INDUSTRIAL PROCESSING AND BASIC PRINCIPLES INCLUDING CRYSTALLIZATION AND LYOPHILIZATION

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INDUSTRIAL PROCESSING AND BASIC PRINCIPLES

What is Pharmaceutical Engineering

It is a branch of pharmaceutical sciences and technology that involves development and manufacture of product, processes and components in pharmaceutical industry. Pharmaceutical engineering is concerned with the study of industrial processes in which raw materials are changed or separated into pharmaceutically useful products such as drugs and excipients.

Pharmaceutical engineering is also the study of chemical engineering principles with special relevance to pharmacy. The objective is to develop an approach of chemical engineering to the field of bulk drug manufacturing and pharmaceutical processing. Some of the applications of pharmaceutical engineerings are as follows:

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 acetyl salicylic 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

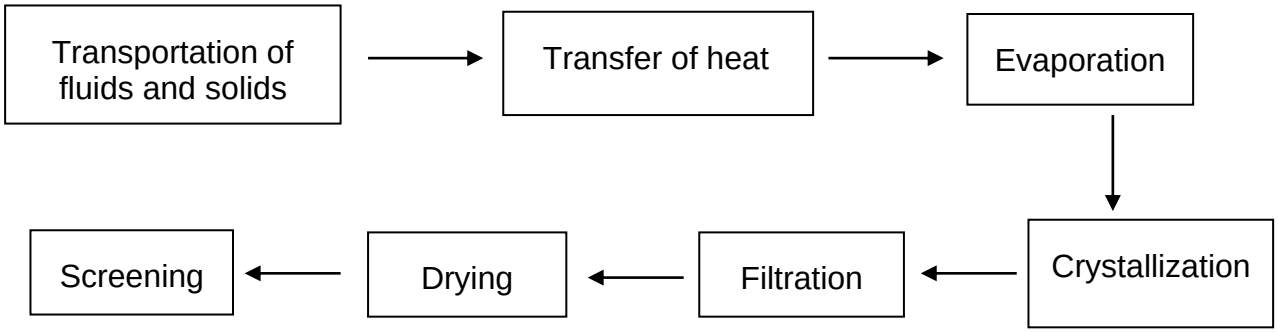
A physical or chemical process frequently consists of a fewer number of distinct individual steps and each step is called as unit operation. Each unit operation follows its own scientific principle. Some of the unit operations with their underlying principles are:

- *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.

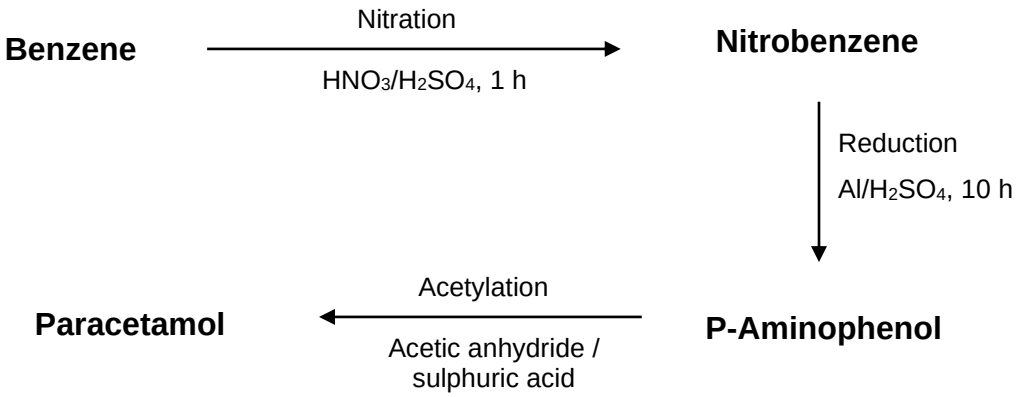
Unit process

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.

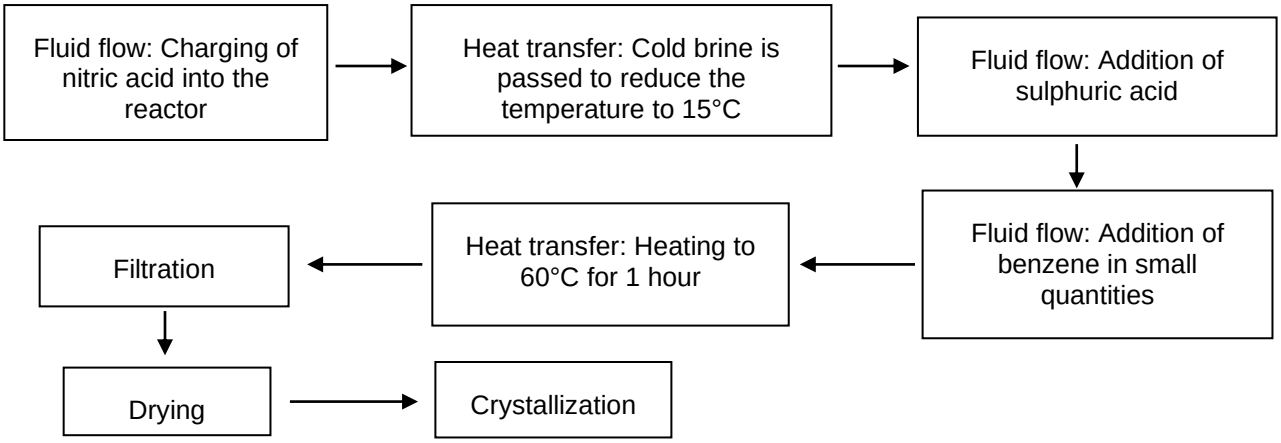
Unit process – Physical process: For example, consider the manufacture of common salt



Unit process – Chemical process: Consider the sequence of reactions for the production ofparacetamol 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 can be defined as a solid particle, which is formed by the solidification process in which structural units are arranged by a fixed geometric pattern or lattice. Crystals are commonly obtained from liquid state. Example: Salt from brine solution.

CRYSTALLIZATION

Crystallization is the spontaneous arrangement of the particles into a Repetitive; Orderly array, i.e., regular geometric patterns.

Crystallization is a chemical solid – liquid separation technique, in which mass transfer of a solute from the liquid solution to a pure solid. The solution is warmed in an open container, allowing the solvent to evaporate, leaving a saturated solution. As the saturated solution is allowed to cool, the solution will separate out of the solution and crystals will start to grow. The crystals can be collected and allowed to dry.

Crystallization differs from precipitation' in that the product is deposited from a supersaturated solution. Precipitation occurs when solutionsof materials react chemically to form a. product whichis sparingly soluble in the liquid and therefore deposits outs.

Drugs are most commonly 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: dusting powders 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.

In many occasions, drugs are supplied in the solid state even in the injection dosage forms from the point of chemical stability.

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 immediatelyin 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.

CHARACTERISTICS OF CRYSTALS

1. Crystal Lattice
2. Crystal Systems
3. Crystal Habit

1. Crystal Lattice

A crystalcan be defined as a solid particle, which is formed by the solidification (crystallization) process (under suitable environment) in which structural units are arranged by a fixed geometric pattern or lattice.

The definition of a crystal lattice is an organised internal arrangement of particles in three dimensions. A crystal's geometric arrangement of structural components is identified by the X-ray diffraction pattern. Space lattice is another name for the three-dimensional arrangement of particles in a crystal.

The units that constitute the crystal structure are ions, atoms or molecules

- Ions with opposite charges are bonded together by electrostatic attractions as in the crystals of sodium chloride.

- Atoms are bonded together by covalent bond as in diamond, and graphite.

- In most organic compounds, molecules are held together by Vander Waalsforces and hydrogen bonding. Examples are naphthalene and p-Hydroxy benzoic acid.

The smallest geometric portion which repeats to build up the whole crystal is called a *unit cell.*

A crystal is bounded by plane surfaces called *faces.*

In the crystal, the angle between the two perpendiculars to the intersecting faces is termed as the *axial angle.*

Axial length can be defined as the distance between the centres of two atoms.

If a crystal is fractured, each fragment of the crystal also possesses plane surfaces with characteristic axial angles of the original crystal.

Certain properties of crystals such as refractive index depend upon the direction in the crystal along which the determinationsare made.

2. Crystal Systems or Forms

A finite number of symmetrical arrangements are possible for a crystal lattice and these may be termed as crystal forms or crystal systems.

Depending upon the axial length and axial angle, crystals formed are designated as cubic, hexagonal, tetragonal, orthorhombic, monoclinic and triclinic as shown in figure 1.

A chemical substance may exist in more than one form, i.e., polymorphism.

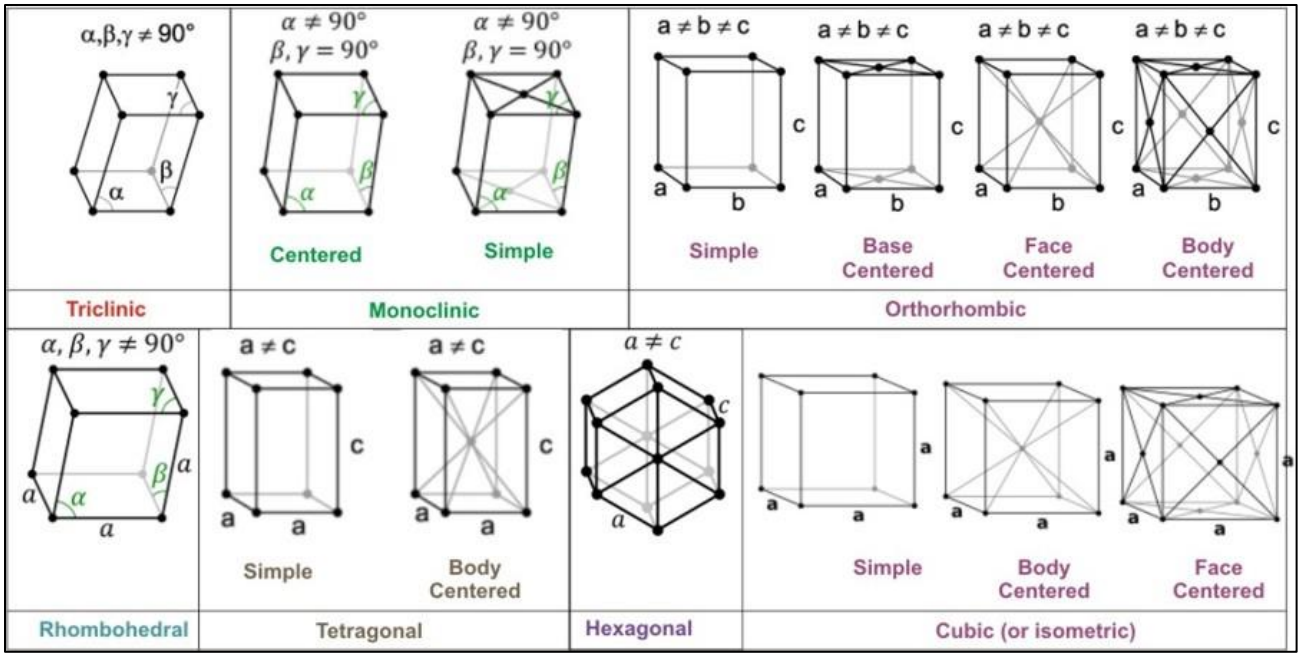


Figure 1. Different types of crystal systems

Crystal Habit

Crystal is a polyhedral solid with number of planar surfaces. A substance crystallizes in such a way that the angle between a given pair of faces is called in all specimens. It is the characteristic of particular substance irrespective of the relative sizes of the faces.

The circumstances under which crystallisation occurs have a significant impact on the size and shape of the crystals that are produced. As opposed to the same medication crystallized from benzene or chloroform, Griseofulvin has a distinct shape when it is crystallized from acetone.

Depending on how the crystals are arranged, numerous descriptions of crystal habits can be made as shown in the figure 2.

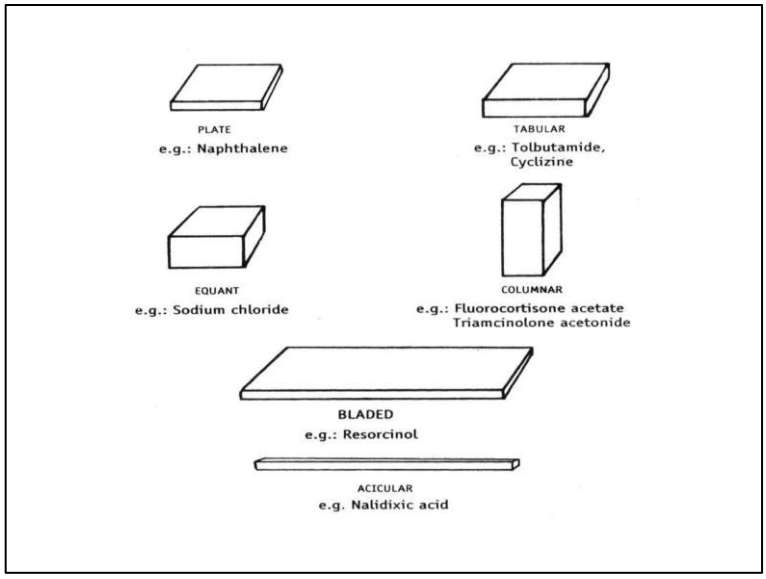


Figure 2. Different types of crystal habit

Plates: Flat, uniformly sized and shaped particles. They can alternatively be described as micaceous or lamellar.

Tabular: Similar in length and width, but with more thickness and flakes of material.

Equant: A group of particles with similar length, width, and thickness.

Columnar: Rod-shaped particles with greater width and thickness than needle-shaped ones. The word prismatic can also be used.

Blade: Long, thin, and flat particles that are also known as lath-shaped particles.

Acicular: Prisms with a needle like appearance.

THEORY OF CRYSTALLIZATION

The formation of crystal from solution involves three steps

A. Supersaturation

B. Nucleus formation

C. Crystal growth

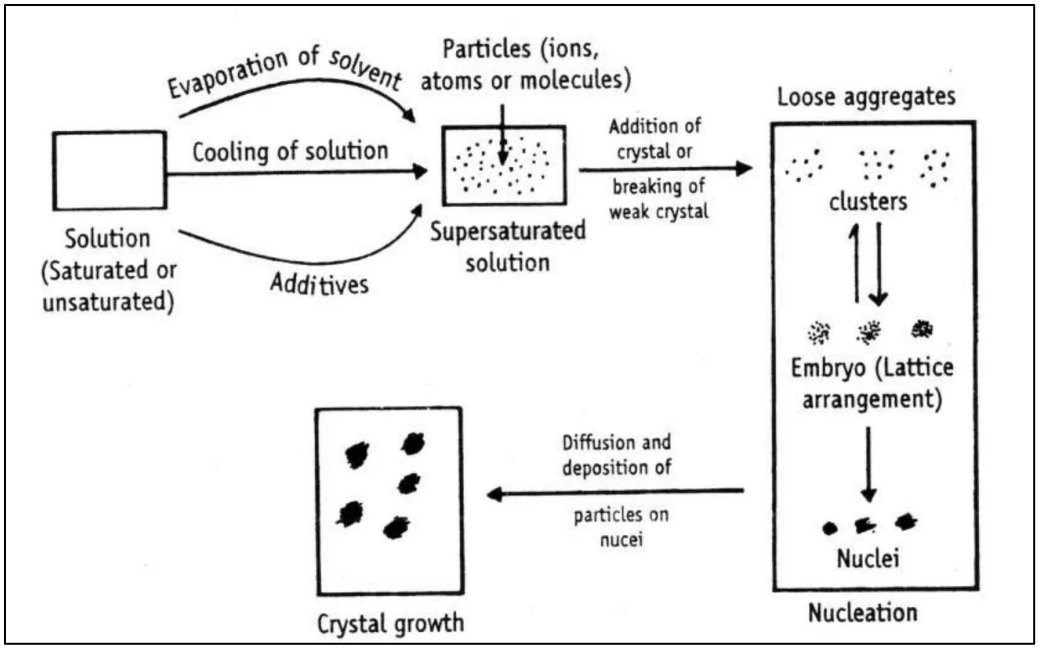


Figure 3. Mechanism of Crystallization

(A) Supersaturation: When the solubility of a compound in a solvent exceeds the saturation solubility, the solution becomes supersaturated and the compound may precipitate or crystallize. Supersaturation can be achieved through:

(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 thanthe solid to be crystallised.

In the absence of seed crystals, significant supersaturation is necessary to initiate the crystallization through the formation of nuclei. The rate of separation, particle size, uniformity and distribution depend on two successive largely independent processes namely, nucleation and growth of nuclei.

(B) Nucleation: The term "nucleation" describes the emergence of tiny new phase bodies within a homogeneous supersaturated liquid phase.

When molecules, ions, or atoms are randomly moving in any tiny volume, rapid local variations at the molecular level have the effect of causing nucleation.

Clusters are first formed by the association of numerous molecules, ions, or atoms. These are merely loose aggregates, and they normally vanish right away.

However, the lattice structure starts to take shape, and a new solid phase forms when enough particles come together to form an embryo. Embryos often have a brief existence and disintegrate right after formation. When an embryo reaches a certain size, it could be in thermodynamic equilibrium with the solution.

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.

Several methods are available for nucleation.

These are:

(1) Soft or weak crystals on impact with moving parts in a crystallizer can break into fragments which act as nuclei.

(2) Small crystals which are formed in the previous process are added to act as nuclei.

(3) In a supersaturated solution or under poor mixing, needle like structures are observed on the ends of crystals. These structures grow faster than the sides of the crystals and come out to give crystals of poor quality.

(C) Crystal growth: Crystal growth is a diffusion process and surface phenomenon. From solution, solute molecules or ions reach the faces of a crystal by diffusion. On reaching the surface, the molecules or ions must be accepted by the crystal and organized into the space lattice. This phenomenon continues at the surface at a finite rate, neither the diffusion nor the interfacial step will proceed unless the solution is supersaturated.

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.

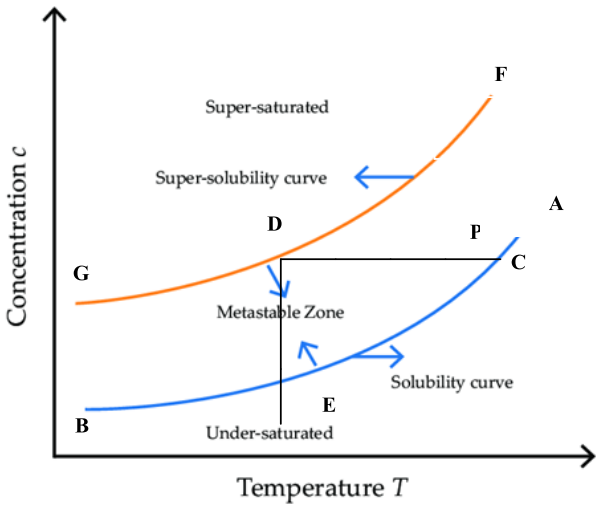


Figure 4. Mier's Supersaturation Theory

A plot of temperature *vs.* concentration of solute is shown in figure 4. The curve AD represents the normal solubility. Any point on the curve represents the solute in equilibrium with the solvent. This is the maximum limit for the solubility of a substance. The curve FG represents the supersolubility, which is roughly parallel to the normal solubilitycurve. It represents the limit at which nucleus formation begins spontaneously. The region enclosed between these two curves AB and FG is referred to as *metastable state,* indicating that the system is unstable and undergoes changes. The liquid may often be cooled a few degrees below its freezing point without crystallization taking place. Crystallization starts if this limit is exceeded. Consider a point C with a definite composition and temperature. On cooling this solution, crystallization is expected to start from point P; however, it does not happen. According to Mier's theory, crystallization do not start at P but it takes place somewhere in the neighborhood of the point D, whencertain conditions are specified.

Mier's states that under ideal conditions of crystallization nucleus formation starts at FG and crystal growth begins.

Then concentration of substance roughly follows the curve DE.

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

Presence of Another Substance

Sodium chloride crystallized from aqueous solutions produces cubic crystals. If sodium chloride is crystallized from a solution containing a small amount of urea, the crystals obtained will have octahedral faces.

Solvent Used

The solvent with moderate solubility is preferred for crystallization. The presence of benzene can help crystal growth. Avoid highly volatile solvents.

Nucleation

Nucleation refers to the formation of the very first atom of a crystal. The first atom that grows is called Nucleus. It acts like a seed that allows the growth of more atoms around it. Crystals initially form via "**nucleating events**". After a crystallite has nucleated it must grow. Nucleation sites are necessary for the formation of crystals. Excess nucleation sites cause smaller average crystal sizes.

Crystal Growth

Crystals grow by the ordered deposition of the solute molecules onto the surface of a pre-existing crystal. Crystal growth is facilitated by the environment changing slowly over time. Keep crystal growth vessels away from sources of mechanical agitation (e.g. vibrations). Set up away from vacuum pumps, hoods, doors, drawers, and so on.

Rate of Cooling

Quality crystals grow best over time in near-equilibrium conditions. The longer the time, the better the crystals. Faster crystallization is not as good as slow crystallization. Faster crystallization, higher chance of lower quality crystals.

EQUIPMENTS

In commercial practice, it is highly desirable tohave the product not only of uniform size, but also of a particular size distribution. It is necessary to control the formation of nuclei, since the number of nuclei controls the size of crystals. Once the nuclei are formed, they start growing.

Depending on the conditions of crystallization, it is possible to control or modify the nature of the crystals obtained.

1. If the solution is cooled slowly just above saturation point, crystals of larger size are formed since the number of nuclei is less.
2. If the solution is chilled rapidly a crop of small crystals is formed, since rapid cooling increases the· degree of supersaturation resulting in a large number of nuclei.
3. When polymorphs exist, careful temperature control and seeding with the desired crystal form are necessary.
4. The habit or shape of a given form is often highly dependent on:
    a) Impurities in solution,
    b) pH,
    c) Rate of stirring,
    d) Rate of cooling,
    e) Solvents.

Very rapid rate of crystallization can result in the entrapment of impurities in the crystals. Crystallization equipment is classified according to the method employed for producing the, supersaturated solution. Some large-scale crystallization equipment's are discussed below.

AGITATED BATCH CRYSTALLIZER

Principle: In agitated batch crystallizer, saturated solution is made supersaturated by reducing the temperature. The crystals are formed from the supersaturated solution. Agitation of the solution facilitates the production of uniform size crystals.

Construction: The construction of an agitated batch crystallizer is shown in figure 5. It consists of a cylindrical container with a conical bottom. A propeller is fixed centrally, which rotates on its own axis with the help· of a motor. Pipes made up of good material for conducting heat are run from right bottom to left top of the crystallizer.

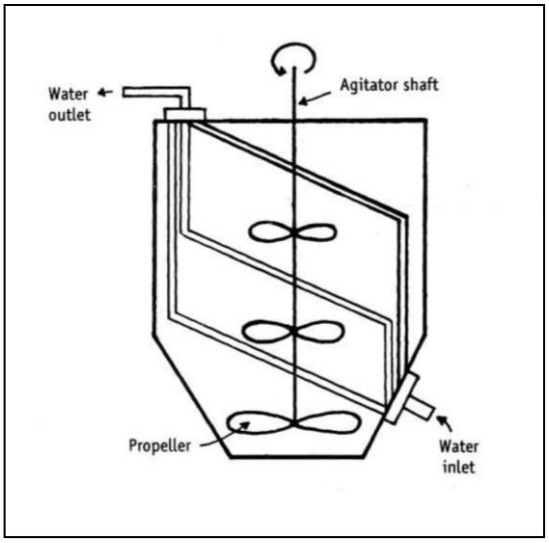


Figure 5. Construction of an agitated batch crystallizer

Working: Solution to be subjected for crystallization is placed in the crystallizer. Cold water is passed through the pipes continuously. Due to cooling the solution becomes supersaturated and crystals are formed. The propeller is allowed to rotate, which serves two purposes. Firstly, it increases the rate of heat transfer thereby helps in maintaining the temperature of the solution almost uniform. Secondly, it keeps fine crystals in suspension, which facilitates them to grow uniformly. Otherwise, large crystals or aggregates may form. The crystals are collected from the bottom by a suitable mechanism for the 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 passing the cold water in a direction opposite to the flow of hot concentrated solution. This results in supersaturation and subsequently crystals are deposited. Agitation prevents the accumulation of crystals

on the cooling surface. The crystals are simultaneously separated from the mother liquor and therefore it can be used as a continuous process.

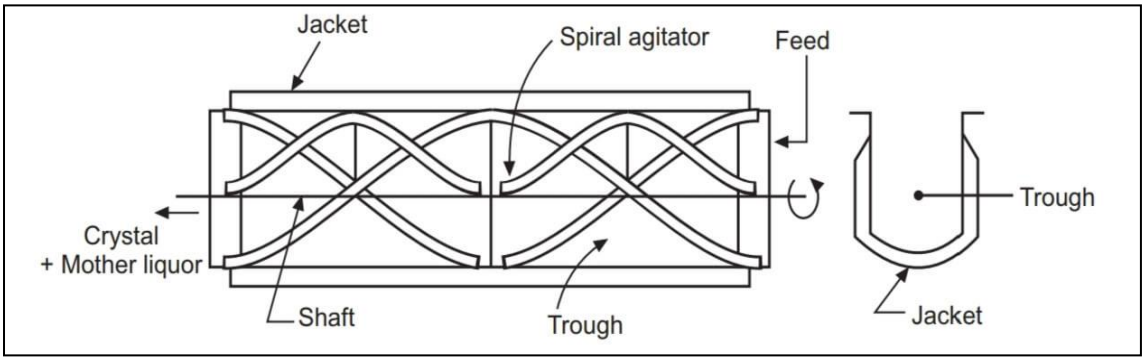


Figure 6. Construction of a Swenson Walker crystallizer

Construction: The construction of a Swenson Walker crystallizer is shown in figure 6. It is a linear type and consists of a long open trough about 0.6 metres wide and 3 metres long with a semi-cylindrical bottom. The trough is welded with water jacket externally. Long pitch spiral scrapper is fixed as close to the bottom of the trough as possible. Spiral scrapper rotates on its own-axis with the help of a motor. For higher capacity, maximum of four such units are joined together. For still higher capacities, several such sets are placed one above the other. In this arrangement the solution flows from one set to its below set.

Working: The hot concentrated solution to be crystallized is fed at left side of the trough. Cooling water enters through right side in the jacket. Due to cooling of the hot solution, supersaturation is achieved and crystals begin to form. If necessary, the size of crystals can be controlled by injecting an extra amount of cooling water into the selected sections. Spiral scrapper rotates on its own axis at a speed of 7 revolutions per minute. It helps in agitating the mixture and conveying of the crystals. It also prevents the accumulation of crystals on the cooling surfaces by lifting them. This results in a suspension, which allows the crystals to grow individually. Thus, aggregation is prevented.

Draining table is attached to one end of the crystallizer. Mother liquor and crystals together overflows into the draining table while crystals are retained, the

mother liquor is sent back to crystallizer. The wet crystals are conveyed to a centrifuge.

Screw conveyor can also be used in place of the draining table. Screw conveyor with a slight inclination lifts the crystals from solution and delivers to a centrifuge. Mother liquor overflows at a convenientpoint.

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

Principal: In Krystal crystallizer, concentration or liquid and crystallization are obtained in different chambers namely vapour head and crystalling chamber. The concentration of liquid (supersaturation) is induced by evaporation of hot solvent with the help of a vacuum pump. In the crystallization chamber, the supersaturated solution and crystals are maintained in a fluidised state for uniform crystal growth. As the crystals of desired size settle down by gravity, the fine crystals and supersaturated solution is recirculated for further crystallization. Crystals of desired size are collected from the crystal growth chamber.

Construction: The construction of a Krystal crystallizer is shown in figure 7. 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 thefeed to enter vapour head on its way to vapour head a heater is provided.

Working: Solution is pumped, which passes through the heater.The hot solution enters the vapour head because of reduced pressurethe hot solution undergoes flashing which results in the formation of solvent vapour and supersaturated solution. Vapour is removed by suction pump. Supersaturated solution passes through long cube belowthe operation is controlled in such a way that crystals do not form in the vapour head but should form in the crystallizing chamber.

The crystallizing chamber consists of a bed of crystals suspended in an upward flowing stream of liquid. Supersaturated liquid flows through the bed of crystals, which are maintained in a fluidized state. A uniform temperature is thereby attained. There is a continuous gradation ofcrystals in the chamber. Coarse crystals settle at the bottom while finecrystals remain above the coarser ones. Very fine crystals overflow throughthe liquid and enter into the recirculating system which then combines with fresh feed from time to time coarse crystals are taken out through the opening at the bottom of the chamber.

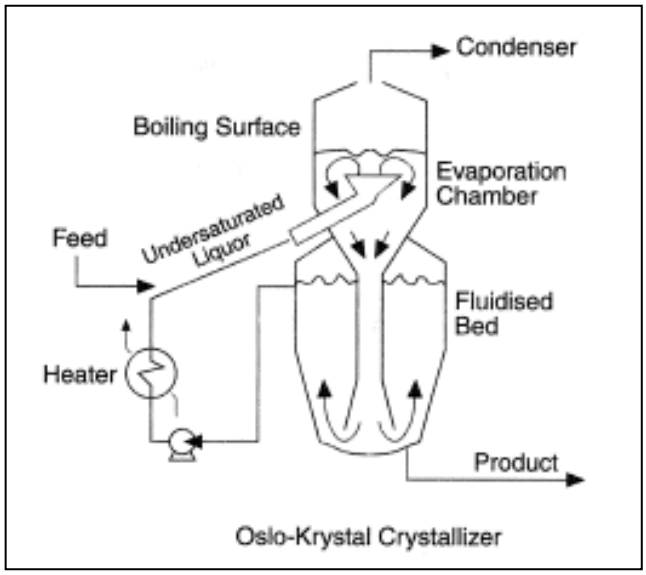


Figure 7. Construction of a Krystal crystallizer

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: In vacuum crystallizer supersaturation is obtained by adiabatic evaporative cooling. When warm saturated solution is introduced into the crystallizer, due to high vacuum the solution undergoes flashing. A part of the solvent gets evaporated, thereby causing cooling of the solution from the resulting supersaturation crystals are produced.

Construction: The construction of a vacuum crystallizer is shown in figure 8. Vacuum crystallizer is a cylindrical body with a conical bottom. A condenser is attached to the crystallizer with a vacuum pump between the bottom of the crystallizer is attached to a discharge pipe internally the body of the crystallizer can be lined with acid resistant material such as lead or rubber. Two propellers are placed above discharge pipe to prevent short circuit of the feed (to the discharge pipe).

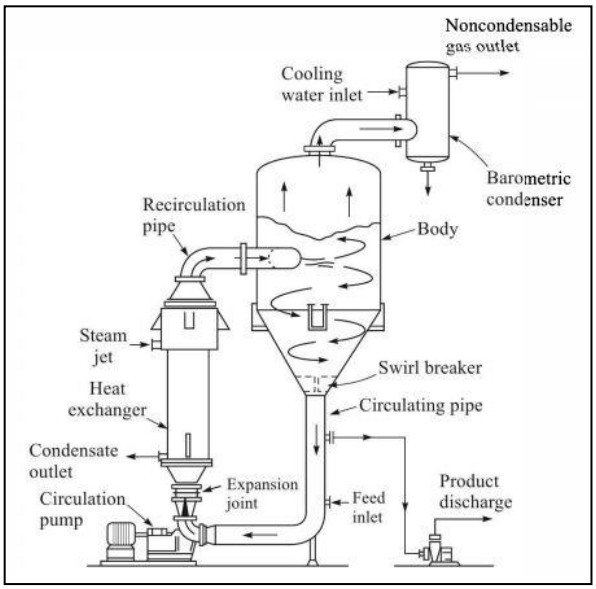


Figure 8. Construction of a vacuum crystallizer

Working: High vacuum is created using a vacuum pump. The vacuum so created must correspond to a boiling point of the solution, but lower than the feed temperature. Hot saturated solution is fed into the crystallizer at a convenient point solution undergoes flashingwhich results in evaporation of solvent. This process is adiabatically so that the crystallizer body is cooled. The resultant cooling causes supersaturation and crystallization. · The evaporation of the solvent enhances the yield. Flashing of the solution in the crystallizer leads to ebullition, which keeps the crystals in suspension, until they become large enough to fall into the discharge pipe. The propellers mix the contents thoroughly and prevent the contents reaching the discharge pipe without flashing. With the help of pump, the product is collected and subjected to filtration or centrifugation to obtain crystals. The filtrate returns to the feed.

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.

After crystallization, crystals must be stored in bulk for either subsequent use, transportation, or the formulation of dosage forms. The crystals must retain good flow properties during storage, for example, they can pass freely from hopper to die in case of tablet punching. During storage, crystals may tend to form a cake. This problem

becomes more serious in the case of small packages than in bulk packages. In some cases, the pressure of a thumb can easily break the crystals.

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.

By absorbing moisture, the crystals develop a saturated layer on their surface. The capillary forces cause the saturated solution to concentrate where the points of contact occur. The solute crystallizes to create a solid bridge when the water evaporates or the temperature drops.

FACTORS AFFECTING CAKING

Size of the crystals: More voids are present in bigger crystals. Smaller crystals, on the other hand, have more points of contact and less void space. The rate of caking will increase as there are more places of contact. As a result, smaller particles tend to cake more than bigger ones.

Shape of the crystals: The smallest possible points of interaction exist between spherical particles. As the crystal structure deviates from a spherical shape, the sites of contacts grow. Deformed crystals hence tend to cake more than spherical crystals.

Humidity: The rate of caking will increase as the humidity of the environment to which the crystals are exposed increases.

Time of exposure: If the exposed atmosphere has humidity over the critical humidity, the caking will increase with exposure time.

Impurities in crystals: The mother liquor's impurities might be used to coat the crystals. This could change the crucial humidity level. When the essential humidity varies, caking's characteristic also changes. For instance, calcium chloride and magnesium chloride are contaminants that can change the critical humidity of sodium chloride crystals.

Melting point of crystals: Certain crystals with melting points close to room temperature may melt. After that, caking results from the melt being solidified by fusion.

Temperature fluctuations: The melting of the crystals occurs as the temperature rises. The temperature drops, later which causes solidification. As a result, temperature changes affect solubility, which may result in caking.

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. Controlled freeze drying keeps the product temperature low enough during the process to avoid changes in the dried product appearance and characteristics

Freeze drying is used in the manufacture of pharmaceuticals and biologicals that are thermolabile or otherwise unstable in water or moisture for prolonged storage periods, but that are stable in the dry state. It is an excellent method for preserving a

wide variety of heat-sensitive materials such as proteins, microbes, pharmaceuticals, tissues & plasma.

SUBLIMATION

Sublimation is when a solid (ice) changes directly to a vapor without first going through a liquid (water) phase. Thoroughly understanding the concept of sublimation is a key building block to gaining knowledge of freeze drying. As shown below on the phase diagram for water, low pressures are required for sublimation to take place, Sublimation is a phase change and heat energy must be added to the frozen product for it to occur. Sublimation in the freeze drying process can be described simply as:

1. FREEZE - The product is completely frozen, usually in a vial, flask or tray.

2. VACUUM - The product is then placed under a deep vacuum, well below the triple point of water.

3. DRY – Heat energy is then added to the product causing the ice to sublime.

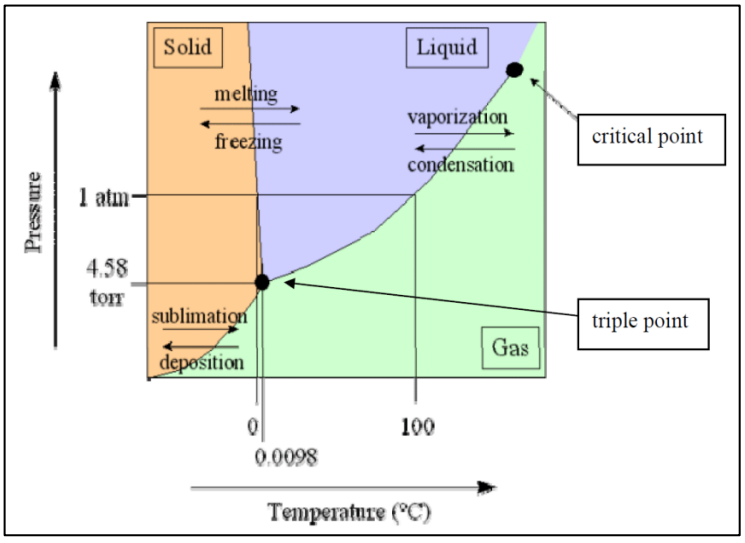


Figure 9. Phase diagram of water

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.

Sublimation of water can take place at pressures and temperatures below the triple point of water (The temperature and pressure at which a substance can exist in equilibrium in the liquid, solid, and gaseous states). The triple point of pure water is at 0.01°C and 4.58 mm Hg.. Under these conditions, any heat transferred is used as latent heat and ice sublimes directly into vapor state. The water vapor is removed from the system by condensation in a cold trap maintained at a temperature lower than the frozen material.

The material to be dried is first frozen and then subjected under a high vacuum to heat (by conduction or radiation or by both) so that frozen liquid sublimes leaving only non-volatile solid, dried components of the original liquid.

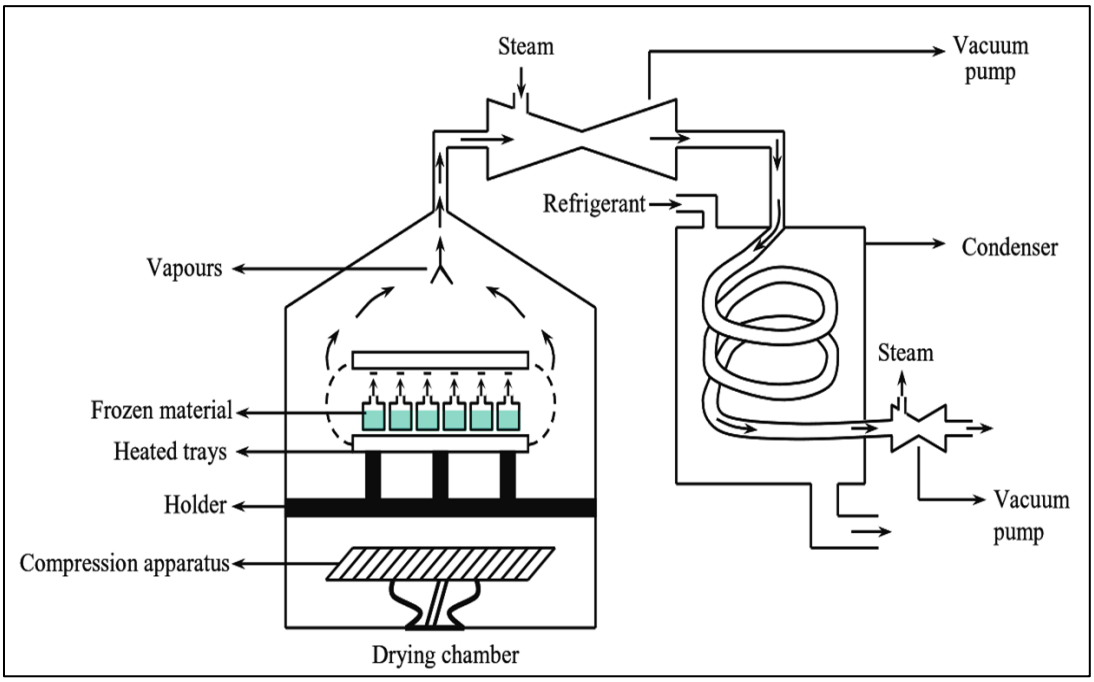


Figure 10. Diagram of Freeze Dryer

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.

WORKING OF FREEZE DRYER

Traditional freeze-drying is a complex process that requires a careful balancing of sample, equipment and processing techniques. In this process, water is removed from a sample after it is frozen and placed under a vacuum, allowing the ice to change directly from solid to vapor without passing through a liquid phase.

Initially, the solution is frozen in cold shelves (1-3 Kelvin/min with solutions). The quantity of the material to be dried should be optimum to facilitate complete freezing. While freezing, low conditions of temperature (-50°C) and atmospheric pressure are maintained in the chamber. Freezing is done at a high rate of 1-3 Kelvin/min facilitating the formation of large ice crystals with large holes. Such large crystals form a porous product on drying.

Freeze drying is performed at temperature and pressure conditions below the triple point of the water (if only water is present), to enable sublimation of frozen

material. When liquids other than water is present, the temperature and pressure are maintained below the eutectic point (-10℃ to 30℃).

Vaccum is applied (about 3mm of Hg) to the frozen material and its temperature is raised then the frozen material sublimes into vapours.

Movement of ice layers is controlled by heat which regulates the formation of vapours above the frozen surface. It also prevents the melting of ice. The vapours formed are eliminated and the driving force is constituted by the difference in temperature of the drying chamber and the condenser. This is usually referred to as primary drying in which the material loses about 98-99% of moisture. The vapour pressure of water increases with an increase in temperature during the primary drying. Therefore, primary drying temperature should be kept as high as possible, but below the critical process temperature, to avoid a loss of cake structure.

Remaining 1-2% of moisture is removed by increasing the temperature to about 50℃ called as secondary drying which takes more than 10 hours of time

The entire process is performed at low temperature and pressure. Steps involved in lyophilization start from sample preparation followed by pretreatment, freezing, primary drying and secondary drying, to obtain the final dried product.

HEAT AND MASS TRANSFER

Freeze-drying is a complex operation where both heat and mass transfer processes occur in the interior of the food product. To generate vapor from the ice, energy in the form of heat is transferred to the sublimation zone. Unlike the mass transfer process, which is constantly taking place through the dried layer (mass flux), heat transfer (heat flux) can occur

(a) by conduction through the dried layer (Figure 11(a)) and in the opposite direction of the mass flux – in this case, near the food product is the heat source that irradiates heat to the dried layer;

(b) through the frozen layer (Figure 11(b)) – in this case, the frozen product is in direct contact with the heat source, and the heat transfer is by conduction; or

(c) within the frozen layer (Figure 11(c)) by heat generation using microwaves – in fact, microwaves are currently preferred as a heat source in freeze-drying due to their capability to infiltrate profoundly into the food product, resulting in a uniform and effective heating.

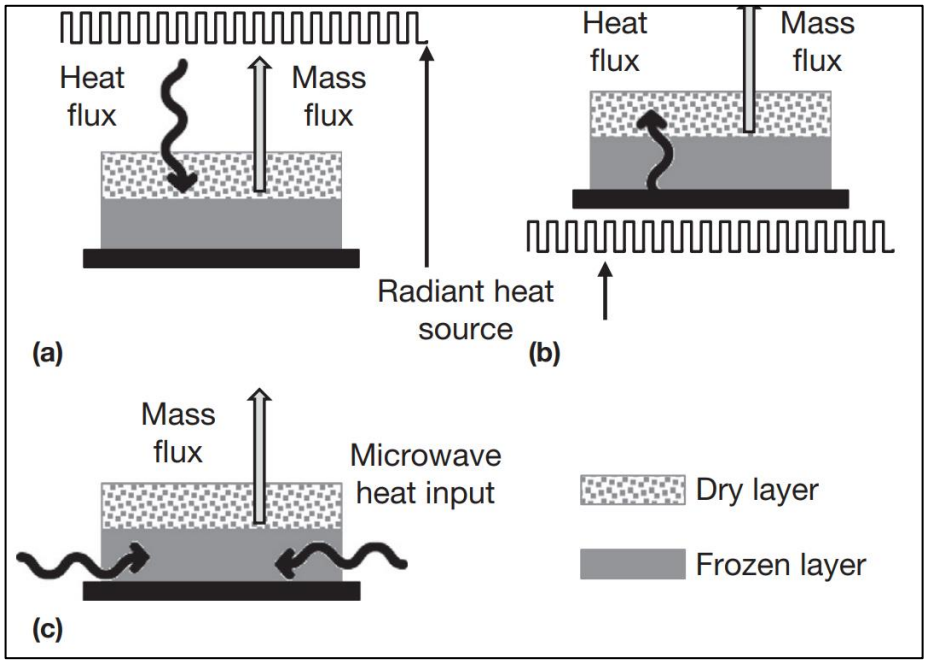


Figure 11. Heat and mass fluxes in different freeze-drying mechanisms.

In addition to providing an extended shelf-life, successful freeze-drying should yield a product that has a short reconstitution time with acceptable potency levels. The process should be repeatable with well defined temperature, pressure and time parameters for each step. Visual and functional characteristics of the dried product are also important for many applications.

Figure 12. Freeze dried products

FREEZE DRYING EQUIPMENT

The main **components of freeze drying equipment** are:

- Refrigeration System
- Vacuum System
- Control System
- Product Chamber or Manifold
- Condenser

The refrigeration system cools the (ice) condenser located inside the freeze dryer. The refrigeration system can also be employed to cool shelves in the product chamber for the freezing of the product.

The vacuum system consists of a separate vacuum pump connected to an airtight condenser and attached product chamber.

Control systems vary in complexity and usually include temperature and pressure sensing ability. Advanced controllers will allow the programming of a complete “recipe” for freeze drying and will include options to monitor how the freeze drying process is progressing. **Choosing a control system** for the freeze dryer depends on the application and use (i.e. lab vs. production).

Product chambers are typically either a manifold with attached flasks, or, a larger chamber with a system of shelves on which to place the product.

The purpose of the condenser is to attract the vapors being sublimed off from the product. Because the condenser is maintained at a lower energy level relative to the product ice, the vapors condense and turn back into solid form (ice) in the condenser. The sublimated ice accumulates in the condenser and is manually removed at the end of the freeze drying cycle (defrost step). The condenser temperature required is dictated by the freezing point and collapse temperature of the product. The refrigeration system must be able to maintain the temperature of the condenser substantially below the temperature of the product.

In shelf freeze dryers, the condenser can be located inside the product chamber (internal condenser) or in a separate chamber (external condenser) connected to the product chamber by a vapor port.

Manifold freeze dryers rely on ambient conditions to provide the heat of sublimation to the product. This heat input does not melt the product because an equivalent amount of heat is removed by vaporization of the solvent. Advanced shelf freeze dryers can provide a heat source to control/expedite the drying process and they can also employ the refrigeration system to allow freezing of product inside the unit.

Freeze dryers can be informally classified by the type of product chamber: (1) Manifold dryers where the product is typically pre-frozen & in flasks (2) Shelf dryers where the product is placed in a tray or directly on a shelf (3) Combination units with both drying options.

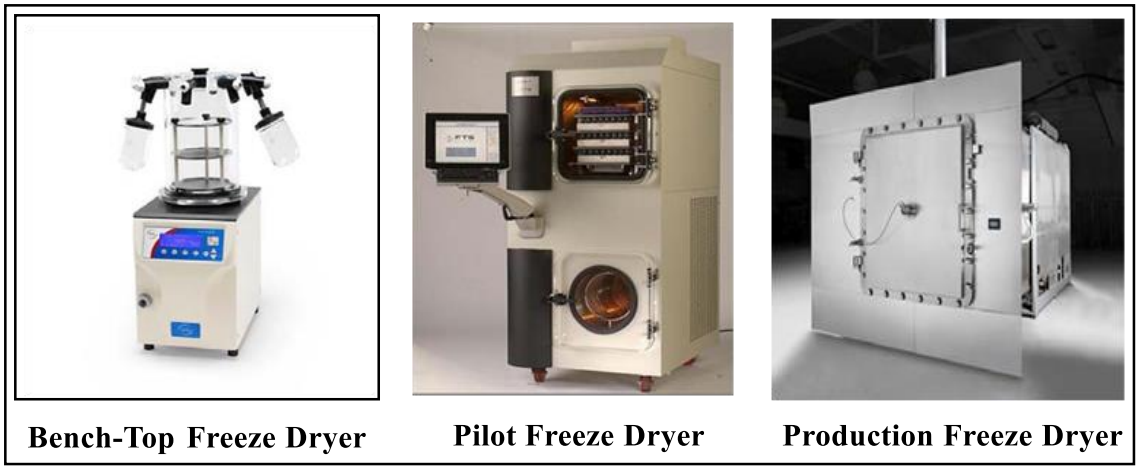


Figure 13. Different types of Freeze dryers

Freeze-dryers can also be grouped by size & use: (a) laboratory bench-top units for R&D (b) pilot units for process development and scale-up, and (c) larger production-sized units. It should be noted that in addition to process scale-up work, pilot-sized freeze dryers are often used for product R&D as well as small volume production applications.

Choosing a freeze dryer depends on the product characteristics as well as many other application-based variables including the container that the product will be dried in, the shelf area or number of ports required to accommodate the quantity to be dried in each batch, the total volume of ice to be condensed and whether there are any organic solvents. The type and shape of product being dried and its end-use also need to be considered.

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 14. 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. This may include concentrating the product, the revision of the formulation (i.e, the addition of components to increase stability and/or improve processing), decreasing a high vapor pressure solvent, or increasing the surface area. 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 pretreat 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 inthat no vacuum is applied. Pre-freezing could also be doneseparately from the dryer.

The freezing step is of paramount importance, as it determinesthe ice morphology and pore size distribution, which isessential for success later in the process. This seems rather elementary, but it is often the least understood and investigated step of the process.

Figure 15. Product that was not fully frozen before starting vacuum & drying

The freezing of the product may result in either a sudden solidification of the liquid at a specific temperature (eutectic former) or a liquid which does not solidify, but rather just becomes more and more viscous (glass formers). The eutectic formers freezing temperature equates to the triple point ofthe product on the phase diagram. In this instance, the productis frozen in the classic sense and the temperature must be maintained below this level during the entire Primary Drying step.

To freeze a product properly, thermal analysis can be used in order 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

Materials that have poor structural stability generally end up shrunken, puffed or may be glassy-looking and sticky. Such samples are said to have collapsed during Freeze Drying.Poor structural stability combined with longer drying times will also result in poor product quality.

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

- Dextran (-9°C)
- Fructose (-48°C)
- Gelatin (-8°C)
- Glucose (-40°C)
- Inisitol (-27°C)
- Lactose (-32°C)
- Maltose (-32°C)
- Sorbitol (-45°C)

Once the freezing point (eutectic point) of the product is determined, the optimal rate of freeze must also be determined. The rate of freezing determines the crystalline size. It is important to remember that as the frozen liquid will eventually be subliming

out of the product, the larger crystalline structure coming from a slow freeze rate, will produce amore porous and quickly dried product. Typically, this is advantageous for the optimization of Freeze Drying cycles but may not result in the best product in terms of rehydration (reconstitution).

On the other hand, a fast rate of freeze will result in a product that turns inactive at a faster rate and has a smaller crystalline structure, which in turn results in it being more granulated and therefore easier to reconstitute, even if it takes longer to freeze dry. A rule of thumb for freezing products in vials, is that the product container should never be filled to more than half of its total volume. Some biological products cannot tolerate large ice crystals and they must be freeze dried with smaller ice crystal sizes.

3. PRIMARY DRYING

Primary Drying phase is where the ice sublimates (turns directly into vapor) under ultra-low pressure, typically downto 0.01 hPa (mBar) or lower, depending on the pre-freezing temperature of the sample. The driving force of sublimation is the pressure difference related to the corresponding temperature difference between the product ice surface and the condenser ice surface. All three methods of heat transfer - conduction, convection and radiation, must be considered when freeze drying a product.

Larger temperature differences mean larger pressure differences, which allow fora faster process. The vacuum speeds up the process by removing air molecules to allow sample vapor molecules to move easier from the sample, through the chamber andinto the condenser. Typically, shelf temperatures during

Primary drying are ramped from –40 to +20°C during the process time, which can vary from a few hours to several days. The shelf temperatures indirectly influence the ice temperature of the sample by conducting heat (contact tothe shelf) as well as the radiating of heat from the shelfabove. Due to the low level of air molecules present in the chamber, highly limited amounts of heating stems from convection. Sample temperature(s) are monitored by tiny sensors inserted into the vials, which then follows the change of shelf temperature accordingly.

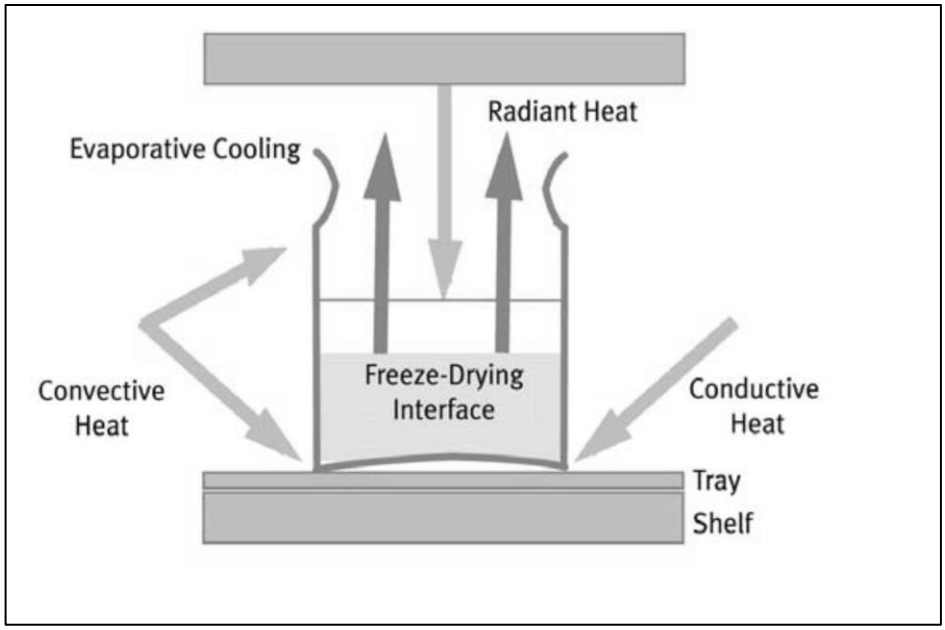


Figure 16. Heat Transfer in a Shelf Freeze Dryer

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.

During the Primary drying phase, it is essential to heat the product as much as possible (without passing theeutectic point) in order to increase the pressure differential between the product and the condenser. This also increases the temperature differential between the freeze-dried ice interface (condenser) and the product-ice barrier. However, it is important to remember that the heat input constraints are often caused by the product's own thermal characteristics. If a product has a eutectic temperature of -10°C, then the product may be taken to a temperature of approximately -15°C. If the condenser is -50°C this will result in a much larger pressure differential (speed of process) than if the product temperature was left at -30°C or even -40°C. Since pressure differentials at very low temperatures are minimal, lowering the condenser temperature will have limited effect on the speed of process.

When using a vial chamber system, the operator can control the energy input to the product via temperature and pressure control. These controls allow the operator to optimize the Freeze Drying cycle. Typically, in Freeze Drying cycles, the product temperature will follow behind the shelf temperature, thus increasing the cycle duration. To overcome this issue, the pressure can be increased to raise the number of molecules available for heat transfer from the heat source (the shelves) to the product. Additionally, using vials with flat bottoms offer the optimal contact,which decreases the amount of heat transfer barriers between the shelves and the product.

Regardless of the Freeze Drying method employed, it is essential to remember that Primary Drying is a delicate balance between the energy input to the product and the pressure differential created between the product and the condenser by the temperature differential.

Also, Primary Drying is typically the part of the process that takes the longest and is therefore subject to optimization.This is typically done by adjusting the temperature and pressure in order to bring the product as close as possible to its collapse conditions, but without crossing the line.

Primary drying is a top-down process with a well-defined sublimation front moving through the product as it dries. Above the ice surface interface is dried product, or “cake”; below the interface is product with ice crystals still remaining to be sublimed. At the end of primary drying when all of the free ice crystals have been sublimed, the product will appear to be dried. However, the moisture content can still be in the 5-10% range due to the presence of “sorbed” water molecules attached to the product.

Pressure & Temperature During Primary Drying

A general guideline is to choose a system pressure that is 20% to 30% of the vapor pressure of ice at the target product temperature. When the vacuum level set point is deeper than the vapor pressure of ice at the current product temperature, sublimation can take place. Typically, vacuum levels for freeze drying are between 50mTorr and 300mTorr with 100mTorr to 200mTorr being the most common range.

With the temperature and pressure parameters set, primary drying is then continued for a length of time sufficient for all of the ice crystals to be sublimed

Because most commercial freeze dryers cannot consistently control vacuum much below 30mTorr, at very cold product temperatures (less than -40ºC), it becomes impossible to have a system pressure set point that is 20% to 30% of the vapor pressure of ice. Freeze drying occurs extremely slowly at these cold product temperatures.

Determination of the End of Primary Drying

Several analytical methods are available for determining that primary drying is complete. The most basic method is to monitor the product temperature with a thermocouple probe. The measured product temperature will be colder than the shelf temperature set point during active primary drying because the heat from the shelf is being used for the sublimation phase change. When sublimation of ice crystals is complete, the product temperature will increase and approach the shelf temperature. When the product temperature equals the shelf temperature, it can be inferred that primary drying is complete.

Note: the specific vial that contains the thermocouple wire will typically dry faster than the other vials on the shelf because the wire will conduct more heat into that specific vial. Similarly, if bulk drying, the area around the thermocouple wire will dry more quickly than other areas in the product tray. It is important to allow a modest amount of additional drying time (30 min to 2 hrs, depending on the product characteristics) after the product thermocouple temperature increases to ensure that all of the ice in the entire batch of product has been completely sublimated.

Because product will dry from the top down, the tip of the thermocouple should always be placed at the very bottom and center of the container. It is OK if the thermocouple touches the bottom of the container. If drying in vials, it is good practice to insert the thermocouple in a vial located in the middle of the shelf. Radiant heating effects will cause vials/product on the perimeter of the shelf to dry more quickly.

Figure 17. Thermocouple Placement Tools

Additional **primary drying endpoint determination** tools are available on larger freeze dryers equipped with advanced process control systems. One such method entails comparison of parallel pressure readings between a Pirani gauge and a capacitance manometer. A capacitance manometer always gives a true pressure reading in the product chamber. The Pirani gauge, however, will give a false high reading in the presence of water vapor. When the Pirani pressure reading decreases and approaches the true pressure reading of the capacitance manometer, little or no water vapor is present and it can be concluded that primary drying is complete.

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.

Secondary drying is continued until the product has acceptable moisture content for long term storage. Depending on the application, moisture content in fully dried products is typically between 0.5% and 3%. In most cases, the more dry the product, the longer its shelf life will be. However, certain complex biological products may actually become too dry for optimum storage results and the secondary drying process should be controlled accordingly.

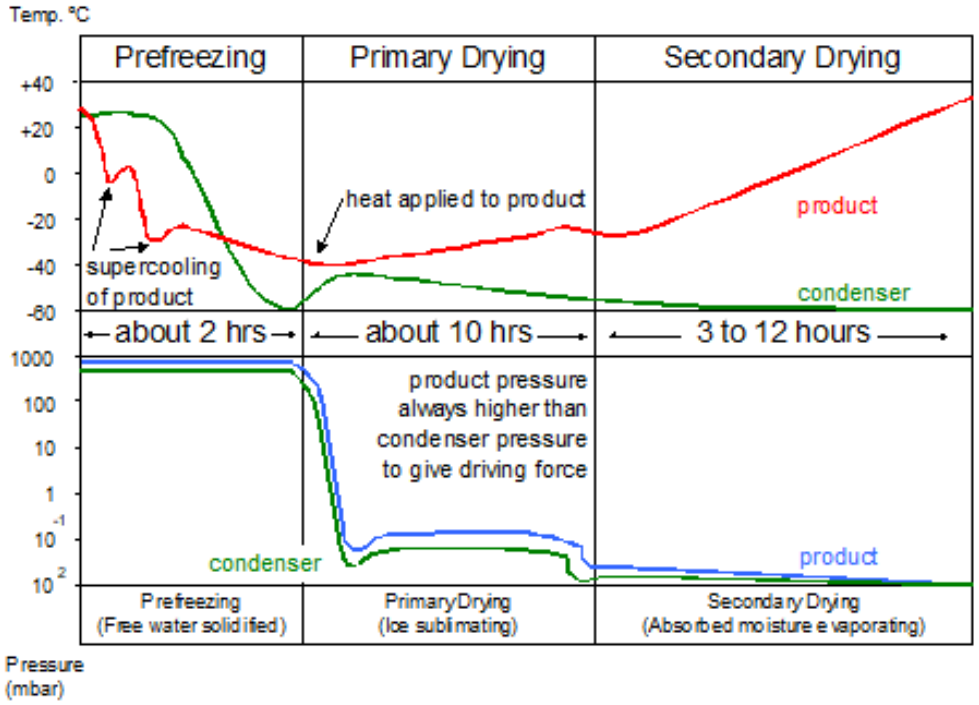


Figure 18. Overview of Lyophilization process

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.

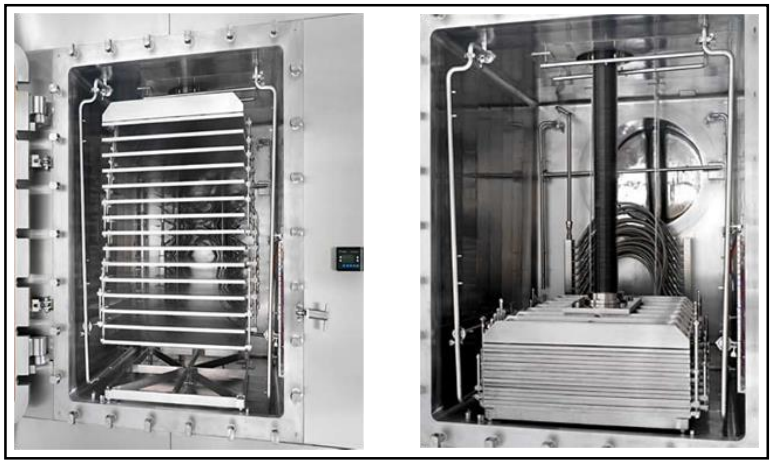


Figure 19. Stoppering mechanism in a production freeze dryer

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.

CYCLE OPTIMIZATION

In addition to designing a recipe that successfully dries a product, it is also extremely valuable to optimize (shorten) the length of the cycle, especially if there is

potential for process repetition or scale-up for production. Freeze drying can be a multi-day process. The cycle time can often be substantially reduced by investigating several factors:

Freezing and annealing – maximize crystal size and crystallization to increase drying rates.

Thickness of product - water vapor molecules experience resistance as they exit from the dried portion of the product. Thinner samples yield less resistance to vapor flow and lead to faster drying. Shell freezing can help when drying bulk product in flasks.

Critical Collapse Temperature – this is the most important piece of information for cycle optimization. The ability to run primary drying at higher product temperatures greatly reduces drying time by creating a larger pressure differential between the vapor pressure over ice in the product and the pressure at the condenser. Each 1℃ increase in product temperature can decrease primary drying time by 13%.

Cycle optimization using eutectic/collapse temperature information requires an iterative approach of taking real-time measurements of the product temperature during primary drying and then making corresponding adjustments to the shelf temperature settings. This can be accomplished manually using product thermocouples or, if drying in vials, an automated **SMART** system can be used.

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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