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Crystallization by Antisolvent Addition and Cooling

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1. Introduction

Crystallization is the second most important separation process in chemical industry after distillation. Crystallization consists of a solid disperse phase formation into a continuous medium, which usually is a liquid solution in industrial systems. This solid phase formation occurs in two main steps: the appearance of transition structures between solid and fluid phase, or nucleation; and the growth of these structures into solid particles, crystals. The solution concentration must be higher than the equilibrium concentration at that temperature (solubility) in order to nucleation and crystal growth occur. The difference between actual concentration and equilibrium concentration is called supersaturation and is the driving force of crystallization. Supersaturation can be generated in the system by cooling, solvent evaporation, or changing of medium – addition of an antisolvent which reduces the solute solubility in the resultant system, or changing the solute by chemical reaction producing another substance with much lower solubility. Frequently other secondary processes occur, as agglomeration and breakage of those particles, which affect the final product (crystal) size distribution.

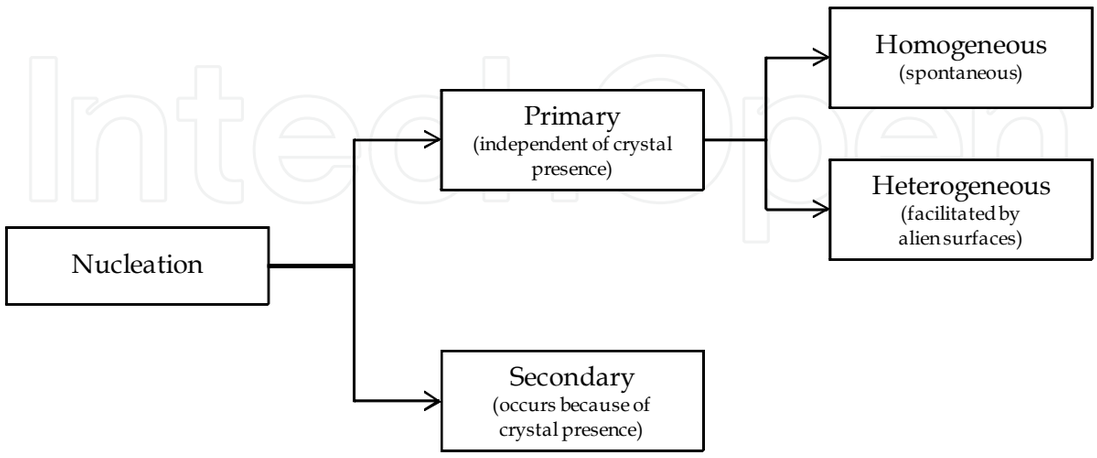

Fig. 1. Mechanisms of nucleation

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Nucleation may occur by different mechanisms. It may be primary, when is independent of crystal presence in solution, or secondary, when occurs as result of crystal presence in solution. When nucleation is primary, it may occur as a homogeneous mechanism, i.e. spontaneous depending only of supersaturation degree, or heterogeneous when is facilitated by alien surfaces (reactor or agitator wall, for instance). These different mechanisms are shown in Figure 1.

Primary homogeneous nucleation is the result of successive equilibrium of solute clustering (Figure 2). When a stable cluster is formed, it remains in solution as a transition structure from which the solid dispersed phase may appear. This stable cluster is called nucleus (Mullin, 2001).

$$\begin{aligned} A + A &\leftrightarrow A_2 \\ A_2 + A &\leftrightarrow A_3 \\ &\vdots \\ A_{n-1} + A &\leftrightarrow A_n \end{aligned}$$

Fig. 2. Solute clustering

The excess Gibbs energy is result of a resistance for the formation of a new surface, or the product of the surface tension and the cluster area, and a tendency to reach equilibrium, product of chemical potential and cluster volume:

$$\Delta G = \Delta G_S + \Delta G_V = \gamma \cdot A_{cluster} - \Delta\mu \cdot V_{cluster} = \gamma \cdot 4\pi r^2 - \Delta\mu \cdot \frac{4}{3}\pi r^3 \quad (1)$$

where γ is the surface energy of the system solute-solvent, $\Delta\mu$ is the chemical potential, $A_{cluster}$ is the cluster surface area, $V_{cluster}$ is the cluster volume, and r is the cluster radius (therefore, there is an implicit hypothesis considering cluster spherical)

Because the clusters start to grow from very small sizes (theoretically from the solute volume), it is possible to infer that initially the surface term of the excess Gibbs energy is larger than the volume term. As clusters continue to grow, they reach a critical size which corresponds to the maximum value of the excess Gibbs energy (the critical Gibbs energy). From this point on, Gibbs energy starts to decrease, and crystals grow from the existent stables clusters (nuclei). Mathematically, the critical size is calculated deriving equation (1) and equating to zero the value:

$$r_{crit} = \frac{2\gamma}{\Delta\mu} \quad (2)$$

The above equations as well as Gibbs-Thomson equation for non-electrolytes (Mullin, 2001) may be manipulated to obtain an expression for the chemical potential:

$$\ln\frac{c(r)}{c^*} = \ln S = \frac{2M\gamma}{RT\rho r} \quad (3)$$

where M is the molecular weight of solute, S is the supersaturation ratio defined as c/c^*, R is the gas constant, T the absolute temperature, ρ the crystal density and r the particle radius.

Manipulating equation (3) and considering equation (2):

$$\ln S = \frac{2M\gamma}{RT\rho r} = \frac{2\gamma\upsilon}{\upsilon\frac{R}{V}T\frac{m}{M}r} = \frac{2\gamma\upsilon}{\frac{Rn}{N_A}Tr} = \frac{2\gamma\upsilon}{kTr} \Rightarrow \Delta\mu = \frac{kT\ln S}{\upsilon} \tag{4}$$

where υ is the molecular volume, N_A is the Avogadro number, n is the number of mols, and k is the constant of Boltzmann.

Considering the homogeneous nucleus radius definition (2) and the obtained expression for the chemical potential (4), the critical Gibbs energy for homogeneous nucleation is:

$$\Delta G_{crit} = \frac{16\pi\gamma^3\upsilon^2}{3(kT\ln S)^2} \tag{5}$$

The critical Gibbs energy may be interpreted as an energy barrier to be transposed to the appearance of the nucleus, as primary nucleation depends on ordered clustering of solute until a critical size (or critical radius if cluster and nucleus are considered spherical). The practical consequences of this barrier are the metastability and the induction time. Metaestability is the state of a clear supersaturated solution, i.e. there is driving force for crystallization but there is no crystal in the system yet. The metastable state may persist for different induction times – time interval between the supersaturation imposition and the appearance of first nucleus – depending on supersaturation degree. As this supersaturation degree increases, smaller induction times are observed until the limit of instantaneous nucleation. At this point, the metastable zone width (abbreviated as MZW), i.e. a region between equilibrium concentration and actual solution concentration, was reached.

In primary heterogeneous nucleation, an alien surface (dust particle, reactor wall etc.) facilitates nucleation (Figure 3):

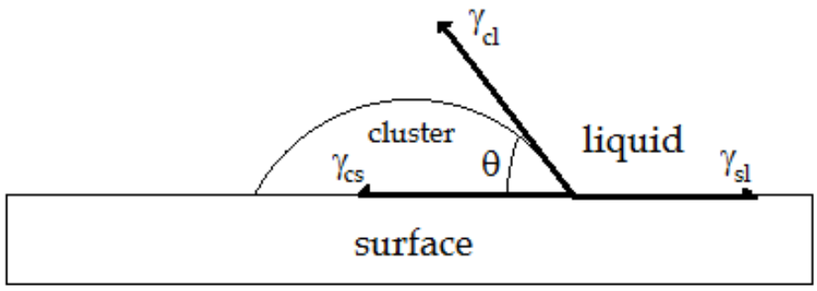

Fig. 3. Surface energies in heterogeneous nucleation. γ_{cs}, γ_{sl}, γ_{cl} are, respectively surface energies between cluster and surface, surface and liquid, and cluster and liquid.

Therefore, in heterogeneous nucleation there is a contact angle θ and a factor Φ which express the affinity between the cluster and the surface (Mullin, 2001):

$$\cos\theta = \frac{\gamma_{sl} - \gamma_{cs}}{\gamma_{cl}} \tag{6}$$

$$\Phi = \frac{(2+\cos\theta)(1-\cos\theta)^2}{4} \tag{7}$$

The factor Φ varies from 0 (total affinity between cluster and surface) to 1 (no affinity). The primary nucleation rate, J, is the rate of appearance of nucleus in a given volume:

$$J = \frac{dN}{Vdt} \tag{8}$$

where N is the number of nucleus, t is time and V is the system volume.

For its characteristics, primary nucleation may be modeled as an Arrhenius thermally activated rate:

$$J = A\exp\left(-\frac{\Delta G}{kT}\right) \tag{9}$$

Equations 5, 7 and 9 allow determining a primary nucleation rate:

$$J = A\exp\left(-\frac{16f\gamma^3\upsilon^2}{3k^3T^3(\ln S)^2}\right) \tag{10}$$

Where f is a factor that equals 1 for homogeneous nucleation or is lower than 1 for heterogeneous nucleation (Bernardo et al, 2004). Consequently, it should be expected that in industrial systems heterogeneous nucleation occurs before homogeneous, and the metastability or the induction times be smaller than in homogeneous nucleation.

It is reported that melts frequently demonstrate abnormal nucleation characteristics – nucleation rate follows the expected exponential curve as supersaturation is imposed to the system, but reaches a maximum and decreases for higher supersaturation values. It was suggested that the viscosity of melts increase starkly with cooling and restricts molecular movement inhibiting the formation of ordered structures. It was modeled by a modification in equation 10, including a 'viscosity' term (Mullin, 2001):

$$J = A\exp\left(-\frac{16f\gamma^3\upsilon^2}{3k^3T^3(\ln S)^2} + \frac{\Delta G'}{kT}\right) \tag{11}$$

where ΔG' is the activation energy for molecular motion across the system, and is very large for viscous liquids and glasses.

When there are crystals suspended in solution, they may be shorn by relative movement of liquid or broken by collision with other crystals or with crystallizer or impellers surfaces. The consequence of these mechanical processes is the appearance in suspension of small embryos which allow the growth of new crystals, i.e. secondary nucleation. As it exists because of physical interactions between crystals and the system, it cannot be modeled by thermodynamic equations, as primary nucleation. The wide-spread solution is to relate secondary nucleation rate B_0 with process variables which may cause secondary nucleation,

as supersaturation ΔC (the difference between C and C*), impeller rotation W, and concentration of solids M_T in a power law equation (Myerson and Ginde, 2002):

$$B^0 = k_N W^i M_T^j \Delta C^n \tag{12}$$

Seeding is a common practice in industry. It consists of adding a small quantity of crystal in the supersaturated solution that will facilitate the crystal growth by the existence of a surface. If the process of crystallization is seeded, it is expected that secondary nucleation be the dominant mechanism of nucleation.

The crystal growth may be defined as the variation in time of the characteristic size of the crystal:

$$G = \frac{dL}{dt} \tag{13}$$

where G is the crystal growth rate and L is the characteristic size of the crystal.

There are many theories to explain and model crystal growth. Briefly explaining, these theories may be grouped in three sets: surface energy theories, that postulate that shape of growing crystals search the minimum energy condition, are limited to molecular modeling studies; diffusion theories, which states that crystal growth is limited by the diffusion of the solute to the crystal surface; adsorption theories, which states that the integration of the solute molecule to the crystal surface is the rate-determining step. For the crystallization of melts, the crystal growth may be limited by heat release. It seems quite obvious that crystal growth may be limited by diffusion of solute to the surface, integration of the solute in the surface, or by the heat release depending on the system composition or the process conditions (Mulin, 2001). In the engineering practice, it is common to describe crystal growth rate as a power law (Myerson and Ginde, 2002):

$$G = k_G \Delta C^g \tag{14}$$

where k_G is a constant which may vary with temperature according to an Arrhenius-like equation, and g is the crystal growth order, generally a number between 1 and 2.

1.1 Antisolvent crystallization

As already mentioned, supersaturation may be generated by changing the solubility of the system by the addition of an antisolvent – a liquid miscible with the solvent which reduces solute solubility in this new mixed solvent. An advantage of the antisolvent crystallization is that the process can be carried out at temperatures near the ambient temperature. It is quite convenient for heat-sensitive substances. Also, the process would demand less energy than a solvent evaporation process. However, the solvent-antisolvent mixture must be separated in order to recover and recycle one or both solvents. Another advantage of antisolvent crystallization is that the change in solvent composition may favor one crystalline structure in those cases where the solute may crystallize in two or more crystalline phases (what is called polymorphism), and only one of them is desired for product application. Because of these characteristics, antisolvent crystallization has been widely used to crystallize

pharmaceutical products, which are generally sensitive to degradation by heating and frequently have polymorphism occurrence.

Takiyama et al. (2010) utilized the antisolvent crystallization to control the formation of two possible polymorphs of indomethacin (alpha and gamma forms).To obtain only the desired stable polymorph, it is required to avoid the precipitation of meta-stable polymorph crystals; they postulate that in the antisolvent crystallization, the solubility profiles are essential data for crystallization operation design to selectively isolate the target polymorph. In antisolvent crystallization, indomethacin was dissolved in acetone and heptane as used as antisolvent. Agitation speed and rate of addition control, as well as seeding gamma crystals were done to obtain the desired gamma form. The experiments were done at 288 and 313 K.

Granberg et al. (1999) investigated the influence of solvent composition on the antisolvent crystallization of paracetamol in acetone-water mixtures where extra water was added as antisolvent and concluded that supersaturation degree and not solvent composition defines induction time. They noticed increasing nucleation and agglomeration rate with increasing initial supersaturation, but at a given initial supersaturation, the solvent composition has no clear influence on the crystalline product characteristics. Crystal growth rate showed good relationship with solubility. Their work concluded that antisolvent modifies solubility and crystal shape, but has low influence in crystallization kinetics, governed by supersaturation degree.

Analyzing data of benzoic acid crystallization in water-ethanol solution by the water addition, Kubota (2008) concluded that solvent composition has no effect on induction time or primary nucleation rate, which could be modeled considering only the supersaturation imposed to the system as water as added.

Antisolvent crystallization may be combined with cooling strategies to enhance crystallization. Sheikhzadeh et al. (2008) implemented an adaptive MIMO neuro-fuzzy logic control for crystallization of paracetamol in isopropanol-water system in which water was added as antisolvent and temperature was varied from 40 to 10°C. When seeds were added, product yield reached 99%, while unseeded experiments reached 95% product yield. Seeding allowed to significantly reduce batch time without reduction in crystal mean size.

In combined cooling antisolvent crystallization, it seems that when antisolvent is added before cooling, the results are better than the opposite. Studying crystallization of paracetamol in isopropanol-water system in which water was added as antisolvent, Knox et al. (2009) increased the yield from 78.4% to 93.5% when antisolvent was added before cooling.

Nagy et al. (2006, 2008) utilized the method of moments to model the combined cooling and antisolvent crystallization in order to obtain the optimum recipe for crystallizing lovastatin (a hypolipidemic agent in drugs) in acetone/water mixture and achieve a maximized crystal size. Compared to cooling-only strategy, antisolvent-only strategy improved the product mean size in 15%, while combined strategy improved the mean size in 22%. The width of particle size distribution was lowered in 17 and 23% when only antisolvent and combined cooling antisolvent was used, respectively, compared to cooling-only strategy.

2. Crystallization of sugars

The major amount of crystallization studies for sugars, sucrose is almost an exception, were made concerning the undesirable crystallization or the need to impose the crystallization of these substances in food formulation (Hartel, 2001; Hartel et al., 2011). Very little research concerns industrial crystallization processes, and even for sucrose, industrial processes remain based on practical operational practice. Fundamental studies on sugars solutions behavior have been being done, almost always concerning the behavior of food formulation.

In fact, the most used sugars in industrial formulations – sucrose, glucose, fructose, lactose – seem to have specific characteristics that become the study of their crystallization quite complex. These substances are all very soluble in water, which implies that their industrial processes of crystallization will have very high initial (feed) concentration. Figure 4 shows the solubility of sucrose, glucose, fructose, lactose in water.

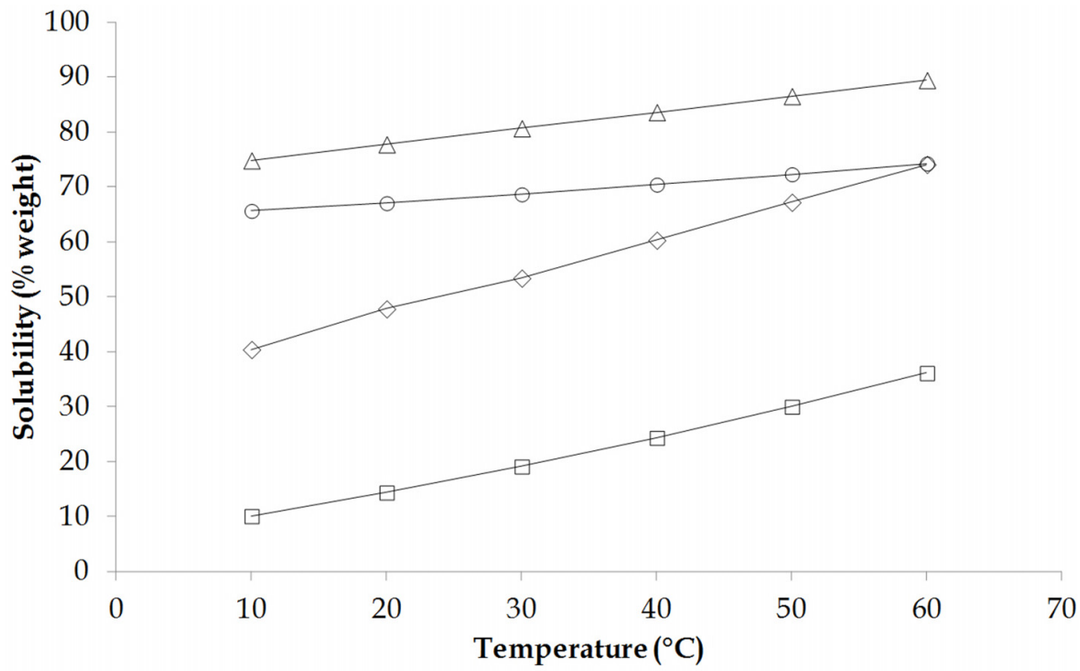

Fig. 4. Solubility in water of fructose △ (Silva, 2010), sucrose ○ (Ouiazzane et al., 2008), glucose ◇ (Alves et al., 2007), lactose □ (Brito, 2007).

It may be observed in Figure 1 that despite of lactose, all the other sugar have solubilities larger than 40 % weight. Even lactose have its solubility larger than 30 % weight at 60°C, where the others haves solubilities larger than 60 % weight.

Other important physical properties to be considered are solution viscosity and glass transition temperature T_g. Chirife and Buera (1997) presented a simple equation to predict the viscosity of sugar solutions at 20°C. Table 1 utilized this equation to calculate viscosities for selected sugars in a 60% weight solution. Hartel et al. (2011) compiled T_g values for different sugars (Table 2). For temperature values around or below T_g, the solution will be expected to exhibit a very low mobility.

Sugar	Viscosity (cP)
Glucose	36,4
Fructose	32,9
Sucrose	59,4
Lactose	65,7

Table 1. Viscosity at 20°C for 60% weight solution of selected sugars

Sugar	T_g (°C)
Glucose	31
Fructose	5-10
Sucrose	62-70
Lactose	101

Table 2. Glass transition temperatures of selected sugars

Considering a sugar crystallization process, if no seed is added, primary nucleation rate will occurs as predict equation (11), i. e. nucleation rate will grow exponentially until a maximum and decrease for higher supersaturation. Crystal growth rate will be limited by diffusion of solute to crystal face, which implies that even seeding policies has limited efficiency.

Further, metastable zone width (MZW) may have reach 30°C as reported in several references (Gharsallaoui et al. (2008); Brito (2007); Silva (2010)). The combination of large MZW, flat solubility curves (Figure 1) and high viscosity makes simple cooling crystallization practically unfeasible. Mathlouthi and Genotelle (1998) compare sucrose crystallization to a 'hurdle race', where viscosity seems to be a minor hurdle and the disassociation of hydration water a major one.

2.1 The role of water affinity in sugar crystallization

Mathlouthi and Genotelle (1998) considered two steps in sucrose crystallization: diffusion of sucrose molecules from the bulk solution to the interface crystal/solution and the incorporation of these molecules to the crystal after releasing their hydration water. Utilizing X-ray diffraction and laser-Raman spectroscopy, they concluded that hydrogen bonds between sucrose molecules in concentrated solutions is so strong that it hinders completely the free diffusion of molecules, and that diffusion in concentrated solutions is not due to viscous flow, but to the transfer of water molecules from one sucrose molecule to another by rotation of these sugar molecules. Consequently, water would diffuse in the concentrated solution and sucrose molecules would remain immobile, becoming the migration of hydration water from the crystal surface to the bulk solution very likely to be the controlling step in sucrose crystal growth.

Gharsallaoui et al. (2008) studied the interactions between water and disaccharides (sucrose, maltitol, and trehalose) in saturated solution and in crystallization conditions. According to them, narrowest metastable zone width was observed for maltitol and the largest for trehalose, because of the higher affinity of trehalose for water. They conclude that the crystallization of anhydrous disaccharides in aqueous solution necessitates that hydration

water be removed and evacuated from crystal integration surface to the bulk solution to allow the growth of crystals. It seems to occur because for disaccharides in dilute or concentrated aqueous solutions, folding around the glycosidic linkage and hydrogen bonding influences very much the solution behavior. Specifically in the case of properties such as solubility, viscosity and molecular arrangements that take place before crystallization. As a general rule, high T_g sugars exhibit a greater degree of freedom to rearrange hydrogen bonds during changes in temperature than low T_g sugars.

Molinero et al. (2004) utilizing atomistic simulations investigated the nature of combination of water and glucose in supercooled solutions and concluded that there is a concentration limit not to have water freezing and keep a glassy state for all system.

Bensoussi et al. (2010) compared the metastable zone width of aqueous solutions of sucrose, maltitol, mannitol and xylitol, and attributed the observed differences to the interactions between water and solute molecules, as well as the conformation of solute molecule in solution. Further, they concluded that these factors are at the origin of solution properties like viscosity, diffusivity and surface tension, which interfere in nucleation and crystal growth. They concluded that nucleation of sugars is affected by their solubility, as it affects viscosity and the consequent solution diffusivity. Besides, the stability of bonds established with water may also affect nucleation. Sucrose and xylitol, for instance, have high potential of forming stable hydrogen bonds with water, as well as more favourable water-sugar interactions than to sugar-sugar interaction, which implies in large MZW, low capacity to form spontaneous nuclei, and high hydrophilic behavior. Mannitol and maltitol have similar MZW despite the difference in their solubility in water, because of, in the case of maltitol, its high viscosity at saturation and flexibility of glucitol moiety which decreases the stability of water-maltitol interactions. On the other hand, mannitol has low affinity for water and low viscosity, which favors the conditions to form spontaneous nuclei; its rigid conformation explains the ease of nucleation and the narrow metastable zone.

Shortly, as general rule, sugars have high affinity with water, which frequently implies in highly viscous, highly soluble solutions with large MZW, low ease of nucleation and small crystal growth rates.

2.2 Antisolvent cooling crystallization of sugars

Sugars are very polar compounds, which explain their affinity with water. The dielectric constant of water is 78.54 at 25°C. A 50 weight percent of sucrose aqueous solution has its dielectric constant equals to 60.19; a similar dextrose solution has a dielectric constant of 63.39 (Malmberg and Maryott, 1950). Dielectric constants of ethanol and acetone at 25°C are 24.55 and 20.7, respectively. As dielectric constant provides a good measure of a system polarity, it is obvious that aqueous solutions of sugars are much more polar that the common organic solvents. The solubility of a solute in aqueous solution should be decreased by the addition of an organic solvent with a dielectric constant lower than that of water. Another factor which contributes to precipitation by organic solvents is the redistribution of water and the organic solvent around solute molecule (Arakawa and Timasheff, 1985). In fact, water-organic solvent mixture cannot be regarded as a continuous medium in the vicinity of a sugar molecule, since the sugar surface may be a mosaic of regions with different polarities and different affinities for the solvent components. Furthermore, large organic molecules as sugars may also be excluded by steric hindrance.

If an organic solvent is mixed to aqueous solution of sugar as antisolvent, it is possible to suppose that it would surround the hydrophobic moieties of sugar molecule surface, dehydrating sugar molecule by a steric hindrance mechanism. This dehydration of sugar molecule, exposed to a less polar medium in which it has little affinity to solvent, would decrease viscosity (increasing solute mobility) and facilitate sugar-sugar interaction. The result would be higher ease of nucleation and higher crystal growth rate.

Following, it is presented results of antisolvent cooling crystallization of fructose utilizing ethanol as antisolvent, and for lactose utilizing acetone, ethanol, and iso-propyl alcohol. Crystallization was evaluated utilizing Nývlt's method to calculate crystallization kinetics (Nývlt et al., 2001).

Nývlt's method utilizes a set of at least nine experiments of no-seeded batch cooling crystallization, with three different cooling rates and three initial concentrations, to determine the apparent average crystal growth rate, expressed as a power-law equation similar to equation (13), and the apparent average nucleation rate $\dot{N}$, expressed as a power-law equation:

$$\dot{N} = k_N M_T^c \Delta C^n \tag{15}$$

where c value allows to comprehend the nucleation mechanism – c = 0 means true primary or secondary nucleation; c = 1 means that crystal-crystal interaction provokes nucleation; c = 2 means that friction between crystals provokes nucleation.

For all experiments, the metastable zone width ΔT_{max} is measured, and from equation:

$$\log \Delta T_{max} = \frac{1-m}{m} \log \frac{dC^*}{dT} - \frac{1}{m} \log k_N + \frac{1}{m} \log \frac{dT}{dt} \tag{16}$$

where m is the apparent nucleation order and C* is the solubility, it is possible to obtain the values of k_N and m by a multiple linear regression.

The cumulative mass distributions of crystals M(L) may be described as the function:

$$M(L) = 100\left(1 + z + \frac{z^2}{2} + \frac{z^3}{6}\right)\exp(-z) \tag{17}$$

where $z = L/(G \cdot t_{batch})$, is the crystal dimensionless size. It is possible to calculate the z values iteratively, and the average crystal growth rate for that experiment may be calculated from the relation between z and L. Crystal mean size L_m is the L value for z = 3, and

$$G = \frac{L_m}{3t_{batch}} \tag{18}$$

The linear coefficient of z-L relation is called z_n and

$$f(z_n) = 100\left(1 + z_n + \frac{{z_n}^2}{2} + \frac{{z_n}^3}{6}\right)\exp(-z_n) \tag{19}$$

The nucleation rate be calculated by the following equation

$$\dot{N} = \frac{27 M_T G}{2 k_v \rho_C f(z_n)(L_m - L_n)^4} \tag{20}$$

A multi-linear regression of $\dot{N}$ as function of G and M_T, gives:

$$\ln \dot{N} = \ln\left(\frac{k_N}{k_g^{n/g}}\right) + c \ln(M_T) + \frac{n}{g} \ln G \tag{21}$$

Nucleation order may be calculated:

$$n = \frac{4(m-1)}{3\frac{g}{n} + 1} \tag{22}$$

2.3 Antisolvent cooling crystallization of fructose

Silva (2010) studied the antisolvent cooling crystallization of fructose utilizing ethanol as antisolvent. She varied the initial concentration of the aqueous solution of fructose, the quantity of added ethanol expressed as ratio ethanol/water (E/S) and the cooling rate. The agitation rate was 500 rpm and the final temperature was 30°C for all experiments. The results of MZW are shown in table 3.

As it was expected, MZW decreases with added ethanol quantity. The crystals yield, not shown in table, was more than 93% of available fructose quantity for all experiments. The obtained crystals had cubic habit, and agglomeration occurred in all experiments. The crystal mean size, and the crystallization kinetics, calculated by Nývlt's method had no significant difference with the quantity of ethanol added (Table 4).

Initial concentration (% weight)	Ethanol (E/S)	Saturation temperature (°C)	Nucleation temperature (°C)	Cooling rate (°C/min)
86,88	1.5	50.5	30 after 40 min	0.60
86,88	4.0	50.5	30 after 30 min	0.55
86,88	6.0	50.5	42	0.55
86,88	9.0	50.5	47	0.58
88,10	1.5	55	30 after 130 min	0.50
88,10	4.0	55	30 after 20 min	0.55
88,10	6.0	55	38.5	0.60
88,10	9.0	55	42	0.55
89,36	4.0	60	38	0.22
89,36	6.0	60	40.5	0.65
89,36	9.0	60	46.5	0.65

Table 3. MZW of antisolvent cooling crystallization of fructose with ethanol as antisolvent

Flood et al. (2000) studying the same system also concluded that ethanol quantity and temperature did not affect significantly the crystal growth rate. They cited other studies that concluded the same.

Initial concentration (% weight)	Ethanol (E/S)	Product mean size (μm)	G (10^6·m/s)	$\dot{N}$ (10^{-11}·#/m^3s)
86,88	1.5	42.50	1.28[1]	202.1[1]
86,88	4.0	109.7	3.14[1]	12.36[1]
86,88	6.0	44.07	1.01	133.5
86,88	9.0	56.75	1.27	49.54
88,10	1.5	51.64	2.82[1]	192.5[1]
88,10	4.0	42.06	1.15[1]	224.1[1]
88,10	6.0	44.02	1.04	156.1
88,10	9.0	63.82	1.46	35.43
89,36	4.0	55.87	1.22	62.32
89,36	6.0	43.95	1.03	177.0
89,36	9.0	60.07	1.36	56.62

[1]As in these experiments nucleation occurred after cooling cessation, calculated kinetic parameters G and $\dot{N}$ must be considered cautiously.

Table 4. Crystallization kinetics of fructose calculated by Nývlt's method

2.4 Antisolvent cooling crystallization of lactose

Brito (2007) studied the antisolvent cooling crystallization of lactose utilizing ethanol (at different pH), isopropanol, and acetone as antisolvents. She varied the initial concentration of the aqueous solution of lactose, the final temperature and the cooling rate; the quantity of added antisolvent was always the same quantity of water in solution (E/S = 1), and the agitation rate was 350 rpm for all experiments. The results of MZW are shown in tables 5, 6 and 7.

C_i (% weight)	pH	Saturation (°C)	Final (°C)	Nucleation (°C)	Cooling rate (°C/min)
25.54	4.00	60	25	52	0.35
36.95	7.00	60	25	55	0.52
33.24	12.41	60	25	53	0.58

Table 5. MZW of antisolvent cooling crystallization of lactose with ethanol as antisolvent

Tables 5, 6 and 7 show that adding the same quantity of antisolvent of water in solution MZW almost disappear for all studied conditions. Tables 8, 9 and 10 present the calculated kinetic parameters (Nývlt's method).

Results presented in tables 8, 9 and 10 allow to conclude that pH has an important role in ethanol cooling crystallization of lactose – crystal growth rate and yield increase with pH, and nucleation rate decreases. For isopropanol, an increase in batch time almost always implies in higher yields and larger mean sizes due to the increase in growth rate. Also, for

the same temperature variation, higher initial concentration (that means higher average supersaturation) implies in larger crystal sizes.

C_i (% weight)	Saturation (°C)	Final (°C)	Nucleation (°C)	Cooling rate (°C/min)
42.86	70	20	68	1.00
42.86	70	30	69	0.34
42.86	70	40	68.5	0.53
35.48	60	20	57	1.10
35.48	60	30	57	0.59
35.48	60	40	58	0.33
31.03	52	10	50	0.33
31.03	52	20	49	0.30
31.03	52	30	51.5	0.42

Table 6. MZW of antisolvent cooling crystallization of lactose with isopropanol as antisolvent

C_i (% weight)	Saturation (°C)	Final (°C)	Nucleation (°C)	Cooling rate (°C/min)
35.06	50	20	50	0.15
35.00	50	20	50	0.17
35.07	50	20	48	0.21
35.07	50	20	50	0.27
35.00	50	20	50	0.51
35.07	50	25	50	0.52
35.07	50	35	50	0.45
33.32	45	20	43	0.61
33.32	45	25	43	1.00
33.32	45	30	43.5	0.44
29.88	40	10	39	0.66
30.00	40	20	40	1.19
29.98	40	25	40	0.50

Table 7. MZW of antisolvent cooling crystallization of lactose with acetone as antisolvent

For acetone, larger concentration experiments had a yield of about 90%, increasing cooling rate (which means to increase average supersaturation) caused nucleation rate to increase and mean crystal size to decrease. For lower initial concentration, increasing cooling rate seems to decrease yield and mean size. Intermediate concentration experiments had an increase of mean size with cooling rate.

The presented results corroborated the expectation that the addition of an organic antisolvent eases the crystallization of sugar, as the antisolvent would decrease sugar-water interaction increasing solute mobility (Miranda et al., 2009). An indirect measurement of this effect is the sugar solubility in the solvent mixture. Figure 5 presents lactose solubility in different pH values and in a mixture of 50 percent weight of water and ethanol. Figure 6 presents solubility of lactose in water and in mixture of water with different solvents.

C_i (%weight)	pH	Cooling rate (°C/min)	L_m (μm)	G (10^5·m/s)	$\dot{N}$ (10^{-11}·#/m³s)	Yield (%)
25.54	4.00	0.35	121.18	0.734	5.683	62.4
36.95	7.00	0.52	115.77	3.473	5.308	46.04
33.24	12.41	0.58	168.37	5.051	2.313	82.46

Table 8. Crystallization kinetics of lactose (antisolvent ethanol) calculated by Nývlt's method

C_i (% weight)	Cooling rate (°C/min)	L_m (μm)	G (10^5·m/s)	$\dot{N}$ (10^{-11}·#/m³s)	Yield (%)
42.86	1	103.5	0.6029	3.6751	86.23
42.86	0.34	91.74	5.5047	7.4673	85.72
42.86	0.53	68.09	7.1675	13.769	80.42
35.48	1.1	81.44	6.1077	11.027	49.60
35.48	0.59	53.27	0.2948	18.195	75.65
35.48	0.33	89.98	6.8336	6.2648	49.20
31.03	0.33	47.00	3.1688	28.797	61.01
31.03	0.3	56.47	5.2936	21.703	73.74
31.03	0.42	80.70	5.6968	8.3657	43.85

Table 9. Crystallization kinetics of lactose (antisolvent isopropanol) calculated by Nývlt's method

C_i (% weight)	Cooling rate (°C/min)	L_m (μm)	G (10^5·m/s)	$\dot{N}$ (10^{-11}·#/m³s)	Yield (%)
35.06	0.15	118.71	0.3458	0.7797	88.74
35.00	0.17	99.04	0.3396	1.6071	92.63
35.07	0.21	53.98	0.2722	21.347	89.81
35.07	0.27	77.31	0.4179	4.0916	91.55
35.00	0.51	70.11	0.7130	11.599	86.60
35.07	0.52	93.24	1.1655	6.2562	47.45
35.07	0.45	106.43	1.9351	5.2757	41.55
33.32	0.61	113.84	1.3940	3.3583	73.74
33.32	1.00	72.96	1.7510	17.515	43.85
33.32	0.44	73.94	0.9859	10.476	82.40
29.88	0.66	114.01	1.2906	2.0553	55.72
30.00	1.19	82.07	2.3449	1.2720	40.91
29.98	0.50	149.77	2.2466	1.5606	58.08

Table 10. Crystallization kinetics of lactose (antisolvent acetone) calculated by Nývlt's method

Figure 5 explains the variation in the obtained yields in experiments of table 8, as solubility of lactose has a maximum value in neutral pH and also decreases with ethanol addition. However solubility curves do not explain the yields themselves. In systems where lactose has very low solubility, it would be expected that lactose has low interaction with solvent system and, therefore, high mobility of lactose molecule. A probable reason why lactose crystal yields are about 40% even in system with low solubility could be mutarotation (Miranda et al., 2009). Lactose molecule has two conformations (anomers), α and β forms,

and below 93.5°C α-form is the constituent of stable crystals. It is known that mutarotation is affected by temperature, pH and solution impurities. Further, α-form crystallization rate may be faster than mutarotation rate, causing mutarotation to be the rate-determining step for crystallization (McLeod, 2007).

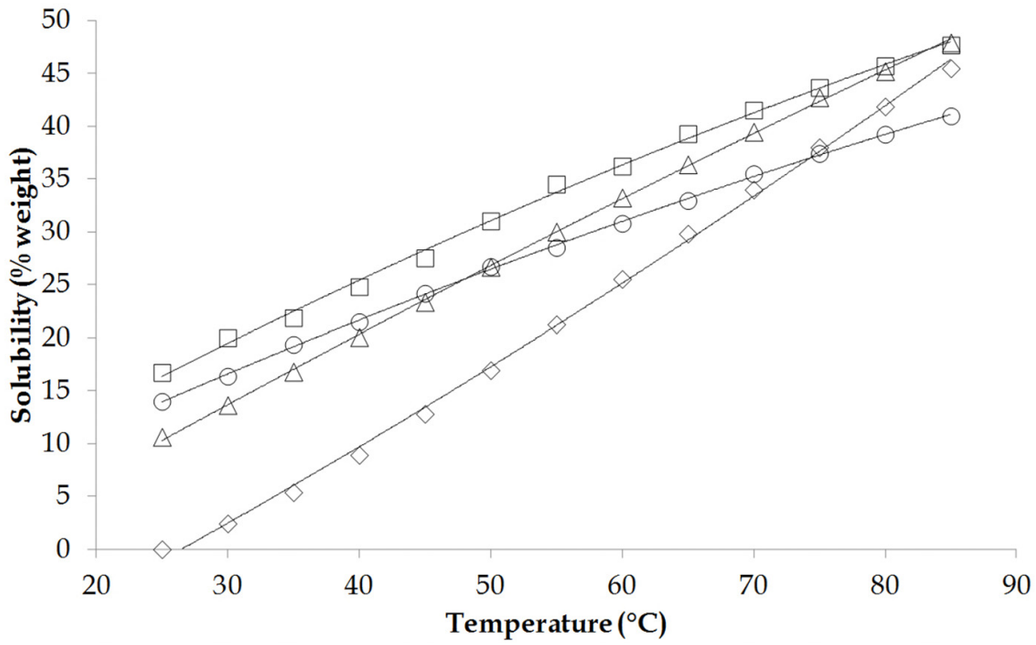

Fig. 5. Solubility of lactose in water at pH 4.0 (◇), water pH 7.0 (□), water pH 12.41 (△), and a mixture 50% weight ethanol water (○).

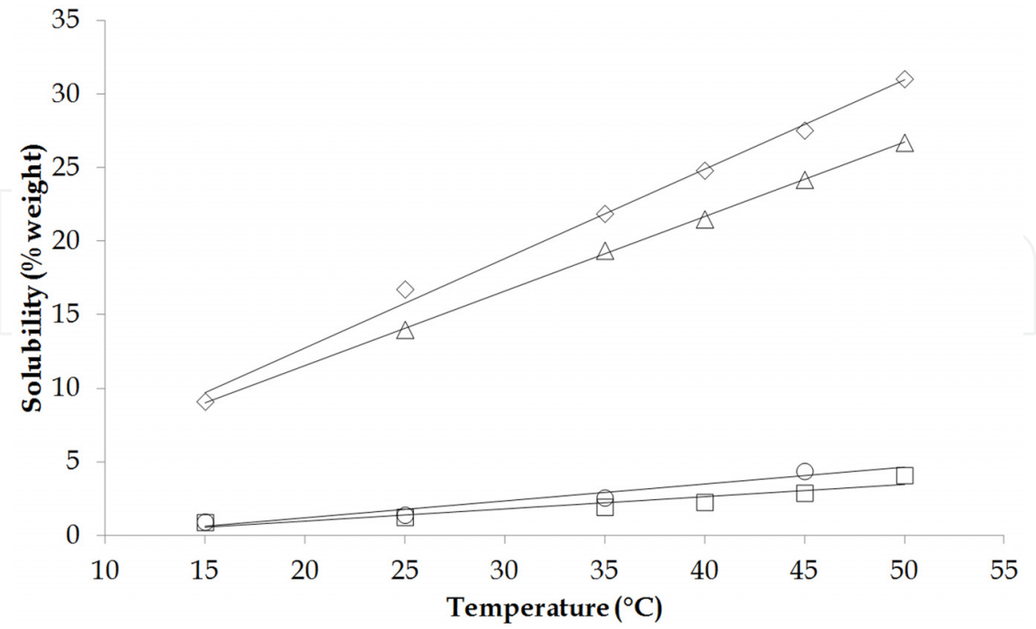

Fig. 6. Solubility of lactose in different solvents: water (◇), solution 50% weight acetone-water (□), solution 50% weight ethanol-water (△), solution 50% weight isopropanol-water (○).

Flood at al. (2000) describes fructose mutarotation issue. According to them, fructose interconverts naturally in solution in five tautomeric forms by mutarotation, but only the β-D-fructopyranose form crystallizes. In aqueous solutions the mutarotation rates would be higher than the crystallization kinetics, but in aqueous ethanolic solutions mutarotation would be sufficiently slow to move the tautomeric equilibrium away from the equilibrium β-D-fructopyranose. So, it would be important express supersaturation in terms of the tautomer, β-D-fructopyranose. In experiments driven by Silva (2010), crystal yield was always higher than 93%, but lower than 100%. In lactose crystallization experiments of Brito (2007), higher yield were about 90%. Therefore, it seems that mutarotation may reduce crystallization yields for lactose and fructose.

From an industrial perspective, in which the maximum crystal yield is an aim, it is important to emphasize that cooling and antisolvent addition must be combined. Figure 7 shows fructose solubility in weight percentage as function of water content in solvent (a mixture of ethanol and water) for the temperatures of 20°C and 60°C.

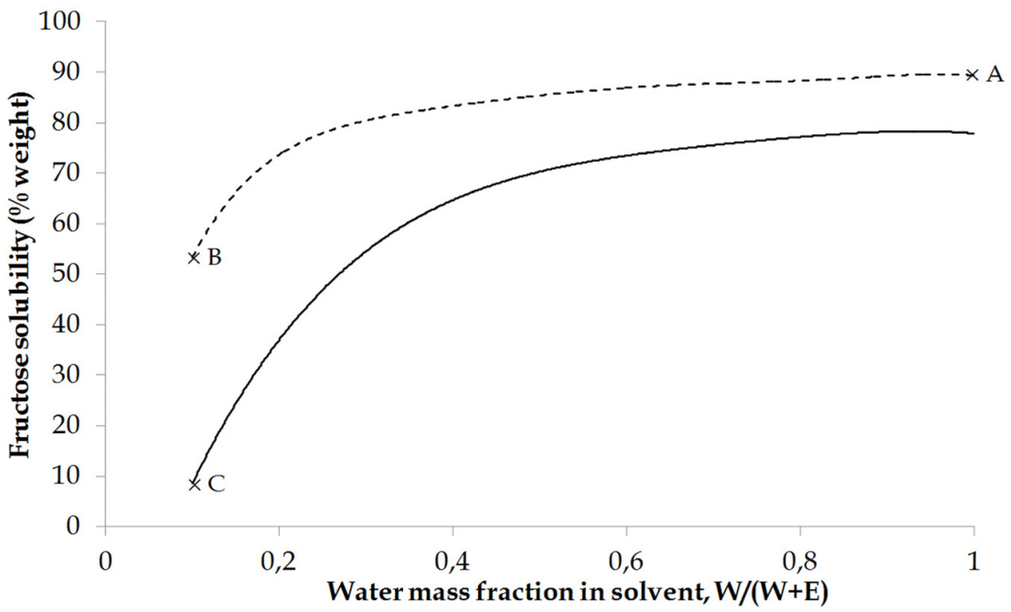

Fig. 7. Fructose solubility in a mixture of ethanol and water at 20°C (continuous line) and at 60°C (dashed line).

The data showed in Figure 7 is based on Silva (2010) work. Figure 7 allows to understand that despite the addition of antisolvent eases crystallization, crystal yield is strongly dependent on final temperature. For 10% of water in solvent (thus 90% ethanol), fructose solubility varies from 53,13% at 60°C to 9,75% at 20°C. For instance, 1000 kg of fructose aqueous solution at 60°C (point A in Figure 7) would contain 106,9 kg of water and 893,1 kg of fructose. Adding 962,1 kg of ethanol to this system, total solvent content would be 1069 kg, with 10% weight of water. In this solvent system, more than 1200 kg of fructose could be dissolved at 60°C (point B in Figure 7) – more than initial quantity with no crystal produced – but only 115,5 kg of fructose would be soluble at 20°C (point C in Figure 7) – giving a theoretical crystal yield of 87% of total fructose, desconsidering possible mutarotation effects, or 81% of total fructose, considering that in Silva's experiments, yield was always more than 93% of available fructose.

3. Conclusion

Crystallization of sugars may be improved by adding an organic liquid antisolvent (as alcohol or ketone) and cooling the system. This addition shuts nucleation hindrance off, as it decreases system viscosity. Simultaneously, the antisolvent competes with solute for water of hydration, throwing solute out of the solution: promoting crystallization. As the solubility of sugars in the mixture water-organic solvent is much lower than in water only, antisolvent addition increases the crystallization rate. Cooling the system maximizes the drowning-out effect.

Sugars may present complex structures which interconvert in solution by mutarotation. As generally only one anomer crystallizes, mutarotation may decrease crystals yield. Mutarotaton may be affected by pH, temperature, and by solvent composition. However, for the studied cases of fructose and lactose, antisolvent cooling crystallization showed to be advantageous even considering mutarotation occurrence.

Fructose was studied utilizing ethanol, and lactose was studied utilizing ethanol, acetone and isopropanol. It is possible to vary antisolvent addition rate and cooling rate simultaneously (Nagy et al., 2008), allowing to optimize crystal quality in industrial operations. The presented kinetic data as well as shape and size distribution measurement for antisolvent cooling crystallization corroborate its utilization in industrial operation.

Combined antisolvent and cooling crystallization is an important technique for obtaining products that are difficult to crystalize due to inherent solution properties like high viscosities, large metastable zone width, low kinetic of nucleation and growth, like sugars and others materials. The good choice of antisolvent must be done carefully with preliminary experiments that can allow to obtain high yields and easiness of solvent recovery. Optimal path to combine the two techniques, antisolvent and cooling, to obtain good crystal size distribution must be evaluated for each particular system, taking into account the couples solvent-antisolvent, solute-mixed solvent. The phase diagram of this ternary system is very important to evaluate that path and possible yield.

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