size particles into two or more portions by means of screening surfaces. Size separation is also known as sieving, sifting, screening.
- *Evaporation:* It involves a process by which liquid water goes directly into the vapour phase due to an increase in temperature *but is usually restricted to the* concentration of solutions by boiling.

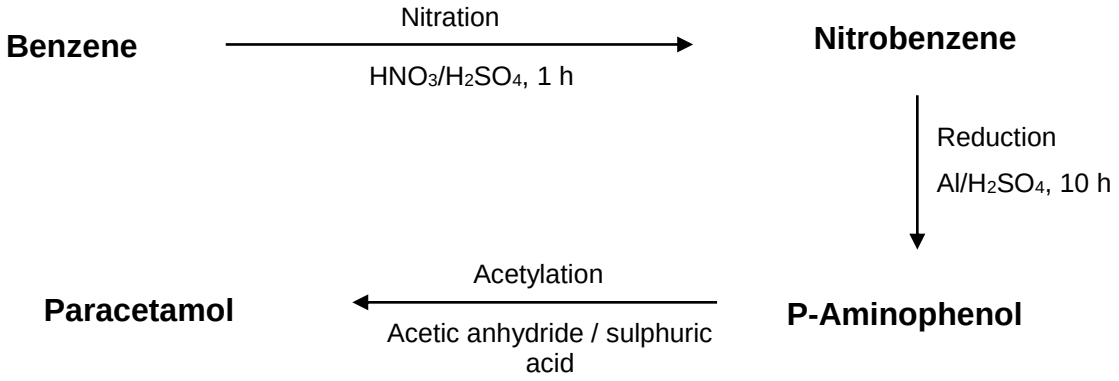
Unit process

Unit process is defined as the one in which several unit operations are combined in a sequence to achieve the objectives of a chemical or physical process.

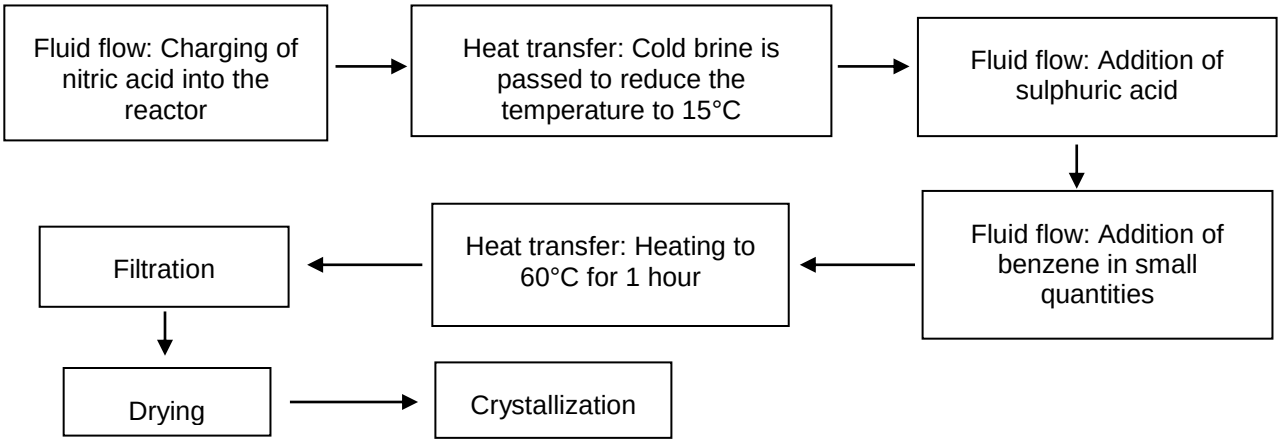
Unit process – Physical process: For example, consider the manufacture of common salt



Unit process – Chemical process: Consider the sequence of reactions for the production of paracetamol from benzene.



In the above process, three unit processes are involved: nitration, reduction and acetylation. Each unit process in turn contains number of unit operations. For example, in the nitration of benzene to nitrobenzene, the unit operations involved are:



These examples illustrate that unit operations are largely used to conduct the physical steps such as:

1. Preparation of reactants
2. Separation and purification of products
3. Recycling of the unconverted reactants
4. Controlling of the energy transfer into or out of the chemical reactor

Thus, several steps are carried in a sequential order to achieve a process efficiently and economically. Here in this chapter, we will such in detail about two critical process namely, crystallization and lyophilization which is widely applicable in industrial processing of pharmaceuticals.

CRYSTALLIZATION

CRYSTALS

A crystal is a solid particle that is formed during the solidification process and has its structural components organised in a rigid geometric pattern, often known as a lattice. The liquid state is a typical source of crystal formation. For example, salt from a brine solution.

CRYSTALLIZATION

The spontaneous arrangement of the particles into a repetitive; orderly array, or predictable geometric patterns, is known as crystallization.

Crystallization is a chemical process that converts a solute from a liquid solution to a pure solid through mass transfer. Heating the solution in an open container causes the solvent to evaporate, leaving the solution completely saturated. If the saturated solution is allowed to cool, the solution will separate from the solution, and crystals will begin to form.

Drugs are most typically used in the solid state (powder forms) in the following dosage forms:

1. Bulk powders for internal use, examples are fine powders and granules.
2. Bulk powders for external use, examples are snuffs: dustingpowders and tooth powders.
3. Simple and compound- powders for internal use.
4. Powders in the form of compressed tablets and tablet triturates.
5. Powders enclosed in cachets and capsules.

OBJECTIVES AND APPLICATIONS

The use of drugs in the solid state has several advantages.

- **Purification of drugs**: Crystallization is used as a purification process. It is used for removing impurities from pharmaceutical products, i.e., recrystallization technique.

- **Better processing characteristics:** Crystallization technique is used to change the micromeritics of drugs such as compressibility and wettability.
- **Ease of handling:** Crystallization facilitates various operations suchas transportation and storage.
- **Better chemical stability:** Crystallization increases the stability of drugs. For example, amorphous penicillin G is less stable than crystalline salt. Amitriptyline is more stable in crystalline form than in amorphous form.
- **Improved physical stability:** Crystalline form play important role in product properties such as suspension stability and hardness of a tablet. Using dehydrating materials such as dehydrated alcohol and glycerol, the stability of hygroscopic substances can be enhanced.
- **Improved- bioavailability:** Some drugs are more effective in their crystalline form. For example, penicillin G does not dissolve immediately in the gastric fluids. Therefore, its degradation decreases. Hence, bioavailability of penicillin G enhances.
- **Sustained release:** Drug substances with different sizes of crystals can be used in the production of sustained release dosage forms. For example, protamine zinc insulin in crystalline form slowly and continuously releases insulin from the site of injection for prolonged periods.
- **Miscellaneous:** Certain crystals are used in the production of semiconductor devices, laser beams and artificial gems.

THEORY OF CRYSTALLIZATION

The formation of crystal from solution involves three steps

A. Supersaturation
B. Nucleus formation
C. Crystal growth

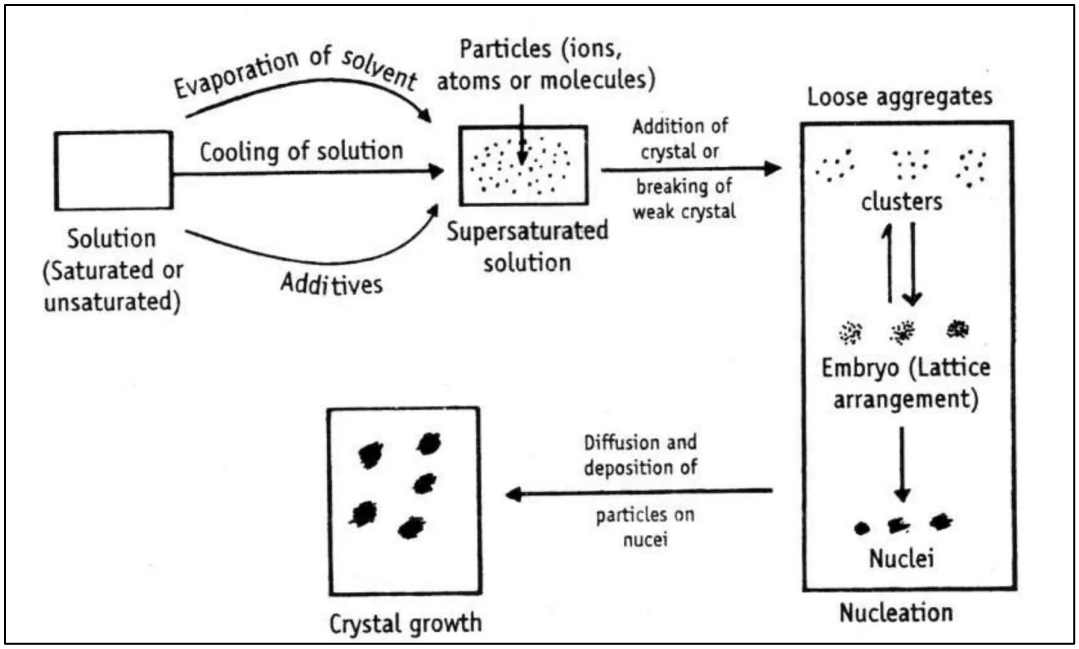


Figure 1. Mechanism of Crystallization

(A) Supersaturation: A substance may precipitate or crystallise when its solubility in a solvent exceeds its saturation solubility, which causes the solution to become supersaturated. Supersaturation may be attained by using:

(1) Evaporation of solvent from the solution.

(2) Cooling of the solution, if the solute has a positive heat of solution.

(3) Formation of a new solute as a result of chemical reaction.

(4) Addition of a substance which is more soluble in solvent than the solid to be crystallized.

Significant supersaturation is required to start the crystallisation process through the production of nuclei in the absence of seed crystals. The nucleation and growth of nuclei are two sequential, mostly distinct processes that determine the rate of separation, particle size, homogeneity, and dispersion.

(B) Nucleation: The formation of microscopic new phase entities inside a homogeneous supersaturated liquid phase is referred to as "nucleation". Rapid variations at the molecular level result in nucleation when molecules, ions, or atoms are randomly moving in any microscopic volume.

Numerous molecules, ions, or atoms initially unite together to create clusters. These are just loose aggregates, and they often disappear immediately. However, when the numbers of particles assemble to form an embryo, the lattice structure begins to take shape and a new solid phase develops. Embryos frequently have a short lifespan and disintegrate soon after formation. An embryo could be in thermodynamic equilibrium with the solution when it reaches a particular size.

The initially formed crystals are of molecular size, which are termed as *nuclei.* On certain occasions, the nuclei grow in dimensions that are limited by the amount of material available and thus form crystals.

(C) Crystal growth: Crystal growth is a surface phenomena and diffusion process. Diffusion is the process by which solute ions or molecules move from solution to the faces of a crystal. The crystal must accept the molecules or ions when they reach the surface and organise them into the space lattice. This event occurs at the surface at a finite rate; unless the solution is supersaturated, neither the interfacial step nor diffusion will take place.

Mier's Supersaturation Theory

Mier's theory of supersaturation postulates a definite relationship between concentration and temperature at which crystals will spontaneously form in an initially unseeded solution. According to it, the supersolubility curve represents the limit at which, nucleus· formation begins spontaneously and consequently the point where crystallization can start in the absence of any solid particle.

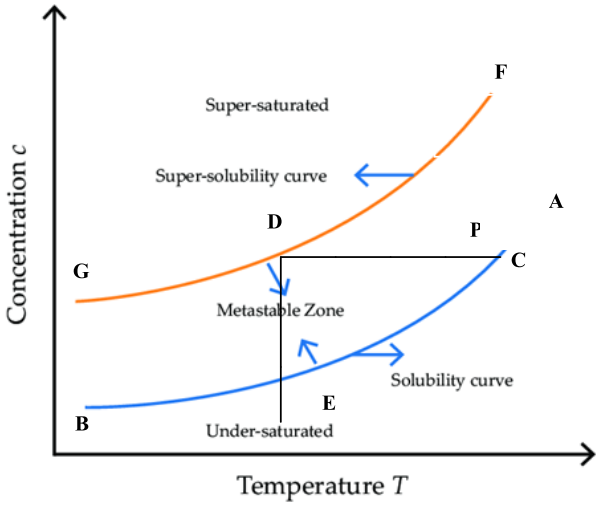


Figure 2. Mier's Supersaturation Theory

Conditions for obeying Mier's theory:

1. The solute and the solvent must be pure.
2. The solution must be free from solid solute particles.
3. The solution must be free from foreign solid matter.
4. The solution must be protected from entry of any particle.
5. Soft or weak crystals must not form during the process.
6. There should not be any fluctuations in maintaining the temperature.

Limitations:

1. According to Mier's theory, crystallization start supersolubility curve. But general tendency is that crystallization takes place in an area rather than a line.
2. If the solution is kept for longer periods, nucleation starts well below the supersolubility curve.
3. If the solution is available-in large volume, nucleation starts well below the supersolubility curve. This is because formation of nuclei depends on accidental collisions of molecules of solute. These collisions are more in large volumes than in small volumes.
4. Mier's theory is applicable when pure solute and pure solvent are used. In practice, it is impossible to get them in pure state.

5. For crystallization, the solution must be stored for longer periods. During storage, millions of dust particles can enter. Nucleation can be initiated not only by solute molecules, but also by dust particles.

FACTORS AFFECTING CRYSTALLIZATION

Various factors affecting the crystallization process are,

- Presence of Another Substance
- Solvent Used
- Nucleation
- Crystal Growth
- Rate of Cooling

TYPES OF EQUIPMENT

AGITATED BATCH CRYSTALLIZER

Principle: The temperature of a saturated solution is reduced in an agitated batch crystallizer to make it supersaturated. The supersaturated solution is used for the formation of crystals. Crystals of a consistent size are easier to produce when the solution is agitated.

Construction: It is made out of a cylinder with a conical bottom. The motor helps a propeller that is fixed in the centre to revolve on its own axis. Pipes constructed of heat-conducting material runs traverse from the crystallizer's right bottom to its left top.

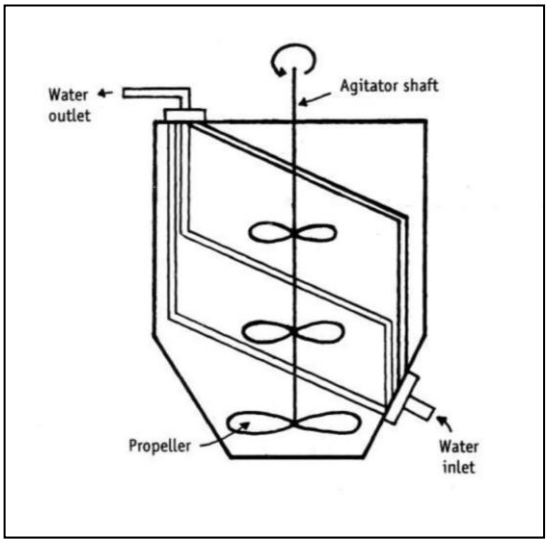


Figure 3. Construction of an agitated batch crystallizer

Working: The crystallizer is filled with the solution that will undergo crystallization. Continuously, cold water is pumped via the pipes. When a solution cools, it supersaturates and crystals start to form. It serves two roles to let the propeller to revolve. Firstly, it speeds up heat transfer, which aids in keeping the solution's temperature nearly constant. Secondly, it helps fine crystals develop consistently by maintaining them in suspension. Otherwise, large crystals or aggregates may develop. By using an appropriate mechanism, the crystals are removed from the bottom for separation of mother liquor.

Advantages: In agitated crystallizer, crystals formed are more uniform and also finer compared to older crystallizer such as tank crystallizer.

Disadvantages: It is a batch or discontinuous equipment. Solubility is least at the surface of the cooling coils. Hence crystal growth is most rapid at this point and the coils rapidly build up with a mass of crystals that decreases the rate of heat transfer.

SWENSON WALKER CRYSTALLIZER

Principle: Crystallization is induced by flowing cold water in the opposite direction of the flow of heated concentrated solution. As a result, supersaturation occurs, and crystals are subsequently deposited. The collection of crystals on the cooling surface is prevented by agitation. Because the crystals are separated from the mother liquor at the same time, it may be employed as a continuous process.

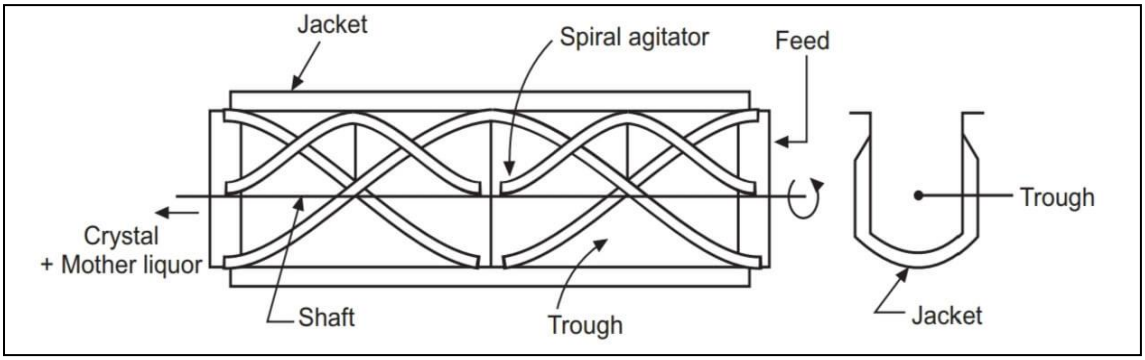


Figure 4. Construction of a Swenson Walker crystallizer

Construction: It has a long, open trough that is about 0.6 metres wide and 3 metres long with a semi-cylindrical bottom and is of the linear kind. The water-jacket is externally welded to the trough. The bottom of the trough has a long pitch spiral scrapper fastened as closely as possible. The motor helps the spiral scrapper revolve on its own axis. A maximum of four of these units are connected for better performance. The placement of many similar sets one on top of the other allows for even larger capacity. In this arrangement the solution flows from one set to its below set.

Working: The left side of the trough is supplied with the hot, concentrated solution that is needed to crystallize. Cooling water enters the jacket on the right side. As the heated solution cools, supersaturation is reached and crystal formation starts. By injecting more cooling water into the chosen areas, one may, if required, adjust the size of the crystals. The spiral scrapper revolves at an average speed of 7 revolutions per minute around its own axis. It aids in stirring the substance and moving the crystals. Additionally, by elevating the crystals, it avoids their buildup on the cooling surfaces. This results in a suspension, which allows the crystals to grow individually. Aggregation is therefore avoided.

A draining table is fastened to the crystallizer's end. While the crystals are retained, the mother liquor is sent back to the crystallizer as the crystals and mother liquor overflow into the draining table simultaneously. The wet crystals are transported to a centrifuge.

The draining table can be also replaced by a screw conveyor. The crystals are lifted from the solution by a screw conveyor with a little incline, and are then delivered to a centrifuge. Mother liquor overflows at a convenient point.

Advantages:

1. Large saving in floor space, material and labour costs can be achieved in Swenson Walker crystallizer.
2. It is a continuous process.
3. Crystals of uniform size and free from inclusions or aggregations can be obtained.

Disadvantage:

The scrapper may breakthe crystals to a little extent, while agitating the suspension.

KRYSTAL CRYSTALLIZER

Principle: In Krystal crystallizer, concentration or liquid and crystallization are obtained in different chambers namely vapour head and crystallizing chamber. A vacuum pump is used to accelerate the evaporation of a heated solvent, which results in the concentration of liquid (supersaturation). The supersaturated solution and crystals are kept fluidized in the crystallization chamber to ensure uniform crystal formation. The fine crystals and supersaturated solution are circulated for further crystallization as the crystals of the required size sink down by gravity. The crystal growth chamber is used to harvest crystals that are of the required size.

Construction: It consists· of a vapour head and crystallizing chamber. Vapour head consists of a long tube, which extends almost to the bottom of crystallizing chamber. Other end of vapour head is connected to condenser and vacuum pump. A pump is provided which allows the feed to enter vapour head on its way to vapour head a heater is provided.

Working: Pumped solution travels through the heater. Due to the decreased pressure, the hot solution flashes as it reaches the vapour head, causing solvent vapour and supersaturated solution to develop. The suction pump is used to remove the vapour. The process is managed such that crystals should form in the crystallizing chamber rather than the vapour head when the supersaturated solution flows through the long cube below.

A bed of crystals floating in an upward-moving stream of liquid makes up the crystallising chamber. The supersaturated liquid flows through the bed of crystals, which are kept fluidized. Thus, a consistent temperature is achieved. There is a continuous gradation of crystals in the chamber. Fine crystals remain above the coarser ones whereas coarse crystals settle towards the bottom. Occasionally, coarse crystals are removed via the hole at the bottom of the chamber as very fine crystals overflow through the liquid and into the recirculating system where they mix with fresh feed.

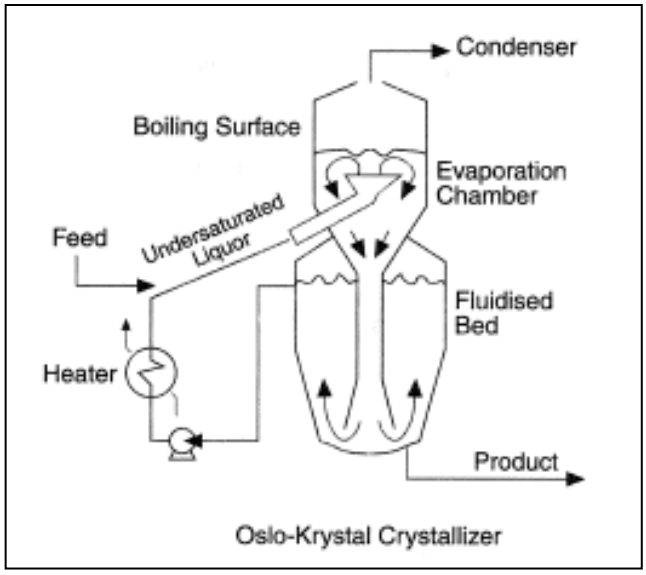


Figure 5. Construction of a Krystal crystallizer

Uses: Krystal crystallizer is used for crystallisation of sodium chloride and magnesium sulphate.

Advantages:

1. Krystal crystallizer is preferred when large quantities of crystals of controlled sizes are required.
2. This crystallizer is available in very large sizes with a body upto 4.5 metres diameter and 6.0 metres height.

VACUUM CRYSTALLIZER

Principle: Supersaturation in vacuum crystallizers is achieved by adiabatic evaporative cooling. Due to the high vacuum in the crystallizer, heated saturated solution flashes when it is added. As a portion of the solvent evaporates, the solution cools and crystals get formed as a result of supersaturation.

Construction: The cylindrical body of a vacuum crystallizer has a conical bottom. The body of the crystallizer can be coated internally with an acid-resistant material such as lead or rubber. A condenser is connected to the crystallizer through a vacuum pump, and the bottom of the crystallizer is connected to a discharge pipe. To

avoid a short circuit of the feed (to the discharge pipe), two propellers are positioned above the pipe.

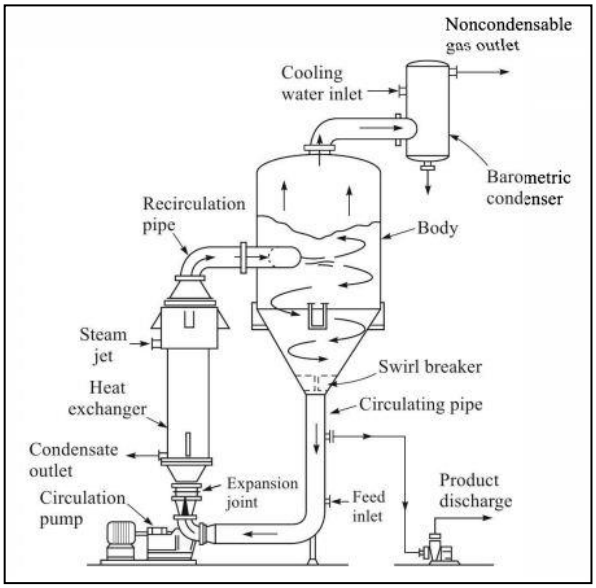


Figure 6. Construction of a vacuum crystallizer

Working: A vacuum pump is used to produce a high vacuum. The vacuum that results from this must be lower than the feed temperature and correspond to the solution's boiling point. Hot saturated solution is fed into the crystallizer at a convenient point solution undergoes flashing which results in evaporation of solvent. The crystallizer body undergoes cooling as a result of the adiabatic nature of this operation. Crystallization and supersaturation are the results of the subsequent cooling. The yield is improved by the solvent evaporation. When the crystallizer flashes the solution, it causes ebullition, which keeps the crystals suspended until they are big enough to fall down the discharge pipe. The contents are fully mixed by the propellers, which also stop the contents from flashing as they reach the discharge pipe.

Uses: Vacuum crystallizer is suitable for thermoliable substances, due to low temperature conditions.

Advantages:

1. Vacuum crystallizer is very simple without any moving parts.

2. Corrosive materials can be used as inner surface can be made acid resistant.
3. It can be constructed as large size as desired.
4. It can be operated either batch wise or continuously.

CAKING OF CRYSTALS

Caking can be defined as the process of formation of clumps or cakes when crystals are improperly stored.

Crystals must be preserved in bulk once they have crystallised in order to be used later, transported, or utilised to formulate dosage forms. The crystals must maintain acceptable flow characteristics while being stored, for instance, being able to readily move from the hopper to the die in the case of tablet punching. Crystals may have a tendency to form a cake while in storage. This problem becomes more serious in the case of small packages than in bulk packages. In certain situations, the crystals can be easily broken by the simple pressure of a thumb.

Critical humidity is the humidity above which crystals absorb moisture and below which they do not absorb moisture.

A crystal remains dry when it comes into touch with air that has a humidity level below the critical humidity. On the other hand, the crystal collects moisture if the air is moister than the critical humidity level.

FACTORS AFFECTING CAKING

- Size of the crystals
- Shape of the crystals
- Humidity
- Time of exposure to humidity
- Impurities in crystals
- Melting point of crystals
- Temperature fluctuations

PREVENTION OF CAKING

1. Crystals must be more spherical in shape, with the least points of contact.
2. Crystals must be larger in size with more voids and must be of anarrow size distribution. Crystals must have highest possible critical humidity.
3. Crystals must be coated with powdery inert material to prevent absorption of moisture. For example, table salt is coated with magnesia or tricalcium phosphate. Similarly, flake calcium chloride is coated with anhydrous calcium chloride.

LYOPHILIZATION

Lyophilization or Freeze drying is the removal of ice or other frozen solvents from a material through the process of sublimation and the removal of bound water molecules through the process of desorption. The equipment used to dry solutions or suspensions at or below freezing points of liquids is called a freeze dryer or lyophilizer.

Lyophilization and freeze drying are terms that are used interchangeably depending on the industry and location where the drying is taking place.

PRINCIPLE OF FREEZE DRYER

The principle involved in freeze-drying is sublimation, where water passes directly from solid-state (ice) to the vapour state without passing through the liquid state. Low pressures are necessary for sublimation to occur, which is a phase shift that requires the addition of thermal energy to the frozen product, as seen below on the water phase diagram.

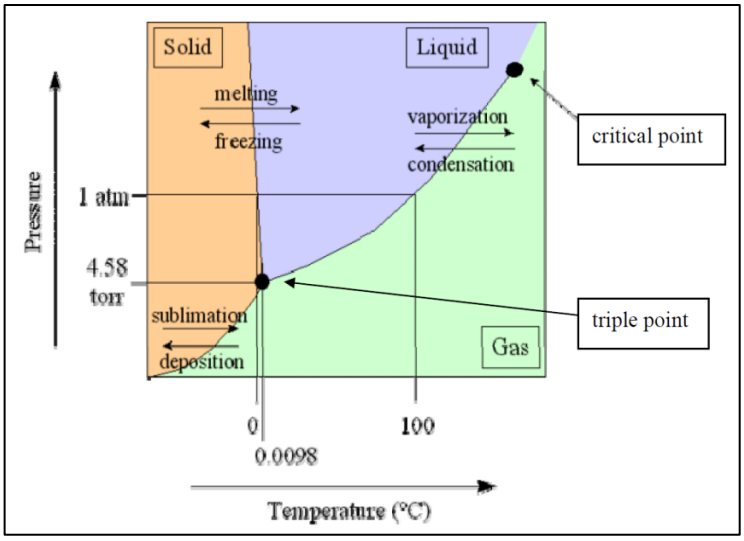


Figure 7. Phase diagram of water

The triple point of water (the temperature and pressure at which a substance may exist in equilibrium in the liquid, solid, and gaseous states) is below which water can sublimate. At 0.01°C and 4.58 mm Hg, pure water reaches its triple point. Any heat that is delivered under these circumstances is utilised as latent heat, causing ice to instantly turn into vapour. Condensation in a cold trap kept at a temperature lower than the frozen substance removes the water vapour from the system.

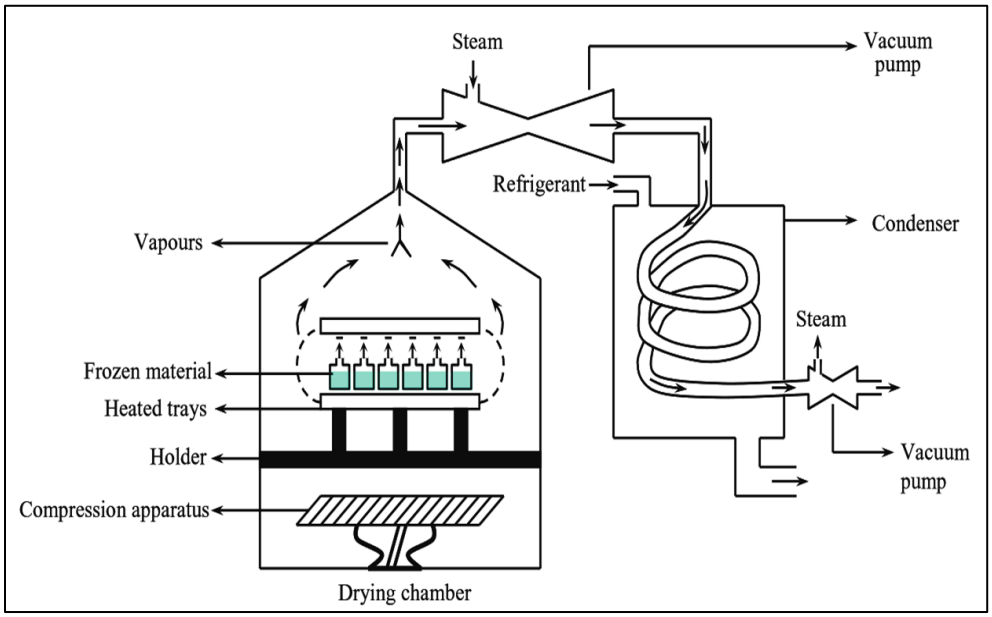


Figure 8. Diagram of Freeze Dryer

CONSTRUCTION OF FREEZE DRYER

Generally, there are three types of freeze dryers, for example, manifold freeze-dryer, rotary freeze dryer and tray-style freeze-dryer.These freeze-dryers differ in the method by which the dried substance is interfaced with a condenser.

The components common to all of them are a vacuum pump to reduce the ambient gas pressure and a condenser to remove the moisture by condensation on a surface cooled to -20 to -80 °C.

1. *Drying chamber*- It is made of stainless steel which has a conical top and a flat bottom. Thermally heated trays are installed horizontally in the centre with the help of a holder. The compression apparatus is placed at the bottom (to carry out the mechanism of compression). A door is attached for the entry and removal of materials from the chamber. A vacuum pipe is connected to the chamber by means of an opening present at the conical top of the chamber.
2. *Vacuum pump*- it is present in between the drying chamber and the condenser and is provided with an inlet for the steam jet.
3. *Condenser*- internally it consists of a coiled pipe surrounded by a mixture of acetone and dry ice (solid CO_2), in order to maintain the temperature lower than the frozen material. Both the ends of condenser are connected by the vacuum pump. Distance between the drying chamber and the condenser must be in such a way that it equals the mean free path travelled by the vapour molecules. This increases the rate of drying.

Figure 9. Freeze dried products

IMPORTANT FREEZE DRYING TERMS

1. **Critical Temperature-** During freeze drying, the maximum temperature of the product before its quality degrades by melt-back or collapse. Thermal analysis **(Differential Scanning Calorimetry** & **Freeze Dry Microscopy**) and Dielectric Resistance analysis and are common methods used to determine this critical temperature of the product.
2. **Collapse temperature (Tc)-** This is the temperature at which the material softens to the point of not being able to support its own structure.This can be a problem for many reasons:
    - Loss of physical structure
    - Incomplete drying
    - Decreased solubility
    - Lots of ablation (splat)
3. **Eutectic temperature (Teu)-** This is the temperature at which the solute material melts, preventing any structure forming after the solvent has been removed.
4. **Glass transition (Tg')-** The temperature of the frozen material changes from a brittle to flexible structure.
5. **Annealing-** Some amorphous products (such as mannitol or glycine) form a metastable glass with incomplete crystallization when first frozen. These products can benefit from a thermal treatment process, which is also called

annealing. During annealing, the product temperature is cycled (for example: from -40℃ to -20℃ for a few hours and then back to -40℃) to obtain more complete crystallization. Annealing has the added advantage of larger crystal growth and corresponding shorter drying times.

6. **Crystalline-** The material forms crystals when frozen; has a eutectic point or multiple eutectic points. Fast freezing creates small crystals which are hard to dry; annealing can help form bigger crystals.
7. **Amorphous-** Multi-component mixtures which do not crystallize and do not have a eutectic point. They turn into a ‘glass." Freeze drying needs to be performed below the glass transition temperature.

Frozen products can be categorized as either crystalline or amorphous glass in structure. Crystalline products have a well defined “eutectic” freezing/melting point that is its collapse temperature. Amorphous products have a corresponding “glass transition” temperature and they are much more difficult to freeze dry. The collapse temperature of amorphous products is typically a few degrees warmer than its glass transition temperature. Although most materials that are freeze dried are actually amorphous, the term “eutectic” is often used (erroneously) to describe the freezing/melting point any product.

Figure 10. Collapsed Product – Critical Temperature was exceeded

STEPS INVOLVED IN LYOPHILIZATION PROCESS

The steps required to lyophilize a product in a batch process can be summarized as follows:

- Pretreatment / Formulation
- Freezing (Thermal Treatment) at atmospheric pressure
- Primary Drying (Sublimation) under vacuum
- Secondary Drying (Desorption) under vacuum
- Backfill & Stoppering (for product in vials) under partial vacuum
- Removal and Reconstitution of Freeze dried Product

1. PRETREATMENT

It includes any method of treatment of the product before freezing. Pretreatment methods include freezing concentration, solution-phase concentration, formulation to preserve the appearance of the product, formulation to stabilize reactive products, formulation to increase the surface area, and decreasing high vapor pressure solvent. In many instances, the decision to pre-treat a product is based on the theoretical knowledge of Freeze Drying and its requirements, determined by the cycle time or product quality considerations.

2. FREEZING

Freezing, also called Pre-freezing, is when the sample is frozen to a temperature below its “eutectic point” or safe freezing point. This is typically in the range of -40 to -60°C, whereas certain applications can go as low as -60° to -80°C. During pre-freezing, the freeze dryer works as a freezer in that no vacuum is applied. Pre-freezing could also be done separately from the dryer.

To freeze a product properly, thermal analysis can be used to help better understand its properties. Thermal analysis to detect the eutectic point can be done in several ways, but none of them are 100% effective.

- Time Versus Temperature Curve

- Differential Scanning Calorimetry
- Cryo Microscopy

Below are some collapse temperatures of typically freeze-dried products and solutions:

- Dextran (-9°C)
- Lactose (-32°C)
- Maltose (-32°C)
- Sorbitol (-45°C)

The ideal rate of freezing must be established when the product's freezing point (eutectic point) has been established. The size of the crystals is determined by the freezing rate. It is essential to keep in mind that the bigger crystalline structure produced by a slow freeze rate will result in a more porous and quickly dried product when the frozen liquid ultimately sublimates out of the product. Normally, this is helpful for optimizing freeze drying cycles, but it might not produce the optimal product in terms of reconstitution (rehydration).

On the other hand, a substance that freezes quickly will become inactive more quickly, have a smaller crystalline structure, and be more granulated, making it easier to reconstitute, even if it takes longer to freeze dry. A general rule of thumb is that the product container should never be filled to more than half of its total content when freezing items in vials. Some biological products must be freeze dried with lower ice crystal sizes because they cannot tolerate huge ice crystals.

3. PRIMARY DRYING

During the primary drying phase, which can last as little as 0.01 hPa (mBar) or less depending on the sample's pre-freezing temperature, the ice sublimates (converts instantly into vapour). Vacuum levels for freeze drying typically vary from 50 to 300 Torr, with 100 to 200 Torr being the most popular range. The pressure differential between the product ice surface and the condenser ice surface, together with the accompanying temperature difference, is what drives sublimation. When freeze drying a product, all

three types of heat transfer—conduction, convection, and radiation must be taken into account.

Larger temperature variations also result in larger pressure differences, which speed up the process. The removal of air molecules by the vacuum quickens the process by facilitating easier passage of sample vapour molecules from the sample through the chamber and into the condenser. During primary drying, the shelf temperatures typically ramp up from -40 to +20°C throughout the course of the operation, which can last anywhere from a few hours to several days. The shelf temperatures indirectly influence the ice temperature of the sample by conducting heat (contact to the shelf) as well as the radiating of heat from the shelf above. Very little heating occurs through convection in the chamber since there are so few air molecules there. Small sensors placed within the vials measures the sample temperature(s) and record changes.

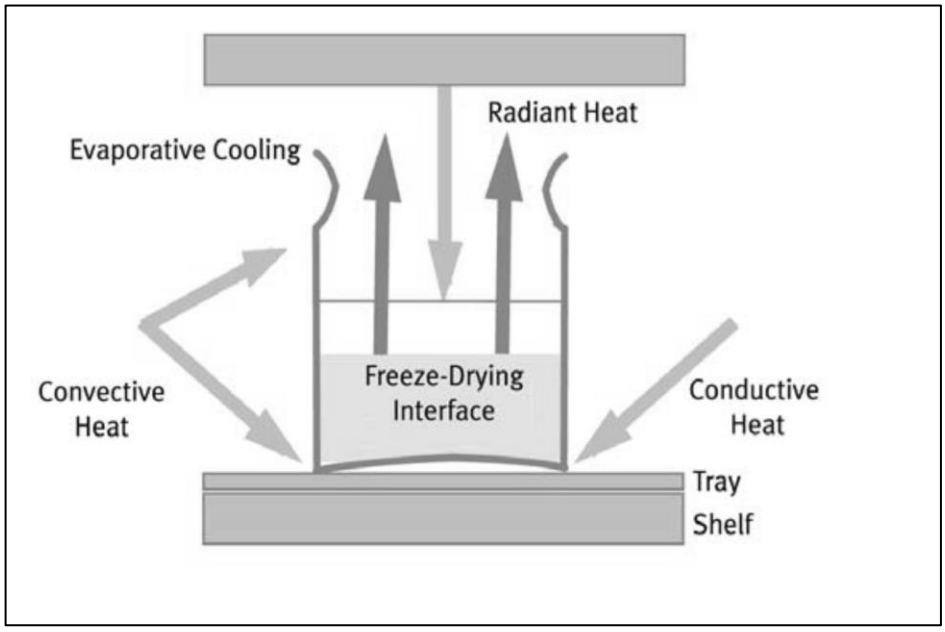


Figure 11. Heat Transfer in a Shelf Freeze Dryer

In order for a freeze dryer to be effective, the temperature of the condenser must be lower than the temperature of the product. This difference in temperature creates a pressure differential and the net migration of water vapor towards the condenser.

Determination of the End of Primary Drying

The status of primary drying may be assessed analytically using a variety of techniques. Monitoring the product temperature with a thermocouple probe is the most fundamental technique. During active primary drying, when the heat from the shelf is being used for the sublimation phase transition, the measured product temperature will be lower than the shelf temperature set point. The product temperature will rise and get close to the shelf temperature after ice crystal sublimation is finished. The conclusion that primary drying is finished can be drawn when the product temperature reaches the shelf temperature.

The comparison of parallel pressure measurements between a Pirani gauge and a capacitance manometer is one such technique. An accurate pressure reading in the product chamber is always provided by a capacitance manometer. The presence of water vapour will, however, because the Pirani gauge to display a falsely high value. Little to no water vapour is present when the Pirani pressure measurement falls and becomes close to the capacitance manometer's genuine pressure reading, and it may be said that primary drying has finished at that point.

Another tool is available with freeze dryer designs that have external condensers. An isolation valve can be added to the vapor port that connects the product chamber to the condenser. This valve can be closed for a short period of time and the subsequent rise in pressure in the product chamber can be measured. When this pressure rise approaches zero, no more water vapor is being generated via sublimation.

4. SECONDARY DRYING

In addition to the free ice that is sublimed during primary drying, there remains a substantial amount of water molecules that are bound to the product. This is the water that is removed (desorbed) during secondary drying. Since all the free ice has been removed in primary drying, the product temperature can now be increased considerably without fear of melting or collapse.

Secondary drying actually starts during the primary phase, but at elevated temperatures (typically in the 30ºC to 50ºC range), desorption proceeds much more

quickly. Secondary drying rates are dependant on the product temperature. System vacuum may be continued at the same level used during primary drying; lower vacuum levels will not improve secondary drying times.

Amorphous products may require that the temperature increase from primary to secondary drying be controlled at a slow ramp rate to avoid collapse.

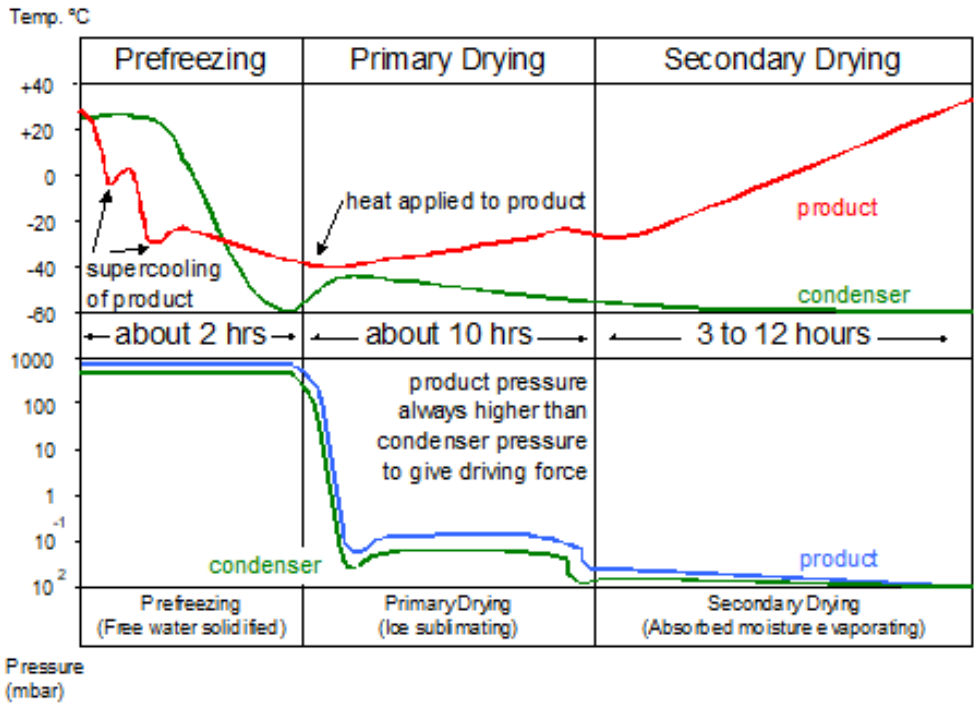


Figure 12. Overview of Lyophilization process

5. STOPPERING AND STORAGE OF DRIED PRODUCT

Lyophilized products are extremely hydroscopic and they must be sealed in air tight containers following freeze drying to prevent rehydration from atmospheric exposure. Both water and air are damaging to a dried sample, causing degradative changes resulting in poor stability and it is therefore prudent to stopper samples within the freeze-dryer prior to removal.

Freeze dryers can be configured with a “stoppering” capability to seal the product while it is still under partial vacuum inside the unit. Typically, stoppering is done on vials with partially inserted stoppers. The shelves are collapsed so that each

shelf pushes down the vials/stoppers located on the adjacent shelf. It is also common to backfill with an inert gas such as dry nitrogen before sealing/stoppering the product.

6. RECONSTITUTING THE PRODUCT

It is often supposed that because freeze-drying only removes water, then all products will be fully active by rehydrating only with water. This may not be the case and freeze-dried products often exhibit enhanced activity when reconstituted in an isotonic medium, such as saline, rather than water.

PROBLEMS TO AVOID DURING FREEZE DRYING

- Heating the product too high in temperature can cause melt-back or product collapse
- Condenser overload caused by too much vapor hitting the condenser.
  - Too much vapor creation
  - Too much surface area
  - Too small a condenser area
  - Insufficient refrigeration
- Vapor choking – the vapor is produced at a rate faster than it can get through the vapor port, the port between the product chamber and the condenser, creating an increase in chamber pressure.

ADVANTAGES OF FREEZE DRYER

1) This is suitable for drying heat sensitive (thermolabile) products.
2) Freeze dried product is porous and easy to be rehydrated and instantly dissolved.
3) Drying takes place at very low temperature, so that enzyme action is inhibited and chemical decomposition, particularly hydrolysis is minimized.
4) Denaturation of protein does not occur.
5) Loss of volatile materials is less.
6) Sterility can be maintained.
7) Moisture level can be kept as low as possible without decomposition.

8) The final product can be stored at ambient temperature if well sealed by providing inert atmosphere.

DISADVANTAGES OF FREEZE DRYER

1) The process is very slow.
2) Expensive process.
3) The period of drying is high.
4) The product is prone to oxidation due to high porosity and large surface, hence it must be packed with vaccum or inert gas.

APPLICATIONS OF FREEZE DRYER

- Freeze-drying is used to increase the shelf life of thermolabile products, such as vaccines, blood plasma and products, bacterial and viral cultures, human tissues, antibiotics, steroids, vitamins and other injectables.
- It is used to enhance stability of products during storage, shipping, and transportation.
- Freeze-drying is used to reduce weight of products.
- It is used to preserve blood products in freeze-dried form.
- It is used in chemical synthesis to make products more stable and easier to dissolve in water.
- Freeze-drying can effectively be used in bio-separations in purification procedures.
- It can be used to concentrate low molecular weight substances that are too small to be removed by a membrane filtration.

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