

PHARMACEUTICAL ENGINEERING

Crystallization

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Keywords

Crystal characteristics, yield, crystallizing equipment, factors controlling crystallization, caking

Introduction

There has been an increasing effort in designing pharmaceutical particles with controllable qualities in terms of purity, size, shape, morphology, size distribution and surface characteristics and pharmacological properties. Polymorphism and particle size distribution of pharmaceutical particles are two very important criteria as per the guidelines of regulatory bodies and requirements of pharmaceutical process and the uses of drugs. So, undergraduate Pharmacy students must understand the process involved in production and purification of medicinal compounds in the laboratory / bulk drug manufacturing industry, characterization of these compounds and stepwise handling of drug materials in formulation industry. A formulation pharmacist has to solve many problems related to undesirable growth of crystalline active ingredients in liquid formulations. As for example, crystal growth in acetaminophen suspension can be prevented by the use of some additives like, polyvinyl pyrrolidone, bovine serum albumin, benzalkonium chloride, sucrose etc. Therefore, pharmacy students must acquire basic knowledge of '**crystals and crystallization**' to encounter and solve various problems in the laboratory and pharmaceutical industry.

Crystallization is a method of formation of solid particles within a homogeneous phase (vapor phase, liquid melt). Most of the crystalline solid substances are prepared either by solidification from liquid melt or by precipitation in chemical reaction. 'Crystallization' is one of the important unit operations that are taught in undergraduate curriculum of **Chemical Engineering** and **Pharmaceutical Engineering**. This unit operation involves knowledge of mass transfer mechanism, diffusion theory, heat transfer mechanism, hydrodynamics, solubility curves, design of equipments and selection of equipments on the basis of principles of crystallization. Each manufacturing plant requires many unique features and these must be evaluated on an individual basis in order to achieve optimum result. It is true that mechanical design of the crystallizer has a significant influence on the nucleation rate due to contact nucleation with the parts of pump, impellor etc. when suspended in a supersaturated solution. This phenomenon yields varying rates of nucleation in scale up and differences in nucleation rate when the same piece of equipment is used to crystallize different materials. All these must be taken care of in order to achieve super saturation of liquid.

Crystallization of a material from solution is important industrially because of the markets' demand due to some advantages of its crystalline solid forms. One of the important advantages of crystallization compared with other means of separation technique is that it produces highly 'pure products with good appearance' from impure solutions. Energy input is low and products with high bulk density are obtained. Drying requirement is minimum due to low moisture content. Commercial crystallization processes manufacture crystalline products from the standpoint of special demands based on definite crystal shape, size and size range of particles (crystal size distribution, CSD). Generally, narrow size range is desired. Of course, requirements of scientific works are solely restricted to yield of crystal as high as possible and its **purity**. Crystalline products have high demand in the market due to some reasons and some advantages over liquid form products.

- Handling of solid-form products with convenience than solution.
- More economical than liquid form.
- Less degradation, less contamination, more stability than solution.
- More sales appeal than liquid.
- Purity of crystalline product is more than that of a solution.

Crystallization process may be analyzed and judged from the standpoint of following aspects in order to produce good products and avoid problems encountered both within the industry and outside the industry.

1. Yield of a given product
2. Quality of product in terms of size, shape and purity of crystals
3. Uniformity in size and CSD
4. Rate of production of the desired crystals.
5. Energy requirements for cooling and evaporation, etc.

High yield and rate of production of a crystalline product at acceptable cost leads to its economical viability. But, purity of a crystalline material as medicinal compound is mandatory requirement in Pharmaceutical industry. So, purity is the first and foremost demand of the purchaser in Pharmaceutical sector. Size, uniformity in size, crystal size distribution and crystal geometry are characteristics of particles that control many physicochemical factors in making of 'formulation drugs', stability and pharmacological factors.

Crystal geometry

A crystal is the most highly organized type of non-living matter. Molecules, atoms and ions are arranged in a crystal in orderly repetitive arrays called crystal lattices and it appears as polyhedrons having sharp corners and flat sides or faces. Although relative sizes of the faces and edge of various crystals of the same materials may vary, the angle between adjacent faces is constant for all crystals of the same materials and that is the characteristics of the material causing difference in physical properties among chemicals. Therefore it is not unexpected that the formation of the crystalline material from its solution or mother liquor is accompanied by unique growth and nucleation characteristics. By limiting the degree of super saturation crystal growth rate and crystal sizes can be controlled. The crystal systems are a grouping of crystal structures according to the axial systems used to describe their lattice. Each crystal system consists of a set of three axes in a particular geometric arrangement. There are seven unique crystal systems. The cubic / isometric system has the symmetry of a cube, that is the three axes are mutually perpendicular and of equal length. The other six systems in order to decreasing symmetry are as follows:

Hexagonal: Three equal axes are in one plane at 60° to each other, one is at right angles to this plane but not necessarily of the same length as the others. Cross section is hexagonal.

Tetragonal: Three axes are at right angles, one is longer than the other two.

Orthorhombic: It is like tetragonal crystals except not square in cross-section (when viewing the crystal on end), forming rhombic prisms or dipyramids (two pyramids stuck together).

Trigonal: There is single 3-fold axis of rotation instead of the 6-fold axis of hexagonal division.

Monoclinic: Two axes are at right angles in one plane and a third axis at some odd angle to this plane like skewed tetragonal crystals often forming prisms and double pyramids.

Triclinic: Three axes are at odd angles to each other; usually it is not symmetrical from one side to the other, which can lead to some fairly strange shapes.

A crystalline substance may have the ability to form more than one form, called polymorphism. Different polymorphs possess different physicochemical properties causing difference in solubility and melting point that affect dissolution, adsorption, absorption and stability. Nowadays, atomic force microscopy (AFM) is used to map the crystal structure by imaging the molecular lattice space in all three directions.

Crystal size and shape factors

Shape factor or sphericity, ϕ_s is used to calculate the ratio of the total surface (S_p) of a crystal to the crystal volume where $S_p = \pi D_p^2$ and $V_p = 1/6 \pi D_p^3$ where D_p is the diameter of crystal.

$$\frac{S_p}{V_p} = \frac{6}{\phi_s D_p} \quad \text{and} \quad L = \phi_s D_p = \frac{6 V_p}{S_p}$$

L is the length of crystal; when $\phi_s = 1$, $L = D_p$. For cubes and spheres, $\phi_s = 1$. For granular materials range of ϕ_s is from 0.6 to 0.95. The ratio S_p/V_p is very important parameter in any surface related phenomenon. Product containing smaller crystals is more soluble than that of bigger crystals since surface area per unit volume (S_p/V_p) is greater in smaller particles. Three dimensional surface morphology, surface area and crystal structure of many therapeutic agents have effects on the manufacturing of crystal, ease of delivery of drug to the system, bioavailability, dissolution rate, absorption and adsorption of drugs.

Uniformity in size or crystals distribution

Particles of uniform size in a product are desirable for the convenience of selection of filter, washing, uniform time of dissolution and good appearance of product. Besides these, caking tendency of crystals during its storage period can be prevented since number of points of contact between crystalline particles is significantly less in uniform crystals. Actually a product batch contains various fractions of particles of different particle sizes. Wide range of particle sizes creates problem in many practical situations. So, crystal size range is made narrow by controlling some process parameters like

- adding seed crystals with desired size range.
- avoiding contact nucleation as far as possible
- removing a fraction of small size /finer particles
- dissolving smaller crystals, nuclei either by heating or adding some solvent
- increasing residence time for larger particles.

The objective is to reduce sharply the number of nuclei present so that bigger crystals formed earlier can grow properly under super saturated condition. The presence of too many nuclei leads to a large surface area and makes the supersaturation small, so the growth rate of individual crystal is low since there is decrease in potential (or concentration) between the bulk of the liquor and saturated liquid film around particle. If the process were carried out without formation of additional nuclei, it would be possible to predict exactly the size distribution of the product from the size distribution of seed crystals, because the rate of growth of a linear dimension of crystal is constant for all crystals in the batch. The size distribution is generally expressed by the mass fractions in a screen analysis rather than number of particles present in particular fraction of sizes.

Yield

In crystallization processes, it is often needed to calculate the theoretical yield so that actual yield can be compared with it. Crystals are allowed to grow for sufficient period to reach targeted growth. Finally, mother liquor sheds its super saturation and attains equilibrium at final temperature. Now, solid crystals are separated from mother liquor and further processed. Computation of yield of crystal involves a material balance. The yield can be predicted from the difference of concentration of feed solution and solubility of mother liquor (saturated). Predicted yield may not match actual yield due to slow growth longer time required to reach equilibrium, insufficient exposure of surface area when heavier particles settle at the bottom, less growth in the location with poor super saturation, viscous nature of solution etc. In such a situation, the final mother liquor may retain appreciable super saturation and actual yield is always less unless mode of nucleation is changed and above-mentioned causes are solved. The solubility is expressed commonly in terms of anhydrous salt per 100 mass of pure solvent or mass fraction. The calculation of yield of a nonhydrated salt (crystal without water of crystallization) from solution is simple since the amount of solvent in the liquid remains unchanged.

$$\text{Yield} = \left(\frac{x_1}{100} - \frac{x_2}{100} \right) \times \text{total amount of solvent, } x_1, x_2 \text{ are the concentration of anhydrous}$$

material and solubility of crystal in feed solution and in mother liquor respectively.

If evaporation loss (z) is accountable and y be the amount of initial solvent

$$\text{Yield} = \frac{x_1}{100} \times y - \frac{x_2}{100} (y - z).$$

If the product is hydrated with water of crystallization, quantity of solvent decreases during the operation, but the amount of water (free water) in excess of that required hydrating total anhydrous material (salt (P) in solid product + salt (S) left in saturated mother liquor) is constant.

A material balance can be carried out on the basis of excess (free) solvent. Solubility is easily expressed in terms of mass of hydrate per unit mass of excess water.

Let w_1 , w_2 be the respective amount of water associated with P lb and S lb of anhydrous material as water of crystallization.

Let w_3 be the amount of free water. Considering no loss due to evaporation, we may write mass balance on the basis of 1000 lb of total water.

$$1000 = w_1 + w_2 + w_3$$

Mass of product salt (hydrated) = $P + w_1$ and Mass of salt (hydrated) = $S + w_2$ in mother liquor.

$(P+S)$ is the total amount of anhydrous substance.

Concentration of total hydrate per unit amount of free water in the solution is $(P + w_1 + S + w_2)/w_3$ and solubility of hydrate in mother liquor is $(S + w_2) / w_3$

$$\therefore \text{yield} = \left(\frac{P + S + w_1 + w_2}{w_3} - \frac{S + w_2}{w_3} \right) \times w_3 = P + w_1$$

Amount of water of hydrate is calculated as follows:–

$$(w_1 + w_2) = (P + S) \times \frac{(\text{number of water of crystallization})}{\text{Molecular weight of anhydrous salt}} \times \text{molecular weight of water}$$

Purity of product

Purity of a crystalline product is judged by many ways, for example determination of melting point of crystalline substance. Generally it is thought that ‘crystal form’ is the purest form of a substance, but it may retain impurities on its surface due to adherence of impure mother liquor on its surface while separating it from final magma. Smaller crystals will retain relatively more impurities than large crystals due to large specific surface area of the smaller crystals. “Washing of crystal’s surface” is done with the same solvent to remove impurities. Sometimes mother liquor is occluded within the empty space of an agglomerate / lump that leads to poor quality product. Proper washing of agglomerated crystal is difficult. Formation of agglomerated crystal during crystallization can be minimized by proper agitation. Even after thorough washing, the product cannot reach the limit of purity, then it is further processed to produce more pure product by the recrystallization method by utilizing the difference in solubility of crystal and unwanted impurities. **Recrystallization** is often practiced both in laboratory research work and industry to achieve high-grade purity in pharmaceutical ingredient. Recrystallization is done by repeated crystallization of the same material by dissolving in solvent to remove the residual soluble impurities that has been adhered to the surface of crystal from mother liquor. It is possible to produce crystals of varying particle shape and of specific polymorph by selection of proper operating variables and design of equipment.

Recrystallization can be explained by the following example:

Purity of benzoic acid (antimicrobial agent) is assessed by assay method and melting point (122°C). If impurities like phthalic acid, benzyl benzoate are present with benzoic acid, dissolving it in hot water and filtering it can remove these. Upon cooling benzoic acid crystals are formed and then crystals are separated by filtration. This step may be repeated unless satisfactory product is obtained. After purification, the amount of final product will have been reduced due to removal of impurities and loss of material in attaining equilibrium during repeated recrystallization. Calculation of percentage yield is done as follows.

$$\% \text{ Yield} = \frac{\text{Mass of final product}}{\text{Mass of initial sample}} \times 100$$

This indicates extent of impurity in the original sample.

Nucleation and Crystal growth

In the formation of crystal two-steps is required (1) generation of a new particle (2) its growth to macroscopic size. The first step is called nucleation. Neither formation of a new crystal nor its growth is possible in saturated or unsaturated solution.

Rate of nucleation is very important for controlling crystal size distribution (CSD). The rate of nucleation is the number of new particles formed per unit time per unit volume of magma or solid free mother liquor. The sequence of stages in the evolution of a crystal is as follows:

Cluster – embryo – nucleus – crystal

Nuclei are in a state of unstable equilibrium if it loses units, it dissolves, if it gains units, it grows and becomes a crystal. Solubility of large crystal is less than that of smaller crystals in the micrometer range because of significant surface energy per unit mass on smaller crystals. Smaller crystals are in a state of unstable equilibrium in a supersaturated solution. As a result larger crystals grow until the small crystals disappear. This phenomenon is called Ostwald ripening. The effect of particle size on solubility is a key factor in nucleation.

At first, a loose unstable aggregate called 'cluster' is formed when several molecules/atoms of solute come into contact due to random collision.

Formation of embryo initiates lattice arrangement and formation of a new and separate phase. Though embryos have short lives but it may grow to a size as that of nucleus, which is the smallest assemblage of particles. Formation of stable nucleus depends on number of units assemble together. Nucleation may be of three types: Spurious nucleation, primary nucleation and secondary nucleation. Spurious nucleation produces crystals of poor quality with abnormal needle like or whisker like growths from the ends of the crystals. It occurs at large super saturation ($\Delta T > 8^{\circ}\text{C}$). This is called needle breeding. Another growth related spurious nucleation called 'Veiled growth' gives the crystal surface 'milky' appearance due to rapid crystal growth and occlusion of mother liquor into the crystal faces. This problem can be avoided by growing crystals at low super saturation and by using well-designed and operated pumps and agitators.

The first, step of 'nucleus' formation is called 'nucleation' or primary nucleation. On an industrial super saturation driving force is necessary to initiate primary nucleation. The second chief mechanism in crystallization is called secondary nucleation. There, crystal growth is initiated with contact. The formation of nuclei is attributable to fluid shear and to collisions between existing crystals with each other or with the walls of the crystallizer and rotary impellers or agitator blades. On impact with these moving parts of crystallizer, soft or weak crystals can break into fragments and so give new crystals. Attrition is the only source of new crystals that is independent of super saturation. No complete theory is available to model secondary nucleation, so its behavior can be anticipated by experimentation. It is the most common type of nucleation in industrial crystallizers and it is influenced by the intensity of agitation. Growth of crystals is optimum at low super saturation. The energy at which a crystal must be struck is very low and no visible effect is observable on the crystal surface.

Crystal growth is a diffusion process; solute molecules reach the growing surface by diffusion through the liquid phase and are organized into space lattice. Growth rate of most crystals is linear with super saturation. The rate of deposition is proportional to driving force between the bulk of the liquor and that wetting the surface of the crystal that is approximately saturated with respect to crystals of that size. The driving force will vary because of the increasing solubility for crystals with lower size range. Crystal growth takes place in metastable zone that lies between saturation and nucleation limits. In this region the solution is supersaturated and no nucleation occurs when crystals are growing.

To tailor the growth process according to requirement, growth parameters such as temperature, pH, concentration and additive levels need to be optimized. Nowadays in situ visualization of growth by 'Atomic force microscopy (AFM)' help to optimize growth conditions in producing crystals with desired characteristics.

Miers super saturation theory

In the year 1927, Miers, SIR, H.A. postulated a theory on super saturation. Miers theory explains growth of nuclei with respect to super solubility and solubility curve under some limitations. Let us know first about solubility curve. When equilibrium is attained at final temperature, mother liquor becomes saturated in crystallization process and rate of formation of nucleus is balanced by the rate of dissolution of nucleus. The equilibrium relationship is the solubility curve. Solubility data for different solids had been expressed as function of temperature. Solubility chart displays various types of profiles like curves with positive and high slope (KNO_3), positive and very low slope (NaCl), negative slope ($\text{MnSO}_4\text{-H}_2\text{O}$). For most of the materials, solubility curves follow firstly i.e. high and positive slope. Solubility curve represents the maximum concentration of solutions that can be obtained by bringing solute into equilibrium with solvent. This curve represents final concentration of mother liquor toward which supersaturated solution approaches. Super saturation is attained by decreasing temperature of highly concentrated solution or decreasing amount of solvent by evaporation or by both.

Miers super saturation theory is explained with the help of following figure.

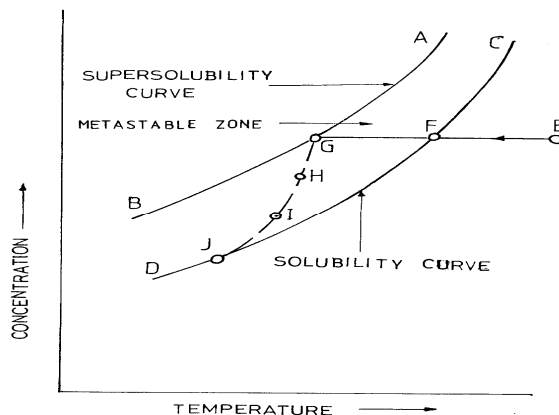


Fig. 1: Miers solubility curve

AB – super solubility curve, CD – solubility curve, E – Feed location, under saturation, F–solution cools to saturation, G – Metastable zone, nucleation begins, H– Concentration

of mother liquor decreases with crystal growth, I – Crystal growth during cooling and decrease of concentration of solution, J – Exit location, saturated solution

Let us consider a concentrated solution that is free of any kind of solute either solute of crystalline material or any foreign substance. Point E represents certain composition and temperature. Now, this solution is cooled gradually in the direction as shown in the figure along EFG. It first crosses the solubility curve at F and it seems that crystallization would begin immediately. But it begins only when it is super cooled sufficiently past the curve CD, somewhere near the point G. When crystal formation begins the concentration of the substance in the solution falls and the curve follows roughly along GHJJ. The curve AB represents super solubility curve. Any short of this line, nuclei formation and its further growth cannot occur in pure solution. The theory explains that formation of nuclei is possible under good extent of super saturation and for its subsequent growth necessary requirement is that concentration of solution should exceed normal solubility.

The exact mechanism of arrangement of randomly moving molecules into a regular crystal lattice is not clearly understood. Both the molecules of solute and solvent move in their various molecular paths, when a group of molecules come in close proximity due to accidental collisions, form a loosely held cluster by mutual attraction. Stability of these clusters depends on high level of super saturation. As soon as crystal grows into appreciable size, it continues to grow due to continuous deposition of solute on the surface of crystal. These crystals have lesser tendency to dissolve in the solution due to its bigger size. The super solubility line according to Miers theory is not restricted to a definite curve like AB, but rather it is confined to an area or zone. So, formation of nucleus begins around the curve within the super solubility zone. Miers theory is based on the postulation that the solution consists of molecules of pure solvent and solute, in which no seed particle or any foreign particle is present, so formation of nucleus depends solely on accidental combination of the solute molecules that form permanent crystal. Formation of nuclei in the large volume of supersaturated solution is very rapid than small volume liquor. In large volume liquid chance of collision is more. Nucleus formation is rather delayed in absence of any particulate matter. In commercial practice, solutions are exposed to the air and dust particles enter the solution and act as nuclei even if seed particles of same substance are not added.

In order to justify the Miers super solubility curve it is necessary to deal with pure solutions completely free of any type of particle of solid matter. The following are the limitations of Miers theory:

1. Time be long enough
2. The volume of the solution be large enough
3. Presence of solute / foreign particle.

If any one of the above three is maintained in crystallization then existence of super solubility curve according to Miers theory is no longer possible and solution does not need super cooling for crystal formation. Practically greater the degree of super saturation, the greater is the probability of nucleus formation and more rapid is the growth of nucleus, whether it is spontaneously formed nucleus or an accidental one.

Super saturation method

1. Super saturation by cooling
2. Super saturation by evaporation of solvent.
3. Super saturation by adiabatic evaporation (cooling plus evaporation)
4. Salting out by adding a substance that reduces the solubility of the substance of interest.

In case of solubility with strong temperature dependencies the cooling method is more attractive whereas with low dependencies on temperature the evaporation method is adopted.

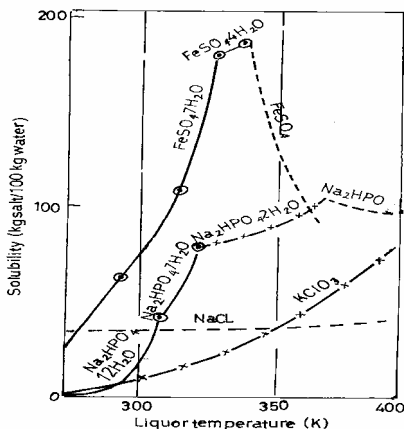


Fig. 2: Solubility curves of salts

When solubility curve decreases appreciably with temperature i.e., rate of decrease of solubility with the decrease of temperature is high, so curve is steeper. KCl, AgNO₃, CuSO₄·5H₂O and Na₂HPO₄·H₂O are the example of crystals that follow Method 1.

Substances like NaCl, Na₂SO₄, and CaCl₂ follow method 2. Solubility curves of these substances are flat type i.e. solubility does not decrease appreciably with the decrease of temperature. In this case, yield will be very poor if method 1 is followed.

The third method, cooling adiabatically under a vacuum is the most important method for large-scale production. If a hot solution is evaporated under a vacuum, the solvent flashes because total pressure is less than the vapor pressure of the solvent at the temperature at which it is introduced. Now, the solution becomes supersaturated due to evaporation of solvent and adiabatic cooling.

The last method is not very much used. In this method, a foreign substance is deliberately added to reduce the solubility to such an extent that the desired solute crystallizes.

Crystallization Equipments

There are different types of equipments used for making crystals. The design of these equipments is based on the method of super saturation.

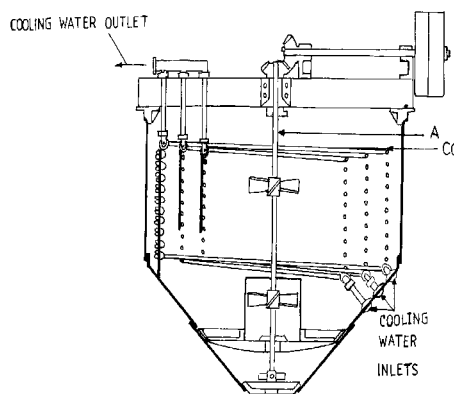
Names of equipments:

1. Super saturation by cooling alone – Tank crystallizer, Agitated batch crystallizer. These two are used in batch process, though tank crystallizer is obsolete one. Swenson Walker crystallizer falls under this category and it is used in continuous process.
2. Super saturation by adiabatic cooling: Different kinds of vacuum crystallizers are used to make crystals by this method.
3. Super saturation by evaporation: Krystal evaporator and salting evaporator are two examples under this type of super saturation.

All these equipments are made of stainless steel.

Description of some crystallizers:

(i) Agitated batch crystallizer: The crystallizer body is equipped with a centrally located agitator, cooling pipes. The upper part of the vessel is cylindrical and closed at the top. The lower part of the vessel is conical and its bottommost part is used to drain out final magma. Magma is defined as the slurry containing **product crystal** and saturated **mother liquor**. Hot concentrated solution of a substance is induced in the crystallizer and it is agitated with the impeller. Cold water flows through the cooling coils to transfer heat from the hot solution. Cold water transfers heat due to heat of crystallization too. As temperature drops, super saturation is achieved that initiates crystallization. Agitator facilitates heat transfer operation throughout the solution and maintains uniformity of temperature in the solution and keeps the growing crystals in suspension so that these can grow uniformly. Thus agitator prevents formation of aggregates.



A – Impellor, CC- cooling coil
Fig. 3: Agitated batch crystallizer

Rate of production of crystals is low due to batch process. Since temperature at the surface of cooling coil is least so rapidly formed crystals get deposited on the surface of cooling coil and cause hindrance in heat transfer rate. These are the disadvantages of agitated batch crystallizer. After certain period of growth, magma is transferred to centrifuge where crystals are separated from mother liquor.

The Swenson–Walker crystallizer: It consists of an open semi cylindrical trough, bottom part of which is welded with a jacket to run cold water through the jacket in counter current direction to that of solution. It is equipped with a slow speed long pitched spiral agitator moving at 7 r.p.m., that is fitted as close to the bottom of the trough as possible i.e. a narrow clearance is maintained. A single unit (trough) is 24 inch wide and 10 feet long. Length of crystallizer may be increased up to 40 feet by joining 4 units. If more units are required, these can be arranged one above another and solution fall from the upper row to the next lower one.

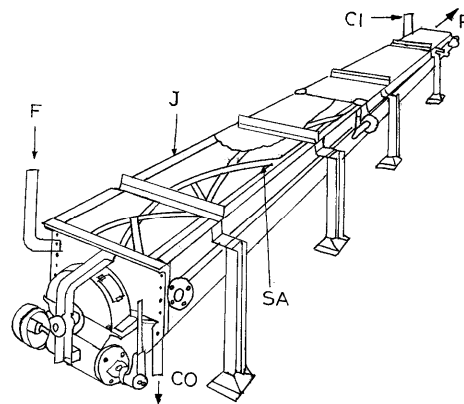


Fig. 4: Swenson Walker Crystallizer: F-feed, J- Jacket, CI-coldwater inlet, CO-coldwater outlet, SA-spiral agitator, P- product.

The hot concentrated solution is fed at one end of the trough and flows to the other end slowly. When solution is cooled to desired degree of super saturation, crystals start forming. At the end of the crystallizer, crystals along with mother liquor overflow to a draining table that separates mother liquor from crystals. Mother liquor is returned to the process and wet crystals are conveyed to a centrifuge.

The spiral agitator functions by conveying crystals in the forward direction and it keeps particles in suspension and prevents accumulation of crystals at the bottom of trough. This agitator lifts the deposited crystals from the bottom and spreads throughout the solution and thus keeps these crystals in suspension facilitating uniform growth of crystals.

Vacuum Crystallizer: This falls in the category of modern type crystallizers. It is closed vessel, at its top vacuum is maintained by a condenser with the help of a steam jet vacuum pump or booster. Large quantity of material can be processed in small floor space and labor cost is also saved in this type of crystallizer.

Vacuum crystallizer consists of a cone-bottomed vessel, which is fitted with a barometric condenser at the top and propellers in the conical part, elutriation leg at the bottom of the vessel. Hot saturated solution (feed) well above the boiling point at the pressure in the crystallizer is introduced into the main crystallizer body via a slow speed low head circulating pump and a heater, through a tangentially cut inlet pipe that causes a swirling motion within solution. Liquid level in the crystallizer body is maintained up to certain mark. At the top of liquid, vacuum is maintained that corresponds to be boiling point of the solution lower than the feed temperature. The solution so introduced into a vessel in which a vacuum is maintained, the solution flashes and solvent, evaporates due to adiabatic evaporation. As a result solution gets cooled spontaneously to equilibrium temperature; since it is adiabatically cooled i.e. both the enthalpy of cooling and the enthalpy of crystallization provide enthalpy of vaporization. Super saturation is generated due to both cooling and evaporation. Temperature gradient and concentration gradient thus formed due cooling and evaporation are two driving potential to create nucleation. Vapors are formed in the empty space above the solution and discharged through the top outlet. It is evident that the vapor from the crystallizer cannot be condensed at low pressure with the usual cooling water temperatures available. This vapor is compressed and then condensed by ordinary cooling water. The crystals so formed in the body due to super saturation, fall through the conical bottom of vessel into elutriation leg that helps to

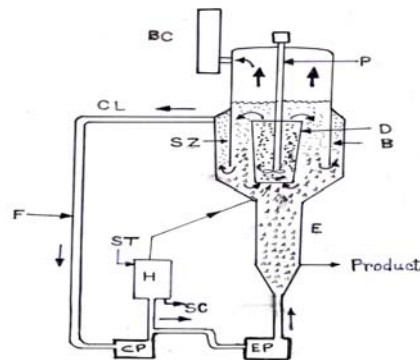


Fig. 5: Vacuum Crystallizer: B- barometric condenser, D- Downpipe, F- feed
ST-steam inlet, SC- steam condensate, H-heater, PM- Pump, C-centrifuge, M-
mother liquor, P-product crystal.

classify and separate bigger size particles. Now, product magma (crystal along with mother liquor) is discharged through outlet and fed to centrifuge, part of mother liquor is re-circulated. Function of tangential inlet of the pipe is that it creates swirling motion and thus facilitates flashing of solvent and equilibrates magma within the vapor. The simple vacuum crystallizers are not equipped with propellers. So, the effect of static head due to solution creates problem in generating adequate nucleation. So, both the evaporation and

cooling are confined to the surface zone. As a result concentration and temperature gradients are formed near the surface. Therefore, super saturation prevails near the surface and crystals tend to settle to the bottom region with little or no super saturation. This problem can be overcome if a stirrer is fitted centrally.

Function of propeller is to prevent the tendency of the feed to be short circuited to the discharge pipe without being flashed. It helps to maintain uniformity of temperature and concentration of solution.

Draft tube baffle (DTB) crystallizer: Draft tube baffle crystallizer is based on the same principle as that of vacuum crystallizer but it is more versatile and effective equipment. The main crystallizer body is equipped with a condenser at the top, elutriation leg at the conical bottom, a recycling loop at the side of the body, a centrally located propeller, a draft tube around the propeller and an annular space within the crystallizer body. A pump assembly is used to maintain circulation of fluid. Hot solution enters the main crystallizer body. The solution is super saturated adiabatically under the vacuum maintained at the top, due to evaporation of solvent and decrease of temperature of solution. Draft tube acts as baffle. It controls circulation by promoting axial flow of fluid thus facilitating maintenance of temperature and concentration gradient throughout the solution and allowing fine particles to flow in the upstream. In this crystallizer, all the fine particles

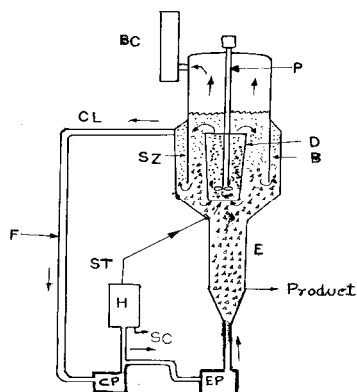


Fig.6 : Draft tube baffle crystallizer: BC- barometric condenser, CL-clear liquor, F-feed, CP- circulating pump, EP- elutriation pump, ST-steam, SC-steam condensate, H-heater, E-elutriation leg, SZ- settling zone, D- draft tube, B-baffle, P-propeller.

are not grown simultaneously. Some fraction of fine particles is removed in the upstream. When fluid enters the annular zone, bigger particles are settled here due to baffling effect and very finer particles float in the upstream and thus unwanted nuclei are removed through the recycle loop. In this way magma density is sharply increased within the body. A part of this recycled liquid is mixed with the fresh feed and is pumped to the main crystallizer body via a heater and another part of liquid is introduced into the elutriation leg via an elutriation pump. Elutriation leg facilitates in classification of crystals according to size while flowing in the upward direction through it. Upward stream carries

away some smaller particles into the main crystallizer body for further growth. Product is discharged through the outlet and fed to the centrifuge to separate out crystals from mother liquor. This type of crystallizer produces crystals with narrow crystal size distribution. Draft Tube Baffle Crystallizer is an elaborated Mixed Suspension Mixed Product Removal (MSMPR) design, which has proven to be well suited for vacuum cooling and for processes exhibiting a moderate evaporation rate. MSMPR is an idealized crystallizer model that follows some stringent requirements. The DTB crystallizer has proven to be suitable for many products such as boric acid, Glauber salt, citric acid.

The Krystal Crystallizer: The Krystal or Oslo crystallizer is extensively used where large quantities of crystals of controlled size are required. The basic principle is to flow a supersaturated solution to bed of crystals which are maintained in a fluidised state. The Krystal crystallizer consists of a vapor head (A) that is attached with a condenser at the top and connected with a long specially designed discharge tube (E) extended well to the bottom of crystal growth chamber B. Feed solution is usually introduced into the suction of pump C and then it is sent to vapor head through heater. Vapor formed at the top is released and discharged into condenser and vacuum pump. The hot solutions in the chamber A become supersaturated due to evaporation but crystals are not formed in this chamber. Super saturation produced in chamber A is discharged on the crystals suspended in an upward flowing stream of liquid at the bottom of Krystal growth chamber. When the liquid becomes saturated at equilibrium, it leaves the chamber through F for recirculation. Coarser particles remain at the bottom and finer particles remain at the top of crystal bed and re-circulated liquid carries away finest particles and enters the vapor chamber via the heater and pump. Coarse crystals are discharged through the bottom (G) at intervals.

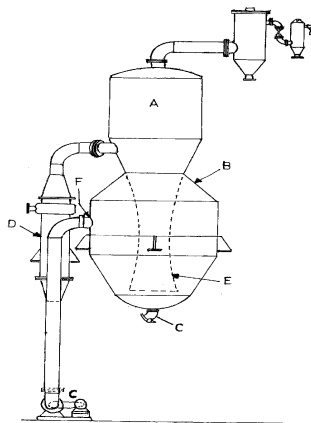


Fig.7: Krystal crystallizer: A- vapor head, B-crystal growth chamber, C- circulating pump, D- heater or cooler, E- discharge tube, F- overflow to circulating pump, G- product outlet.

A typical Oslo crystallizer for the production of $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$ is fed with saturated solution at 393°K and the temperature of the plant is 313°K with a feed rate of 2000 kg/h and a circulation rate of 50000 kg/h, the circulating liquid becomes heated to 316°K .

Mass balance in crystallization

Mass balance in any operation acts as a monitor that facilitates quantification of converted products. In crystallization yield of product is calculated by mass balance let us consider an example of hydrated magnesium sulphate ($\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$).

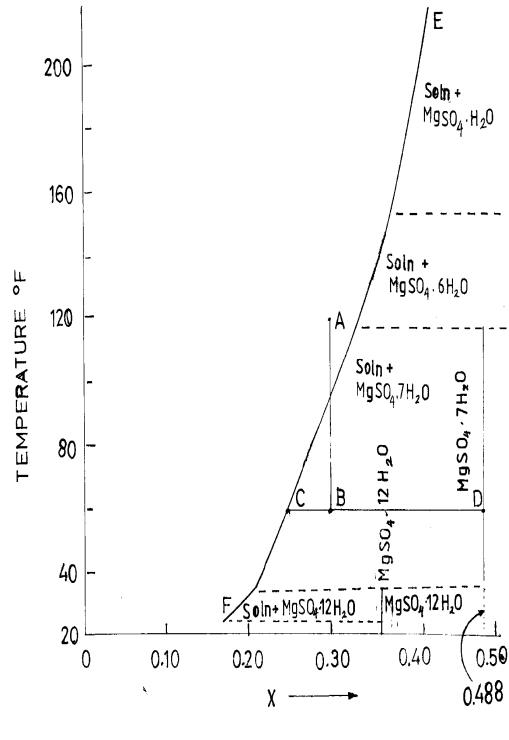
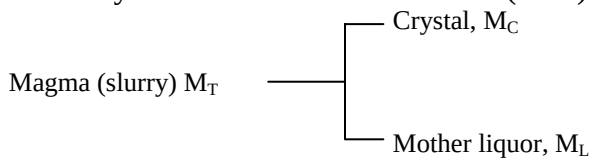


Fig. 8: Solubility curve (ACF) of MgSO_4 , X-mass fraction

In solubility diagram (Fig.8) various hydrated forms of magnesium sulphate are displayed at various zones under the curve i.e. $\text{MgSO}_4 \cdot 12\text{H}_2\text{O}$; $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$; $\text{MgSO}_4 \cdot 6\text{H}_2\text{O}$; $\text{MgSO}_4 \cdot \text{H}_2\text{O}$. These zones are in relation with concentration and temperature of magnesium sulphate. Let us consider a point A (0.3, 120°) that represents hot unsaturated solution. It is cooled to 60°F (B) to achieve super saturation and kept at 60°F for long period to form crystal. Now, magma is split to crystal and mother liquor (saturated liquor at 60°F). Co-ordinate of crystal or mass fraction (x_c) is obtained at D, where BD intersects vertical line. Co-ordinate of mother liquor is obtained at C where CB intersects solubility curve. CD is isothermal line (60°F).



$$\therefore M_T = M_L + M_C$$

Considering crystallization by cooling method without any loss due to evaporation, we may write material balance equation for anhydrous magnesium sulphate

$$M_T x_T = M_L x_L + M_C x_C$$

$$\text{Or, } (M_L + M_C) x_T = M_L x_L + M_C x_C$$

$$\text{Or, } \frac{M_L}{M_C} = \frac{x_C - x_T}{x_T - x_L}$$

Now, adding 1 on both sides we get

$$\frac{M_T}{M_C} = \frac{x_C - x_L}{x_T - x_L} \quad \text{or, } \frac{M_C}{M_T} = \frac{x_T - x_L}{x_C - x_L} \quad \dots(1)$$

x_F, x_L, x_C are mass fractions of anhydrous magnesium sulphate in feed, mother liquor and crystal. x_c can be obtained by the following ratio or from solubility chart.

$$x_c = \frac{\text{Molecular weight of } \text{MgSO}_4}{\text{Molecular weight of } \text{MgSO}_4 \cdot 7\text{H}_2\text{O}} = 0.488$$

Above equations help to calculate yield of crystal, when mass fraction are known.

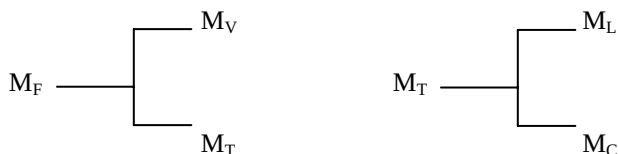
There is easy way to determine any ratio of masses ($M_L/M_C, M_L/M_T, M_C/M_T$) i.e. by the center of gravity principle.

Let us consider now, crystallization by adiabatic evaporative or adiabatic cooling method where loss of solvent due to evaporation is accounted in mass balance. Mass of feed (M_F) is not same as mass of magma or slurry (M_T).

Table 1

Item	Mass, lb	Mass fraction	Enthalpy, BTu/lb
Feed, F	M_F	x_F	h_F
Evaporated solvent, V	M_V	y	H_V
Slurry, T	M_T	x_T	h_T
Mother liquor, L	M_L	x_L	h_L
Crystal, C	M_C	x_c	h_c

Following are the mass balance equations for solution and anhydrous substance.



$$\therefore M_F = M_V + M_T; \quad M_T = M_L + M_C$$

$$\text{and } M_F x_F = M_V y + M_T x_T;$$

$$M_T x_T = M_L x_L + M_C x_C$$

By algebraic method, above equations is solved and ratio of different masses can be expressed as before:

$$\frac{M_V}{M_T} = \frac{x_T - x_F}{x_F - y} \text{ adding 1 on both sides, we get}$$

$$\frac{M_F}{M_T} = \frac{x_T - y}{x_F - y}, \quad \dots(2)$$

Ratio of masses can be expressed with the help of enthalpy of different items.

$$\frac{M_F}{M_T} = \frac{h_T - H_V}{h_F - H_V} \dots(3)$$

$$\text{and } \frac{M_V}{M_F} = \frac{h_T - h_F}{h_T - H_V} = \frac{h_F - h_T}{H_V - h_T} \dots(4)$$

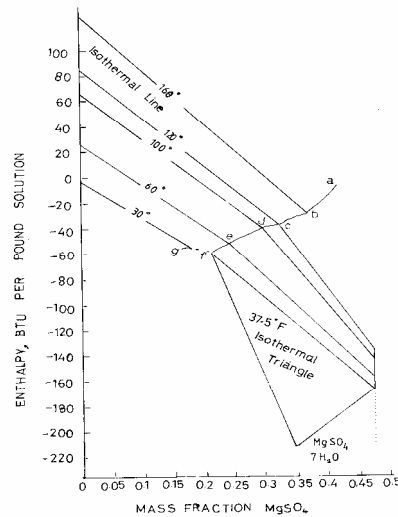


Fig.9: Enthalpy –concentration diagram

The above expressions (equation 2, 3 and 4) can be written easily with the help of center of gravity principle. In the Fig.10 (Enthalpy – concentration diagram), V, F and T are in equilibrium so these three points are on the same straight line. It is true for the L, T and C.

Table 2

Items	Mass fraction and mass	Numerator L.H.S.	Denominator L.H.S.	Ratio	Numerator R.H.S.	Denominator R.H.S.
V,F,T	y, x _F , x _T M _V ,M _F ,M _T	M _F	M _T	M _F /M _T	x _T - y	x _F - y

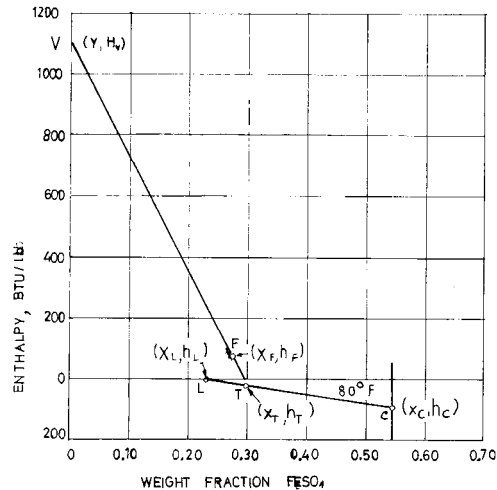


Fig.10: Enthalpy concentration diagram

When numerator of L.H.S. involves mass of feed (M_F) then numerator of R.H.S. is equal to difference of mass fractions of slurry (x_T) and vapor (y). Similarly, when denominator of L.H.S. involves mass of slurry (M_T) then denominator of R.H.S. is equal to difference mass fractions of feed (x_F) and vapor (y), (see equation -2).

By knowing required data from enthalpy concentration chart as for example Fig.9, any unknown item can be calculated. There is another equation based on mass balance, for the estimation of yield of crystals produced by cooling method.

$$y = RW_1[C_1 - C_2(1-E)] / [1 - C_2(R-1)]$$

y – yield of crystal,

R = (molecular weight of hydrate / molecular weight of anhydrous salt).

E = (mass of solvent evaporated / mass of solvent in the initial solution)

W_1 – mass of initial solvent

C_1, C_2 – Initial and final concentration of solution in terms of mass of anhydrous salt per unit mass of solvent.

Energy balances

Energy balances are used to calculate the cooling requirements. In Swenson Walker crystallizer-cooling method is used and no evaporation occurs. Solution is split into solid crystal and mother liquor. If quantities and corresponding enthalpies are known then heat balance can be carried out.

$$M_F h_F = M_L h_L + M_C h_c + q$$

M_F, M_L, M_C is the mass flow rate (lb/hr) of feed solution, mother liquor and crystal. h_F, h_L and h_c are their respective enthalpies in BTU/lb, q is the amount of heat withdrawn by cooling.

$$q = \text{Mass of water (cooling agent)} \times \text{specific heat} \times \text{temperature difference} + M_C h_c$$

$q = M \times c_p \times t + M_C h_c$, here h_c is called heat of crystallization, it is latent heat evolved when solid crystals are formed from a solution. It is exothermic and numerically it is

equal to heat of solution i.e. heat absorbed by crystals dissolving in a saturated solution. h_c is negative of heat of solution for particular compound. q can be calculated from heat transfer equation

$$q = U \times A \times \Delta t_{lm}$$

U is overall heat transfer coefficient and Δt is the log means temperature difference.

$$\therefore m c_p \Delta t + M_c h_c = U A \Delta t_{lm}$$

A is area of heat transfer. The amount of heat to be removed by cooling could be visualized as the heat required to cool the feed solution from the initial to final temperature without any solid phase precipitating out, plus the heat liberated due to heat of crystallization. Enthalpy data can be obtained from enthalpy concentration chart.

Enthalpy concentration diagram illustrates various enthalpy concentration zones according to concentration, temperature of solution. It displays isothermal lines, isothermal triangles, unsaturated zone, and solubility curve.

Problem:

1. A solution of 1000 kg of Na_2SO_4 in 5000 kg of water is cooled from 333 to 283°K in an agitated mild steel vessel of mass 1500 kg, the specific heat of steel being 0.5 KJ/kg deg k. At 283°K the stable crystalline phase is $\text{Na}_2\text{SO}_4 \cdot 10 \text{H}_2\text{O}$ and at 291°K the heat of solution is – 78.5 MJ/k mol. The mean heat capacity of the solution is 3.6 kJ/kg deg K. If during cooling, 2% by mass of water is lost by evaporation, estimate the yield of crystals formed and the heat to be removed. The solubility of anhydrous salt at 283°K is 8.9 kg/100 kg water.

Solution:

The heat of crystallization

= – heat of solution

$$= 78500 \text{ kJ/kmol} = \frac{78500}{322} = 244 \text{ kJ/kg}$$

The latent heat of vaporization of water = 2395 kJ/kg

$$M_F = 6000 \text{ kg}, \quad x_F = \frac{1000}{6000}$$

2% water is evaporated

$5000 \times 0.02 = 100 \text{ kg } (M_v)$; Therefore, 100 kg of water is evaporated.

$$M_F = M_T + M_v$$

$M_T = 5900 \text{ Kg}$ = weight of slurry

$$X_C = \frac{142}{322} = 0.44099; \quad X_F = 0.1666; \quad X_T = \frac{1000}{5900} = 0.16949; \quad y = 0;$$

$$X_L = \frac{8.9}{108.9} = 0.08172 \quad \therefore \frac{M_C}{M_T} = \frac{x_T - x_L}{x_C - x_L},$$

$$\text{Therefore } M_C = M_T \times (x_T - x_L) / (x_C - x_L)$$

$$M_C = 1441.37 \text{ kg}$$

$$\text{Heat of crystallization} = 1441.37 \times 244 = 351694.28 \text{ kJ}$$

$$\begin{aligned} \text{The heat to be removed from the solution} &= M_F \times \text{mean heat capacity} \times \text{temperature drop} \\ &= 6000 \times 3.6 (333 - 283) \end{aligned}$$

$$= 1080000 \text{ kJ}$$

$$\text{Heat removed from the vessel}$$

$$= 1500 \times 0.5 (333 - 283) = 37500 \text{ kJ}$$

$$\text{The heat lost by evaporation}$$

$$= 100 \times 2395 = 239500 \text{ kJ}$$

$$\text{and therefore, the heat to be removed} = 10,80000 + 35700 - 239500$$

$$= 1229694.3 \text{ kJ} = 1229.76 \text{ MJ (approx.)}$$

Yield of crystal can also be calculated by using the following equation.

$$Y = RW_1 [C_1 - C_2 (1 - E)] / [1 - C_2(R - 1)]$$

$$[R = \frac{322}{142}, C_1 = \frac{1000}{5000} = 0.2 \text{ kg/kg of water}, C_2 = 0.089 \text{ kg/kg of water at } 283^\circ\text{K},$$

$$W_1 = 5000 \text{ kg water}, E = 0.02 \text{ kg/kg water}]$$

$$Y = \frac{322}{142} \times 5000 [0.2 - 0.089 (1 - 0.02)] / [1 - 0.089 (2.27 - 1)]$$

$$= 1441.65 \text{ kg}$$

2. An aqueous solution of NaNO_3 (M.W.85) is fed to a continuous crystallizer at a rate of 5000 kg/hr. The solution is cooled from 90 to 40°C . The cooling agent is water. Loss of water from feed due to evaporation in the crystallizer is 3% of the feed solution. Determine the quantity of heat (kilo watt) that must be withdrawn by the cooling agent.

Data:

Mass fraction of NaNO_3 in feed (x_F), mother (x_L) liquor and crystal (x_c) are 0.5763, 0.5111 and 0.5941 respectively.

Heat capacity of feed solution (c_p) = 2469.57 J/kg $^\circ\text{K}$

Latent heat (λ) of vaporization of water 2345 kJ/kg

Heat of crystallization of NaNO_3 (h_c) = 21100 kJ/k mole.

Solution: Basis – 1 hr.

Amount of crystal produced = M_c

By mass balance we get,

$$M_T x_T = (M_T - M_c) x_L + M_c x_c \dots (1)$$

M_T is the mass of slurry. $M_T = M_F - M_V$

M_V is the mass of vapor evaporated.

$M_V = 5000 \times 0.03 = 150$ kg, therefore, $M_T = 4850$ kg.

Amount of NaNO_3 in feed = $M_F x_F = 5000 \times 0.5763 = 2881.5$ kg.

5000 kg feed = 2881.5 kg (NaNO_3) + 2118.5 kg (water)

$$\therefore x_T = \frac{M_F x_F}{M_F - M_V} = \frac{\text{Amount of NaNO}_3 \text{ in solution}}{M_T}$$

$$\text{or, } x_T = 0.5941$$

From equation (1) we get, $M_c = 823.21$ kg

Heat withdrawn by cold water, q

$$= M_F \times c_p \times t + M_c h_c - M_V \times \lambda$$

$$= 5000 \times 2469.57 \times (90 - 40) + 823.21 \times \frac{2100000}{85} - 150 \times 2345 \times 1000$$

$$= 4.69992 \times 10^8 \text{ Joule / hr} = 130553.41 \text{ J/S} = 130.5534 \text{ kW.}$$

Therefore, heat withdrawn from the crystallizer by the cooling is equal to 130.55 kW (Approx).

Factors controlling crystallisation

(i)Concentration gradient and Temperature gradient: The rate of growth of a crystal in a solution is dependent on the temperature and concentration of the liquid at the crystal face. These conditions are not generally the same as those in the bulk of the solution because concentration gradient and temperature gradient are necessary conditions for growth and dissipation of the heat of crystallization. Heat of crystallization is exothermic. For crystallization from a solution, very less super cooling of within $1-2^\circ \text{K}$ is possible in comparison to crystallisation from melt and so it involves much mass transfer rather than heat-transfer since the resistance to heat and mass transfer lies predominantly in the laminar sub-layer close to the surface of the crystal, the rate of growth of the crystal is improved by increasing the relative velocity between the solid and the liquid. Rate of growth initially rises very rapidly in some cases with the increase of r.p.m. of impellor by overcoming the resistance in the solution but rate ceases after certain r.p.m. The temperature at the interface (T_i) is greater than that of the bulk of the liquid (T_L) otherwise there would not be any heat transfer. The higher the heat transfer coefficient, the smaller is the required temperature difference $T_i - T_L$ and so T_i approaches T_L when solution is agitated at high r.p.m.

Noyes and Whitney [Noyes, A.A. and Whitney, W.R. J. Am. Chem. Soc. 19(1897) 930], the rate of solution of solid substances in their own solutions] assumed that the diffusion of material to the crystal face is controlled almost entirely by the resistance of the laminar

layer near the face, $\frac{dm}{dt} = \frac{DA}{b}(C_A - C_B) \frac{dm}{dt}$ is rate of growth where m is the mass of material deposited on the surface and t is time D is diffusivity, A is area of crystal surface, b is thickness of laminar layer, C_A is the concentration in the bulk of liquid and C_B is the concentration at equilibrium. In many instances, presence of soluble impurities affect both rate of nucleation and rate of crystal growth, substances like glue, tannin, dextrin prevents nucleation and growth of calcium carbonate crystal in boiler in order to reduce scaling on the wall.

(ii)Effect of Temperature on solubility: The rate of crystallization is a function of the degree of super saturation. There are different principles of super saturation. Accordingly methods as well as equipments have been designed and classified. Particular method of super saturation adopted for a specific substance depends on the effect of temperature on the solubility of that substance. In general, solubility increases with the increase of temperature. Fig.2 shows profiles of solubility of different substances at various temperatures $KClO_3$ has a large positive temperature coefficient, so spontaneous crystallization is possible by cooling saturated solution. In contrary, sodium chloride has a small coefficient; very little crystals are obtained by cooling method. Sodium hydrogen phosphate shows discontinuous profile due to changes in stable crystal form. At temperature less than $50^\circ C$ ferrous sulphate solution yields $FeSO_4 \cdot 7H_2O$; whereas solution gives $FeSO_4 \cdot 4H_2O$ in the range ($65 - 50^\circ C$). Anhydrous salt at temperature higher than $338^\circ K$ and temperature coefficient is negative in this case.

Caking of crystals

Increasingly there has been a trend towards improving quality of bulk solids in the industry in order to maintain a competitive advantage. It is often found that lumps/ aggregates are formed in the bulk products during its storage period or its transport from chemical / pharmaceutical / food industry tries due to effects of environmental conditions. This phenomenon is called caking. Caking of crystals caused by migration of moisture, create problems to such an extent that quality and handling properties are compromised. The caking tendency of crystalline materials arises due to liquid layer formation and evaporation of moisture from thin liquid layer (saturated with the crystal material) around the crystal surface when exposed to environmental condition that varies during storage and this fact leads to bonding together of crystals at points of contacts. If a crystal is brought into contact with air containing high amount of moisture (i.e. above the critical humidity) that would be in equilibrium with its saturated solution then the crystal will become damp. When these crystals are exposed to air with humidity less than critical humidity, then moisture present within saturated liquid layer in the interstices – evaporates and it results locking of crystal particles with each other and formation of dry aggregates or cakes. For instance, vapor pressure of water at $70^\circ F$ is 18.76 mm and vapor pressure of saturated sodium chloride solution at $70^\circ F$ is 14.63 mm. Now, critical humidity of this sodium chloride solution is $[(14.63/18.76) \times 100 = 78\%]$ 78 percent, if NaCl crystal is exposed to air over 78% relative humidity for long period, salt will become damp and dissolve. So critical humidity of a solid salt is defined as the relative humidity above which it will always become damp and below which it will always stay

dry. The critical humidity of a commercial grade of a crystalline material may differ appreciably from the critical humidity of a pure substance.

Prevention of caking of crystal

Caking of crystals is formed as a result of absorption and desorption / evaporation of moisture from the surrounding of crystals at various condition of air and ultimately it leads to locking of crystals at points of contacts. Formation of cake can be prevented if following measures are considered

1. Increasing the critical humidity of the product crystal by removing impurities so that its relative humidity is higher than the humidity of air.
2. Making of uniform grains with maximum percent of void and fewest points of contacts. To increase % voids it is not necessary to produce larger crystals but to produce more uniform mixture. Percent void is more or less same for absolutely uniform crystals with any particle size. Non-uniformity causes decrease in percent of void. Fine particles greater tendency to cake due to more number of points of contacts.
3. Coating of crystal particle by a powdery inert material that can absorb moisture, example – dusting of table salt with magnesia or tri-calcium phosphate. This remedy is not always possible.

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