An Executive Summary

How Well Should You Understand Your Crystallization Process (and Solid-State Properties)?

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Exploring the critical nature of crystallization process development and key factors for success.

Overview

Crystallization is the most common unit operation for the isolation and purification of solid intermediates and active pharmaceutical ingredients (APIs), and the quality of the output directly affects drug formulation development and manufacturing.

Well-designed crystallization processes and an understanding of the solid-state properties of a drug substance are essential to achieving a high-purity product and consistent delivery of the desired crystal modification. Particle size distribution (PSD) of the crystallization product depends upon the solvent/solute system, process parameters, and equipment properties. Crystallization processes are therefore used to engineer particles precisely. Having reliable and well-understood processes helps avoid issues in later product development.

Approaches to Crystallization

Crystallization has three main purposes. The first is to generate a solid product from a complex liquid matrix, ideally at high yield and with the required crystal modification. Second, and especially important in the pharmaceutical industry, crystallization purifies the product, removing any by-products and solvent to a given specification. Third, crystallization gives the product form, generating particles with the required size distribution, mean size, and shape. Thus, crystallization requires knowledge of the physical properties involved.

The basic approaches to crystallization process development involve working towards either a one-step or a two-step process. A one-step process isolates, purifies and produces the right powder specification in a single process. It has the advantage of being lower cost than a two-step process and having a faster turnaround. However, it can be difficult to control all the process parameters and deliver the desired product properties. A high level of process understanding and control is vital for success, and there is a risk of failure or of compromising purity or powder specification.

A two-step approach normally comprises a first crude crystallization for isolation and purification, followed by a second for form-giving and any further purification needed. The benefits are that fewer parameters require optimization in each process (compared with single step), it may be possible to eliminate shape-directing or growth-inhibiting by-products, and generally better process control. However, since two operations are involved, there are additional process steps with associated costs and a slower turnaround.

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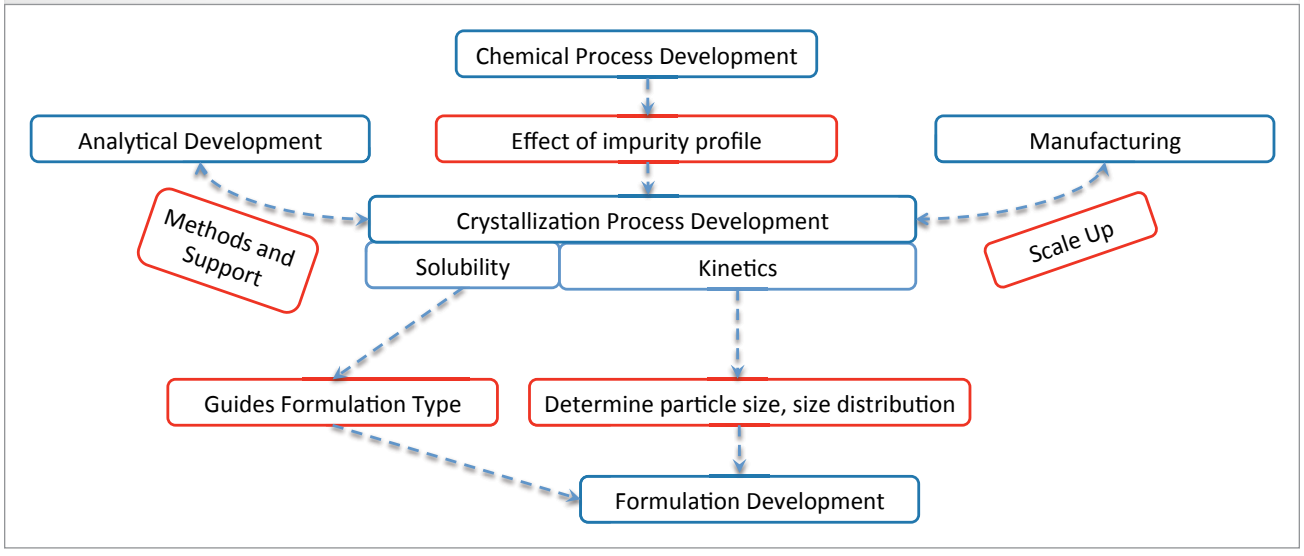
Figure 1: Rational process development.



Factors Governing Crystallization

Essentially, two factors govern crystallization, the first being thermodynamics. For crystallization, the thermodynamics are expressed in terms of the solubility of the target compound. The second, and more complicated factor, is kinetics. Four different competing kinetics—nucleation, growth, attrition (secondary nucleation), and agglomeration—must be considered and often the details are insufficiently understood to direct the properties from first principles.

Crystallization process development hinges on prior chemistry. Impurities can affect the thermodynamics and the kinetics, so it is important to have some knowledge of both the chemistry up to this point and by-product formation. In pharmaceutical processes, crystallization is never the final stage and formulation will be required to deliver a final drug product. The API properties themselves will guide formulation, with solubility, for instance, influencing formulation type, and particle size and PSD influencing dissolution characteristics and administration methods. **Figure 1** summarizes the considerations when taking a rational approach to crystallization process development, from initial chemistry to manufacturing and scale-up.

The Importance of Solubility

The solid–liquid equilibrium, or the maximum amount of a solid material that will dissolve in a given solvent, is a thermodynamic parameter characteristic of the solid under investigation and is a function of temperature, pressure, and composition. Since composition refers to everything that is in the starting solution, this includes any impurities from the initial synthesis. In principle, these must be known if solubility is to be fully understood. In practice, the effects of small amounts of impurity are often negligible and ignored unless it becomes clear during development that they have a role. Pressure dependence is generally noticeable only when operating at very high pressures, which is not an issue in most cases. For most systems then, equilibrium concentration is a function of temperature.

The graph in **Figure 2** plots solubility versus temperature for sucrose. At room temperature, solubility is just under 2 Kg anhydrous sucrose/Kg solvent, increasing to about 5 Kg/Kg solvent at higher temperatures. The blue dashed line indicates the starting (far right) and finishing (far left) temperatures for crystallization; the y-axis in between gives the theoretical yield. In this case, crystallization from around 370 Kelvin down to about 280 Kelvin yields approximately 3 Kg sugar per Kg of solvent, a yield of about 60%.

If the sucrose example were a pharmaceutical industry process, the aim would be for yields of more than 91% and a different type of process would be sought. The difference in equilibrium concentration is insufficient for this simple cooling crystallization to give a high yield. Instead, it might be possible to modify the solubility by adding an anti-solvent or to consider a reactive, or possibly evaporative, crystallization. Real-life processes are usually combinations of all of these.

So, solubility is important in understanding process yield. Since by extension it is part of the phase diagram and is part of the description of the phase behavior of a system, it also provides information about polymorphs, solvate, crystals and co-crystals.

Standard approaches to measuring solubility, including the classic “shake-flask” method and manual polythermal solubility measurement, tend to be somewhat error prone. More modern “dynamic solubility” measurement relies upon automation of polythermal solubility measurements. Several commercial instruments offer this, generally using light transmission. A turbid solution will scatter light, reducing the intensity of transmission, while a clear solution allows maximum transmission, and the transitions are usually sharp. The methodology can also detect nucleation upon cooling, providing information on the metastable zone width (MSZW), the working range for the crystallization. By definition, primary nucleation signifies the upper concentration limit of the metastable zone.

Solubility and the Metastable Zone

At concentrations below the equilibrium solubility line, the solution is undersaturated; at concentrations above the line, it is supersaturated. The metastable zone is the region between the solubility (blue line in **Figure 3**) and the metastable zone limit (red line in **Figure 3**). In the simple crystallization represented here, as nucleation occurs concentration decreases because of crystal growth, indicated by the red curved arrow.

A more complicated scenario emerges when dealing with polymorphs and solvates, where more than one crystal modification can be generated. Two classes of polymorphs exist: *monotropic* and enantiotropic. With *monotropic* forms, the free energies of both phases intersect at a temperature higher than that of the melting temperature of either solid, so the free energy of the metastable phase is always higher than that of the stable phase in the solid state. In turn, the solubility of the stable phase is always lower than the metastable phase.

For *enantiotropic* polymorphs, the free energies of the phases intersect at a temperature lower than the melting temperature for either solid, so there is a defined transition

Figure 2: Solubility versus temperature for sucrose.

Solid-Liquid Equilibrium

- $c^* = f(T, p, C)$

Determines type of process

- Cooling crystallization
  If Δc^* sufficiently large
- Antisolvent crystallization
  Solvent/antisolvent mixture, increase Δc^*
- Reactive crystallization
  For salts, co-crystals
- Evaporative crystallization
  If substance sufficiently stable and process controllable
- Real-life processes usually combinations of above

Extension – Phase behaviour (Polymorphs, Solvates, Salts, Co-Crystals...)

Determines yield

Theoretical yield (simplest case)

$$\Delta c^* = c^*(T_{in}) - c^*(T_{fin})$$

Aim for > 90 %

Below: yield ca. 3 kg/kg solvent = 61 %

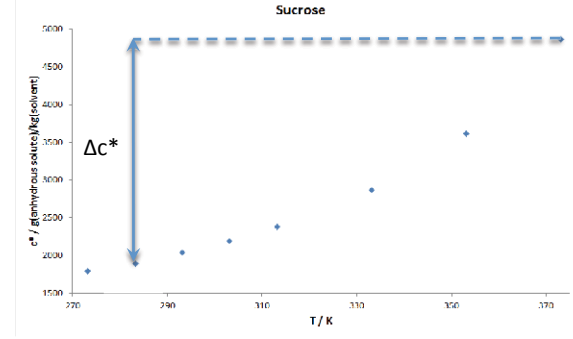


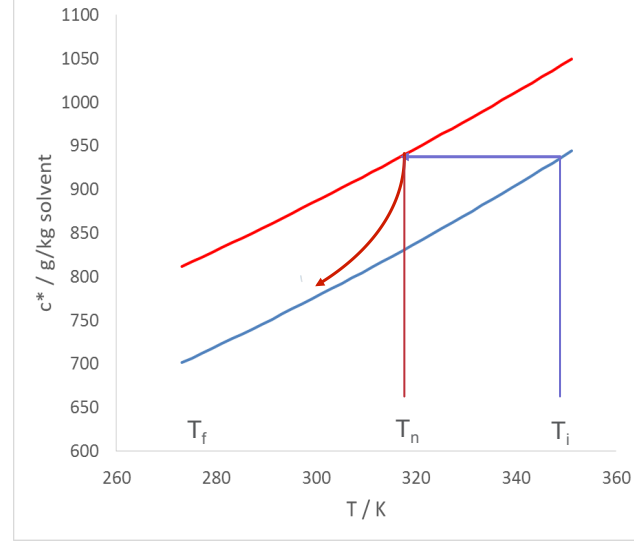
Figure 3: Solubility and metastable zone.

Metastable Zone

- Defined as T where primary nucleation occurs
- Labile solution unobtainable using this definition
- Working range for crystallization process

Simple Cooling Crystallization

- Cool from T_i
- Nucleation occurs at T_n
- Growth reduces supersaturation
- Cool further until final Temperature T_f



temperature between the two different solids. The risk here is that working in an incorrect temperature range will generate the wrong phase and means relying upon this wrong crystal modification transforming to the desired form within the process time. This requires sufficiently fast kinetics.

Competing Kinetics

With four types of kinetics competing in a crystallization, it is important to understand the influence they exert, beginning with the kinetics of formation of the first particles or primary nucleation. Primary nucleation may be homogeneous, where nuclei form without external stimulus, or heterogeneous involving the formation of nuclei on foreign surfaces such as dust, impurities, or equipment surfaces. In contrast, secondary nucleation is the formation of crystal nuclei as the result of attrition that causes breakage and leads to the production of two or more particles from an original single one.

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Primary nucleation is normally characterized by classical nucleation theory, and while there is debate about the theory itself, it is currently the best tool. Factors affecting the time taken from supersaturation to nucleation include surface tension, temperature, and the supersaturation itself. At lower supersaturations, there is little chance of nucleation but a very rapid rise in nucleation rates occurs as supersaturation increases. This rise is so rapid that even at moderate supersaturation levels subtle changes in the process may give rise to the generation of different numbers of particles as nucleation progresses. Nucleation is a kinetic process and is therefore also subject to changes in impurities, the solvents used, materials of construction, mechanical perturbations, cooling rates, and antisolvent or reactant addition rates. For all these reasons, the metastable zone will never appear as a clean line, but more as a cloud of different nucleation points and is not exactly reproducible from experiment to experiment.

The stochastic nature of nucleation means that small variations in conditions result in large differences in nucleation rates. Consequently, particle size becomes difficult to control, depending on both growth rates and the number of particles growing. A higher nucleation rate is likely to produce smaller particles and vice versa. Therefore, it is advisable to control the crystallization process by seeding, which circumvents primary nucleation. Designing the seeding process to ensure it takes place in middle of the metastable zone requires accurate knowledge of the zone width.

The next stage, crystal growth, determines the duration of a batch process. In continuous processes, crystal growth rates influence the choice of equipment size as they determine the mean residence time of the particles in the crystallizer. Crystal growth kinetics are complex and depend upon the level of supersaturation. At low levels, step growth is usual, occurring in the form of spiral growth due to dislocations in the crystal. Other models include birth and spread, where pre-formed clusters of the solid in solution deposit on the surface of the crystal and then organize into the crystal structure. At very high supersaturations, rough or dendritic growth (as seen in snowflakes) may occur. The growth mechanism impacts product quality. Rapid growth can lead to liquid inclusions that affect residual solvents and purity profiles. Rough surfaces are prone to secondary nucleation, changing the final particle size distribution. Also, depending on the supersaturation level, the aspect ratio of the crystals may change, with implications for downstream processing.

In terms of crystal growth kinetics, there is a question of which growth rate to measure, since different ones can be defined: growth rate of an individual crystal face, overall linear growth rate, or mass deposition rate. Mass deposition rate is probably the most useful as it describes growth of an assembly of crystals over time and provides information on process duration. When designing a continuous process there is a clear need for measuring crystal growth rates, but for batch processes it is easier to simply perform a few experiments, varying process duration and comparing yields.

Process Design

Building on the knowledge gained above, the next step is to select the solvent, or solvent mixture, based on solubility and its ability to purify. Selecting the process type then becomes a case of elucidating the best process parameters to ensure the right crystal modification, purity, size and size distribution. Here the use of an automated reactor with various probes that help understand exactly what is happening during the crystallization is an advantage. Typically, probes may deliver focused beam reflectance measurements (FBRM) for particle sizing that allows observation of changes in the process and process video microscopy (PVM) for inline image acquisition and limited image analysis.

Figure 4: Typical experimental output using the Optimax Reactor (Mettler Toledo).

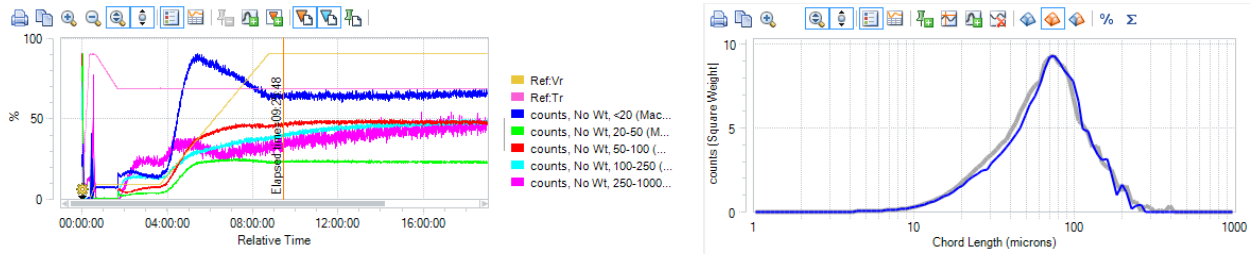

Figure 5: Variation of crystallization conditions.

One and the same substance crystallized from different solvents, solvent compositions, addition rates

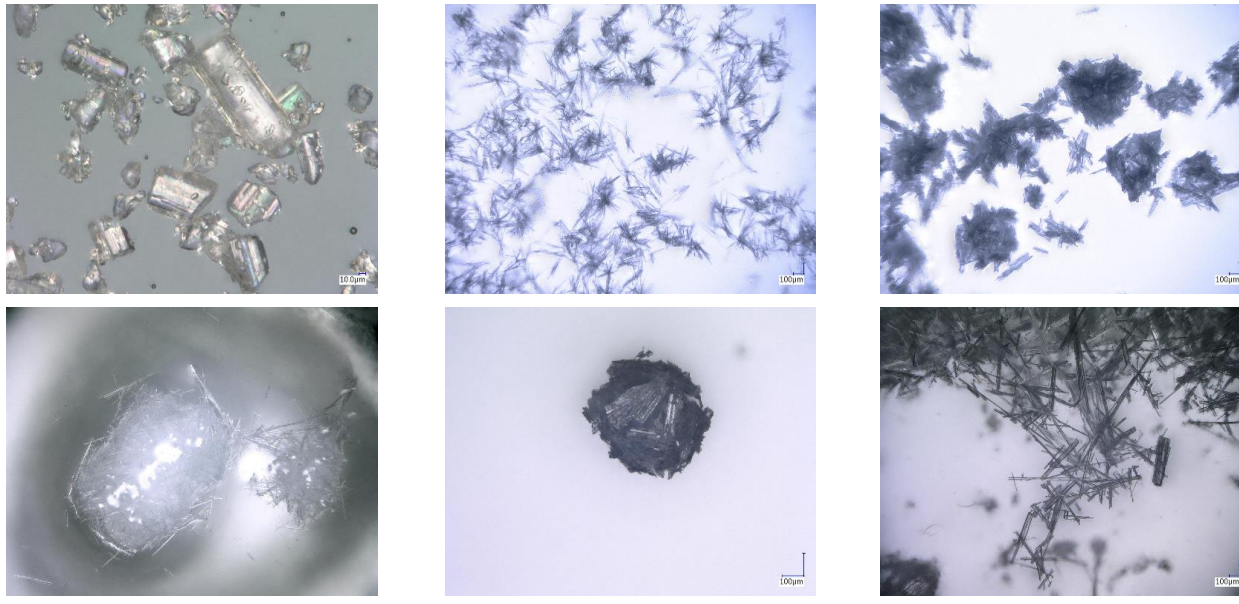

Figure 4 shows a typical experimental output using the Optimax Reactor (Mettler Toledo). The trace in the bottom right hand corner shows particle size distributions (measuring chord length) and the bottom left graph shows changes in the size classes over the course of the process. Alongside these are images taken from the PVM at different times in the process.

In the bottom left graph, the early high signal level indicates material dissolving. This is followed by a low signal, which increases once the process is seeded at between 1.5 and 2 hours. The addition of antisolvents (yellow line) at 4 hours results in a major change in fine particles (blue line), which then decreases over time. After around 8 hours, roughly coinciding with the point at which no further antisolvent is added, very little changes in the process. So, there is a very long hold period, with a little increase in large particles but where the signal for the lower size classes remains constant. This indicates the hold period is unnecessarily long. The result of varying crystallization conditions is illustrated in **Figure 5**, demonstrating the need to fully understand process parameters before going into manufacturing.

Scale-Up Challenges

With continuous processes, there are established scale-up procedures. These do not apply for batch processes, where technology transfer is not straightforward. **Figure 6**, which compares a pilot-scale and plant-scale reactors, illustrates why and how the different parameters change with scale. The one constant is impeller diameter since that is defined by the geometry at the pilot scale. For scale-up, it is therefore important to know which parameter influences the process the most, something that can only really be determined with laboratory experiments. The effects of different processing equipment can also lead to different behaviors and to changes in the PSD of the product.

Figure 6: Pilot-scale versus plant-scale reactors.

		Pilot Scale	Plant Scale			
		30 L	10 000 L			
Power Input	$P \propto N^3D^5$	1	333.3	100 000	100	0.1
Power to Volume Ratio	P/V	1	1	300	0.3	0.0003
Impeller Rate	N	1	0.15	1	0.1	0.01
Impeller Diameter	D	1	10	10	10	10
Tip Speed	ND	1	1.5	10	1	0.1
Reynolds Number	ND^2	1	15	100	10	1
Pumping Capacity Impeller	ND^3	1	150	1000	100	10

Crystallization is never an isolated unit operation, so there are other factors to consider. The chemical synthesis prior to crystallization can influence the outcome through variable concentrations or changes in chemistry that may affect concentrations and purity profiles. Ineffective removal of transition metal catalysts, for example, can inhibit crystal growth or nucleation.

Processes following crystallization include solid-liquid separation. This is influenced by crystal shape, the mechanical properties of the crystals and the nature of the solid phase, whether it is single or multi-component, for example, and its stability under processing. Grinding of crystals may take place at this stage with consequences for particle size and stability of the end-product. Similarly, washing efficiency depends upon solids' characteristics in the process, with the potential to affect yield, size specification, and the solid form. Drying efficiency too may depend on particle and residual liquid characteristics, and can influence purity and particle size, especially if agitated.

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Working with Incomplete Knowledge

In the pharmaceutical industry, it is common to work with incomplete knowledge, largely due to lack of information about the phase behavior of solids and the difficulty of identifying all possible solid forms. While computational technology has made great strides, it cannot tell you how to make a specific modification. So, it is necessary to prepare for the possibility that the modification being crystallized is not thermodynamically stable and may go through unexpected phase transitions and instability on further processing. Consulting phase diagrams may help here, especially when encountering impurities.

Conclusion

Rational crystallization process development relies upon understanding the nature of both the solid phase and solution phase behavior. This understanding reduces the possibility of unexpected events during process development and in later manufacturing. Judicious measurement of appropriate physical properties can free resources to focus on the process rather than on problems.