Crystallization is recognized as a common unit operation used to isolate and purify product in a number of industries. However, the scientific fundamentals of crystallization are typically not as well-known as they are for other unit operations such as distillation or absorption. The crystallization step directly influences product attributes such as crystal size, shape, yield and purity which offers great potential to improve both the quality of the final product and the efficiency of the process.

In the first part of this two-part white paper the fundamentals of crystallization will be introduced and common-sense guidelines for the design of a high quality crystallization process will be presented. Using case studies and references from industry and academia, key crystallization topics such as solubility, supersaturation and crystallization kinetics will be explained with examples of how each can be utilized to make informed decisions regarding effective crystallization process development. The role of technology in crystallization development, from effectively controlling crystallization process parameters to monitoring crystal size and supersaturation in situ, will also be presented.
1 Introduction to Crystallization and Precipitation

Crystallization touches every aspect of our lives from the foods we eat and the medicines we take, to the fuels we use to power our communities. The majority of agrochemical and pharmaceutical products go through many crystallization steps during their development and manufacture, key food ingredients such as lactose and lysine are delivered to humans and animals as crystals and the unwanted crystallization of gas hydrates in deep sea pipelines is a major safety concern for the petrochemical industry.

Scientists and engineers working in many industries around the world are required to understand, optimize and control crystallization processes every day. The purpose of this guide is to introduce key crystallization concepts and highlight the many resources available for those working in this exciting field.

**Crystallization**: A process whereby solid crystals are formed from another phase, typically a liquid solution or melt

**Crystal**: Solid particles in which the constituent molecules, atoms or ions are arranged in some fixed and rigid repeating three-dimensional pattern or lattice

**Precipitation**: It is a little bit difficult to define the term precipitation. For some, it is simply a very fast, perhaps uncontrolled, crystallization process. For others it is crystal formation resulting from a chemical reaction. It can also vary by industry; in the pharmaceutical industry “crystallization” is common and in the chemical industry “precipitation” is the vernacular.

The prevalence of crystallization processes in industry can likely be attributed to the fact that crystallization acts as both a separation and purification step. In a single step, crystal product of the desired purity can be created and then isolated. Despite this obvious advantage, crystallization processes still need to be understood and controlled to the desired crystal product quality and to ensure an efficient and cost-effective crystallization process.

While crystals have many important attributes the crystal size distribution probably has the greatest impact on the quality and effectiveness of the final product (and the process needed to deliver it). Crystal size and shape directly influence key steps downstream from the crystallizer with filtration and drying performance being particularly susceptible to changes in these important attributes. Similarly the final crystal size can also directly influence the quality of the final product. In a pharmaceutical compound, bioavailability and efficacy are often related to particle size with smaller particles often desired for their enhanced solubility and dissolution characteristics.

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**Product Performance**
“Crystallization of an API [active pharmaceutical ingredient – the crystal product] in particular is critical for product qualities such as chemical purity and correct polymorphic form, which need to be strictly controlled to meet set specifications”.

**Process Performance**
“The API crystallization process and crystal properties have a significant effect on downstream processing. For example, excess fines or wide particle size distribution may cause slow filtration and inefficient drying, which may be a major bottleneck of the entire manufacturing process”.

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Crystallization and Precipitation
The crystal size distribution of ice plays a vital role in the taste and mouthfeel of ice cream with crystals smaller than 50 μm better than crystals larger than 100 μm. For agrochemicals it is vital to ensure that particles are small enough to be sprayed without blocking nozzles while large enough not to drift into neighboring fields.

Crystal size distribution is influenced by a number of variables which can be optimized and controlled during crystallization development and manufacturing. In turn, crystal size distribution influences both product and process performance. Figure 1-1 highlights how choosing the correct input properties and process parameters for a crystallization can influence the transformations that occur and the product and process attributes that result once the crystallization is complete.

Figure 1-1. Relationship between common crystallization parameters, transformations and attributes

2 Common Ways to Reduce Solubility and Drive Crystallization

Crystallization is generally achieved by reducing the solubility of the product in a saturated starting solution by cooling, adding antisolvent, evaporation or some combination of these methods. Another common method used to induce crystallization is via a chemical reaction where two or more reactants are mixed to form a solid product insoluble in the reaction mixture; a common example of this would be the reaction of an acid and a base to form a salt.

The method chosen to crystallize product can vary greatly depending on a number of factors. For example, protein crystals are temperature-sensitive ruling out cooling and evaporation and leaving antisolvent addition as the most common crystallization method. For many crystallization processes, cooling can be advantageous as it is reversible; the saturated solution can be reheated in the event of a non-optimal operation. Many large scale industrial crystallization processes rely on evaporation to produce common products such as potassium nitrate and ammonium chloride.

Regardless of the method chosen a common feature is starting with a saturated solution.

**Saturated Solution and Solubility:** At a given temperature there is a maximum quantity of solute that can be dissolved in a given solvent. At this point, the solution is saturated. The quantity of solute dissolved at this point is the solubility.

**Units:** Solubility is usually reported as:
- g of solute/100 g of solvent
- g of solute/L of solution
- mole fraction
- mole %

Solubility curves (Figure 2-1) are commonly used to illustrate the relationship between solubility, temperature and solvent type. By plotting temperature vs. solubility, scientists create the framework needed to develop the desired crystallization process.

In Figure 2-1, the solubility of the given material in Solvent A is high – meaning more material can be crystallized per unit mass of solvent. Solvent C has a low solubility at all temperatures, indicating it could be a useful antisolvent for this material.
Solubility curves also reveal the theoretical yield for a given crystallization process. In Figure 2-1 if a saturated solution containing 50 g of product per 100 g of Solvent A is cooled from 60 °C to 10 °C then it is clear that 10g of product per 100 g of solvent will remain in solution. In other words exactly 40 g of product per 100 g of solvent should crystallize. This allows scientists to compare the theoretical yield with the actual yield and define the efficiency of the crystallization process.

Once an appropriate solvent is chosen, the solubility curve becomes a critical tool for the development of an effective crystallization process. With this information the starting concentration and temperature (or antisolvent ratio) can be chosen and the first important decisions regarding how the crystallization will be developed can be made. For example if seeds are to be used to induce crystal nucleation it is critical to add them at a temperature lower than the solubility point – otherwise they will dissolve.

Example Case Study

ParticleTrack (a probe based instrument that tracks the rate and degree of change to particle size and count as particles exist in process) can be used to measure the solubility curve and MSZW by accurately identifying the point of dissolution (point on the solubility curve) and point of nucleation (point on the MSZW) at various solute concentrations. In Figure 2-2, an undersaturated solution is cooled at a slow, fixed rate until the point of nucleation is measured by ParticleTrack, indicating a point on the MSZW. Next, the solution is heated slowly until the point of dissolution is measured indicating a point on the solubility curve.

Solvent is then added to the system to reduce the concentration and the process is repeated. In this way, the solubility curve and MSZW can be measured rapidly over a wide range of temperatures. This process can be automated using a synthesis workstation, such as EasyMax® or OptiMax™ by introducing a feedback loop where the ParticleTrack signal can be used to initiate the heating, cooling and dilution steps.

Figure 2-2. Points of nucleation and dissolution during cooling and heating

Figure 2-3. Automated crystallization workstation with tight control over process parameters and probe based tools for real time unattended characterization (ParticleTrack and ParticleView probes monitoring in an EasyMax synthesis workstation)
In Figure 2-4, the solubility curve and metastable zone width(s) for potassium aluminum sulphate is shown. While the solubility curve is thermodynamically fixed for a given solvent-solute system the MSZW is a kinetic boundary and can change depending on process parameters such as cooling rate, agitation or scale. Characterizing the MSZW under a range of process conditions can help scientists understand how a crystallization process may behave at different scales - or in the event of a process upset. Variability in the MSZW under different conditions may indicate that the system may not behave consistently in terms of nucleation point and kinetics. Such a result may justify investigating the possibility of seeding the process in order to fix the nucleation point for every experiment or batch.

Dynamic approaches to solubility determination, such as this one, are sometimes limited in their accuracy since a fast heating rate means the exact point of dissolution can be overestimated. Static methods, such as gravimetric analysis may offer more accuracy – but are more time-consuming and cumbersome to implement. Many techniques can be used to measure solubility curves and recent research aimed at predicting solubility in different solvents is showing promise. The references below offer a good starting point for more in depth study.

3 Supersaturation: The Driving Force for Crystal Nucleation and Growth

Crystallization scientists gain control of crystallization processes by carefully controlling the prevailing level of supersaturation during the process.

**Supersaturation**: The difference between the actual concentration and the solubility concentration at a given temperature is defined as the supersaturation ($\Delta C$)

Figure 3-1 illustrates the concept of supersaturation and expands on the role of the metastable zone width, the kinetic boundary at which crystallization occurs. When a saturated solution is gradually cooled crystals will “crash out” at a given temperature. It seems intuitive to think that this temperature may be the same as the solubility temperature – the temperature at which the last crystal dissolved during heating. However, when a saturated solution is cooled the system enters a metastable region where the solution becomes supersaturated, in other words, more of the solute is in solution than the solubility curve predicts. As cooling continues, a certain temperature will be reached where crystal nucleation will occur. This point is called the metastable limit and the difference in temperature between this point and the solubility curve is called the metastable zone width. Once the metastable limit is reached and crystallization starts supersaturation is consumed and eventually the liquid phase concentration will reach equilibrium at the solubility curve.

It is critical to understand the concept of supersaturation because it is the driving force for crystal nucleation and growth, and as such, will ultimately dictate the final crystal size distribution. Nucleation is the birth of new crystal nuclei – either spontaneously from solution (primary nucleation) or in the presence of existing crystals (secondary nucleation). Crystal growth is the increase in size (or more accurately “characteristic length”) of crystals as solute is deposited from solution. The relationship between supersaturation, nucleation and growth is defined by a well known set of (somewhat simplified) equations (Table 3-1).

$$ G = k_G \Delta C^g $$

<table>
<thead>
<tr>
<th>Equation</th>
<th>Variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>$G$</td>
<td>Growth Rate</td>
</tr>
<tr>
<td>$k_G$</td>
<td>Growth Constant</td>
</tr>
<tr>
<td>$g$</td>
<td>Growth Order</td>
</tr>
<tr>
<td>$\Delta C$</td>
<td>Supersaturation</td>
</tr>
</tbody>
</table>

$$ B = k_B \Delta C^b $$

<table>
<thead>
<tr>
<th>Equation</th>
<th>Variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>$B$</td>
<td>Nucleation Rate</td>
</tr>
<tr>
<td>$k_B$</td>
<td>Nucleation Constant</td>
</tr>
<tr>
<td>$b$</td>
<td>Nucleation Order</td>
</tr>
<tr>
<td>$\Delta C$</td>
<td>Supersaturation</td>
</tr>
</tbody>
</table>

Table 3-1. Equations that define relationship between supersaturation, nucleation and growth rate.1
For organic crystallization systems, the value of the growth order (g) is typically between 1 and 2 and the value of the nucleation order (b) is typically between 5 and 10. When we plot these equations for a theoretical organic crystallization process the importance of supersaturation becomes clear. At low supersaturation, crystals can grow faster than they nucleate resulting in a larger crystal size distribution. However, at higher supersaturation, crystal nucleation dominates crystal growth, ultimately resulting in smaller crystals. Figure 3-2, relating supersaturation to nucleation, growth and crystal size clearly illustrates how controlling supersaturation is vitally important when it comes to creating crystals of the desired size and distribution.

**Example Case Study**

Supersaturation can be monitored *in situ* and in real time by measuring the liquid phase concentration with ReactIR (ATR-FTIR). In this example, researchers looked at the cooling crystallization of benzoic acid from ethanol water mixtures and utilized ReactIR to monitor supersaturation *in situ* and in real time. A novel approach is to eliminate the need for a calibration step and simply monitor a peak in the ReactIR spectrum that is characteristic of the solute concentration (Figure 3-3). By heating a crystal suspension slowly a solubility trace (peak height as a function of temperature) can be created. As temperature increases, crystals dissolve and solute goes into solution. If the heating rate chosen is slow enough it can be assumed that the system is effectively at the solubility point at each temperature, and that a plot of temperature vs. peak height is an effective way to trace the solubility curve without calibration (Figure 3-4). While this approach may not be as accurate as using a static method (outlined in section 2) the simplicity and real time nature of this method make it a valuable approach that can be deployed routinely during crystallization development.
Once a solubility trace is determined, crystallization processes can be run under varying process conditions and the effect of these conditions on supersaturation can be observed. Faster cooling rates result in nucleation at lower temperatures and the highest level of supersaturation throughout the process. A very slow cool down results in a higher nucleation temperature and low supersaturation throughout the process. A one-hour cubic cool down (slow at first and fast at the end) has a medium level of supersaturation throughout.

The influence of varying supersaturation on crystal size and shape distribution can be clearly observed by comparing ParticleView (a probe based real-time microscope) images for each experiment. Higher supersaturation results in the smallest crystals – since nucleation will be favored over growth. The opposite is true for the slowest cool down.

The fundamentals of crystallization and the relationship between supersaturation and crystallization kinetics are covered in great detail in these references.

5. Mark Barrett, Mairtin McNamara, HongXun Hao, Paul Barrett, Brian Glennon, Supersaturation tracking for the development, optimization and control of crystallization processes, Chemical Engineering Research and Design, Volume 88, Issue 8, August 2010, Pages 1108-1119.
4 The Importance of Crystal Size and Shape Distribution

This set of ParticleView images (Figure 4-1) neatly illustrates the complex size, shape and structure of various crystals. From large round “boulders” to beautifully delicate “dendrites”, crystal product is often varied, posing challenges to effective separation and downstream manipulation.

Filtration or centrifugation is typically the step that comes after crystallization and the crystal size and shape can greatly affect the efficiency of this unit operation. It is not much use to design a crystallization that is complete in one hour if it ends up taking 24 hours to filter! Looking at the ParticleView images some clues as to how these different crystal products will filter can be gathered:

a. These crystals will likely filter quickly and consistently. The larger boulders will leave plenty of space for the filtrate to pass through rapidly.

b. Flat plates like these can be some of the most difficult to filter. Plates tend to stack on top of each other creating a layer of crystals that the filtrate cannot get through. This leads to long and potentially variable filtration times, depending on how the crystals are discharged from the crystallizer.

c. This is another case where filtration times can be long. Small crystals will plug the gaps left by the larger crystals making it difficult for the filtrate to pass through the bed of crystals. This is a common problem because many crystallization processes are designed with a fast cool, or antisolvent addition step at the end of the crystallization (to increase yield) that leads to excessive secondary nucleation. Additionally, in many cases the agitation is increased at the end of the batch to help with discharge and this leads to crystal breakage.

d. This image is more common than many would expect, at least in organic crystallization systems that are seeded. A structure such as this would be difficult to observe using an offline microscope as it will be crushed during sampling and preparation. However, ParticleView reveals a beautiful dendritic structure. A dendrite such as this often forms when a crystallization is seeded with milled seed. Imperfections on the crystal surface lead to crystal growth from these areas and long crystal branches growing from a seed core. It is difficult to predict how something like this will filter but it is likely to break apart resulting in variable filtration times.

Figure 4-1: ParticleView real-time microscope images
Filtration is just one aspect of crystallization where particle size is important. For many products, the crystal size impacts the effectiveness of the product; for example the rate of absorption of a pharmaceutical drug in the body or the burn rate of a highly energetic material. Other aspects of the process can also be influenced by particle size and shape – for example flowability. Table 4-1 highlights some other areas where crystal size plays a key role in various applications.

<table>
<thead>
<tr>
<th>Application</th>
<th>Product Quality</th>
<th>Process Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active Pharmaceutical Ingredients</td>
<td>Speed of action (small crystals dissolve faster allowing medicines to work faster)</td>
<td>Drying rates (large crystals have a lower surface area to volume ratio and may dry more slowly)</td>
</tr>
<tr>
<td>Energetic Materials</td>
<td>Burn rate (small crystals burn faster and with higher energy)</td>
<td>Safe handling (small crystals can be volatile and unsafe)</td>
</tr>
<tr>
<td>Agrochemicals</td>
<td>Segregation (large crystals sink to the bottom of formulation tanks and are not sprayed evenly)</td>
<td>Yield (small crystals can bind or block filters resulting in multiple washes and the reduction in yield)</td>
</tr>
<tr>
<td>Sugar</td>
<td>Flowability (uniform crystal size makes for better product flowability)</td>
<td>Poor control (small crystals, resulting from excessive nucleation, can destabilize a process)</td>
</tr>
<tr>
<td>Amino Acids</td>
<td>Bioavailability (small crystals dissolve faster)</td>
<td>Throughput (wide crystal size distributions can be difficult to stir and transport through a process)</td>
</tr>
<tr>
<td>Bulk Chemicals</td>
<td>Price (crystals of different size can be sold at different prices for different purposes)</td>
<td>Centrifugation (small crystals can reduce centrifuge performance and cause breakdowns)</td>
</tr>
</tbody>
</table>

Table 4-1. Crystal size vs product and process quality for various applications

**Example Case Study**

The process conditions chosen can greatly influence crystal size, either by affecting supersaturation and kinetics (Chapter 3) or by more physical mechanisms such as crystal breakage or agglomeration, which are both influenced by mixing conditions in the crystallizer.

Figures 4-2 and 4-3 show how increasing the cooling rate at the end of a crystallization experiment results in a secondary nucleation event and a more rapid increase in fine crystal counts (less than 20 μm). An increase in cooling rate generates more supersaturation - which is consumed by nucleation rather than growth. Careful control of cooling rates at every point in a crystallization is vital to ensure the target crystal size distribution is obtained.

**Figure 4-2.** ParticleTrack data: time vs. temperature and counts (0-20μm) showing faster cooling causes secondary nucleation

**Figure 4-3.** ParticleTrack data with confirmation from ParticleView images show how more small crystals appear after the second cooling ramp
In Figure 4-4, the influence of a high shear wet mill is shown on crystal size and shape. Initially rod-like crystals are present but as wet-milling progresses the crystals size decreases and the crystal count increases. ParticleTrack and ParticleView monitor this progression and can support targeting an endpoint that delivers crystals of the most appropriate size and shape in a repeatable way.

Figure 4-4: a. Time vs. Counts and mean chord length for a wet-milling process; b. ParticleView images taken at 7 mins (left) and 30 mins (right) for the same process.
5 Conclusion

In the preceding chapters some of the fundamental aspects of crystallization development have been covered - with special attention paid to manipulating crystal size and shape distribution. Sound understanding of the fundamentals is vital to ensure an effective crystallization process can be developed and scaled up to manufacturing, however a number of topics have not been addressed. In a follow up white paper, a number of other crystallization challenges and solutions will be addressed including seeding, scale-up and how to choose the correct process parameters to ensure target process and product attributes are obtained.

White Paper: Best Practice for Inline Particle Size Characterization

This white paper outlines how scientists and engineers can improve process understanding, product quality and process performance by applying inline particle size and count measurements. By implementing inline technologies, measurement errors and variability caused by offline sampling and sample preparation methods are eliminated.

www.mt.com/wp-E25

White Paper: Understand Crystallization with In Situ Microscopy

This White Paper demonstrates that in situ microscopy offers a faster alternative to traditional offline visualization methods and discusses how GlaxoSmithKline, Merck, Sintef, and University College Dublin (UCD) use in situ microscopy to gain a unique perspective of their crystallization processes.

www.mt.com/wp-PVM
Appendix A: ParticleTrack with FBRM® (Focused Beam Reflectance Measurement)

Measurement for optimization in real time – ParticleTrack is a precise and sensitive technology which tracks changes to particle dimension, particle shape, and particle count. Over a wide detection range from 0.5 to 2000 µm, measurements are acquired in real time while particles are forming and can still be modified enabling process optimization and control. No sampling or sample preparation is required – even in highly concentrated (70 % and higher) and opaque suspensions.

www.mt.com/ParticleTrack

How does ParticleTrack work?
The ParticleTrack probe is immersed into a dilute or concentrated flowing slurry, droplet emulsion, or fluidized particle system. A laser is focused to a fine spot at the sapphire window interface (Figure a). A magnified view shows individual particle structures will backscatter the laser light back to the probe (Figure b). These pulses of backscattered light are detected by the probe and translated into Chord Lengths based on the calculation of the scan speed (velocity) multiplied by the pulse width (time). A chord length is simply defined as the straight line distance from one edge of a particle or particle structure to another edge. Thousands of individual chord lengths are typically measured each second to produce the Chord Length Distribution (CLD) (Figure c). The CLD is a “fingerprint” of the particle system, and provides statistics to detect and monitor changes in particle dimension and count in real time (Figure d).

Unlike other particle analysis techniques, ParticleTrack measurement makes no assumption of particle shape. This allows the fundamental measurement to be used to directly track changes in the particle dimension, shape, and count.
Appendix B: ParticleView with PVM® (Particle and Vision Microscope)

Vision for understanding and optimization – ParticleView is a real-time probe based vision tool which provides instant critical insight into crystal, particle, and droplet systems. ParticleView enables chemists and engineers to detect and understand process changes that could take months to discover with traditional offline microscopy techniques.

www.mt.com/ParticleView

How does ParticleView work?
ParticleView uses a high resolution camera and internal illumination source to obtain high quality images even in dark and concentrated suspensions or emulsions. With no calibration needed and easy data interpretation, ParticleView quickly provides critical knowledge of crystal, particle, and droplet behavior.
References and Further Reading


5. Mark Barrett, Mairtin McNamara, HongXun Hao, Paul Barrett, Brian Glennon, Supersaturation tracking for the development, optimization and control of crystallization processes, Chemical Engineering Research and Design, Volume 88, Issue 8, August 2010, Pages 1108-1119.


