

One-Dimensional modeling of Batch Cooling Crystallization Process

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1 Introduction

Crystallization is widely used by the chemical industry as a means of preparing chemicals in solid form. Many materials, including pharmaceuticals, dyestuffs, agrochemicals and polymers are synthesized by reactions which occur in the liquid phase to yield either solutions or melts containing the required products. Crystallization from these reaction media allows the separation of products in convenient solid form. These solids may then be further processed to yield dispersions, tablets, pastes, powders etc. for sale to customers.

Crystallization is also a chemical solid–liquid separation technique, in which mass transfer of a solute from the liquid solution to a pure solid crystalline phase occurs. In chemical engineering crystallization occurs in a crystallizer. Crystallization is therefore an aspect of precipitation, obtained through a variation of the solubility conditions of the solute in the solvent, as compared to precipitation due to chemical reaction.

The crystallization process consists of two major events, *nucleation* and *crystal growth*. *Nucleation* is the step where the solute molecules dispersed in the solvent start to gather into clusters, on the nanometer scale, that become stable under the current operating conditions. These stable clusters constitute the nuclei. However, when the clusters are not stable, they dissolve. Therefore, the clusters need to reach a critical size in order to become stable nuclei. Such critical size is dictated by the operating conditions. It is at the stage of nucleation that the atoms arrange in a defined and periodic manner that defines the crystal structure.

The *crystal growth* is the subsequent growth of the nuclei that succeed in achieving the critical cluster size. Nucleation and growth continue to occur simultaneously while the supersaturation exists. Supersaturation is the driving force of the crystallization, hence

the rate of nucleation and growth is driven by the existing supersaturation in the solution. Depending upon the conditions, either nucleation or growth may be predominant over the other, and as a result, crystals with different sizes and shapes are obtained. Once the supersaturation is exhausted, the solid–liquid system reaches equilibrium and the crystallization is complete, unless the operating conditions are modified from equilibrium so as to supersaturate the solution again.

Many compounds have the ability to crystallize with different crystal structures, a phenomenon called polymorphism. Each polymorph is in fact a different thermodynamic solid state and crystal polymorphs of the same compound exhibit different physical properties, such as dissolution rate, shape (angles between facets and facet growth rates), melting point, etc. For this reason, polymorphism is of major importance in industrial manufacture of crystalline products. The important properties of these crystallized products will vary but include purity, phase, composition, crystal shape and size distribution.

The overall objectives of a crystallization process are threefold: (Davey, 1989)

1. To produce solid particles.
2. To produce these particles with specified properties.
3. To achieve this at minimum operating costs and optimum profit margins.

Chapter 2 and Chapter 3 gives the basic understanding of crystallization and the mechanisms involved in the process. Chapter 2 briefly describes the crystal properties and their importance, latter deals with the mechanisms like nucleation and crystal growth. (Mullin, 2001; Mersmann . A, 2001)

2 Physical Properties of crystals

In this section, a general review on crystal properties is discussed based on the present literature. In understanding the process of crystallization or during the modeling the crystallization process crystal properties come into picture. So, here we have dedicated a section to review the Physical properties of crystals.

2.1 Density

Density is one of the very significant properties of the crystals. In crystallization it is important to know the density of the crystals(solute), solvent and slurry. The densities of actual crystallized substances, however, may differ from the literature values on account of the presence of vapor or liquid inclusions or adhering surface moisture. The theoretical density, ρ_c^* , of a crystal may be calculated from the lattice parameters by means of the relationship:

$$\rho_c^* = \frac{nM}{VN} \quad (1)$$

- ρ_c^* - Theoretical density
- n - Number of formula units in the unit cell
- V - Volume of the unit cell
- N - Avagadro number
- M - Molar mass of the substance

Solid densities have a very small temperatures dependence, but this can be ignored for industrial crystallization purposes. The calculation needs a knowledge of coefficient of thermal expansion.

The density of liquid is significantly temperature dependent. The ratio of the density of the given liquid at one temperature to the density of water at the same, or another, temperature is known as specific gravity of the liquid. The simplest instrument for measuring liquid density is hydrometer. Densities may be determined more accurately by the specific gravity bottle method, or with a Pycnometer or Westphal balance. In recent years, several high-precision instruments have become available, Oscillating sample holder is one in those advanced instruments.

The Bulk density of a quantity of particulate solids is not a fixed property of the system since the bulk volume occupied contains significant amounts of void space, normally filled with air. The relationship between the density of the solid particles, ρ_s , and the bulk solids density, ρ_{BS} , is

$$\rho_{BS} = \rho_s (1-\epsilon) \quad (2)$$

ϵ - volume fraction of the voids

For special case of an industrial crystallizer, it is sometimes possible to assess the slurry density by chemical analysis.

2.2 Viscosity

Viscosity is not exactly the property of crystals but the very reason that viscosity of the liquid also depends on the solids dispersed in it made this property important in the study of crystallization.

The viscosity of the fluid is the measure of its resistance to gradual deformation by shear stress or tensile stress. Viscosity is due to the friction between neighboring parcels of the fluid that are moving at different velocities. The instrument used to measure viscosity is called viscometer. Several high-precision viscometers are available in the market.

The viscosity characteristics of liquids can be altered considerably by the presence of finely dispersed solid particles, especially of colloidal size. The viscosity of a suspension of rigid spherical particles in a liquid, when the distance between the spheres is much greater than their diameter, may be expressed by Einstein equation:

$$\eta_s = \eta_0(1 + 2.5\phi) \quad (3)$$

η_s = Effective viscosity of the disperse system.

η_0 = Viscosity of the pure dispersion medium.

ϕ = ratio of the volume of the dispersed particles to the total volume of the disperse system.

We can also find some modifications to the above equation in the literature like Guth-Simha and Frankel-Acrivos etc.,

2.3 Crystal hardness :

Crystals vary in hardness not only from substance to substance but also from face to face on a given crystal. One of the standard tests for hardness in non-metallic compounds and minerals is the scratch test. The hardness calculated by scratch test is called Mohs hardness. The hardness of metal is generally expressed in terms of their resistance to indentation. A hard indenter is pressed into the surface under the influence of a known load and the size of the resulting indentation is measured. There are many instrument that measure hardness of the crystals, one of the widely used is Vickers indenter.

The relation between Mohs hardness, M, and the Vickers hardness, V, is given by the equation

$$\log V = 0.2M + 1.5 \quad (4)$$

This equation is only valid for the values of M lesser than 9. Diamond ($M=10$) is omitted.

Hardness appears to be closely related to density and to atomic or molecular volume, but few reliable data are available. Density is directly proportional to the hardness of the crystal. So, greater the density of the crystal greater the hardness which makes sense.

2.4 Heats of solution and crystallization :

Solution temperature drops if the dissolution occurs adiabatically. When a solute dissolves in a solvent without reaction, heat is usually absorbed from the surrounding medium. When a solute crystallizes out of the solution, heat is usually liberated and the solution temperature rises.

The magnitude of the heat effect accompanying the dissolution of solute in a given solvent or under-saturated solution depends on the quantities of solute and solvent involved, the initial and final concentrations and the temperature at which the dissolution occurs. The standard reference temperature is nowadays generally taken as 25°C .

In crystallization practice, however, it is usual to take the heat of crystallization as being equal in magnitude, but opposite in sign, to the heat of solution at infinite dilution.

2.5 Size classification of crystals :

The most widely employed physical test applied to a crystalline product is the one by means of which an estimate may be made of the particle size distribution. For many industrial purposes the demand is for a narrow range of particle size. Uniformity in the size of crystals results in the crystals having good storage and transportation properties, a free flowing nature. For pharmaceutical products, however, some guidance is available from recommendations in the International Pharmacopoeia.

Important procedures associated with the characterization of particulate solids are outlined below :

- a) Sampling
- b) Particle size and surface area
- c) Shape factors
- d) Size data analysis

2.6.Solubility:

Solubility is the property of a solid, liquid or gaseous chemical substance called solute to dissolve in a solid, liquid or gaseous solvent to form a homogeneous solution of the solute in the solvent. The solubility of the substance fundamentally depends on physical and chemical properties of the solute and as well as on temperature, pressure and the pH of the solution. The extent of the solubility of a substance in a specific solvent is measured as the saturation concentration, where adding more solute does not increase the concentration of the solution and begin to precipitate the excess amount of solute.

The extent of solubility ranges widely, from infinitely soluble such as ethanol in water, to poorly soluble, such as silver chloride in water. Solubility is not to be confused with the ability to dissolve or liquefy a substance, because the solution might occur not only because of dissolution but also because of a chemical reaction. For example zinc, which is insoluble in hydrochloric acid, does dissolve in hydrochloric acid but by chemical reaction into hydrogen gas and zinc chloride, which in turn is soluble in the acid. Solubility does not also depend on particle size or other kinetic factors; given enough time, even large particles will eventually dissolve.

2.7 Solubility correlations :

In the majority of cases the solubility of a solute in a solvent increases with temperature, but there are a few well known exceptions to this rule. The solubility characteristics of a solute in a given solvent have a considerable influence on the choice of a method of

crystallization. It would be useless, for instance, to cool a hot saturated solution of sodium chloride in the hope of depositing crystals in any quantity. A reasonable yield could only be achieved by removing some of the water by evaporation, and this is what is done in practice.

The general trend of a solubility curve can be predicted from Le Chatelier's Principle which, for the present purpose, can be stated: when a system in equilibrium is subjected to a change in temperature or pressure, the system will adjust itself to a new equilibrium state in order to relieve the effect of the change. Most solutes dissolve in their near-saturated solutions with an absorption of heat and an increase in temperature results in an increase in the solubility. An inverted solubility effect occurs when the solute dissolves in its near-saturated solution with an evolution of heat. Solubility is also a function of pressure, but the effect is generally negligible in the systems normally encountered in crystallization from solution.

Many equations have been proposed for the correlation and prediction of solubility data. Some are better than others, but none has been found to be of general applicability. In any case, an experimentally determined solubility is undoubtedly preferred to an estimated value, particularly in systems that may contain impurities. Nevertheless, there is frequently a need for a simple mathematical expression of solubility to assist the recording and correlation of data.

One of the most commonly used expressions of the influence of temperature on solubility is the polynomial

$$c = A + Bt + Ct^2 + \dots \quad (5)$$

t = Temperature.

c = Solution composition

A,B,C etc are constants

2.8 Theoretical crystal yield :

If the solubility data for a substance in a particular solvent are known, it is a simple matter to calculate the maximum yield of pure crystals that could be obtained by cooling or evaporating a given solution. The calculated yield will be a maximum, because the assumption has to be made that the final mother liquor in contact with the deposited crystals will be just saturated. Generally, some degree of supersaturation may be expected, but this cannot be estimated. The yield will refer only to the quantity of pure crystals deposited from the solution, but the actual yield of the solid material may be slightly higher than that calculated, because crystal masses invariably retain some mother liquor even after filtration. When the crystals are dried they become coated with a layer of material that is frequently of a lower grade than that in the bulk of the crystals.

The calculation of yield for the case of crystallization by cooling is quite straightforward if the initial concentration and the solubility of the substance at the lower temperature are known. The calculation can be complicated slightly if some of the solvent is lost, deliberately or accidentally, during the cooling process, or if the substance itself removes some of the solvent. All these possibilities are taken into account in the following equations, which may be used to calculate the maximum yields of pure crystals under a variety of conditions.

2.9 Effect of impurities on solubility

Pure solutions are rarely encountered outside the analytical laboratory, and even then the impurity levels are usually well within detectable limits. Industrial solutions, on the other hand, are almost invariably impure, by any definition of the term, and the impurities present can often have a considerable effect on the solubility characteristics of the main solute.

If to a saturated binary solution of A and B a small amount of the third component C is added, one of four conditions can result :

- a) Nothing may happen
- b) React chemically with A
- c) Makes the solution super-saturated with respect to A
- d) Makes the solution un-saturated with respect to A

2.10 Measurement of solubility

There are innumerable techniques proposed for the measurement of the solubility of solids in liquids. No single method can be identified, however, as being generally applicable to all possible types of system. The choice of the most appropriate method for a given case has to be made in a light of system properties, analytical techniques, precision required, and so on. The accuracy required of a solubility measurement depends greatly on the use that is to be made of the information. Extensive reviews of the literature on the subject of experimental solubility determination have been made by Vold and Vold (1949) and Zimmerman (1952).

There are different kinds of methods available in the literature for measuring solubility. In general the techniques can be divided into different types :

- a) Polythermal methods
- b) Isothermal methods
- c) Measurement under pressure
- d) Thermal and dilatometric methods

2.11 Prediction of solubility :

Accurate solubility measurements, however, demand laboratory facilities and experimental skills and can be very time-consuming on account of the need to achieve equilibrium and the fact that large numbers of individual measurements may be necessary to cover adequately all the range of variables. There will always be a need, therefore, for methods of solubility prediction that can avoid these difficulties, but it has

to be pointed out that in employing such methods some other more serious problems may well be incurred in return. A good number of solubility correlation and prediction methods are available ranging from simple techniques of interpolation and extrapolation to some quite complex procedures, based on thermodynamic reasoning, that have considerable computational requirements.

A group contribution method called UNIFAC, has been developed for estimating liquid-phase activity coefficients in non-electrolyte mixtures. To estimate the solubility of an organic solid solute in a solvent it is only necessary to know its melting point, enthalpy of fusion and relevant activity coefficient. Solid-liquid solubility data, i.e. those which report experimental measurements, are those of Stephen and Stephen and the continuing multivolume IUPAC solubility data series.

2.12 Supersaturation :

The term super-saturation refers to the solution that contains more of the dissolved material than could be dissolved by the solvent under normal conditions. A saturated solution is in the thermodynamic equilibrium with the solid phase, at a specified temperature. It is often easy, however, e.g. by cooling a hot concentrated solution slowly without agitation, to prepare solutions containing more dissolved solid than that represented by equilibrium saturation. Such solutions are said to be supersaturated. The state of supersaturation is an essential requirement for all crystallization operations.

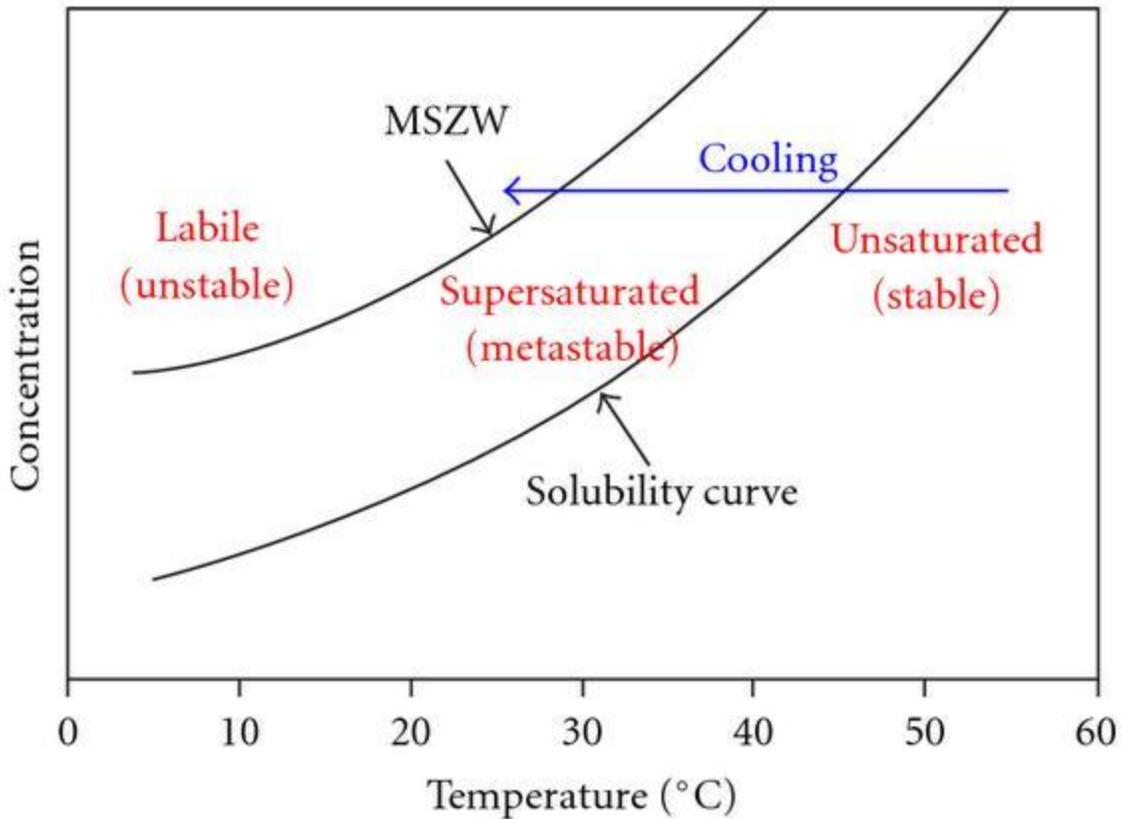


Figure 1: Solubility Curve and Metastable zone plotted against temperature and concentration.

In the above figure 1 we can see two curves which divided the graph into three areas. The area below solubility curve are the solutions which lower concentrations and are called under-saturated. No crystallization occurs in this solution. The second area which is between the curves is called metastable zone. In this region there is no nucleation however crystal may grow. The third region above metastable curve is the Supersaturated or Labile zone, spontaneous nucleation or rapid crystal growth occurs in this region.

Supersaturation can be expressed in a number of ways.

a) Concentration driving force

$$\Delta c = c - c^*$$

b) Supersaturation ratio

$$S = c/c^*$$

c) Relative supersaturation

$$\sigma = \Delta c/c^* = S - 1$$

c - solution concentration

c* - equilibrium saturation

3 Nucleation and Crystal Growth:

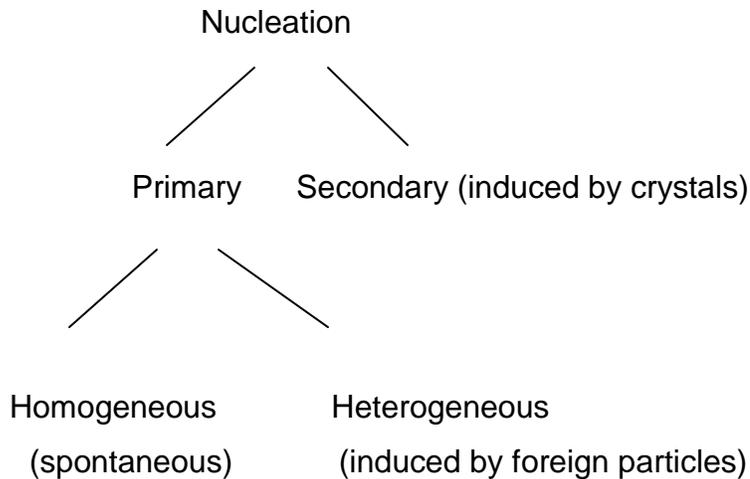
3.1 Nucleation

Crystals are developed in the solution from a number of minute solid particles, embryos, nuclei or seeds. These minute bodies act as centers of crystallization and the process of formation of these minute bodies in the solution is called Nucleation. It may occur spontaneously or may be induced artificially.

Agitation, Mechanical shock, friction and extreme pressures within solutions and melts cause Nucleation. Cavitation in an under-cooled liquid can also cause nucleation. Very high pressures are generated when a cavity is collapsed, the change in pressure lowers the crystallization temperature of the liquid and results in nucleation.

Nucleation that occurs in the systems that do not contain crystalline matter is called primary nucleation. Nuclei are often generated in the vicinity of crystals present in a supersaturated system is referred as secondary nucleation. Thus a simple nomenclature is considered

Nomenclature

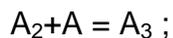
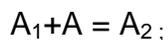


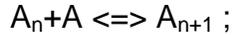
3.1.1 Primary nucleation

3.1.1.1 Homogeneous nucleation:

Exactly how a stable crystal is formed within a homogeneous fluid is not known with any degree of certainty. The formation of crystal nuclei is a difficult process to imagine. The number of molecules in a stable crystal nucleus can vary from about ten to several thousand.

In homogeneous nucleation impurities and foreign particles are absent so small embryos act as interface in order for a new phase to appear. These embryos are formed due to spontaneous density or composition fluctuations. The creation of nuclei can, therefore, be described by a successive addition of units (molecules) and it is generally bimolecular addition





If supersaturation is sufficiently high, more and more elementary units can join together and create increasingly large nuclei known as clusters. Excessive super-cooling does not aid nucleation. There is an optimum temperature for nucleation of a given system and any reduction below the value decreases the tendency to nucleate. Therefore, if the system has set to highly viscous or glass-like state, further cooling will not cause crystallization. To induce nucleation the temperature would have to be increased to a value in the optimum region.

The new technologies developed have been devised for studying the kinetics of homogeneous nucleation. The main problem in studying homogeneous nucleation is the preparation of the experimental setup without any impurities, which might act as nucleation catalysts, and the elimination of the effects of the retaining vessel walls which frequently catalyze nucleation.

In 1963 Garten and Head reported a interesting technique, showed that crystalloluminescence occurs during the formation of a three-dimensional nucleus in solution, and that each pulse of light emitted lasting less than 10^{-7} s corresponds to a single nucleation event. Nucleation rates thus measured were close to those predicted from classical theory.

Agitation is frequently introduced to induce crystallization. The super-solubility curve tends to approach the solubility curve more closely in agitated solutions, i.e., the width of the metastable zone is reduced. However, the relation between agitation and nucleation is very complex. Below figure 2 shows the relationship between critical supersaturation and agitation. The graph tells us that gentle agitation cause nucleation in solutions that are otherwise stable, and vigorous agitation considerably enhances nucleation, but the transition between the two conditions may not be continuous; a portion of the curve may a reverse slope indicating a region where an agitation actually reduces the tendency of nucleate.

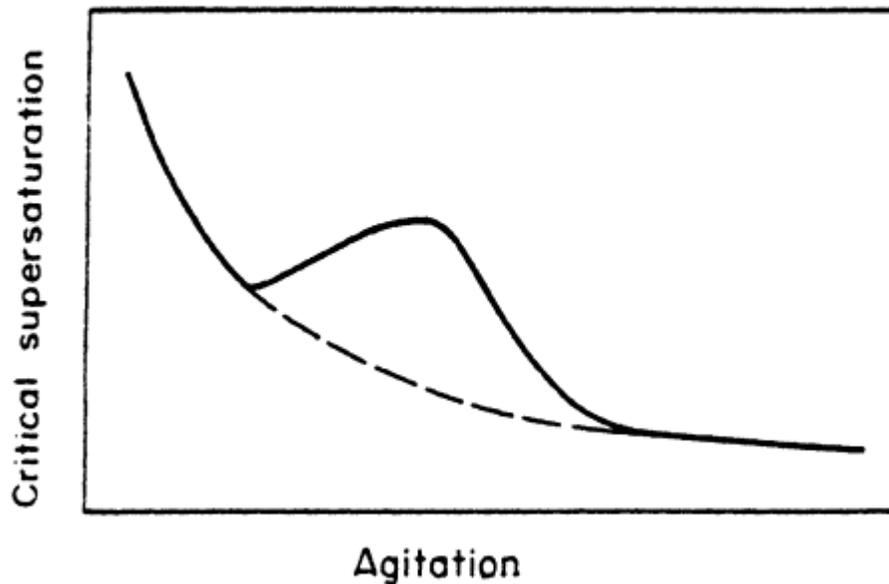


Figure 2 : Influence of agitation on nucleation

3.1.1.2 Heterogeneous nucleation

If the rate of nucleation is affected by the presence of traces of impurities in the system, this type is called Heterogeneous nucleation. Aqueous solutions prepared in the laboratory may contain small solid particles and it is impossible to achieve a solution completely free of foreign bodies. It is generally accepted that true homogeneous nucleation is not a common event. The size of the solid foreign bodies is important and there is evidence to suggest that the most active heteronuclei in liquid solutions lie in the range 0.1 to 1 μm .

As the presence of a suitable foreign body can induce nucleation at degrees of supercooling lower than those required for spontaneous nucleation, the overall free energy

associated with the formation of a critical nucleus under heterogeneous conditions $\Delta G'_{crit}$, must be less than the corresponding free energy change, ΔG_{crit} , associated with homogeneous nucleation, i.e

$$\Delta G'_{crit} = \phi \Delta G_{crit} \quad (6)$$

where the factor ϕ is less than unity.

Interfacial tension, γ , is one of the important factors controlling the nucleation process. The three interfacial tensions of the three phases (two solid and a liquid) in the fig.3 are denoted by

γ_{cl} , γ_{sl} and γ_{cs} . Resolving these forces in a horizontal direction

$$\gamma_{sl} = \gamma_{cs} + \gamma_{cl} \cos \theta \quad (7)$$

γ_{sl} = Interfacial tension between foreign solid surface and liquid

γ_{cs} = Interfacial tension between foreign solid surface and solid crystalline phase

γ_{cl} = Interfacial tension between solid crystalline surface and liquid

θ = angle of contact between the crystalline deposit and the foreign solid surface.

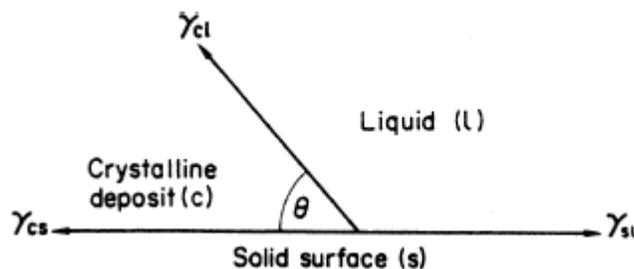


Figure 3: Interfacial tensions at the boundaries between three phases

From the above equation (7) we can also develop the relation between θ and ϕ . As the values of θ changes ratio of free energies changes and the figure 4 below indicates the relation between θ and ϕ .

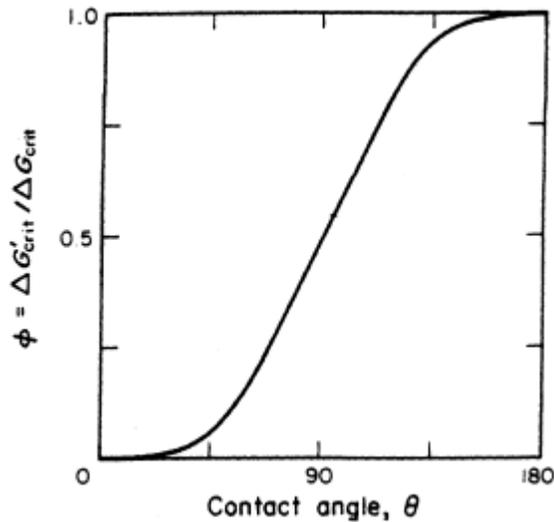


Figure 4: Relation between θ and ϕ .

ratio of free energies of homogeneous and heterogeneous nucleation as a function of contact angle

3.1.2 Secondary nucleation

A supersaturated solution nucleates much more readily, i.e. at a lower supersaturation, when crystals of the solute are already present or deliberately added. Several possible mechanisms of secondary nucleation were reported in the literature, such as Initial breeding, Needle breeding, Polycrystalline breeding and Collision breeding.

Crystal-agitator contacts are prime suspects for causing secondary nucleation in crystallizers, although only those crystals that manage to penetrate the fluid boundary layer around the blade will actually be hit. The probability of such an impact is directly proportional to the rotational speed of the agitator (Nienow, 1976).

Probably the best method for inducing crystallization is to inoculate or seed a supersaturated solution with small particles of the material to be crystallized. Deliberate seeding is frequently employed in industrial crystallization to effect a control over the product size and size distribution.

Fluid shear nucleation occurs when liquid travels across a Crystal at a high speed, sweeping away nuclei that would otherwise be incorporated into a Crystal, causing the swept-away nuclei to become new crystals. Contact nucleation has been found to be the most effective and common method for nucleation. The benefits include the following :

- Low kinetic order and rate-proportional to supersaturation, allowing easy control without unstable operation.
- Occurs at low supersaturation, where growth rate is optimum for good quality.
- Low necessary energy at which crystals strike avoids the breaking of existing crystals into new crystals.
- The quantitative fundamentals have already been isolated and are being incorporated into practice.

3.2 Crystal growth

Crystal growth is a major stage of a crystallization process, and consists in the addition of new atoms, ions, or polymer strings into the characteristic arrangements of a crystalline lattice. The growth typically follow an initial stage of either homogeneous or heterogeneous nucleation, unless a "seed" crystal, purposely added to start the growth, was already present.

There are few proposed crystal growth mechanisms in the literature which are discussed below

3.2.1 Surface energy theories :

The surface energy theories are based on the postulation that the shape of a growing crystal assumes is that which has minimum surface energy. This approach, although not completely abandoned, has largely fallen into disuse.

The total free energy of the crystal in equilibrium with its surrounding at constant temperature and pressure would be a minimum for a given volume. If the volume free energy per unit volume is assumed to be constant throughout the crystal, then

$$\sum a_i g_i = \text{minimum} \quad (8)$$

a_i = area of the i th face of the crystal

g_i = Surface free energy per unit area of the i th face.

Therefore, if a crystal is allowed to grow in a supersaturated medium, it should develop into an equilibrium shape, i.e., the development of the various faces should be in such a manner to ensure that the whole crystal has a minimum total surface free energy for a given volume. Later research showed that the crystal faces would grow at rates proportional to their respective surface energies.

The velocity of growth of a crystal face is measured by the outward rate of movement in a direction perpendicular to that face. In face to maintain constant interfacial angles in the crystal, the successive displacements of a face during growth or dissolution must be parallel to each other. Except for the special case of a geometrically regular crystal, the velocity of growth will vary from face to face. Crystal that maintains its geometric pattern as it grows are called invariant crystals.

In practice, a crystal does not always maintain geometric similarity during growth; the smaller, faster-growing faces are often eliminated, and this mode of crystal growth is

known as 'overlapping'. Surface energy theories fail to explain the well-known effects of supersaturation and solution movement on the crystal growth rate.

3.2.2 Adsorption layer theories :

In 1939 Volmer suggested the concept of a crystal growth mechanism based on the existence of an adsorbed layer of solute atoms or molecules on a crystal face. Volmer's theory is based on a thermodynamic reasoning. When units of crystallizing substance arrive at the crystal face they are not immediately integrated into the lattice, but merely lose one degree of freedom and are free to migrate over the crystal face.

Many Scientists came up with their own theories on the relationships between the various surface and bulk diffusion models of crystal growth, and their relevance to the crystal growth.

3.2.3 Kinematic theories

In 1958 Frank developed a Kinematic theory of crystal growth. Considerations of the movement of macrosteps of unequal distance apart led to the development of this theory.

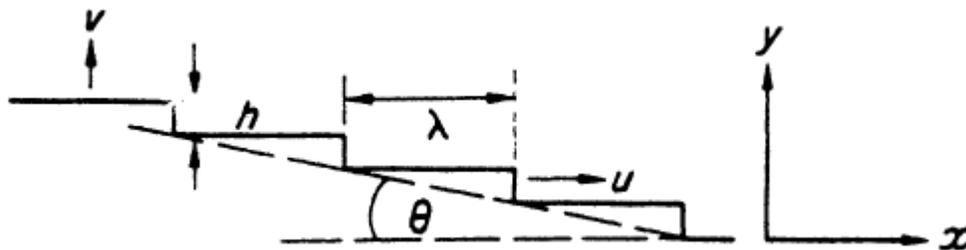


Figure :4 Two-dimensional diagrammatic representation of steps on a crystal face.

The step velocity, u , depends on the proximity of the other steps since all steps since all steps are competing units. Thus

$$u = q/n \quad (8)$$

$$\rho = \tan\theta = hn \quad (9)$$

q = the number of steps passing a given point per unit time.

n = the number of steps per unit length in a given region.

λ = distance between steps.

ρ = slope of the surface with reference to the close packed surfaces.

h = step height.

The maximum velocity is seen if the steps are far apart, and the diffusion fields do not interfere with one another. The velocity, u , reaches to minimum as the step spacing decrease and at $\theta = 45^\circ$.

Step bunching is the another problem that can be treated on the basis of the kinematic theory. The steps that flow across the a face are usually randomly spaced and of different height and velocity.

3.2.4 Diffusion-reaction theories

Deposition of solid on the face of a growing crystal was essentially a diffusional process. It assumes that crystallization was the reverse of dissolution, and the rates of both processes were governed by the difference between concentration at the solid surface and in the bulk of the solution. An equation for crystallization was proposed in the form

$$\frac{dm}{dt} = K_m A (c - c^*) \quad (10)$$

m = mass of solid deposited in time.

A = surface area of the crystal.

c = solute concentration in the solution.

c^* = equilibrium saturated concentration.

K_m = coefficient of mass transfer.

On the assumption that there would be a thin stagnant film of liquid adjacent to the growing crystal face, through which molecules of the solute would have to diffuse, the equation can be modified to the form

$$\frac{dm}{dt} = \frac{D}{\delta} A(c - c^*) \quad (11)$$

D = coefficient of diffusion of the solute.

δ = length of the diffusion path.

As this could imply an almost infinite rate of growth in agitated systems, it is obvious that the concept of film diffusion alone is not sufficient to explain the mechanism of crystal growth. Assuming crystallization to be the reverse of dissolution may not be a valid assumption. A substance generally dissolves at a faster rate than it crystallizes at, under the same conditions of temperature and concentration.

It is known that the solution in contact with a growing crystal face is not saturated but super-saturated. So, a considerable modifications was made to the diffusion theory of crystal growth that there were two steps in the mass deposition, a diffusion process, followed by a first-order 'reaction' when the solute molecules arrange themselves into a crystal lattice. These two stages, can be represented by the equations

$$\frac{dm}{dt} = K_d A(c - c^*) \quad \text{- Diffusion} \quad (12)$$

$$\frac{dm}{dt} = K_r A (c - c^*) \quad - \text{Reaction} \quad (13)$$

k_d = coefficient of mass transfer

K_r = rate constant for the surface reaction process

c_i = solute concentration in the solution at the crystal-solution interface.

The above equations (12) and (13) are not easy to apply in practice because they involve interfacial concentration that are difficult to measure. It is usually more convenient to eliminate the term c_i by considering an overall concentration driving force, $c - c^*$, which is quite easily measured. A general equation for crystallization based on this overall driving force can be written as

$$\frac{dm}{dt} = K_G A (c - c^*)^g \quad (14)$$

K_G = overall crystal growth coefficient

g = order of the overall crystal growth process

3.2.5 Birth and Spread models

The models like "Nuclei on Nuclei" and "Polynuclear growth" seen in the literature also describe virtually the same behavior. The growth develops from the surface nucleation that can occur at the edges, corners and on the faces of a crystal.

The B+S model results in a face growth velocity-supersaturation relationship of the form

$$v = A_1 \sigma^{5/6} \exp(A_2/\sigma) \quad (15)$$

A_1 and A_2 are system related constants. The above equation is the only growth model that allows a growth order, g , greater than 2.

4 Crystallization techniques (Mullin, 2001)

Salting-out crystallization

The process of addition of another substance which effectively reduces the original solute solubility is called 'salting out'. A slow addition of the salting-out agent can change a fast precipitation of the solute into a more controlled crystallization process. This technique is used more often for aqueous inorganic solutions.

Reaction Crystallization

In the preparation of many industrial chemicals, the production of solid crystalline product as the result of chemical reaction between gases and or liquids is a standard method. Reaction crystallization is practiced widely, especially in industries where valuable waste gases are produced.

Desulphurization of flue-gas is an example of reaction crystallization process. This process is employed for the removal of SO_2 from coal-fired power station flue gases. One widely used method is to absorb the SO_2 in an aqueous suspension of finely crushed limestone in a n agitated vessel or spray tower. The resulting CaSO_3 solution is passed to an air-sparged tank where it is oxidized to precipitate $\text{CaSO}_4 \cdot 2\text{H}_2\text{O}$.

Adductive Crystallization

The simple crystallization of a binary eutectic system only produces one of the components in pure form, while the residual mother liquor composition progresses towards that of the eutectic. A typical sequence of operation would be as follows. A certain substance X is added to a given binary mixture of components A and B so that a solid complex, say $\text{A} \cdot \text{X}$, is precipitated. Component B is left in solution. The solid and

liquid phases are separated, and the solid complex is split into pure A and X by the application of heat or by dissolution in some suitable solvent.

This type of crystallization technique is mostly used in fertilizer industry. For example, if a saturated aqueous solution of urea in methanol is added to an agitated mixture of cetane and iso-octane, a solid complex of cetane-urea is formed almost immediately, deposited from the solution in the form of fine needle crystals. The iso-octane is left in solution. After filtration and washing the complex is heated or dissolved in water, and pure cetane is recovered by distillation. If thiourea is used instead of urea, iso-octane can be recovered leaving the cetane in solution.

Extractive Crystallization

The process of altering the solid-liquid phase relationships by introducing a third component is known as Extractive Crystallization. Usually the third component is liquid called solvent. Provided a suitable solvent Extractive crystallization has a large number of potential applications.

Freeze Crystallization

Mainly used in petrochemical industry, particularly for p-xylene. Large scale crystallization by freezing has been practiced commercially. The preference of freezing over evaporation for the removal of water from solutions is the potential for saving heat energy. The enthalpy of crystallization of ice is only one seventh of the enthalpy of vaporization of water.

Emulsion Crystallization

Organic substances may be purified by fractional crystallization from the melt or from organic solvents, but these operations frequently present difficulties in large-scale production. So, a method known as emulsion crystallization appears to overcome this problems. Briefly, crystallization is carried out by cooling from an aqueous emulsion. Impurities, in the form of eutectic mixtures, remain in the emulsion, from which they may be recovered by further cooling.

Spray Crystallization

In this process technique, solid is simply deposited from a very concentrated solution by a technique similar to that used in spray drying. The spray method is often employed when difficulties are encountered in the conventional crystallization techniques, or if a product with better storage and handling properties can be produced.

5 Population balance modeling

5.1 Introduction :

In the industries like chemical/pharmaceutical, engineers encounter particles in an innumerable variety of systems. Particles often significantly affect the behavior of such systems. Particulate-based manufacturing processes need to be better understood so that they can be properly controlled and scaled up. The last decade has seen a shift from empirical formulation efforts to an engineering approach based on a better understanding of particulate behaviors in the process, facilitated by technological advances in computer modeling, manufacture and measurement techniques.

In a large number of industrial production processes such as crystallization, precipitation, liquid–liquid-extraction, polymerization and granulation, dispersed phase systems play an important role. A modeling approach particularly well suited for dispersed phase systems is the concept of population balances, which was developed about 40 years ago (Hulburt and Katz, 1964). Since then, a large number of articles was published dealing with the numerical solution of the resulting partial–integral–differential equations, with aspects concerning the identification of model parameters and with the application of population balances to a wide variety of processes.

Particulate processes are characterized by the co-presence of and strong interaction between a continuous (gas or liquid) phase and a particulate (dispersed) phase and are essential in making many high-value industrial products. The industrial importance of particulate processes and the realization that the physicochemical and mechanical properties of materials made with particulates depend heavily on the characteristics of the underlying particle-size distribution (PSD) have motivated significant research attention. (Panagiotis et al., 2008)

Specifically, population balances have provided a natural framework for the mathematical modeling of PSDs in broad classes of particulate processes (see, for example, the tutorial article (Hulburt and Katz, 1964) and the review article (Ramakrishna, 1985)), and have been successfully used to describe PSDs in emulsion polymerization reactors, crystallizers, aerosol reactors (e.g., Friendlander, 2000) and cell cultures (e.g., Daoutidis and Henson, 2001).

In this article, we will review how population balance is used to model particulate systems with a case study on a crystallization process.

5.2 Population balance framework

Population balance is a well established approach as the mathematical framework for dealing with particulate systems. Population balance modeling has received an unprecedented amount of attention during the past few years from both academic and industrial quarters because of its applicability to a wide variety of particulate processes. A population balance on any system is concerned with keeping track of numbers of entities, which may be solid particles, drops, bubbles, cells or, more abstractly, events whose presence or occurrence may dictate the behavior of the system under study.

The particulate system can be characterized using internal and external coordinates. The external coordinates are simply the ordinary rectangular coordinates specifying the location of the particle, while the internal coordinates represent the particle size and other aspects of particle quality as may be relevant. This theory leads to the deterministic description of the full dynamic distribution of particle sizes of the process unit being analyzed. The external coordinate is generally neglected in the by assuming a perfectly mixed tank and the PBE is expressed only with the internal coordinates.

Consider one dimensional (1-D) population balance equation (Gunawan, 2004)

$$\frac{\partial n(L,t)}{\partial t} + \frac{\partial \{G(L,t)n(L,t)\}}{\partial L} = h(L, t, f) \quad (16)$$

where $n(L, t)$ is the distribution (also called the population density), t denotes the time, L is an internal coordinate, $G(L, t)$ is the growth/dissolution rate, and $h(L, t, f)$ is the creation / depletion rate.

The entities in the distribution can be molecules, cells, crystals, cloud particles, amorphous globs, and so on. The internal coordinate L , often referred to as the size, is typically the characteristic length, volume, or mass, but it can also represent age, composition, and other characteristics of an entity in a distribution. The creation/depletion rate $h (L, t, f)$ includes nucleation, aggregation, breakage, attrition. Since the expression $h (L, t, f)$ is an integral term, PBE typically is an integrodifferential equation.

The generic concept of population balances has existed for well over three decades, its rightful place as a standard modeling tool has not occurred until more recently. (Ramakrishna and Mahoney, 2002) In recent times, there has been considerable industrial interest in the use of population balances for modeling crystallization, precipitation, and polymerization systems towards control of particle size distributions. The capacity to identify population balance models from experimental data is therefore considerably enhanced in view of sophisticated on-line measurement techniques. Consequently, it is not surprising that interest in population balance modeling has risen steeply in recent times.

In his book on "Population balance - Theory and applications to particulate systems in engineering", Ramakrishna devoted a whole chapter on population balance framework where, various features of formulation of population balance are discussed with several examples.

Birth and death terms :

Birth and death events are generally a consequence of particle breakage or aggregation processes. The birth (B) and death (D) terms represented in Eq. (16) by h correspond to breakage and agglomeration mechanisms, which are commonly expressed as integral functions.

$$h = B - D \quad (17)$$

Aggregation:

A binary aggregation is assumed to make the simulations efficient for the purpose. So we could define aggregation is the collision of two entities producing a particle of new size.

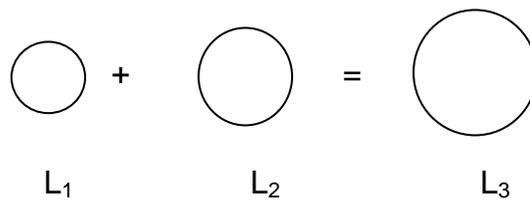


Figure.6 Process of aggregation

Let us say there is a collision between two particles of size L_1 and L_2 results in a larger particle of size L_3 . So, in this case there a birth of a new particle with the death of two particles. The effective number of particles decrease due to aggregation holding the law of conservation of mass.

Expressions of Birth and death terms using volume as the internal coordinate :(costa et al)

$$B'_{agg}(v) = \frac{1}{2} \int_0^v \beta'(v - \varepsilon, \varepsilon) n'(v - \varepsilon, t) n'(\varepsilon, t) d\varepsilon \quad (18)$$

$$D'_{agg}(v) = n'(v, t) \int_0^\infty \beta'(v, \varepsilon) n'(\varepsilon, t) d\varepsilon \quad (19)$$

The agglomeration kernel, $\beta'(v, \varepsilon)$, is a measure of the frequency of collisions between particles of volumes v and ε which produces a particle of volume $v + \varepsilon$. Some researchers also use length as an internal coordinate.

Breakage:

A mother particle breaking down into two particles, may or may not be of same size is known as Breakage. Breakage is the reverse process of aggregation. Mathematical formulations are similar to Aggregation.

$$B'_{br}(v) = \int_v^\infty \gamma(\varepsilon) b(\varepsilon) p\left(\frac{v}{\varepsilon}\right) n'(\varepsilon, t) d\varepsilon \quad (20)$$

$$D'_{br}(v) = -b(v) n'(v, t) \quad (21)$$

where,

$\gamma(\varepsilon)$ is the number of daughter particles generated from the breakup of a particle of size ε .

$b(\varepsilon)$ is the breakup rate of a particle with size ε .

$p(v/\varepsilon)$ is the fraction of daughter particles with size between v and $v + dv$, generated from breakup of particles of size ε .

5.3 Solution of Population balance equation

In this section, discussion is limited to numerical solutions of population balance equations. In practice, analytical methods are rarely used. A particular attractive approach that has evolved more recently is that of discretizing population balance equation and solving the discrete equations numerically. A brief review of numerical solution of Population balance equations are discussed in this chapter.

The numerical methods for solving PBE is classified into three different groups:

- Method of moments
- Discretization of the size domain interval
- Weighted residuals

5.3.1 Method of moments

The idea here is to transform the PBE into a set of Ordinary Differential Equations (ODEs) of the distribution's moments. It is one of the oldest method for solving PBE. PBE is transformed into a set of ODEs by multiplying the populations balance equation by L^j (length based. V^j , if the PBE is volume based) and integrating it giving in terms of moments (Randolph & Larson, 1971). The solution of set of equations gives the moments of the distribution as function of time, considering size independent growth and mean birth and death terms.

$$\int_0^{\infty} L^j \left[\frac{\partial n}{\partial t} + \frac{\partial}{\partial L} (Gn) + D - B \right] = 0 \quad (22)$$

$$\frac{d\mu_0}{dt} = B_0 + \bar{B} - \bar{D} \quad (23)$$

$$\frac{d\mu_1}{dt} = \mu_0 G + \bar{B} - \bar{D} \quad (24)$$

$$\frac{d\mu_2}{dt} = 2\mu_1 G + \bar{B} - \bar{D} \quad (25)$$

$$\frac{d\mu_3}{dt} = 3\mu_2 G + \bar{B} - \bar{D} \quad (26)$$

n = Number density function.

B_o = Nucleation rate

G = Growth rate

\bar{B} and \bar{D} birth and death rates respectively

The great disadvantage of the method is the mathematical compilation in the equations when the growth rate is a size dependent mechanism. (costa 2006). This method of solution cannot be used if it is necessary to generate the entire particle size distribution.(Ma et al, 2002)

5.3.2 Discretization of size domain interval

In the present study, a batch crystallization process is modeled and solved using Discretization (Method of classes) technique. In this method, spectrum of the independent variable is discretized into a number of intervals and subsequently use the mean-value theorem to transform the continuous PBE into a series of equations in terms of either number or average population density in each class. This method turns the PBE in the so-called discretized population balance (DPB) and the resulting set of ODEs has so many equations as the number of granulometric classes.

Marchal et al (1988) introduced the Method of Classes, applicable to a general case, making possible to consider agglomeration, breakage and length-dependent growth rate. The method discretizes the size domain interval in a free of choice grid, generating granulometric classes or bins (C_i). The mean size in each class is assumed as the characteristic size for all particles belonging to that class. The set of ODEs can be

solved using a numerical method like Runge-Kutta or Euler methods. The method of classes was vastly used in the literature to solve PBE in crystallization for simulation of experimental results, determination of kinetic parameters, modeling of process optimization of operation conditions (Costa et al., 2006)

The major drawback of the Method of Classes is its dependency of the number or density functions on the adopted grid. Finer the grid higher the computational time. Self-adaptive Discretization has already been proposed in order to reduce the number of differential equations, without affecting the result.

Discretization equations for the Method of Classes have the potential to produce negative values for the number of particles in each class and that the results from this technique oscillate about the analytical solution. (Kumar and Ramakrishan 1997)

Assumption of a geometric progression for the grid can reduce the computational effort for the numerical solution. (Rigopoulos & Jones, 2003). Costa et al reports two drawbacks for Discretization technique. Conservation of both number of particles and mass is only guaranteed in the limit of infinite resolution and a discontinuity can arise along the separatrix, which is the curve that divides states deriving from initial conditions from those arising from boundary conditions. A sharp discontinuity can be created, which quickly broadens by numerical diffusion in simulation.

5.3.3 Weighted Residuals

The weighted residuals comprise methods that retrieve the distribution by approximating the solution with a series of trial functions, whose coefficients are to be determined so that their sum will satisfy the PBE. There are two types of weighted residual methods. Weighted residual methods with global functions were among the first to be tried in PBE numerical solution. The problem is that global functions cannot capture the features of an arbitrarily shaped distributions, especially if it exhibits sharp changes and

discontinuities. If a priori knowledge of the shape of the resulting distribution is available, the trial functions can be tailored to accommodate it; in that case, the method converges and may even be computationally attractive. The second type is weighted residual with finite elements approximate the solution with piecewise low-order polynomials that are only locally nonzero, and are, thus, flexible and capable of capturing highly irregular solutions. (Costa et al., 2006)

6 One-dimensional PBM - Simulation case study

Crystallization processes are very crucial for the efficient manufacturing of pharmaceutical drugs. Purification and separation can be done in a single step using crystallization. The current work is not assigned to the crystallization of a specific function. We would like to implement material attributes of well known substances to simulate a realistic process.

A seeded batch cooling crystallization process is considered and modeled with certain assumptions. The model relevant material properties and process setting are listed and described in table 1.

Material constants	Value	description
Molecular weight API	$MW_{API} = 180.16 [g/mol]$	Molecular weight of acetylsalicylic acid (Aspirin®)
Molecular weight solvent	$MW_{Sol} = 46.07 [g/mol]$	Molecular weight of ethanol
Density crystalline phase	$\rho_{cp} = 1 [kg/L]$	For simplification we assume an equal density for the crystalline phase, the pure solvent and the solvent containing dissolved species of the crystalline phase
Density pure solvent	$\rho_{sol} = 1 [kg/L]$	
Density solvent with dissolved species	$\rho_{sol+ds} = 1 [kg/L]$	
Reactor volume	$V_r = 1 [L]$	In the present work We used the same the initial mass for the solvent and the API (solid & dissolved) for all simulated experiments
Overall mass of pure solvent in the reactor	$m_{sol} = 0.5 [kg]$	
Overall mass of API in the reactor	$m_{API} = 0.5 [kg]$	

Table :1 Material Properties and process settings

To establish the solubility of our model API in our model solvent we used the solubility of acetylsalicylic acid dissolved in pure ethanol. The latter can be described by a Nyvlt model for the temperature measured in Kelvin

$$\log(X_{cp}) = N_1 + \frac{N_2}{T} + N_3 \cdot \log(T) \quad (27)$$

$$N_1 = 27.769$$

$$N_2 = -2500.906$$

$$N_3 = -8.323$$

In the present study we use the supersaturation S defined as

$$S = \frac{c \text{ [mol/L]}}{c^* \text{ [mol/L]}} \quad (28)$$

where c^* is solubility of the API in the Solvent and c its current concentration. The conversion of the molecular fraction to the amount of moles per liter was performed according to the given supersaturation equation which describes the latter for the initial process conditions. For this work we used a common expression for a size independent growth rate shown in equation 2 with the parameter $k_{g1,2,3}$.

$$G(S, T) = k_{g1} \cdot \exp\left(\frac{-k_{g2}}{R \cdot T}\right) \cdot (S - 1)^{k_{g3}} \quad (29)$$

Model parameters (growth)	Value
k_{g1}	$= 10 \left[\frac{m}{s} \right]$
k_{g2}	$= 10^4 \left[\frac{J}{mol} \right]$
k_{g3}	$= 1 [-]$

Table: 2 Model parameters of the Growth equation

Substance	Temperature [°C]	Value [m/s]
model API (equation 2, parameters from Error! Reference source not found.)	$T = 40$	$G \approx 2 \cdot 10^{-7}$
L-Glutamic Acid [39]	$T = 70$	$G \approx 3 \cdot 10^{-8}$
Ibuprofen [36]	$T = 25$	$G \approx 1 \cdot 10^{-7}$
acetylsalicylic acid [35]	$T = 40$	$G \approx 3 \cdot 10^{-6}$

Table : 3 growth rate at a level of supersaturation value of S=1.5

In the present work we only consider experiments starting with the same mass ratio of *API* and *sol*. Therefore the initial seed mass (non dissolved amount of the API being already in the crystalline phase) of the model API $m_{cp\ initial}$ as well as the initial concentration of the dissolved species $c_{API\ initial}$ depends only on the solubility at the initial temperature $T_{initial}$.

$$c_{API\ initial} \text{ [mol/L]} = \left(\frac{\rho_{sol+ds} \cdot X_{cp}(T_{initial})}{MW_{cp} \cdot (X_{cp}(T_{initial})) + (1 - X_{cp}(T_{initial})) \cdot MW_{sol}} \right) \cdot 10^3 \quad (30)$$

$$m_{cp \text{ initial}} [\text{kg}] = m_{cp} - c_{cp0} \cdot MW_{cp} \cdot 10^{-3} \quad (31)$$

For all the simulated experiments we assumed an equal CSD. We used a logarithmic distribution of

$$n(L) = \frac{1}{L \cdot \sigma_{\ln} \cdot \sqrt{2 \cdot \pi}} \cdot \exp \left(-\frac{1}{2} \left(\frac{\ln(L/L_{50})}{\sigma_{\ln}} \right)^2 \right) \quad (32)$$

with $\sigma_{\ln} = 0.4$ and $L_{50} = 100 \mu\text{m}$ to defining the seed crystals' CSD (Stieß, 2009)
Furthermore we assumed cubic crystals (for the entire process) and defined the length as the characteristic length for a particle defined by L . Therefore the total amount of particles of a specific size L could be computed from $m_{cp \text{ initial}}$ if we assume cubic particles by using the constraint

$$\int_0^{L_{\max}} n(L) \cdot L^3 \cdot \rho_{cp} \stackrel{\text{def}}{=} m_{cp0} \quad (33)$$

Here the aggregation and breakage kernels are not used in the simulation for the case of simplicity. Initial temperature and final temperature of the process is set at 50°C and 25°C respectively. Experiments are designed in which the supersaturation does not exceed a level of $S = 1.5$. We assume that our growth rate mechanism is surface integration limited for which the solubility equation remains valid.

Process settings of simulation experiments and Discussion :

$$T_{\text{initial}} [^{\circ}\text{C}] = 45$$

$$m_{\text{cpinitial}} = 0.388$$

$$t_{\text{process}} = 1666$$

Figure 8 shows the supersaturation profile as well as the final and initial CSD of the experiments. Results seem to look correct as we can see the distribution of final CSD shifted right. Here, a simple validation can be done by checking the mass balance over the simulation time. Constant solute mass balance shows that there is no loss in the API and figure 7 shows the balance for the given process conditions.

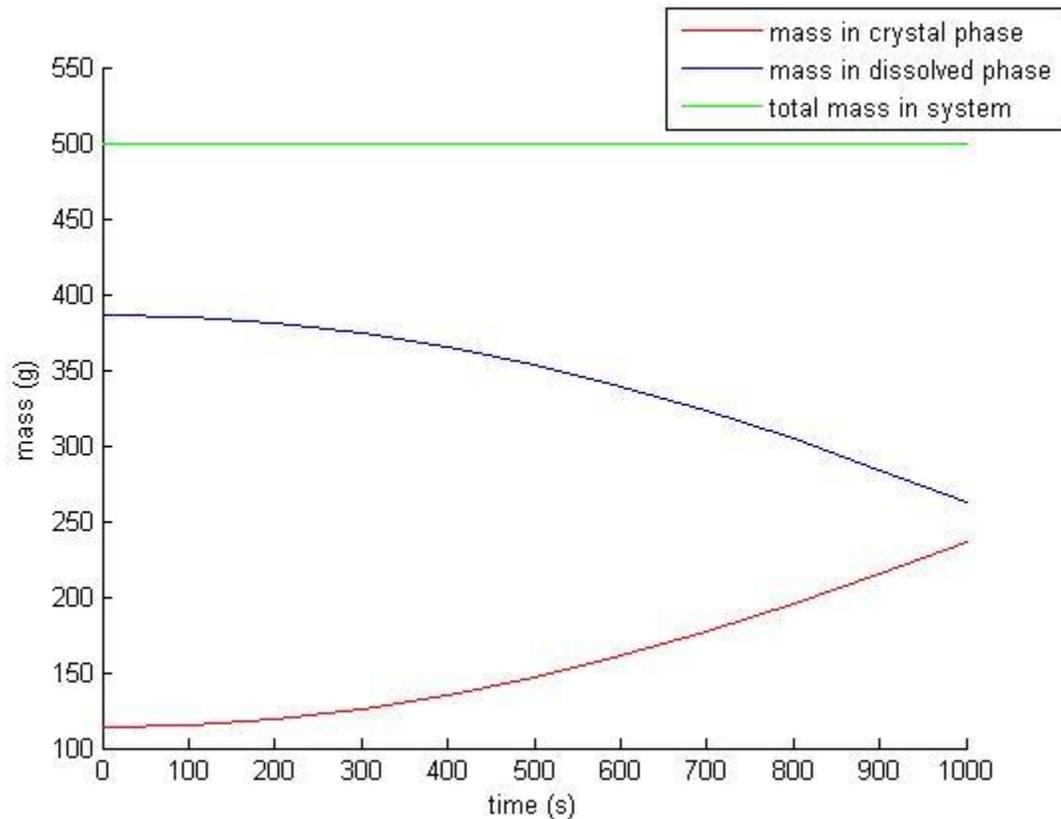


Figure 7 : Mass Balance of API

Further validation can be done by experimentation which are planned to perform later due to the time constraint. PBE solution, method of classes technique is developed on MATLAB platform and is generalized for any number of classes.

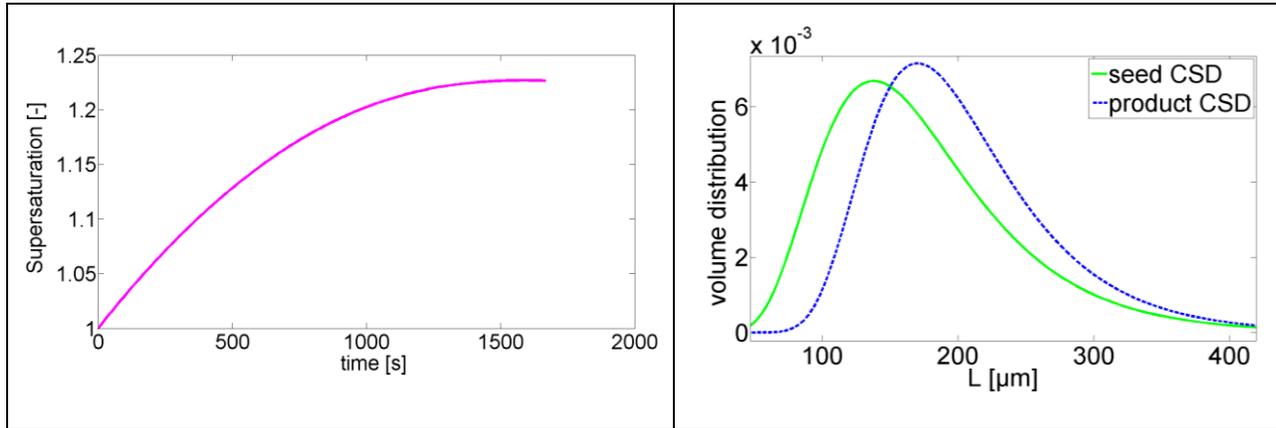


Figure 7: left: Supersaturation profile during the crystallization

right: simulated change in the CSD caused by crystal growth only

7 Conclusion and Future work

I had successfully started my study on modeling of crystallization processes. This report consists of the literature review and a case study of simulation of a pharmaceutical crystallization process. The fundamentals of the crystallization process are studied and are briefly described in this report. The main properties of crystals, models of nucleation and crystal growth are described. In this study, a crystallization process is modeled using population balance equation and the simulation is carried out on MATLAB. For the sake of simplicity we only included the crystal growth in the simulations.

Further studies can be carried out by including Aggregation and Breakage kernels. Experimental studies can be performed to validate the present model. Decreasing the computational time by different techniques like using clusters or GPU can be valuable in process control applications. A multi-scale modeling can be performed for advanced simulation and operation of crystallization process which supports the ultimate challenge of efficient separation, purification and control over crystallization process.

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