

Crystallization Development

A QbD Approach to PSD Control using Modelling

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A QbD Approach to Particle Size Control using Modelling

Abstract

An approach to crystallization development is described, based on a mixture of theoretical modelling and experimentation that provides a deep understanding of the process factors that influence PSD and improves efficiency in development and optimization.

Introduction

Nearly all synthetic steps in industrial chemical manufacturing end with a crystallization. This is because it is almost always the most efficient method to purify and isolate the material. While most chemists are proficient at formulating a basic procedure, when it comes down to the fine details, often crystallization is seen as a mysterious process and subject to factors beyond our control. Various quality attributes may be important: purity, residual solvents, filtration speed, polymorph, crystal habit and particle size distribution (PSD). ***An in-depth understanding of the crystallization process will help reduce risks on scale-up.*** In this article we discuss the use of modelling tools for solubility and supersaturation and how they can aid crystallization development, with an emphasis on PSD.

Basic Concepts

A crystallization consists mainly of two basic processes: ***crystal growth and nucleation.*** Other factors such as attrition and agglomeration may also play a role, and should be considered, but first we need to understand growth and nucleation. These two processes

occur throughout the crystallization with rates that depend on many factors including supersaturation, crystal surface area, collision rate, viscosity and temperature. Several of these factors are changing throughout the crystallization and therefore, the relative rates of growth and nucleation that determine the final PSD are also variable throughout the process. ***The fundamental driving force for crystallization is supersaturation.*** In simple terms this is defined as how far the solution concentration is from the thermodynamic equilibrium or solubility.

Thermodynamics

Since the solubility is the reference with which to determine supersaturation, this is the starting point. The solubility of the product changes during the course of the process, leading to supersaturation, the driving force for the crystallization. Therefore, we need to know the solubility at all times. For a simple, cooled, classical crystallization this is provided by a solubility curve. In other systems the solvent may be changing by anti-solvent addition and a solubility model that considers both temperature and composition is more

appropriate. **The solubility model is an essential map to help us navigate through the process.** A typical model that gives solubility (C) as a function of temperature (T) and antisolvent fraction (X_1) might be based on a modified **van't Hoff equation**, as shown in Equation 1, where A, B, C and D constants to be determined from experimental data.

Equation 1

$$\ln C = \ln A_0 - \frac{B_0}{RT} - C_0 x_1 - \frac{D_0 x_1}{RT}$$

Kinetics

The kinetics of crystallization, that is the rates of growth and nucleation, depend on supersaturation and the **relative rates of these two processes will determine PSD**. The solubility model guides us in setting solvent volumes and seeding points, but to evaluate effects on PSD we also need to model the supersaturation. This problem becomes complex due to continuously changing solubility, PSD and amount precipitated throughout the crystallization. However, despite the seemingly impossible challenge of these calculations, valuable information can be gained by making some simplifying approximations.

Supersaturation modelling

In the first approximation we could model a process without nucleation, only considering crystal growth. This greatly simplifies our crystallization kinetics and leads to an expression as shown below in Equation 2, where M_t and V_s represent crystal mass and crystal volume at time t , and $C_L - C^*$ is the

supersaturation. The solubility, C^* , is calculated using the model described earlier in Equation 1.

Equation 2

$$M_t = \int_{t=0}^t K_G V_S (C_L - C^*) dt$$

The unknown in this equation is the crystal growth rate constant, K_G . However, without even determining this constant, using this model we can start to explore hypothetical situations of slow and fast growth rates and the effects of different process parameters on supersaturation.¹

In the following examples we consider a crystallization process for an API, in which the product is first dissolved in a mixture of 2-propanol and water and, after polish filtration, is cooled to seeding temperature, seeded, aged at constant temperature and then further cooled before filtration and drying. We might consider many different process parameters that could influence product quality, including solvent volumes, seeding temperature, seed amount and PSD, ageing time, cooling ramp, agitation and final temperature.

To study all of these factors experimentally, using for example a statistical design, would require significant resources. One advantage of a theoretical model is that the effects of every factor and their combinations can be simulated rapidly, simultaneously and at many more levels than experimentally feasible. In addition, **the model provides a deeper understanding of the underlying process** than obtained from a statistical analysis of experimental results. A point to emphasize is that the theoretical model

should not replace the experimental DoE; moreover, it is a valuable addition to our understanding of the process and helps guide our DoE in a more efficient manner.

Returning to the crystallization process described above, different process scenarios were simulated using Equation 2, at two different crystal growth rates ($K_G = 0.01$ and 0.2 s^{-1}). The main effects on the maximum supersaturation were evaluated for different process factors. We see in Figure 1 that if the growth rate is fast, then the cooling rate is most important for maximum supersaturation level.²

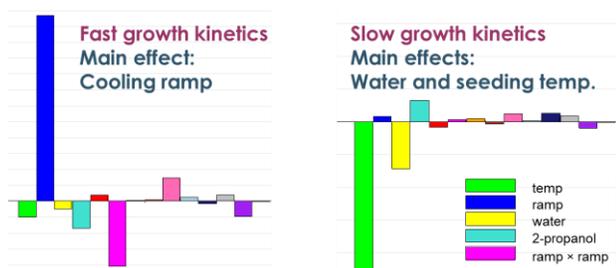


Figure 1: Main Effects of Process Parameters on Maximum Supersaturation

However, if the growth rate is slow then the seeding temperature and water content become significant and cooling rate is unimportant. A few, carefully chosen experiments would allow us to determine which scenario is closer to reality and guide further process development.

The approximation can be taken further by estimating a value for K_G . Nucleation is much more sensitive to supersaturation than growth, and therefore, by operating under conditions of low supersaturation, the initial premise of no nucleation that we made in the derivation of

Equation 2, becomes valid and allows us to calculate K_G . Because we are investigating the kinetics of crystallization, it is necessary to determine either the amount precipitated, or remaining in solution, as a function of time. This is normally performed using process analytical technology (PAT), or by sampling and filtration.

In Figure 2 below are shown experimentally determined solution concentration values (dark blue dots), together with the temperature profile (grey line), solubility curve (yellow), and simulated growth kinetics according to the above equation for three different growth rates, slow (purple), fast (red) and intermediate blue).² The curve can be fitted to estimate K_G ; in this case to give 0.08 s^{-1} .

We should always keep in mind that the model is erroneous due to the approximations we have made, but despite this, it can still be extremely useful. An example is shown below, in which the supersaturation model shows the effects of seeding temperature and ageing time. The K_G value that was determined previously has been introduced into the simulation.

The model allows us to perform a **virtual DoE** on our computer, exploring many different seeding and temperature profiles in very little time.

Solubility, and therefore crystallization kinetics, are often extremely sensitive to temperature and the optimum values could be missed by experimenting with a range that is too wide. The interpretation of this approximation can

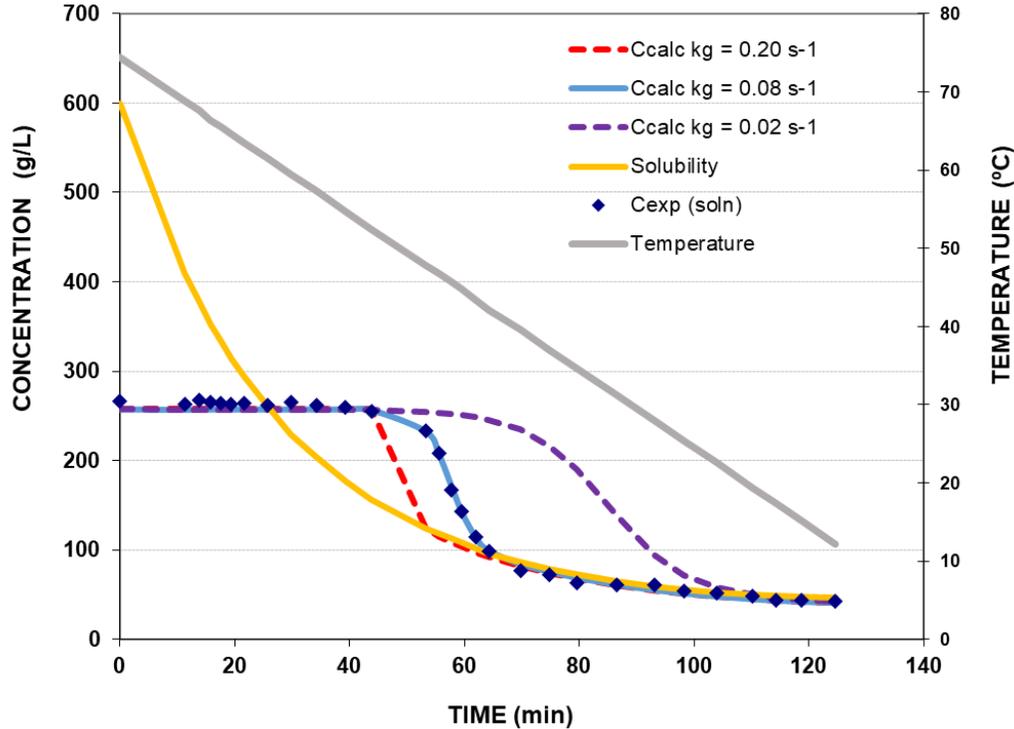


Figure 2: Effect of Crystal Growth Coefficient (K_G) on Crystallization Kinetics

give insights into PSD control. Because nucleation has a higher dependence on supersaturation than growth, the process with **higher maximum in supersaturation will give smaller particles**.

Using the model and virtual DoE method, we are able to explore the effect of seeding temperature at many levels, and different ageing regimes (15 and 60 minutes in the following example).

In Figure 3 we see the effect on supersaturation with time for the different scenarios. Although many combinations were explored only a few are shown in the graph for clarity. Interestingly, the simulation that gave lowest supersaturation is not one that was seeded at

higher temperature. Seeding at lower temperature, 56°C, and ageing for 60 minutes results in a lower maximum in the supersaturation curve. Therefore, **the model is predicting larger particles for the experiment seeded at lower temperature. A subsequent experimental DoE confirmed the effect of seeding temperature on PSD**, in agreement with the supersaturation model.

A clue to the explanation lies in the initial gradient of the curve after seeding. When seeding at lower temperature the initial supersaturation is higher, which results in more precipitation during the ageing process, when compared with an experiment seeded at higher temperature. The largest value of supersaturation occurs during the cooling

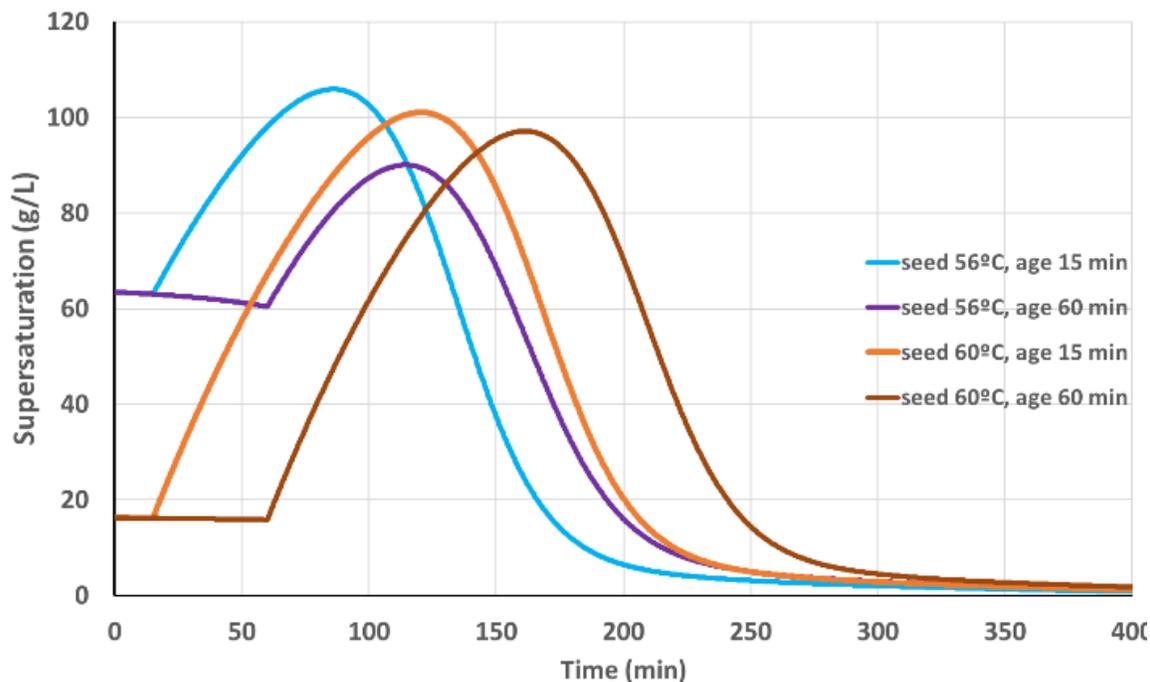


Figure 3: Effect of Seeding Temperature and Ageing Time on Supersaturation

ramp, but if more crystal density is already present at this moment, the growth rate is higher and the resulting jump in supersaturation is lowered.

This result is probably not obvious at first sight and is due to the changing crystal mass and kinetics throughout the crystallization process. It is an example of using simulation tools to bring understanding to our process, and underpinning the concept of **Quality by Design**, in a way that, perhaps, a purely statistical approach could not.

Particle size distribution modelling

The above supersaturation model can be further improved if required by taking into account the temperature dependence of K_G .

However, we would love to be able to model how the PSD changes with process profile and, perhaps more importantly, on scale-up. This becomes challenging, requiring models for solubility, growth and nucleation kinetics (and possibly attrition and agglomeration) together with a population balance model and correlation to the type of distribution used by the analytical method (e.g. spherical equivalent diameter).

Again, we would initially opt for a more simple, practical approach. As part of the crystallization process optimization, chemical engineering parameters (e.g. power/unit mass, shear, Reynolds number, tip speed) for different reactor designs, agitation and scale can be calculated. For processes involving reactive crystallizations (e.g. salt formation) or dominated by antisolvent addition, the meso-

mixing time may also be influential. Some targeted lab experiments based on these calculations can help identify potential factors and reduce risk on scale-up.

Conclusions

To paraphrase the famous statistician George Box, all models are wrong, but some models are useful. In the example described in this document solubility and supersaturation models were used to guide optimization of the crystallization process and understand the factors that affect PSD. In Solitek we believe that modelling is extremely valuable for crystallisation development and these models add to the knowledge base that is the foundation for Quality by Design. We recommend a practical approach using a mixture of simple semi-empirical models and targeted experimentation.

About the Author

Steve has over 20 years' experience in the pharmaceuticals and fine chemicals industry, with a large proportion of his time dedicated to solid form and crystallization. Much of his research has been dedicated to developing and transferring processes to production and troubleshooting historical processes.

About Solitek

Based in the Parc Científic of Barcelona, Spain, Solitek brings a new concept in solid state development, combining an excellent understanding of the diversity of the solid form landscape exhibited by small molecule organic compounds, with experience and practical know-how, increasing the chances of success, while reducing the overall cost of development.

References

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