13

Crystallization

Characteristics of Crystals
Pharmaceutical Solids – Terminology
Theory of Crystallization
Equipment
Caking of Crystals

Crystallization is the spontaneous arrangement of the particles into a repetitive orderly array, i.e., regular geometric patterns.

In matter, particles are present randomly due to thermal agitation. In gases the disorderliness is highest and in liquids it is moderate. The liquids can solidify into crystalline forms, whenever attraction forces between particles are strong enough to overcome the disorderliness. Crystallization can take place directly from vapour of a substance. Examples are solid camphor from camphor vapour, solid iodine from iodine vapour. Such a process is known as *sublimation*. Crystals are commonly obtained from liquid state. Example is salt from brine. This chapter of crystallization deals with the later type, i.e., from solution to solid state.

Crystallization differs from precipitation in that the product is deposited from a supersaturated solution. Precipitation occurs when solutions of materials react chemically to form a product, which is sparingly soluble in the liquid and therefore deposits out.

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.

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 such as transportation and storage.

Better chemical stability : Crystallization increases the stability of drugs. For example, amorphous penicillin G is less stable than crystalline salt. Amitryptyline is more stable in crystalline form than in amorphous form.

Improved physical stability : Crystalline forms play an 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.

CHARACTERISTICS OF CRYSTALS

Crystal Lattice

A *crystal* can 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.

Crystal lattice is defined as an orderly internal arrangement of particles in three-dimensional space.

The geometric form in which structural units are arranged in a crystal is determined by means of X-ray diffraction pattern. The three dimensional arrangement of particles in a crystal is also known as *space lattice*.

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 van der Waals forces 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*.

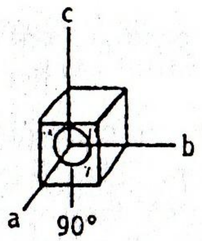
Axial length can be defined as the distance between the centres of two atoms.

- 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 determinations are made.

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, crystal forms are designated as cubic, hexagonal, tetragonal, orthorhombic, monoclinic and triclinic. They are shown in Figure 13-1. A chemical substance may exist in more than one form, i.e., polymorphism.

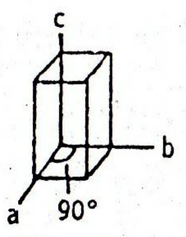


CUBIC

$\alpha = \beta = \gamma = 90°$

a = b = c

Eg. Sodium chloride
Potassium chloride

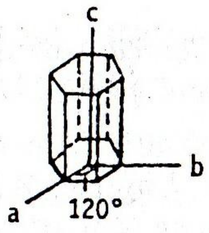


TETRAGONAL

$\alpha = \beta = \gamma = 90°$

a = b ≠ c

Urea, Potassium dihydrogenphosphate

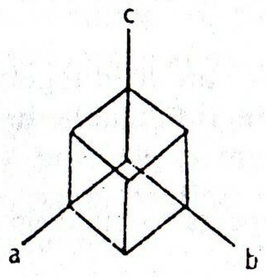


HEXAGONAL

$\alpha = \beta = 90°, \gamma = 120°$

a = b ≠ c

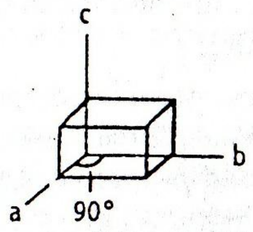
Ice
Thymol



RHOMBOHEDRAL

$\alpha = \beta = \gamma \neq 90°$

a = b = c

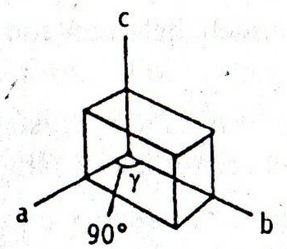


ORTHORHOMBIC

$\alpha = \beta = \gamma = 90°$

a ≠ b ≠ c

Eg: Barium sulphate
Sulphacetamide

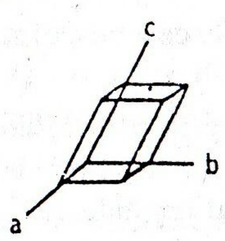


MONOCLINIC

$\alpha = \beta = 90°, \gamma \neq 90°$

a ≠ b ≠ c

e.g.: Sucrose
Ephedrine hydrochloride



TRICLINIC

$\alpha \neq \beta \neq \gamma = 90°$

a ≠ b ≠ c

e.g.: Phenolphthalein
Copper sulphate

Figure 13-1. Different types of crystal systems with characteristics and examples.

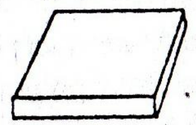
Crystal Habit

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 same in all specimens. It is the characteristic of a particular substance irrespective of the relative sizes of the faces.

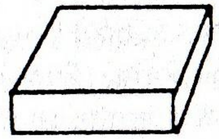
The shape and size of the crystals formed are markedly dependent on the conditions under which crystallization is carried out. For example, griseofulvin crystallized from acetone has a different form from the same drug crystallized from benzene or chloroform.

Depending on the arrangement of faces, crystal habits are described in different ways. These are shown in Figure 13-2.



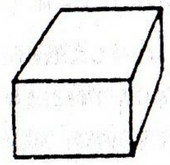
PLATE

e.g.: Naphthalene



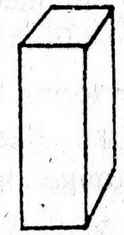
TABULAR

e.g.: Tolbutamide,
Cyclizine



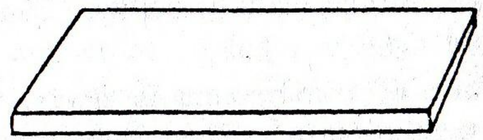
EQUANT

e.g.: Sodium chloride



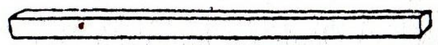
COLUMNAR

e.g.: Fluorocortisone acetate
Triamcinolone acetonide



BLADED

e.g.: Resorcinol



ACICULAR

e.g. Nalidixic acid

Figure 13-2. Different types of crystal habits with examples.

Columnar : Rod like particles having a width and thickness exceeding that of needle type particles. The term prismatic may also be used.

Blade : Long, thin and flat particles, which can also be referred to as being lath shaped.

Plate : Flat particles of similar length and width. They are also denoted as being lamellar or micaceous.

Tabular : Flat particles of similar length and width, but possessing greater thickness and flakes.

Equant : Particles of similar length, width and thickness.

Acicular: Needle like prisms.

PHARMACEUTICAL SOLIDS—TERMINOLOGY

Pharmaceutical powders are available either in amorphous form or in crystalline form. Further crystalline solids such as polymorphs, hydrates and solvates are used in the manufacture of dosage forms.

Crystalline Solids

Crystalline solids have definite shapes and an orderly arrangement of units. These are incompressible. These show definite melting point. Examples are sodium chloride, urea, benzylpenicillin and aspirin.

Crystalline forms have low solubility and dissolution. This fact has been taken as an advantage to produce sustained release products. Example is protamine zinc insulin suspension for injection.

Amorphous Solids

Amorphous solids do not have specific shape (Greek: *amorphe* meant without form). The structural units are arranged randomly in the solid. These do not have definite melting points. Examples are glass, pitch, plastics and novobiocin.

Amorphous form of a compound is always more soluble than the corresponding crystalline form. Therefore, it may exhibit better therapeutic activity than the crystalline form. For example, amorphous novobiocin (antibiotic) has significant biological activity than crystalline novobiocin.

It is not always possible to determine the solids as crystalline or amorphous by casual observation. For example, beeswax and paraffin although appear to be amorphous assume crystalline arrangements when heated and allowed to cool slowly.

Polymorphs

Certain drugs can exist in more than one crystalline form. Such a phenomenon is known as *polymorphism.* About 63% of barbiturates, 67% of steroids and 40% of sulphonamides exhibit polymorphism. Al-

though the drug is chemically indistinguishable in each form, polymorphs differ significantly with respect to a number of properties such as density, melting point, solubility and dissolution rate.

Metastable polymorphs : These polymorphs slowly convert into stable polymorphs. If the rate of conversion is so slow as to be negligible during the expected life of a drug product, metastable polymorphs are preferred because of their unique physicochemical properties.

The metastable polymorphs have lower melting points, higher solubility and higher dissolution than their stable polymorphs. Therefore, these are preferred in the production of dosage forms. For example, riboflavin can exist in three different crystalline forms, which vary in water solubility at 25°C from 60 mg per litre to 1.2 g per litre. The increased solubility of metastable polymorph ordinarily results in increased dissolution and absorption.

Stable polymorphs : These are employed when metastable polymorphs are not suitable on account of rapid decomposition.

Crystal Hydrates

Some drugs have greater tendency to associate with water. The resulting substance is referred to as *drug hydrate.* Examples are caffeine hydrate, theophylline hydrate, ampicillin monohydrate etc. The anhydrous form dissolves more readily and gives better bioavailability than hydrous form. Therefore, anhydrous forms are the preferred ones. Water can combine with positive ions and neutral molecules. Sodium carbonate decahydrate, $Na_2CO_3.10H_2O$ is official in IP and BP. Some substances form a number of crystal hydrates. For example, sodium carbonate is available as $Na_2CO_3.10H_2O$, $Na_2CO_3.8H_2O$, $Na_2CO_3.6H_2O$, $Na_2CO_3.5H_2O$ and $Na_2CO_3.H_2O$. Similarly, ampicillin monohydrate and ampicillin trihydrate are available.

Crystal Solvates

Certain drugs have greater tendency to associate with solvents to produce crystalline forms of *solvates.* These solvates are also known as *pseudomorphs.* Examples are fluorocortisone with n-pentanol or ethyl acetate. Succinylsulphathiazole with n-pentanol dissolve much more rapidly than non-solvated form of succinylsulphathiazole. Therefore, for better bioavailability, solvate forms of drugs are preferred.

Isomorphs

When two or more substances possess the same crystalline form, the crystals of one such substance can be grown in the saturated solution of

the other. This phenomenon is known as *isomorphism*. Such substances are said to be isomorphs (having the same shape). For example, chrome alum $K_2SO_4.Cr_2(SO_4)_3.24H_2O$ is isomorphic with potash alum $K_2SO_4.Al_2(SO_4)_3.24H_2O$. The chromium in chrome alum has the same valency as aluminium in potash alum.

THEORY OF CRYSTALLIZATION

Mechanism of Crystallization

The mechanism of the crystallization of substances from the solution is explained using Figure 13-3.

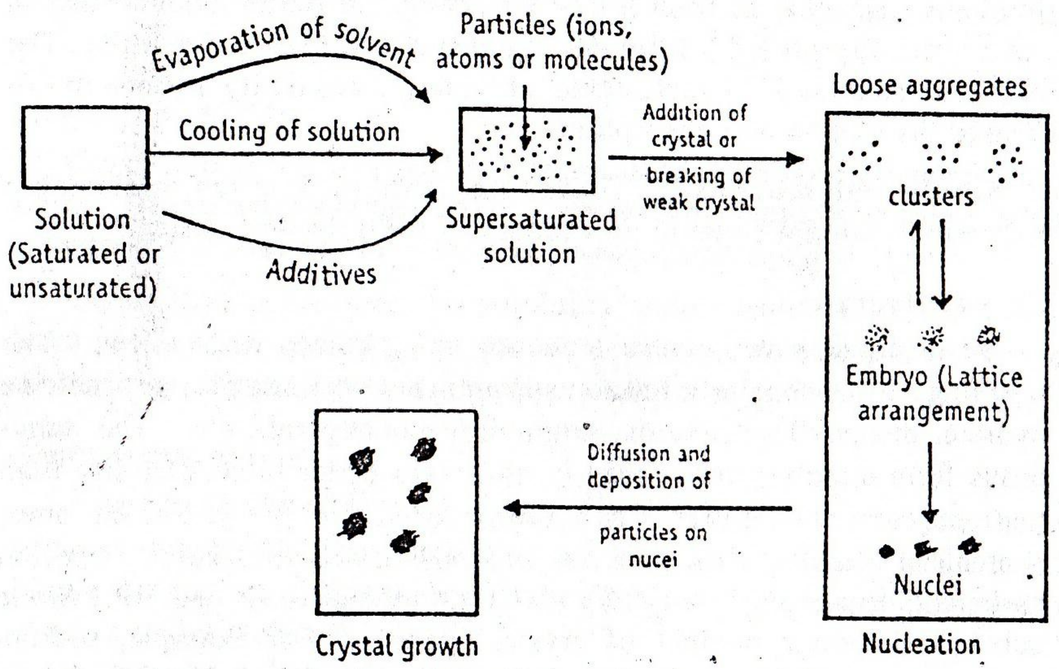


Figure 13-3. Mechanism of crystallization of solutes from a solution and the steps involved.

The formation of crystals from solution involves three steps.

(A) Supersaturation
(B) Nucleus formation
(C) Crystal growth

(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 than the solid to be crystallised.

In the absence of seed crystals, significant supersaturation is necessary to initiate the crystallization through 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 : *Nucleation* refers to the birth of very small bodies of a new phase within a homogenous supersaturated liquid phase.

Nucleation is a consequence of rapid local fluctuations at the molecular level when molecules or ions or atoms are in random motion in any small volume.

Initially several molecules or ions or atoms associate to form clusters. These are loose aggregates, which usually disappear quickly.

However, when enough particles associate to form an embryo, there is a beginning of the lattice arrangement and the formation of a new solid phase. In most of the cases, embryos have short lives and dissolve as soon as they form. An embryo may grow to such a size that it is 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.

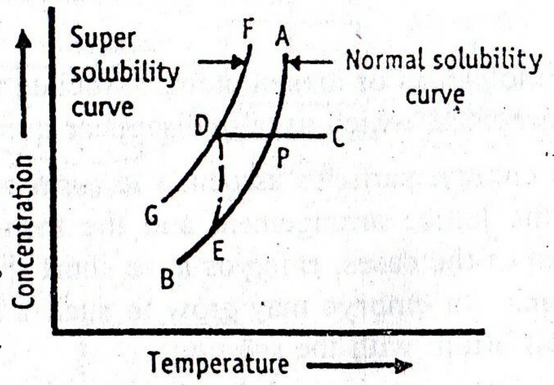


Figure 13-4. Mier's supersaturation theory, CPDE represent the path of cooling.

A plot of temperature vs. concentration of solute is shown in Figure 13-4. The curve AB 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 solubility curve. 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 neighbourhood of the point D, when certain conditions are specified.

Mier 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:

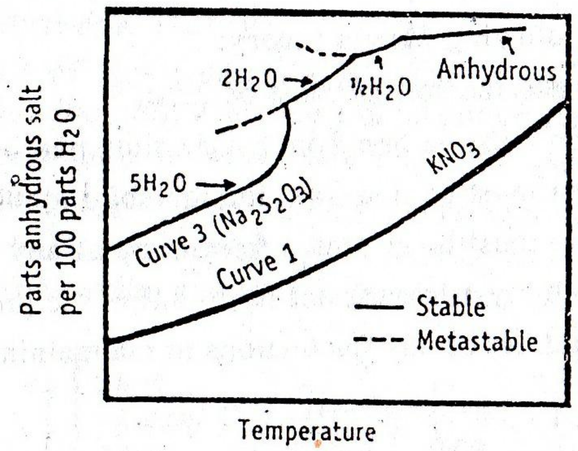
(1) According to Mier's theory, crystallization starts at supersolubility curve. But general tendency is that crystallization takes place in an area rather than a line.
(2) If the solution is kept for longer periods, nucleation starts well below the supersolubility curve.
(3) If the solution is available 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.

Solubility Curves

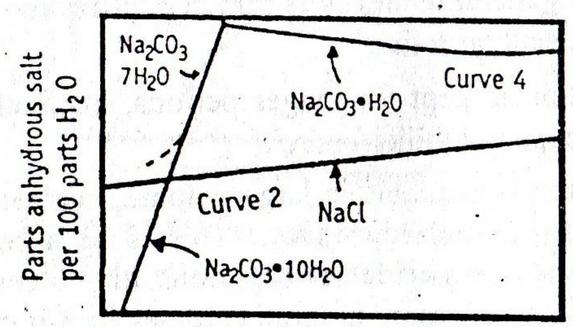
Solubility curves are useful in predicting the experimental conditions desired for crystallizing a substance. Since supersaturation is achieved by reducing the temperature, the influence of temperature on the solubility of a substance is important.

A substance dissolves and goes into solution, if the solution is not saturated. If the solution is supersaturated, crystallization takes place. Equilibrium is attained when the solution is saturated. The graph drawn by taking temperature on *x*-axis and solubility on *y*-axis gives the

solubility curve, which represents stable equilibrium conditions. The metastable condition of the substance is also represented in dotted line. The solubility patterns of some substances are shown in Figures 13-5(a) and (b).



(a)



(b)

Figure 13-5. Typical solubility curves of certain substances.

The following conclusions can be drawn regarding the effect of temperature on the solubility.

(1) Curve 1 represents potassium nitrate. This is the most common type in which the solubility of a substance increases with temperature.

(2) Curve 2 represents sodium chloride. The solubility increases with increase in temperature, but to a marginal extent.

(3) Curve 3 represents sodium thiosulphate. Here solubility increases rapidly with temperature. But inflections are observed in the curve to represent different hydrates.

(4) Curve 4 represents sodium carbonate. This curve is unusual. Here solubility of sodium carbonate increases with temperature, if it is in hydrated form. Once the compound turns into monohydrate form, its solubility decreases.

EQUIPMENT

In commercial practice, it is highly desirable to have 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,
   (d) 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 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 13-6. 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.

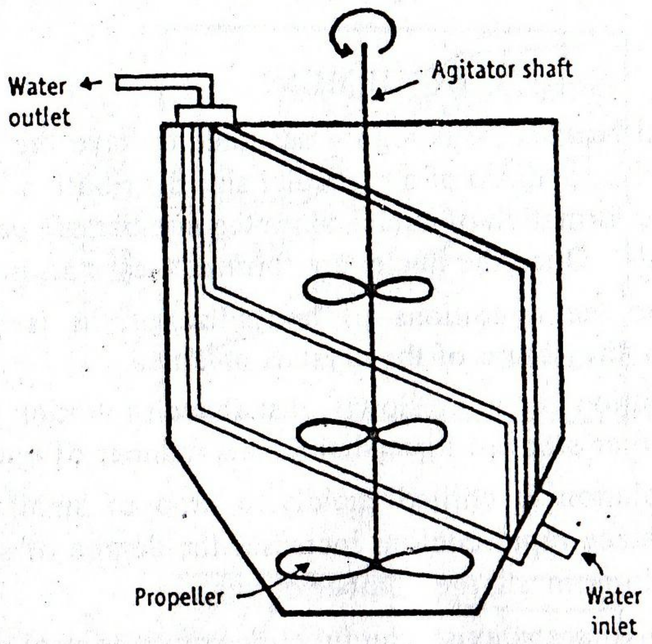


Figure 13-6. Construction of agitated batch crystallizer.

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 more fine 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.

Construction : The construction of a Swenson Walker crystallizer is shown in Figure 13-7. 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 (side view of Figure 13-7). The trough is welded with a water jacket externally. Long pitch spiral scrapper is fixed as close to the bottom of the trough as possible (top view of Figure 13-7). 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.

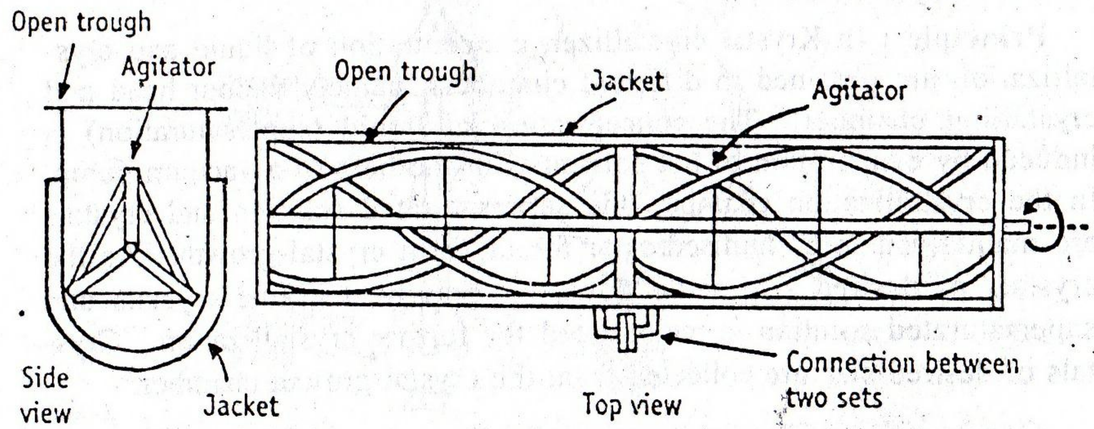


Figure 13-7. The construction of Swenson Walker crystallizer.

Working : The hot concentrated solution to be crystallized is fed at left side of the trough. Cooling water enters through (other end) 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 over flows into the draining table. While crystals are retained, the mother liquor is sent back to crystallizer. The wet crystals are conveyed to a centrifuge.

A 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 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 break the crystals to a little extent, while agitating the suspension.

Krystal Crystallizer

Principle : In Krystal crystallizer, concentration of 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 13-8. 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 : Solution is pumped, which passes through the heater. The hot solution enters the vapour head. Because of reduced pressure, the 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 tube below. The 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 of crystals in the chamber. Coarse crystals settle at the bottom, while fine crystals remain above coarser ones. Very fine crystals overflow through the liquid and enter into the re-circulating system, which then combine with fresh feed. From time to time, coarse crystals are taken out through the opening at the bottom of the chamber.

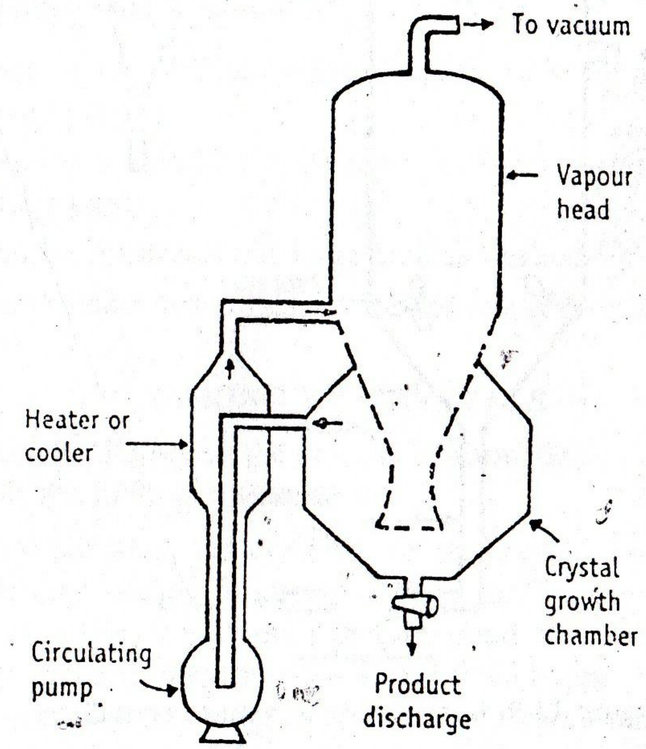


Figure 13-8. Krystal crystallizer.

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 up to 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 13-9. Vacuum crystallizer is a cylindrical body with a conical

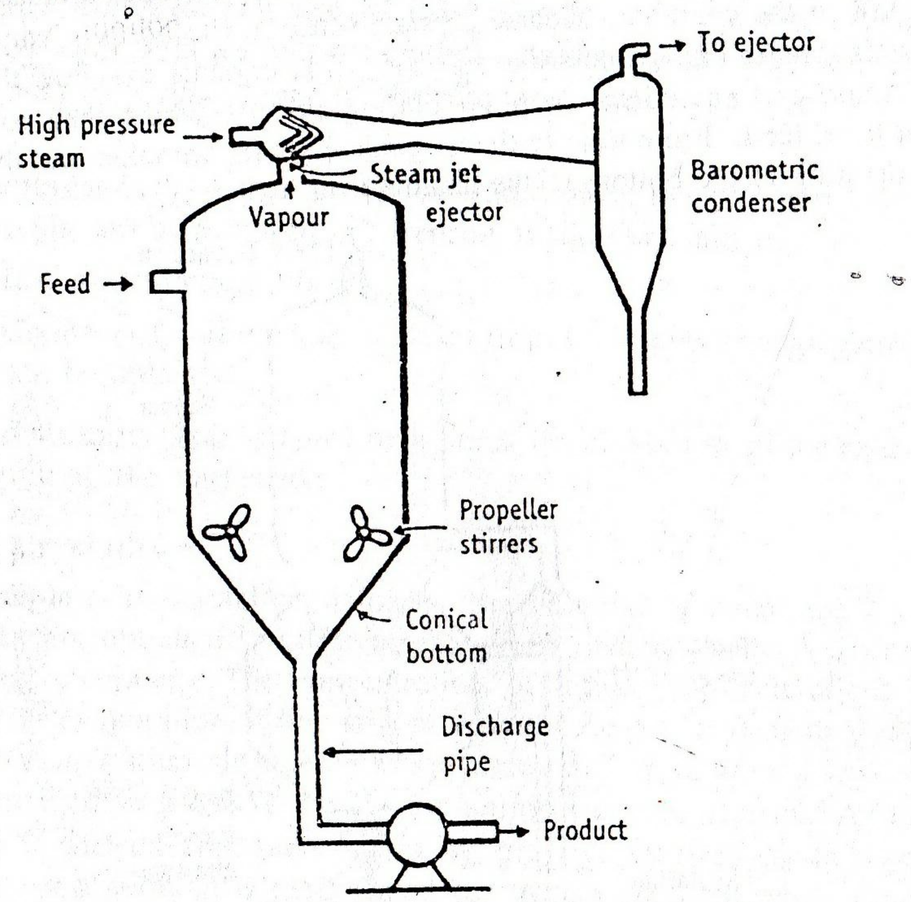


Figure 13-9. Construction of vacuum crystallizer.

bottom. A condenser is attached to the crystallizer with a vacuum pump in 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).

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 flashing, which results in evaporation of solvent. This process is allowed 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 thermolabile 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, the crystals are required to be stored in bulk either for further use or for transportation or for 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 is serious in case of small packages than in bulk packages. In some cases, the pressure of a thumb can easily break the lumps, but considerable pressure is required to break the cake in some other cases.

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

When a crystal is placed in contact of air, whose humidity is below the critical humidity, the crystal remains dry. On the other hand, if the air contains more moisture than critical humidity, the crystal absorbs moisture.

The crystals get a saturated film on the surface by adsorbing moisture. So formed saturated solution concentrates at the points of contact by capillary forces. When water evaporates or when the temperature decreases, crystallization of solute takes place to form a solid bridge.

Factors Affecting Caking

Size of the crystals : Crystals of larger size contain more void spaces. On the other hand, crystals of smaller size contain less void space and possess more points of contact. The more the points of contact, the higher will be the rate of caking. Hence, smaller sized particles tend to cake more than the larger particles.

Shape of the crystals : Spherical particles possess the least possible points of contact. The points of contact increase as the crystal shape deviates from spherical shape. Hence, distorted crystals tend to cake more than the spherical crystals.

Humidity : The higher the humidity of atmosphere to which crystals are exposed, more will be the rate of caking.

Time of exposure : The higher the time of exposure, the more will be the caking, provided the exposed atmosphere has humidity more than critical humidity.

Impurities in crystals : The crystals can be coated with the impurities derived from mother liquor. This may increase or decrease critical humidity. Once the critical humidity changes, the property of caking also changes. For example calcium chloride and magnesium chloride are the impurities for sodium chloride crystals to alter it's critical humidity.

Melting point of crystals : Melting point of certain crystals is near room temperature, crystals may melt. Then solidification by fusion of the melt leads to caking.

Temperature fluctuations : When temperature is increased, melting of the crystals takes place. Subsequent decrease in temperature leads to solidification. Therefore, temperature fluctuations cause variations in the solubility, which may lead to 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 a narrow size distribution.

(3) Crystals must have highest possible critical humidity.

(4) 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.

QUESTION BANK

Each question carries 2 marks

1. Define crystal lattice and crystal habit.
2. Enumerate the characteristics of crystals.
3. Define crystal and critical humidity.
4. Enumerate different types of crystals.
5. Name a suitable crystallizer for the following.
   (a) to get large sized crystals.
   (b) to crystallize large quantity of substance.

Each question carries 5 marks

1. Describe the working of agitated batch crystallizer.
2. What is caking of crystals? List the factors affecting and preventive measures for caking.
3. Describe the salient features of vacuum crystallizer.
4. Describe different methods by which super-saturation can be brought about.
5. Draw the solubility curves and explain its relevance in crystallization.
6. Describe the operation of a suitable crystallizer to produce large crystals.
7. What are the different forms of crystals?
8. What are the conditions to be taken during crystallization to obtain large sized crystals?
9. Describe how nucleation and crystal growth take place during crystallization.
10. What are the pharmaceutical applications of crystallization?

Each question carries 10 marks

1. Discuss the Mier's super-saturation theory of crystallization. What are the limitations of the Mier's theory?
2. Explain the principle, construction, working and advantages of vacuum crystallizer.
3. Giving neat diagram, describe the construction and working of Krystal crystallizer. Write its advantages and applications.
4. Draw a neat labelled diagram of Swenson Walker crystallizer. Discuss the construction, working, advantages and disadvantages.