White Paper

Crystallization of CBD

Steps for Successfully Scaling Up

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METTLER TOLEDO

1. Introduction and Definition

Over the last several years cannabidiol (CBD) from hemp experienced a phenomenal upsurge in acceptance with the general population. The change in regulations around CBD–rich hemp, the FDA approval of Epidiolex (an epilepsy drug containing CBD) and the non-intoxicating nature of CBD, have fueled the increase in cultivation, production and demand of this substance. CBD is only one of the many cannabinoids produced by hemp and cannabis plants. Due to regulations on limits of THC contamination, isolation of purer forms of CBD is one of the most important steps of the production process. The isolation of pure CBD from less pure mixtures is commonly accomplished by recrystallization.

Understanding the crystallization process is critical to successfully scale up CBD isolation. Since the cannabis and CBD–hemp industries are relatively young, very little research has been performed optimizing CBD recrystallization. Poor understanding of the process tends to cause inconsistencies in yield, particle size of crystals and purity of CBD. In this regard, most cannabinoid isolation efforts do not leverage Process Analytical Technologies (PAT) to provide a more thorough understanding of crystallization mechanics.

Therefore, it is not surprising that current recrystallization methods are highly inefficient. In addition to decreased yield and purity of CBD, such inefficient recrystallization methods also effect downstream processing such as filtration times, drying, milling and formulating. Fortunately, these issues can be mitigated by a more thorough understanding of the solubility of the system.

There are a few basic concepts that need to be understood for efficient CBD recrystallization, also see figure 1:

- CBD **solubility** represents the amount of CBD fully dissolved in a given amount of solvent at a specific temperature.
- **Supersaturation** is when the solution contains more CBD than could normally be dissolved by the solvent at a particular temperature.
- **Nucleation** is the first step of crystallization when the first CBD crystals form from the solution.
- The **Metastable Zone Boundary** represents the "cloud point" for a given CBD concentration or where the system spontaneously nucleates to form crystals.
- Metastable Zone Width (MSZW) is the 'area' between the solubility and metastable zone boundary.

Introduction and Definition

2. Importance of CBD MetaStable Zone Width Determination

For precise and efficient CBD recrystallization it is important to control both the CBD concentration in the solvent and the rate of cooling. Runaway cooling rates generate supersaturation faster which leads to spontaneous nucleation. This can be problematic because it generates lots of fines (very small particles) and agglomerates that generally have lower purity, lead to poor filtration and lower product quality. Careful control of cooling rate is critical to ensure the desired crystal size distribution specification can be achieved. An example for the important of crystal size distribution would be ice cream. Crystals smaller than 50 µm being better than crystals larger than 100 µm for the taste and consistency. Most crystallization optimization studies are focused on designing a cooling curve that stays within the MSZW (Figure 1).

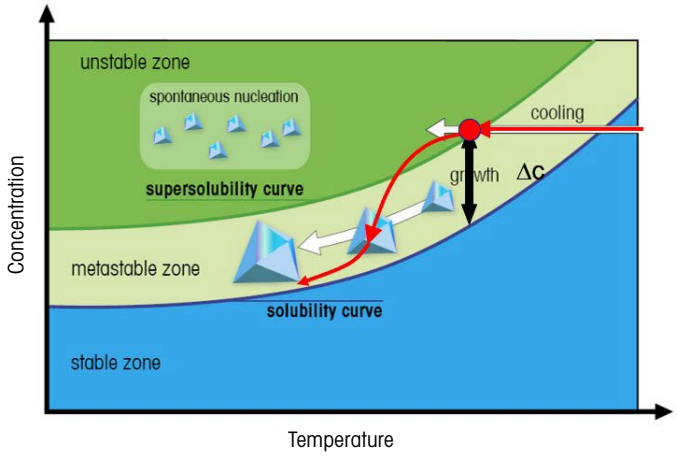


Figure 1: Metastable Zone Width – the region between the supersolubility and solubility curves.

Conducting studies that monitor nucleation and dissolution at varying CBD concentrations allow the processor to determine critical process parameters like the MSZW. Mettler Toledo Particle Size Characterization technologies have been specifically designed for these types of studies since they measure relative crystal concentration in situ while displaying clear images of crystal shape and size. These technologies enable efficient crystallization optimization R&D as well as controlled process monitoring at scale. Crystal morphology improvements can be attained using controlled cooling crystallization which improves filtration time, increases throughput and minimizes issues with impurities. Processors that choose to use this type of PAT will position themselves to produce higher-quality product more efficiently in an increasingly competitive marketplace.

Before commencing MSZW studies, the solvent system needs to be chosen with the correct ratio of solid to solvent. The solids need to be able to dissolve at higher temperatures and then crystallize in a controlled way without needing to go to very low temperatures (sub–ambient). There will be an ideal solvent, or mixture of solvents and amount of CBD that will allow crystals to form without going to sub-ambient temperatures which will become costly when scaling up the process. One should also consider the solvents based upon safety for running at scale, costs and also potential contaminants to the resulting product. For these reasons one wants to avoid solvents that have very low boiling points (reactor overpressure), chlorinated solvents (toxic when captured within crystals) and regulated solvents such as ethanol.

One should select suitable solvents with these factors in mind and add small amounts of CBD into vials and test solubility at room temperature. If CBD is excessively soluble in the solvent, then it will be difficult to form crystals unless the mixture is very concentrated and very low temperatures can be reached. The same goes for sparingly soluble systems in that high temperatures may be required with large amounts of solvent which can degrade CBD and may need huge production crystallizers at scale. In this study we chose petroleum ether rather than hexanes (where CBD is extremely soluble) or alcohols (not soluble enough). After a quick screen as to the correct solids loading, meaning soluble when warmed and then crystallizes when cooled to room temperature, MSZW studies were then performed.

3. Experimental Set-up, Methodology and Results

The MSZW studies were performed with a Mettler Toledo EasyMax 102 automated reactor system equipped with a 100 mL glass reactor, overhead stirrer, temperature sensor and automated syringe pump (provides precise control of reactor temperature, stirring and solvent additions). A Mettler Toledo EasyViewer in situ camera was placed inside the reactor to acquire high quality images and to automatically determine clear and cloud points. As an additional data stream, we also installed a ReactIR 702L mid–IR spectroscopic probe to record the rate of dissolution of solids since it only records the mid–IR spectra of species in the liquid phase. Since the three technologies are interoperable, the following studies were preprogrammed and allowed to run automatically without the need for end user intervention.

9.05 g of amorphous pure CBD solids and 25 mL of petroleum ether were placed in a 100 mL glass reactor in an EasyMax 102 automated laboratory system. The mixture was heated at 2 K/minute until approximately 36 °C where the chosen mid–IR peak (1631 cm-1) for CBD stabilized while images were captured with the EasyViewer probe. As the mixture contents increased in temperature, the trend for dissolved CBD increases while the declining turbidity trend from the EasyViewer probe shows solids dissolving.

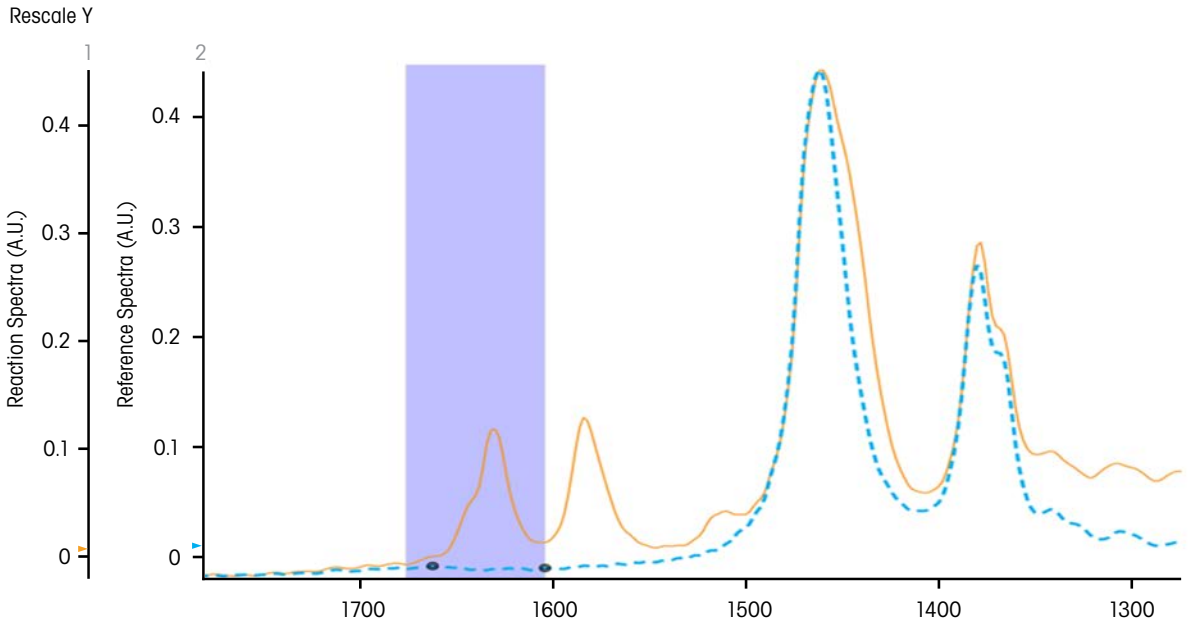


Figure 2: ReactIR spectra of CBD dissolved in petroleum ether (orange) and pure petroleum ether (light blue) and the chosen peak followed during experiments (purple region).

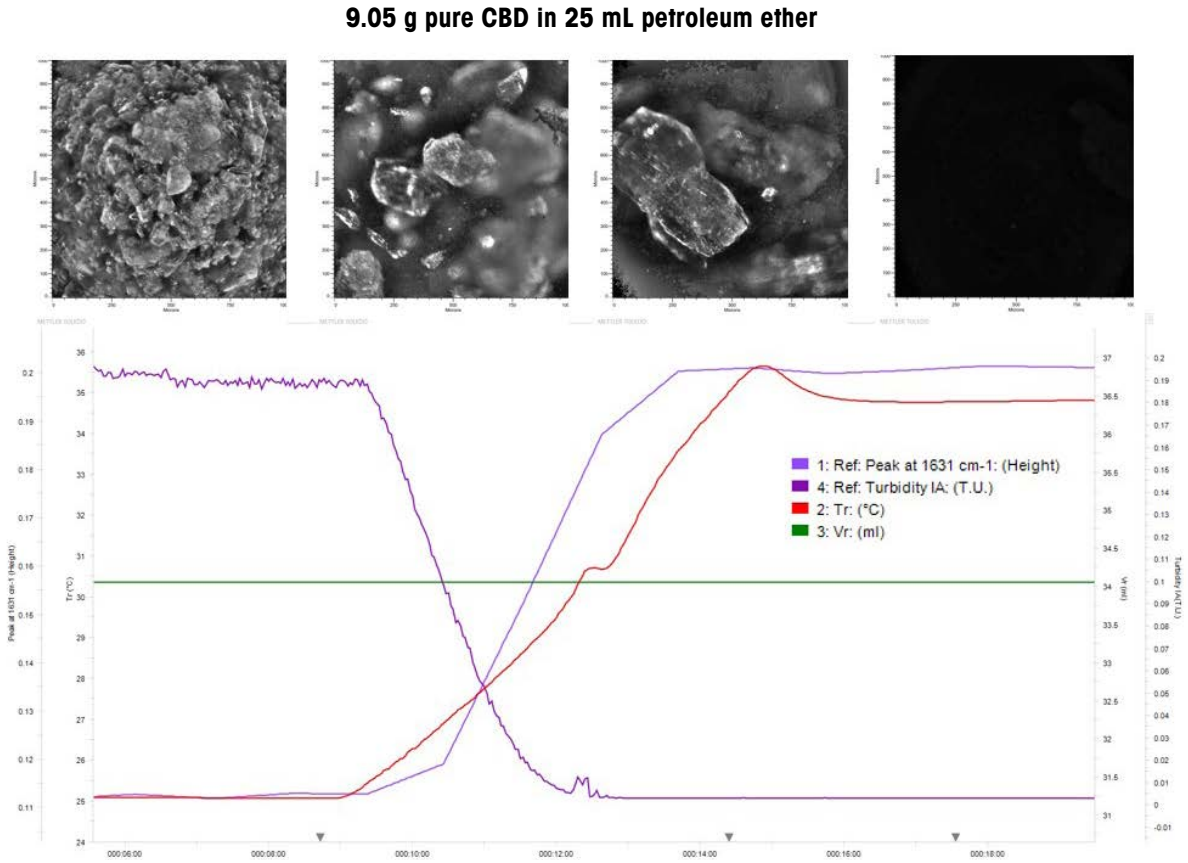


Figure 3: ReactIR trend decreasing while turbidity signal increases during temperature ramp and EasyViewer images during the various stages of the process.

Since images were taken throughout the temperature ramp, the shape and size of the various particles in the system can be observed (Figure 3) along with the rate of change of particle size and count using online image analysis software (iC Vision). This information is critical when studying crystallizations to understand which critical process parameters are controlling the rate of nucleation and growth so the optimal particle size and range of size can be consistently achieved. During the temperature ramp the smaller particles can be seen to dissolve more quickly than the larger particles as expected.

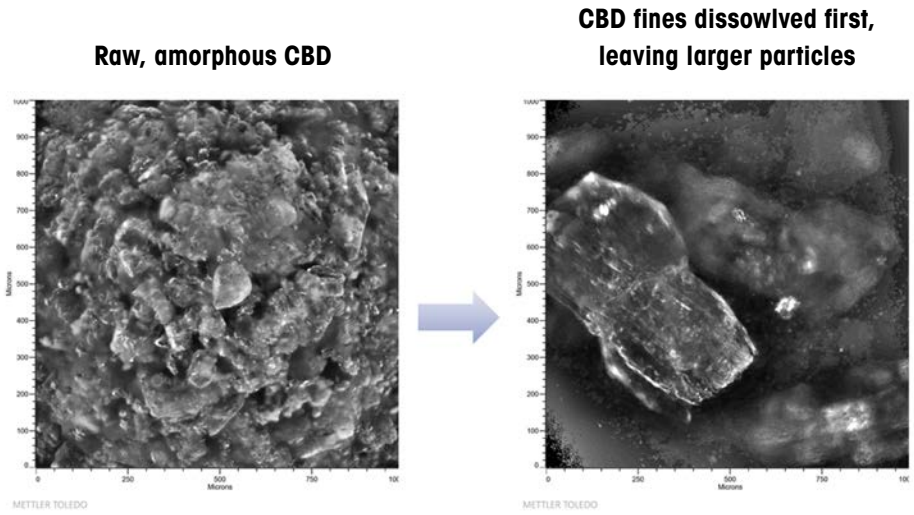


Figure 4: Before and after images of CBD for the recrystallization process.

Once solids are dissolved, six temperature cycles were performed utilizing the turbidity signal from the EasyViewer to end the temperature ramps automatically at the clear and cloud points (% turbidity used as a condition in the EasyMax iControl software procedure). After each cycle 10% additional solvent was added automatically with the connected Dosing Unit to change the concentration of the system. The temperature cycles were performed in reaction mixture temperature mode (vs. jacket mode) at 0.5 K/minute with a condition to end heating/cooling steps using the turbidity signal from the EasyViewer probe. Temperature values at each of these points along with the corresponding concentrations were transferred to Microsoft Excel to create the MSZW curves. Images were recorded throughout the experiment providing greater detail as to the nature of the crystals (size and morphology).

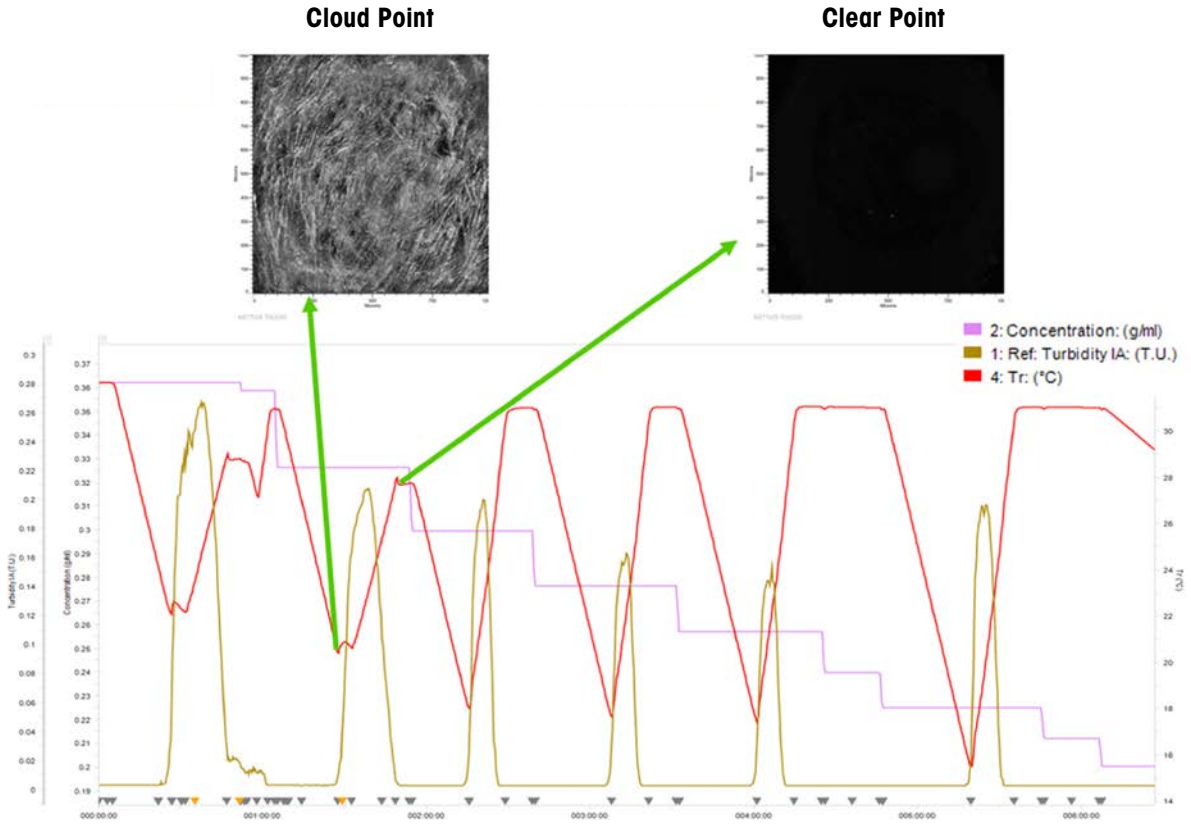


Figure 5: Automated temperature cycles performed by the EasyMax with ramps automatically ending with conditions based upon turbidity signals from the EasyViewer probe.

The optimal cooling rate lies within the two curves of the MSZW graph below. The region to the right of the solubility curve is where CBD remains in solution and the region to the left of the metastable zone boundary is where uncontrolled nucleation and oiling out typically occur. The MSZW also shifts with purity of the CBD material in the system so an understanding of the effect of various impurities should also be understood before moving to larger scales. The tighter the two boundaries the more readily the CBD crystals will crystallize out within small cooling changes and with greater consistency. The boundaries tend to widen with less pure starting CBD material leading to more challenging crystallization processes making PAT advantageous when installed in the production scale vessel.

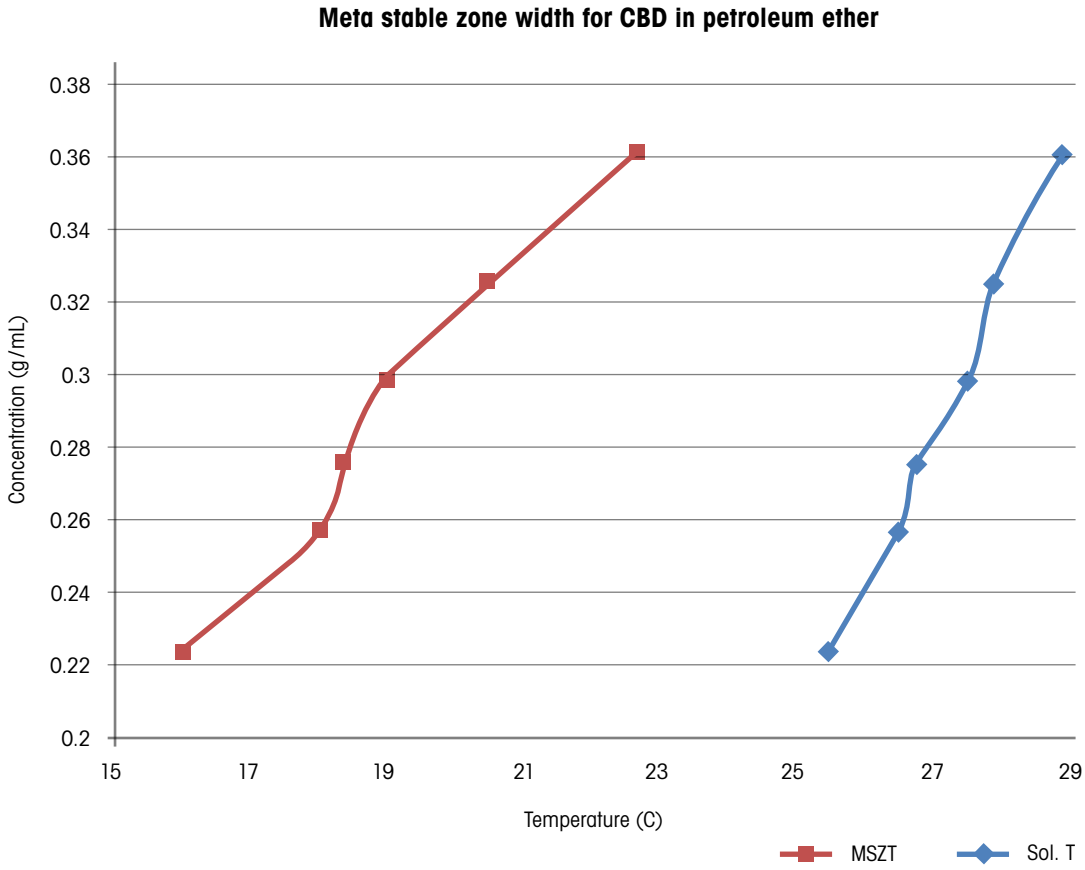


Figure 6: Metastable Zone Width of pure CBD in petroleum ether.

As an additional study, a series of crystal ripening steps were performed immediately after the MSZW experiment. This has the effect of increasing crystal size since the short increases in temperature of the mixture favors dissolution of the fines over the larger particles and slow cooling can then grow existing larger particles in favor of initiating nucleation events. An optimal temperature region along with optimal heating/cooling rates will exaggerate this effect. The resulting crystal form in this case were thick needles with some dendritic agglomerates as viewed from the EasyViewer images taken in situ.

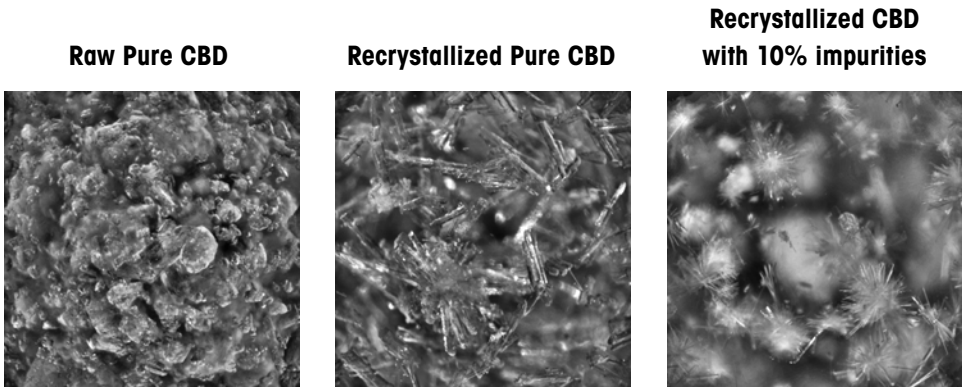


Figure 7: EasyViewer images of raw pure CBD and recrystallized CBD with and without impurities.

4. Conclusion

We demonstrated that the crystallization of CBD can be challenging but this means that there is a lot of potential for improvements. These challenges are amplified as one moves to larger scales so a thorough understanding of the solvent–CBD system necessitates data rich experimentation with precise control of the critical process parameters. Automation of these process parameters and implementing PAT provides greater insight with each experiment performed in the laboratory. Potential issues can then be anticipated and corrected during the scale up of the process to allow higher quality production of CBD and the elimination of delays along the way.

5. Addendum: Definitions and Further Information

5.1. Key Crystallization Definitions

Crystallization
Crystallization is a process whereby solid crystals are formed from another phase, typically a liquid solution or melt.

Crystal
Crystal is a solid particle in which the constituent molecules, atoms, or ions are arranged in some fixed and rigid, repeating three–dimensional pattern or lattice.

Precipitation
Precipitation is another word for crystallization but is most often used when crystallization occurs very quickly through a chemical reaction.

Solubility
Solubility is a measure of the amount of solute that can be dissolved in a given solvent at a given temperature.

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

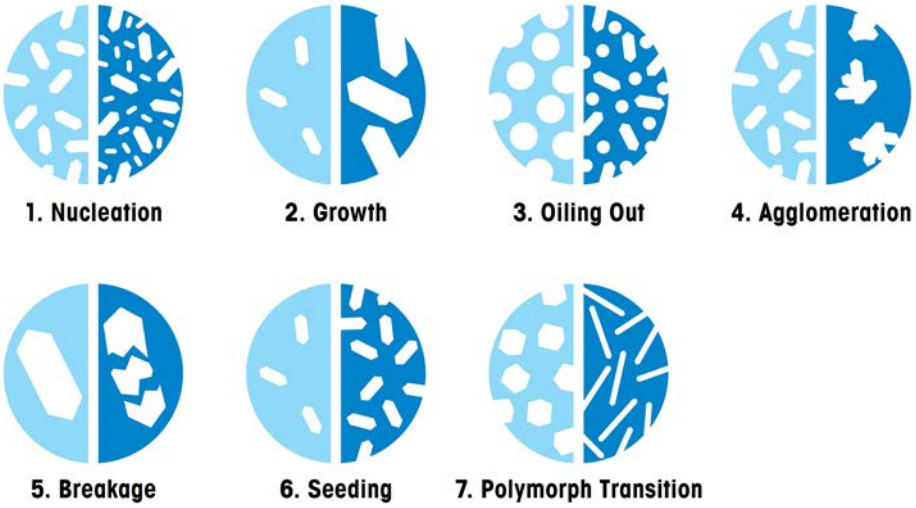
Supersaturation
Supersaturation is the difference between the actual solute concentration and the equilibrium solute concentration at a given temperature.

5.2. Types of Crystallization

Crystallization occurs when the solubility of a solute in solution is reduced by some means. Common methods to reduce solubility include:

- Cooling
- Antisolvent Addition
- Evaporation
- Reaction (Precipitation)

The choice of crystallization method depends on the equipment available for crystallization, the objectives of the crystallization process and the solubility and stability of the solute in the chosen solvent.



5.3. Common Crystallization Challenges

Crystallization proceeds through a series of interdependent mechanisms that are each uniquely influenced by the choice of process parameters:

- Nucleation
- Growth
- Oiling Out
- Agglomeration
- Breakage
- Polymorphism Chemistry

These mechanisms, which are often hidden form scientists, play a dominant role in defining the outcome of a crystallization process.

5.4. Crystallization Steps

1. Choose an appropriate solvent. Common considerations included how much solute can be dissolved (solubility) and how practical the solvent is to handle (safety).
2. Dissolve the product in the solvent by increasing the temperature until the last product molecule disappears. At this insoluble impurities may be filtered from the hot solution.
3. Reduce solubility via cooling, anti-solvent addition, evaporation or reaction. The solution will become supersaturated.
4. Crystallize the product. As solubility is reduced a point is reached where crystals will nucleate and then grow. Highly pure product crystals should form and impurities should remain in solution.
5. Allow the system to reach equilibrium after cooling (or another crystallization method stops).
6. Filter and dry the purified product.

6. References

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