Controlled Crystallization Process for high quality API

Taming the nucleation for intensified crystallization processes

Executive summary

- Controlled nucleation for the crystallization of small molecules
- From low to high particle size with narrow distribution
- Robust technology resulting in quality-by-design production using specific reactor design and parameter control

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FLUIDIFY PHARMA

Introduction

Crystallization is one of the most common phase transformations in pharmaceutical production processes as 90% of the active pharmaceutical ingredients (APIs) are crystallized small molecules (1; 2). Despite the popularity of crystallization, many aspects concerning the creation of solid particles from solutions are not fully mastered, leading often to an empirical approach. Two separate phrases from trustworthy scientists that can be heard at crystallization conferences are: "never trust a spontaneous nucleation event, it will run out of hand" and "that is where the magic happens". Both are related to shortcomings understanding of the crystallization mechanisms and provoke quotes like: "In industrial crystallizers, however, homogeneous nucleation is usually not desired at all and, for the production of large crystals in particular, it has to be avoided. Only for the crystallization of very fine or even nano-sized materials may this mechanism be useful." (3).
This paper reviews the basics of the crystallization transformation and explains more specifically how the theory is implemented to master nucleation for a successful intensified crystallization of small molecules.

Common issues with crystallization process

A solute-solvent phase diagram, as shown in Figure 1, is determined by the thermodynamic solubility line *C**; for a defined concentration at temperatures above this line, the solute is in solution. At temperatures lower than *C**, the solute is partially in solid state and the liquid has a concentration of solute equal to *C**. When a solution at initial concentration is cooled down from high temperatures, it can start to crystallise through nucleation, once a threshold undercooling as opposed to the solubility value has been overcome. Depending on the degree of undercooling, different nucleation mechanisms may dominate:

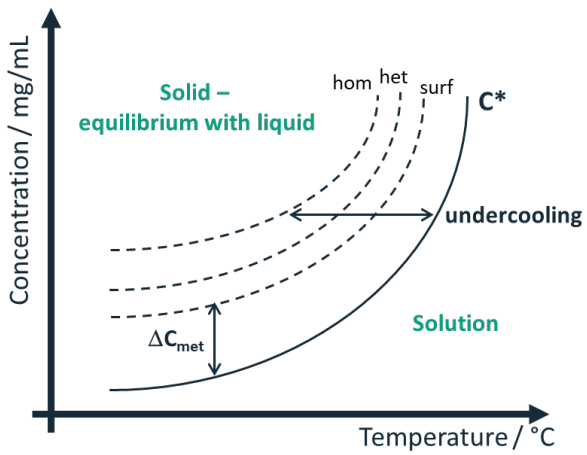

Figure 1: Phase diagram of a solute in contact with a solvent (in mg solute per mL solvent) as a function of temperature, solubility line C; undercooling and metastable zone width ΔC_{met} are indicated. Three exemplary metastable zone widths for different nucleation regimes are shown: homogeneous, heterogeneous, of foreign material, and on crystal surfaces present in the solution. Image is a rework from Mersmann (3).*

- homogeneous nucleation where only solute molecules interact to create a viable nucleus;
- heterogeneous nucleation on foreign particles like wall surfaces and impurities;
- nucleation on crystals present in the solution;
- nucleation by splitting existing crystals – called attrition (4).

This degree of undercooling can also be expressed by the difference between solubility concentration *C** and the concentration at which nucleation starts in isothermal conditions. This difference is typically referred to as the metastable zone width or ΔC_{met}. As clearly depicted by Mersmann and Bartosch in Figure 2, different nucleation regimes can become

dominant at different combinations of product solubility and degree of supersaturation σ at a given temperature. Supersaturation is defined as $\sigma = \frac{C_s - C^*}{C^*}$ with C_s being the solution concentration (4).

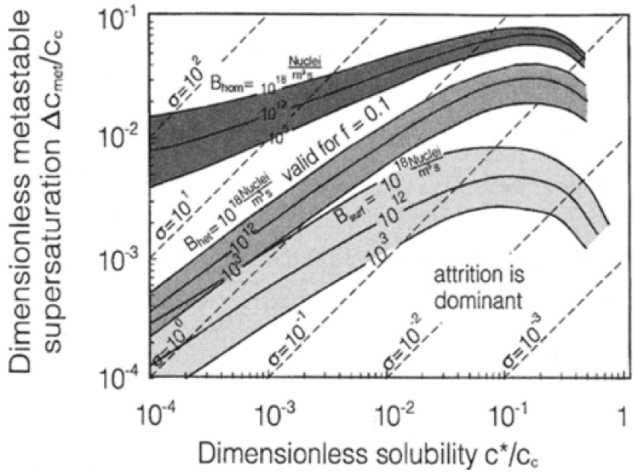

Figure 2: Metastable zone widths for various activated nucleation mechanisms. ΔC_{met} is the width of the metastable zone, C solubility concentration, C_c the molar concentration of the crystal, B_{hom}, B_{het} and B_{surf} the nucleation rates: homogeneous, heterogeneous on foreign materials, and on crystal surfaces present in the solution. Image adapted from Mersmann and Bartosch. (4)*

Theoretical average nucleation rate values per unit of time and volume are 10^{12} nuclei/(m^3 s) for the production of crystal nuclei, as shown in Figure 2 (3). This value means that in a volume of 1 liter, 1 billion of crystals are generated per second. Secondly, as it can also be observed in the figure, one nucleation mechanism can compete with other mechanisms, especially at low supersaturation values sigma. All these crystals grow rapidly. In large batch volume, with its inherent inhomogeneities in temperature and in composition, the different spontaneous nucleation mechanisms will occur simultaneously, thus heavily disturbing the product consistency and leading to batch-to-batch variability.

Nucleation remains an important issue with common continuous crystallization process setups, like the mixed suspension mixed product removal (MSMPR) and oscillated baffled crystallizers (OBC): once nucleation conditions are met or sought for, encrustation on the walls of tubing or vessels does occur and lead to failures in the production processes. A literature overview pinpointing these fouling issues is given by Wood *et al.* (5)

One of the main reasons for the occurrence of the encrustation events is the difference in timescale between the rate of production of crystals and the total residence time in these continuous crystallization technologies. For both setups the residence time of crystallising material inside the reactors may run up to several hours (5; 6; 7; 8). As a result, the creation and growth of several billions of crystal nuclei inside these reactors will lead to highly different crystal sizes and size distributions (4). In addition, the operational time of these reactors will be limited as well (5).

Continuous crystallization studies mostly apply to seeded methodologies to master crystal growth and create narrow crystal size distributions with desired average crystal size (9; 10; 11; 12; 13; 8). However, being outside of nucleation conditions means that in the temperature-concentration profile, the process is to assure that the crystallising solution stays inside the limits of the metastable zone width. The same principle is usually applied for crystallization in large batch systems, as schematised in Figure 3 left hand side. As such,

concentrations, flow rates, cooling rates and yields are generally quite low, and therefore requested industrial output remains difficult to obtain.

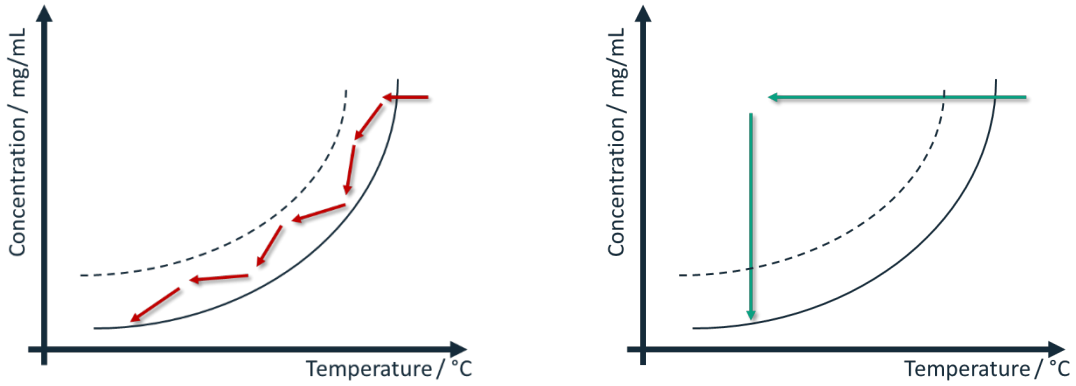

Figure 3: typical temperature-concentration profile for a solute in solution, with the solubility line C (full line) and metastable zone width (dashed line). Left: Arrows indicate the desired concentration evolution as a function of temperature for seeded crystallization methods avoiding entering in the spontaneous nucleation region. Right: Arrows indicate targeting the spontaneous nucleation zone using tubular reactors.*

The use of tubular reactor enables the control over nucleating conditions

What would occur when the size of the reactor is fully adapted to the number of nuclei generated per second per unit volume once nucleation conditions are reached?

Mastering the nucleation process is achieved by combining two parameters: an important reduction of the reactor size through the use of tubular reactors and a controlled residence time – through adjusted length of the tubular reactor – enabling a continuous evacuation of the produced nuclei. Actually, the selection of a thin-walled tubular reactor comes with benefits important to comply with the needs for fast nucleation and nuclei removal:

- **Fast cooling and temperature control.**

  With temperature drops between 15 and 30°C/s at the start, the desired nucleation temperature is imposed rapidly on the liquid passing through the reactor, see Figure 4 (14). The small inherent volume of such reactors ensures the liquid to follow a predetermined modelled temperature evolution, reducing the number of uncontrolled variables. Targeting very specific zones in the phase diagram, as shown in Figure 3 right hand side, can also lead to the spontaneous nucleation of selected polymorphs as demonstrated for the API Brivaracetam (15).

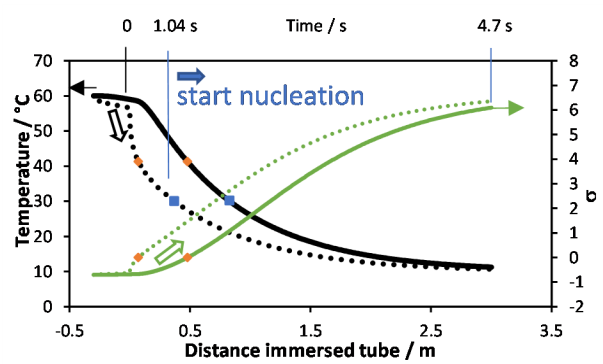

Figure 4: Calculated spatial and temporal evolution of temperature (black) and supersaturation value σ (green) at the centreline (solid lines) and at the wall (dashed lines) for an Aspirin solution. Orange dots indicate the crossing of the solubility line; blue points entering spontaneous nucleation zone. (14)

- **Uniform residence time inside the tubing**

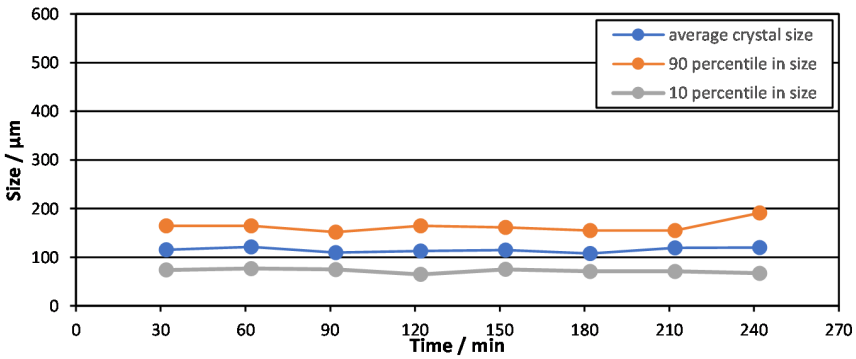

Figure 5: Size analysis of adipic acid crystals produced using the tubular crystallization device during a 4-hour production test.

With a typical reactor volume of about 5 mL and flow rates of 30 mL/min, average residence times inside the reactor are in the order of 10 seconds. The material inside the reactor is continuously refreshed. Therefore, all solute molecules undergo the same temperature evolution, in identical conditions and surroundings. The production consistency is guaranteed for long runs as shown in Figure 5. The quality of the produced material is guaranteed by the combination of the reactor design and the control of the process parameters – the standards for a quality-by-design production are therefore fulfilled.

- **Fast and continuous evacuation of produced nuclei**

For a given set of conditions in tubular reactors, flow velocity of the liquid reaches 50 to 100 cm/s. Nuclei are formed once ΔC_{met} has been overcome and start to grow. Key factor is to evacuate these nuclei before they grow "out of hand". Small enough nuclei are subjected to the Ségré-Silberberg effect, meaning that they will bounce off the tube wall towards the equilibrium position at around 0.6 times the radius away from the tube center (16), as demonstrated by *Park et al*. (17) as shown in Figure 6. For as long as the crystals do not grow up to the point that they sediment as a function of fluid velocity, they will be evacuated from the reactor, without fouling the tube walls.

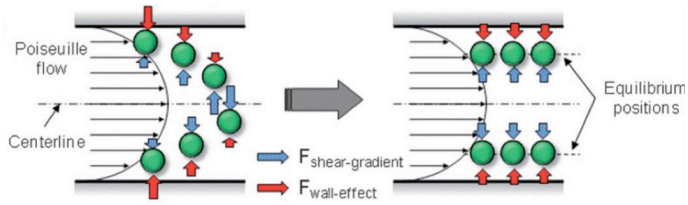

Figure 6: Solid particles reaching equilibrium position while flowing through a narrow capillary, taken from Park et al. (17)

- **Spatial occupation in a plant – Secoya's crystallization pilot unit**

The Secoya Crystallization Technology (18) uses tubular nucleation devices, optimised for both process output and nucleation control. The reactor devices are placed individually inside 10x15x15cm^3 modules in order to assure a fast and uniform cooling, as shown in figure 7. Each module of the automated pilot unit is individually controlled. The pilot itself is expandable up to 10 modules for a production capacity up to 15 tons/year and a

footprint of $3m^2$, buffer tanks included. The unit is transportable, facilitating servicing and maintenance or delocalised production.
The piloting algorithm is constructed in such a way that the system only uses the preselected number of modules, which can even be modified in the middle of a run to guarantee full production versatility.

The molecules that were investigated up to now using the single cooling mode setup are Brivaracetam, adipic acid, salicylic acid, aspirin and Lamivudine (14; 15; 19; 20). Achieved nucleation rates are in the range of 10^4 and 10^7 nuclei/(mL.s), equivalent to 10^{10} and 10^{13} nuclei/(m^3.s). These are regarded as average nucleation rates (4). Given the σ values we obtain inside Secoya's crystallization units and the way the reactors are constructed, the two most uncontrolled nucleation mechanisms - attrition and nucleation on top of existing crystals - are to be neglected. Following the curve of Mersmann in Figure 2, the conditions where nucleation is executed are right on and above the homogeneous nucleation zone (4).

Figure 7: The Secoya process unit with 5 modules.

How to control the PSD?

With a million crystals per mL present in the collected suspensions, the actual time for crystals to grow until the saturated state in suspension is reached is short. As an example, the different growth times for adipic acid crystals in Figure 8 point out that about 90 s between sample collection and filtration are sufficient to obtain a maximum average crystal size since the saturated state is reached. Due to these short growth times and the identical history of each crystal, the crystals cannot grow to very different sizes. That situation is important as it provides freedom for the subsequent steps without impacting crystal size. The product can be collected in a vessel, can be further processed in a continuous reactor to precisely monitor crystal growth or can be casted in/on a filtration device where the time before filtration is freely selected.

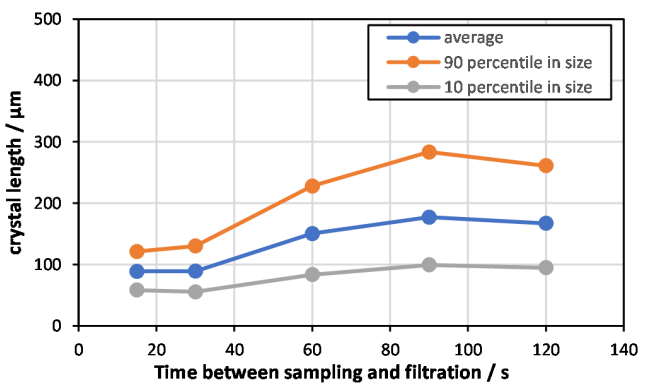

Figure 8: Crystal size analysis as a function of time between nucleation and filtration for adipic acid crystallised in water.

Even though crystallization production by means of continuous nucleation remains complex, the development and use of tubular reactors is a promising way for industrial production of well-defined solids products. Using the proper process design, the crystalline product suited for the target application will always be obtained.

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