WHITE PAPER

Crystallisation in pharmaceutical processes

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radleys
accelerating chemistry

Crystallisation in pharmaceutical processes

Abstract

The different aspects of crystallisation development have been described in detail in the literature and this paper aims to provide an overview of the crystallisation process.

The background to crystallisation processes is described, as well as the four main types of crystallisations: cooling, anti-solvent, reactive and pH controlled. Examples of each crystallisation type are given including developments and applications.

The significance of impurities and purification in the crystallisation process is emphasised along with the different types of impurities-including residual solvents and how they can be incorporated into the final product. The importance of developing a good seeding strategy for crystallisation is also discussed. The current state of PAT (Process Analytical Techniques) is described along with the significance of good control and monitoring of various parameters during experiments. Scale-up of crystallisations and the use of appropriate equipment, including the Radleys Reactor-Ready Filter Lab Reactor, is outlined. A summary of how Design of Experiments (DoE) and Quality by Design (QbD) are integral to any modern crystallisation process is given. The usefulness of single crystal structures, particularly for hydrates and solvated crystals, along with modelling and phase diagrams are also discussed.

Contents

Introduction

Crystallisation is a ubiquitous process that is used in numerous applications, from the food industry, in speciality chemicals, and especially in the pharmaceutical industry. Crystallisation is often a critical process in the food industry e.g., in the making of ice cream and chocolate, in order to obtain the right characteristics of the product. The same applies to the pharmaceutical industry where crystallisation is still the most widely accepted method of producing good quality drug substances with desired physical properties, which are suitable for formulation and product manufacture. This paper presents some of the fundamentals of crystallisation, especially in the context of final product manufacture.

There are 4 main types of crystallisation processes:

Cooling: This is based on the changing solubility of the final product with temperature in a given solvent or solvent mixture. Most organic molecules have increased solubility with increasing temperature, and this is the most common crystallisation method employed.

Anti-solvent: This is based on the changing solubility of the final product with the addition of a second solvent (anti-solvent) to a solvent that the final product is highly soluble in. This is often the preferred crystallisation process for isolation of material from the final step in a chemical synthesis. Following isolation of the crude material, a recrystallisation is employed to optimise the final product properties.

pH adjustment: This is based on the changing solubility of the final product with pH. Often an acid, base or amphoteric molecule can be solubilised by converting to its appropriate salt, and then the neutral/free form crystallised by readjusting the pH. If the salt is the desired product, then the salt can be prepared by dissolving the neutral/free form of the final product in a suitable solvent and then adjusting the pH with, say, hydrochloric acid to crystallise the hydrochloride salt.

Reactive: This is based on the lower solubility of a product compared to a reactant in a particular solvent. An example of this is the hydrolysis of an ester to a carboxylic acid or a carboxylate anion and concomitant crystallisation of the acid product.

Drug substance manufacture has evolved over the years from simply isolating material with the right purity, to now isolating the material with the right purity, in the correct solid form with the desired physical properties: particle size, morphology etc., for down-stream processing and product manufacture. Crystallisation development is the crucial step in meeting this goal.

Background – know the basics

Gaining an understanding of a final product's behaviour and having background information on the drug substance, such as solubility, polymorphism, purity (both chemical and chiral) etc., are vital for developing a crystallisation process. Often, in the early stages of crystallisation, development chemists will obtain anecdotal information from medicinal chemists or early process chemists, such as "This crystallisation works best in acetone at low temperature." This sort of information should not be overlooked and is often very valuable. In this case, the fact that the crystallisation performs best in acetone in cold conditions may mean that at low temperature a transient acetone solvate is formed, which provides the best purification/crystallisation of the material. However, as soon as the material is isolated and dried, it converts to another solid form so the solvate is never actually observed but is the species facilitating the purification.

In the early stages of crystallisation, solvates can be beneficial in terms of obtaining pure material, this is because solvates are often good at rejecting impurities from the crystal lattice and thus producing pure material. The purified material can then be converted to the desired solid form with the required properties in a further recrystallisation process.

Crystallisation Methods

Cooling crystallisations: Understanding solubility

Thermodynamic solubility is often seen as an easy parameter to measure, but in practice it can be very difficult as it is dependent on a number of factors such as polymorphic form particle size, purity, mixing kinetics, solvent evaporation and accurate temperature control. Due to this, understanding the MSZW (Meta Stable Zone Width) of a crystallisation process (Figure *1*), which is integral to any cooling/anti-solvent/ seeded crystallisation, can be very difficult.

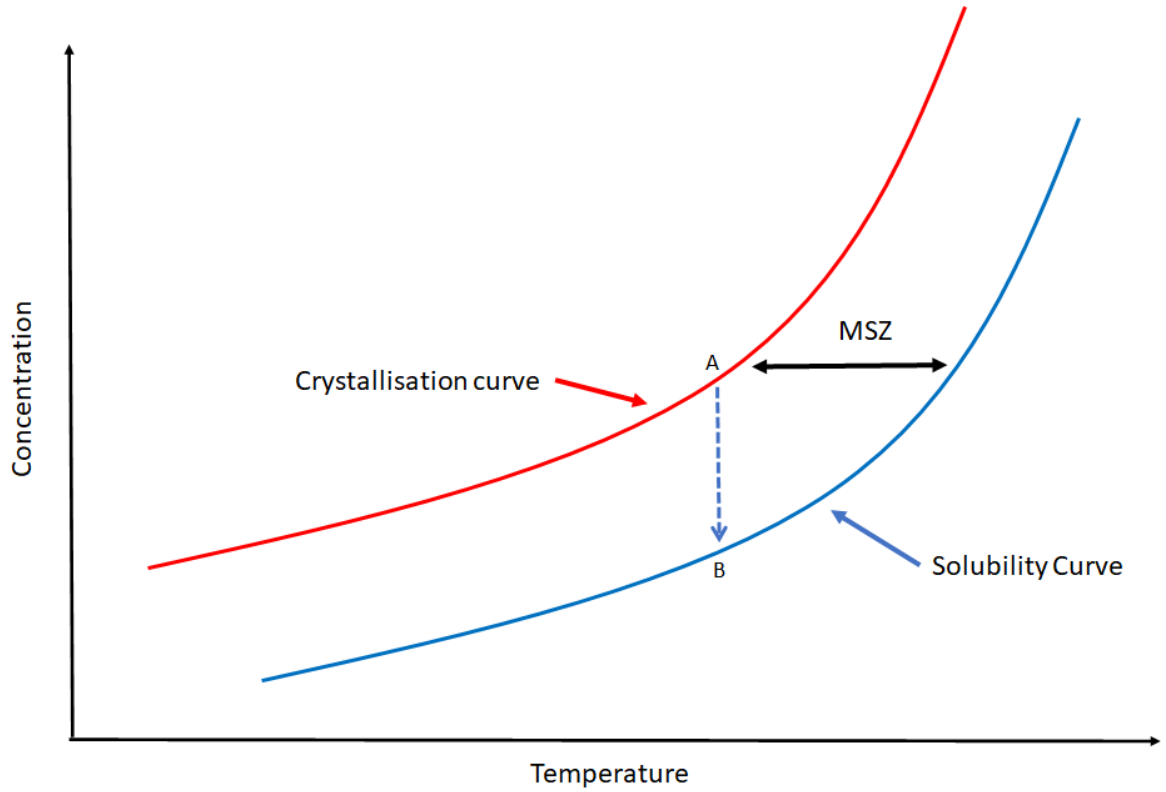


Figure 1. Diagram showing the Meta Stable Zone which exists between the solubility and crystallisation curves, and is dependent on the temperature and concentration of the process

During a crystallisation the mixture is heated to completely dissolve the product at the appropriate temperature. After which, the solution is slowly cooled to point A (Figure 1) ensuring no crystallisation occurs and the solution stays within the MSZ. After this the solution is held at the desired temperature and the material is allowed to crystallise until the equilibrium solubility at point B is reached. The slurry is then cooled to the final crystallisation temperature and the final product material harvested.

Numerous in silico solubility measurements can be performed on the final product, and these provide a very quick way of gauging the solubility of a material and reducing the number of practical solubility experiments. Solubility measurements are typically performed by weighing an appropriate amount of the final product into a vial along with the specified solvent volume and then allowing the vials to equilibrate at the appropriate temperature for 24 h. After this time the solution is analysed, typically by HPLC (High-Performance Liquid Chromatography), to determine the solubility. Often the mass of final product used in a solubility experiment is not considered an important parameter, but by changing the mass of final product in an experiment, factors such as the pH of the media and/or the water content can be altered and as a consequence the solubility is affected. The final product often deviates from ideal behaviour in solution and some micelle formation or ion pairing can occur, which may significantly change the solubility behaviour.

As well as measuring the solubility, determining the crystallisation temperature of the final product is essential to obtaining a good crystallisation, but like solubility this can be dependent on numerous factors such as cooling rate, stirring rate. The crystallisation

temperature can be determined by any method that detects the presence of solid particles in a solution e.g., turbidity or particle sizing. However, without the presence of seed crystals, crystallisation generally takes place by heterogeneous primary nucleation, meaning that crystallisation takes place on a dust particle, stirrer bar, over-head stirrer or surface within the vessel. As a result, the crystallisation temperature and MSZW varies with scale and process conditions, so obtaining an understanding of how wide the MSZ is and how supersaturation (defined below) can be generated under any given set of conditions is paramount for a crystallisation process.

Supersaturation, Δc, is simply defined as the difference between the experimental concentration and the equilibrium solubility, with the supersaturation ratio, S, being the ratio of the two concentrations.[1]

$$\Delta c = c - c^* \text{ or } S = \frac{c}{c^*}$$

Δc = supersaturation
c= solute concentration
c*= equilibrium concentration (under the same conditions)
S = supersaturation ratio

In the majority of controlled cooling crystallisations, the solution is cooled to point A (Figure 1) and then seeded prior to further cooling, in order to desaturate the solution and drive the crystallisation to completion. Simply cooling the solution to induce primary nucleation (nucleation without any seed material present), point B (Figure 1), by moving outside the MSZ, is normally avoided due to its uncontrolled nature. However, this method can be used in certain cases if a particular particle size or property of the final product is desired.

Normally, in the final crystallisation step a clarification filtration is used to remove any undissolved material prior to cooling the solvent or the addition of the anti-solvent. This is similar to a hot filtration in a standard laboratory recrystallisation. Having a wide MSZ (no uncontrolled crystallisation) where the solution can be cooled significantly without any solid being present makes this clarification filtration much easier, especially if high temperatures are used during the process.

Yield is often the most important factor in a crystallisation process; nobody wants to throw away value final product material, so knowing a theoretical value of the recovery of the material from any given solvent is critical. Another important factor in cooling crystallisation is the stability of the final product, i.e., can the material be heated for an extended period of time. These factors often determine whether an anti-solvent is needed or if a single solvent will have the desired properties.

It is rare, but some organic molecules have an inverse or retrograde solubility, i.e., higher solubility at lower temperature, which has a significant impact on crystallisation process development. Inverse solubility is more common in inorganic molecules such as caesium sulphate and sodium sulphate, and is often associated with a change in polymorphic form or hydration level. One of the simplest molecules, sodium chloride, falls in the middle of this

solubility continuum and has virtually no change in aqueous solubility with change in temperature.

A classic example of the difficulties involved in measuring the solubility and selecting a solvent for crystallisation are summarised by the solid-state landscape of Axitinib. Axitinib (Figure 2) is a relatively simple molecule with an incredibly complex solid-state landscape with very low solubility in a number of solvents and the formation of numerous solvates. The low solubility of the compound and the numerous solvates make this a very challenging crystallisation problem, and numerous papers have been published describing the issue.[2]

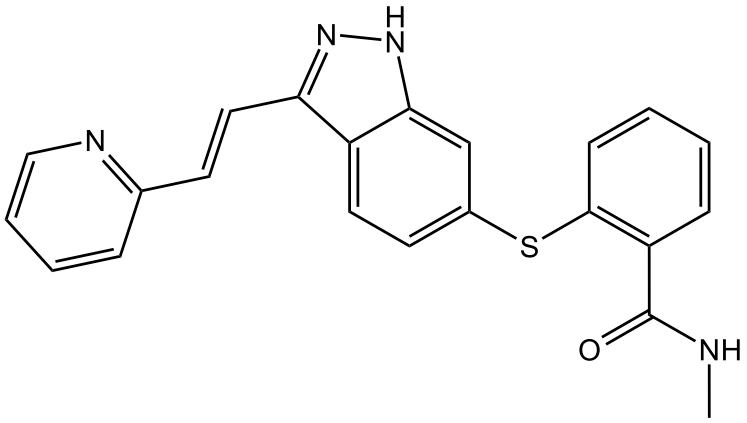


Figure 2. Axitinib structure

Anti-solvent crystallisations

Anti-solvent crystallisations tend to be developed if the desired product attributes and yield cannot be met by a cooling crystallisation, as added complications such as solvent mixing can arise. Mixing of the two solvents, either normal addition (addition of the anti-solvent to the solvent, such as in Figure 3) or reverse addition (addition of the solvent to the anti-solvent) requires a thorough investigation of a number of crystallisation parameters, such as solubility changes, temperature variations, mixing and oiling out. Generally staying within the MSZ and seeding will allow crystal growth and desaturation to occur in a controlled manner, theoretically leading to a more controlled crystallisation process. A typical strategy in anti-solvent crystallisations is seeding at point A in the MSZ, controlling the addition of the anti-solvent and allowing the solution to desaturate and come to equilibrium at point B on the solubility curve. After this time, sufficient seed crystals are present, and further anti-solvent can be added and the crystallisation driven through to completion.

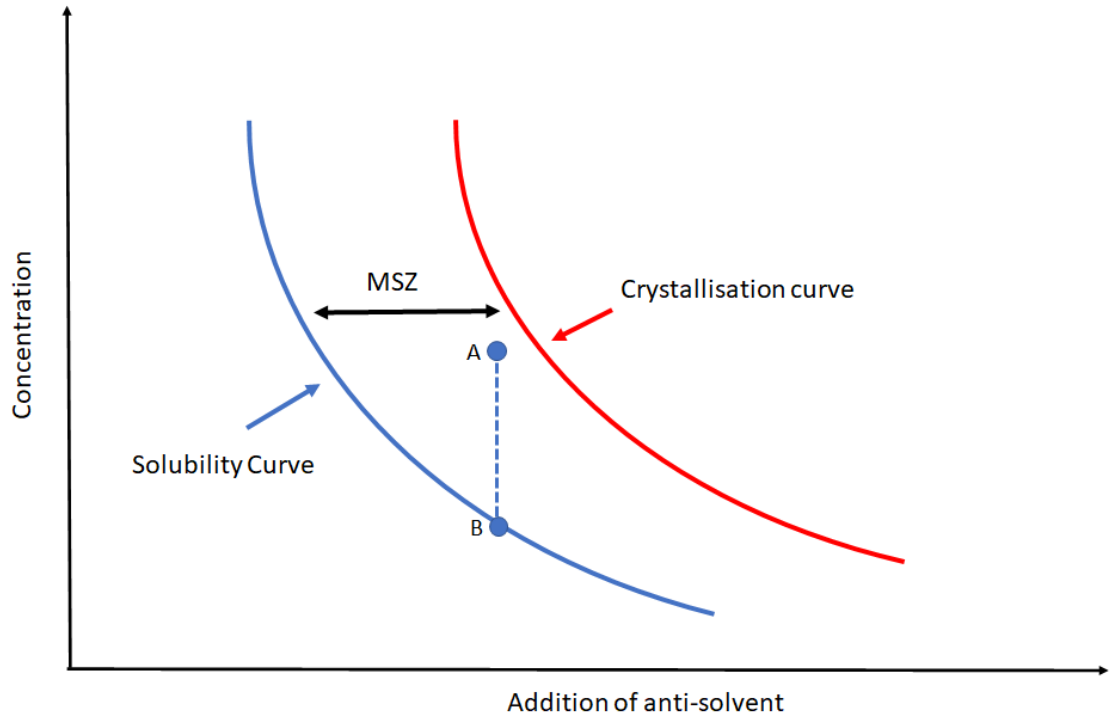


Figure 3. Normal anti-solvent addition scheme

Reverse anti-solvent addition can also be carried out, where a solvent solution of the final product is added to an anti-solvent in a controlled manner. In theory, this can produce a final product with a particular property profile, but reverse addition can be complicated by a number of factors, such as oiling-out, low crystallinity of the final product if rapid precipitation occurs, and impurities becoming trapped in the final product.

Mixing effects are more prevalent in both types of anti-solvent crystallisations, and the position within the reactor where the anti-solvent is added can have a significant effect on the outcome. Addition of the anti-solvent should be in a region where good mixing is present in the reactor. Often, dip tubes are used to add anti-solvent below the liquid level of the solvent and into a region where good mixing is observed.

As stated previously, seeding should still be carried out in anti-solvent crystallisation. Determining the MSZ and the crystal growth/nucleation rates can be more difficult in an anti-solvent crystallisation, but in a number of ways are more important, as knowing where you are within the metastable zone during anti-solvent addition is paramount.

During crystallisation development, due to differences in solvent volatilities and boiling points, working with mixed solvents systems can result in solvent loss, and thus changes in the composition of the solvent as well as to the overall volume of the solvent. This can lead to misleading solubility and crystallisation results, unless the experiments are carefully controlled.

Generally, there is a temperature difference between the solvent and anti-solvent during addition, which means a crucial feature for anti-solvent crystallisations is accurate temperature control during the addition, and ensuring that very little temperature variation

occurs during that time. Having a reliable feedback loop so that addition can be controlled by the temperature and not only by the rate of addition is important for a good, controlled crystallisation process. Anti-solvent crystallisations are sometimes not as volume-efficient as single solvent cooling crystallisations, requiring higher volumes due to the solvent/anti-solvent mixture, and as a result lead to lower throughput of material.

One significant advantage of anti-solvent crystallisations, though, is the final product need not be heated at elevated temperatures for extended periods of time. This is obviously very important for thermally labile final products and the clarification filtration that is usually employed in the final crystallisation step can be made much easier if the solvent is not heated and the final product is very soluble in a particular solvent.

An article in the journal, Crystals, gives some good recent examples of anti-solvent crystallisation processes.[3]

pH Adjustment crystallisations

pH adjustment crystallisations are most appropriate in aqueous based solutions as pH is only formally defined in an aqueous environment and they are often developed in situations where salt formation is possible. Salts such as the sodium salt often have higher solubility in aqueous solvents and if the free acid is the desired final product, then the pH can be adjusted downwards and the free form crystallised. Most of the variables that affect cooling and anti-solvent crystallisations also apply to pH adjustment crystallisation, but obtaining solubility data on both species, the free form and the salt form, is vital, as is having a thorough understanding of the amount of each species present as the pH of the solvent changes. In pure aqueous environments, the concentration of each species, a weak acid and its conjugate base is given by the simple Henderson-Hasselbalch equation:

$$pH = pKa + log_{10} \frac{[A^-]}{[AH]}$$

Where AH is a weak acid and A^- is its conjugate base.

The pKa of the final product will vary with changes in temperature and solvent composition, so these should be considered when developing any crystallisation process. pH adjustment crystallisations can be particularly important in the case of amino acids (Figure 7) or other amphoteric molecules that exist as zwitterions. These often have significant changes in solubility with pH (both acidic and basic), and with judicious control of the pH, a very efficient crystallisation method can be developed. Addition of acid or base into the final product solution is generally controlled by a pH monitoring feedback loop that prevents extreme changes in pH and ensures that the crystallisation stays within the MSZ throughout.

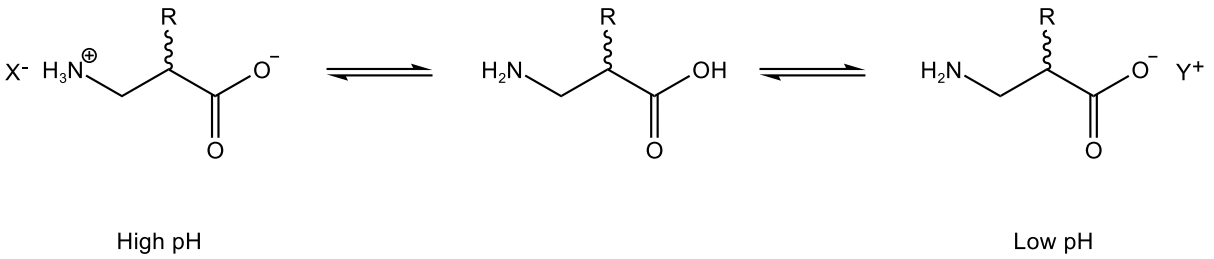


Figure 7. Variation of amino acid forms with pH

Antibiotics such as amoxicillin (Figure 8), ampicillin and cephalexin, which are amphoteric in nature, can be crystallised by pH adjustment, and indeed amoxicillin is crystallised at pH 4.7 (isoelectric point) at 4°C as its tri-hydrate. The fact that amoxicillin tri-hydrate is the desired final product also necessitates the use of an aqueous rich solution as well.

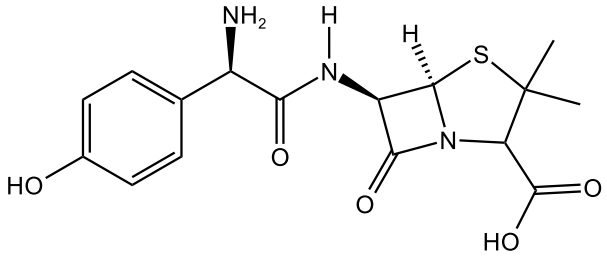


Figure 8. Structure of amoxicillin

Often, an advantage of pH adjustment crystallisations is that they can be conducted isothermally and in low solvent volumes, which can enable a high throughput of material. If thermal stability of the molecule is an issue, such as in the case of amoxicillin, the crystallisation can be carried out at sub-ambient temperature. The obvious disadvantage for pH adjustment crystallisations is the pH stability of the molecule. So, as well as the solubility of the final product changing with pH, the stability of the final product needs to be reasonably robust to changes in pH.

Reactive crystallisations

Reactive crystallisations are often divided into two groups:

1) Crystallisations where a counterion is added to an acidic or basic final product to form the appropriate salt (e.g., chloride or sodium salt) can be classed as reactive crystallisations. Normally, salt formation is assumed to be an instantaneous process, and as a result, many of the factors that affect anti-solvent crystallisations also affect these types of reactive crystallisations.

2) Where a reaction other than salt formation occurs, such as hydrolysis of an ester to form an acid (Figure 9), and a covalent bond is either formed or broken, and crystallisation occurs, then these are described as reactive crystallisations. As well as knowing the fundamental crystallisation factors, such as solubility, supersaturation, crystal nucleation and growth, the chemical kinetics of the reaction need to be incorporated into the process as a factor affecting the crystallisation.

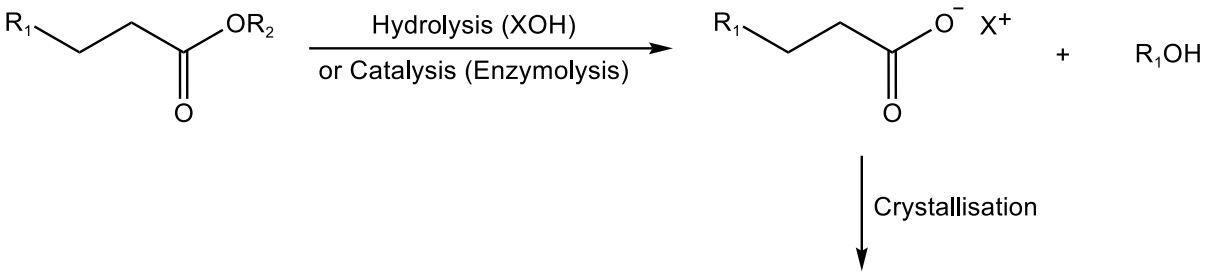


Figure 9. Reactive crystallisation: base catalysed hydrolysis of an ester to form a carboxylate anion and subsequent crystallisation

In the example shown in Figure 9, hydrolysis of the ester can be carried out with a base such as NaOH or LiOH with subsequent crystallisation of the appropriate salt. Alternatively, the hydrolysis can be carried out by an appropriate catalyst such as an enzyme. Antibiotics can be prepared by enzymatic reactive crystallisation as this does not involve elevated temperatures and is often a cleaner and more specific reaction than a chemical hydrolysis and leads to material of higher purity. Often in crystallisations of this type, the product crystallising out of solution provides a driving force for the reaction and, as such, can change the kinetics of the reaction.

An area where reactive crystallisation plays an important role is in chiral resolution. In a classical diastereomeric salt resolution of a chiral final product, the desired enantiomer crystallises and the unwanted enantiomer (in this case S) left in solution can racemise to afford essentially 100% of the desired enantiomer in the solid. This prevents the loss of up to 50% of the material during the crystallisation. As well as understanding the crystallisation process, the rate of racemisation in the solution needs to be well understood.

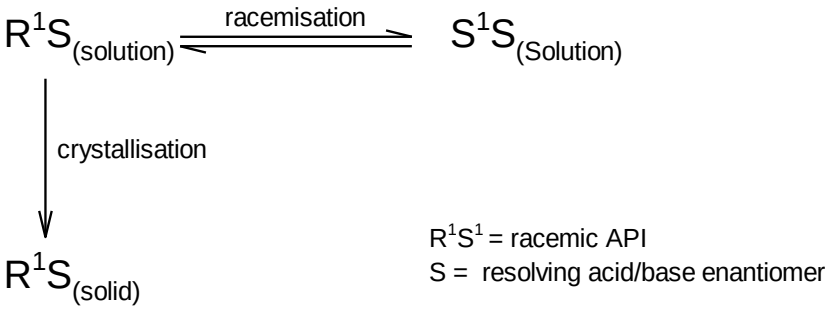


Figure 10. Typical diastereomeric salt resolution

A recent review gives a great summary of a wide range of reactive crystallisations.[4]

The most important factor in any crystallisation, be it cooling, reactive, pH adjustment or anti-solvent, is to know what species you have present at any one time, the thermodynamic solubility of those species present and at what concentration they begin to crystallise, i.e., the level of supersaturation.

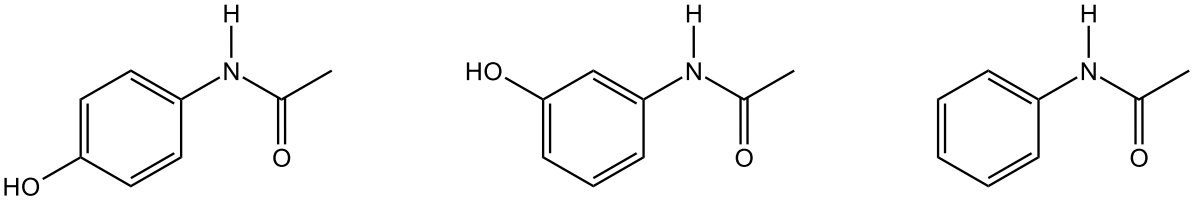
Purification

Hard to remove impurities

The aim of an initial crystallisation process is to obtain material of sufficient purity for further development and as such, an understanding of the impurities present can be crucial for developing a suitable crystallisation method that provides material of the desired purity. Generally, impurities can contaminate the final product in three ways:

1) Impurities can be incorporated into the desired crystalline form via a solid solution.
2) Impurities can crystallise separately as a unique crystalline form or on the surface of the desired final product.
3) Impurities can be present in the final product due to impurity-rich liquors becoming trapped in the crystalline final product.

Solid solutions are often observed if the impurity and the final product have a similar structure, e.g., paracetamol and its impurities (Figure 3).[5]



Paracetamol Metacetamol Acetanilide

Figure 4. Paracetamol and its impurities

In the example below (Figure 5), Impurity A present in the final product shows no change in purity level with crystal yield, indicating that the impurity is crystallising within the final product crystal and a partial solid solution is formed making the impurity difficult to remove. In order to obtain the desired purity, either an alternative solvent system is needed or a different crystalline form should be targeted in which a solid solution is not so prevalent.

The proportion of impurity B present in the final product changes with crystal yield, indicating that the impurity is crystallising out separately, in its own crystal form, and is not significantly incorporated into the final product. Impurities such as these can be more easily removed by recrystallisation, but may still be present in the final product due to impurity-rich liquors

becoming trapped in the final product as it crystallises or due to inadequate washing that does not remove surface-bound impurities.

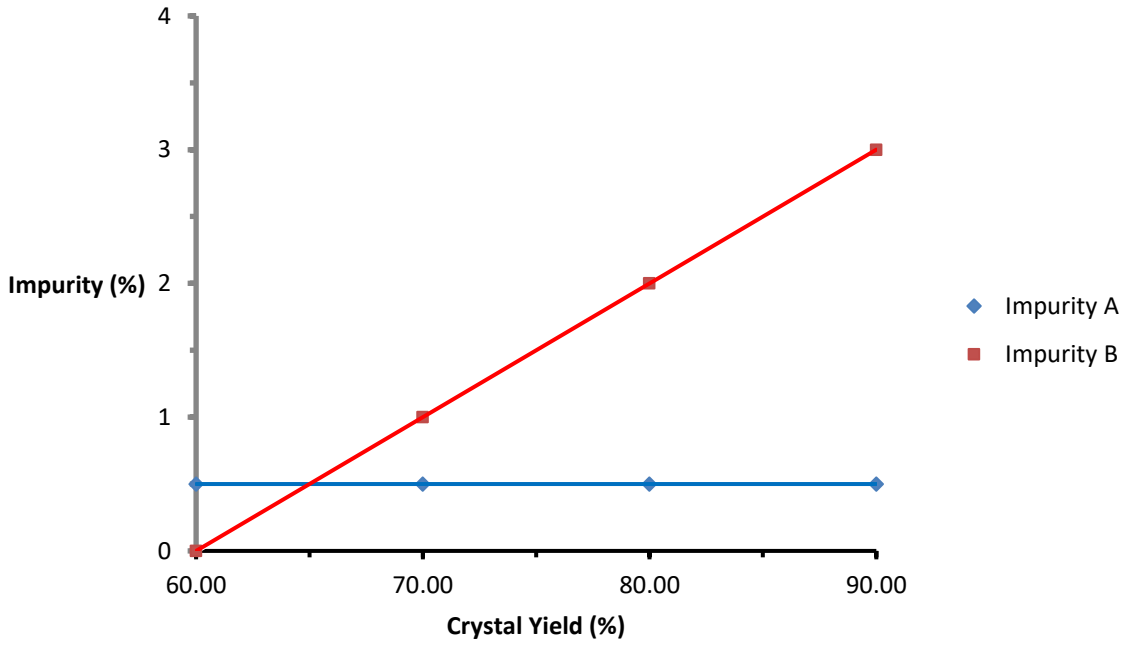


Figure 5. Change in Impurity level with crystal yield

Preferential crystallisation

Preferential crystallisation is the term given to crystallising one compound in preference to another during a crystallisation process. It may be possible to crystallise the desired final product without the impurities present utilising this method. This method is more common in a chiral resolution environment where one enantiomer or diastereomer crystallises in preference to another, but it can sometimes be used as a purification tool in an achiral environment. It is very important to know whether purification of the final product is achieved by this method as it is a kinetic process and as such is time dependent. As the purification is time dependent filtration and isolation of the batch needs to take place before the impurity starts to crystallise. Due to the kinetic/time dependent nature of the purification, the method can break down on scale-up, due to the extended time scales employed, leading to crystallisation of the impurity and contamination of the batch.

Residual solvents

Residual solvents can be classed as liquid impurities, and this is a key consideration when developing a crystallisation process. Nearly all the factors applicable to solid impurities can apply to residual solvents and sometimes even volatile solvents can be difficult to remove in the final product drying process. Residual solvent levels should be monitored closely

throughout crystallisation development, and this is often a consideration when selecting a solvent or solvent mixture for crystallisation. Sometimes solvents can be part of the structure, such as ethanol, dimethyl sulfoxide (DMSO), or isopropanol (IPA), and these solvates have all been approved in marketed drugs. Over the years, more toxic solvents, such as chlorinated solvents, have been removed from a chemist's toolkit of available crystallisation solvents due to the trend towards green/sustainable chemistry, and the use of more environmentally friendly solvents in the final crystallisation.[6]

An often critical and overlooked factor in terms of achieving the desired chiral and achiral purity and residual solvent levels of the final product is having a good filtration and washing regime for the material. This is important as impurity rich liquors can become trapped in the final product, or impurities can nucleate on the surface of the drug substance, and the only time these can be removed is during the washing process. If any liquid impurities do remain during drying of the final product, significant levels of impurities can remain once the solvent is evaporated. The washing regime should be developed in conjunction with the crystallisation process. Jacketed filter reactors are ideal for this process as they allow for crystallisation and filtration in the same vessel, avoiding the unnecessary transfer of slurries between vessels or vessel and a filtration apparatus. Filter vessels (Figure 6) allow for the slurry to be washed while being agitated for effective removal of impurities from the final product surface while being accurately temperature controlled. As well as the ability to remove the filter cake easily, after filtration.

Figure 6. Radleys 2000-ml Filter Lab Reactor

Crystallisation development tends to be carried out with one particular batch of material with a given purity profile as well as other physical properties such as polymorphic form, particle

size and morphology, which can all affect the crystallisation process. As a result, the crystallisation process should be checked for robustness using different input batches with different impurity profiles. Having input batches with different purities can give useful information as to whether an impurity can be removed in the final crystallisation process or needs to be controlled in the final synthetic or isolation step.

An excellent recent paper describes the effect of impurities on the crystallisation process,[7] and a great summary of how impurities can be incorporated into a final product and how they can be removed is given here.[8]

Other Considerations

Polymorphism

Ritonavir (Figure 11) is often quoted as an example of how batch variability can affect drug product manufacture.[9] Ritonavir is an antiretroviral drug first developed by AbbVie (formally Abbott), inc. and FDA approved in 1996. It was originally manufactured as a capsule, with a crystal form of the drug called Form I, but some production batches of Ritonavir started to fail dissolution testing, which would mean a decrease in the bioavailability of the drug. This decreased solubility was due to a new polymorphic form (Form II) of the drug being produced. It has been hypothesized that the new polymorph produced was due to of the presence of an impurity with a similar chemical structure, such as the product formed from the base catalysed degradation of ritonavir, acting as a template, or seed, for Form II. The formation of the new polymorph and subsequent lowering of the bioavailability forced Abbot to withdraw the oral capsule from the market resulting in the loss of ca. $250M. The capsule was replaced by a refrigerated gel cap, made via a new formulation method, which solved the problem.

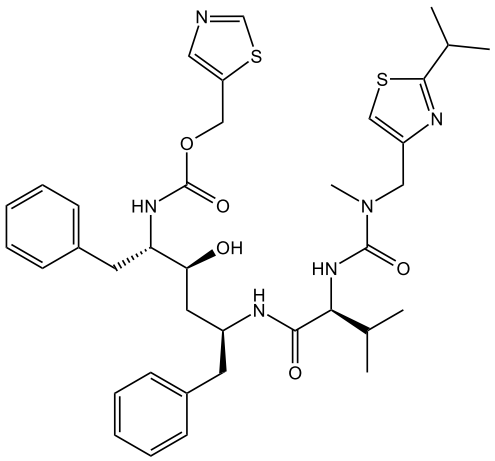


Figure 11. Structure of Ritonavir

Seeding in crystallisations

Nearly all types of crystallisation processes use some sort of seeding regime in order to gain control of the crystallisation process and obtain the desired particle size and morphology. Seeding with the desired polymorphic form of the final product is carried out in order to ensure the desired polymorph is produced in the crystallisation process. Addition of seed crystals generally enables crystal growth to be controlled over uncontrolled nucleation and allows a more robust process to be developed. Developing a seeding regime for any crystallisation process requires a number of factors to be investigated, such as quantity of seeds, quality of seeds, particle size, adding the seeds as a slurry or a solid, temperature of seed addition, and hold time after seeding.

Most crystallisation processes are dominated by secondary nucleation (nucleation where crystalline seeds are present) or crystal growth. Secondary nucleation can be modelled using a simplified empirical equation.

$$\frac{dN}{dt} = k_1(S)^b$$

Where:

$\frac{dN}{dt}$ = nucleation rate
S = supersaturation ratio
k_1 = nucleation rate constant
b = experimentally determined nucleation order

A similar equation can be used for crystal growth. Secondary nucleation normally occurs via collisions which cause breakages of existing crystals, or by the presence of seed crystals reducing the energy barrier for the formation of new crystals from a saturated solution. Both of these vary greatly for each final product, and experimental measurement of the number of new crystals formed and the size of the crystals (crystal growth) are essential factors to determine when developing a crystallisation. In some cases, modelling predicts that large crystals of a final product will form, but in reality, this is never the case due to attrition of the crystals or impurities preventing crystal growth. In other instances, like the case of sucrose, very little secondary nucleation occurs due to the high viscosity of the solution, and hence very low attrition of the crystals occurs. Crystal growth then becomes the dominant mechanism leading to larger crystals.

As with crystallisation, development seeding is often carried out with one batch of material, often with high purity, but with a particular particle size and distribution. Designating a “seeding batch” of material with the right physical properties can be very important in developing a crystallisation process.

The importance of crystal structures

Although not essential for the development of a crystallisation process, crystal structure determination is always help to understand a final product landscape and give a rationale as to why solvate or hydrate formation is prevalent within a given system, even if these are not the ultimate solid forms of the final product that are desired. Crystal structures can also help to understand morphology, i.e., how different solvents may change the growth rate of different crystal surfaces and hence the morphology.

The Cambridge Crystallographic Data Centre (CCDC) gives a case study on how crystal structures and understanding the polymorphism landscape can be used to guide solid form selection of a final product and direct the crystallisation process for the drug substance.[10]

PAT (Process Analytical Technology)

A vital part of any modern crystallisation development process is PAT (Process Analytical Technology). Turbidity probes and pH probes have been used for many years in order to obtain good quality MSZ curves and basic pH solubility information. Since then, a plethora of probes have been developed, such as in-situ particle size measurement (FBRM-Focussed Beam Reflectance Microscopy) and PVM (Particle Video Microscopy), which provide actual pictures of what is happening in any crystallisation process. This information can help to explain a variety of measured parameters, such as particle size and solvent content. Video microscopy gives information on whether oiling out is taking place, if the particles are agglomerating or if significant attrition, or breakage, is involved in the crystallisation process.

Probes have also been developed for solid form identification (Raman spectroscopy probes) and these can provide valuable information on whether any polymorphic transition is taking place during the crystallisation process and whether the seeding is actually controlling the polymorphic form.

ATR-FTIR probes have been used to measure the concentration of species in solution, but these can be difficult to use due to temperature effects and the sensitivity of certain molecules. However, if suitable, they give a good measure of crystal growth (i.e., how quickly the solution desaturates) under a given set of conditions.

Having a number of probes in a reactor can significantly change the crystallisation process, as they can act like baffles and provide various nucleation points for the crystallisation process. As well as performing the crystallisation process without any probes present, using the largest reactor appropriate to the volume needed, that has geometry similar to those of the manufacturing plant, is another essential step. Jacketed reaction vessels (Figure 12), which have a torispherical (dished) bottom, mimic the geometry of pilot plant and kilo lab reaction vessels, as well as allowing a variety of PAT probes to be used to collect data.

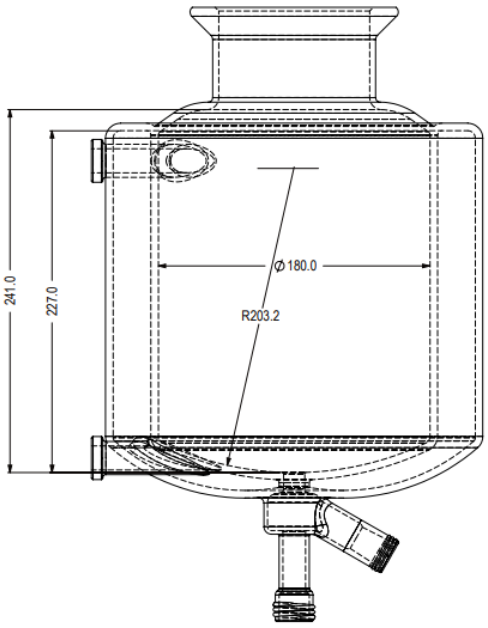


Figure 12. Radleys Process Vessel (torispherical geometry)

Phase diagrams and hydrate formation

For systems where three components are involved in the crystallisation; two solvents and the final product, or one solvent, the final product and water of crystallisation, phase diagrams can be of vital use when developing a crystallisation. For anti-solvent crystallisations and where hydrate formation of the final product is known to exist, constructing a ternary phase diagram (three components) for the system and understanding the domain where the desired solid form exists, and can be reliably produced, is vitally important. Around 33% of all final product molecules are known to form hydrates and often for salts this number is much higher, sodium salts can be particularly prone to hydrate formation due to water coordination with the sodium counterion.

Sodium diclofenac (Figure 13) is a very common NSAID (non-steroidal anti-inflammatory drug) and an example of a final product that can exist in a number of forms, both hydrated (with different levels of hydration), and an anhydrous form, so constructing a phase diagram for such a system is paramount for developing a robust crystallisation. Hydrate formation of a final product is governed by the water activity in a particular solvent as well as the temperature. Hydrates tend to be more stable at lower temperatures so during cooling crystallisation it is very important to ensure that the crystallisation doesn't cool into the region where the hydrate is more stable - if the anhydrous form is the desired form. Seeding with the desired form (anhydrous or hydrate) is also crucial to ensure that the correct form is manufactured, as either cooling or anti-solvent addition significantly lowers the solubility and under those conditions the rate of conversion to the desired form can be very slow.

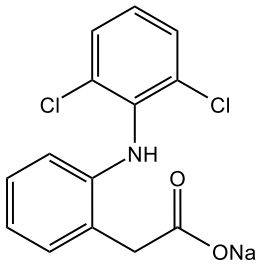


Figure 13. Sodium Diclofenac

In order to experimentally construct a phase diagram, accurate temperature and stirring is essential as thermodynamic conditions need to be established and the composition of the experiment needs to remain constant throughout. Mixtures of the two solvents and the final product are prepared with a defined composition, and these are allowed to equilibrate at the appropriate temperature and the solid form present analysed, typically by XRPD (X-ray powder diffraction) analysis.

In Figure 14 below, point A is composed of 40 mol% final product, 20 mol% water and 40 mol% solvent A, and the solid present is the anhydrate. Point B is composed of 40 mol% final product, 40 mol% water and 20 mol% solvent A, and the solid present is the hydrate.

Usually, phase diagrams such as these are only constructed at the isolation temperature and the seeding temperature of the crystallisation to ensure the process is in the correct domain to produce the desired final product form. However, in order to maintain the correct composition of the 3-component mixture during equilibration, no significant evaporation or loss of solvent must occur during the experiment.

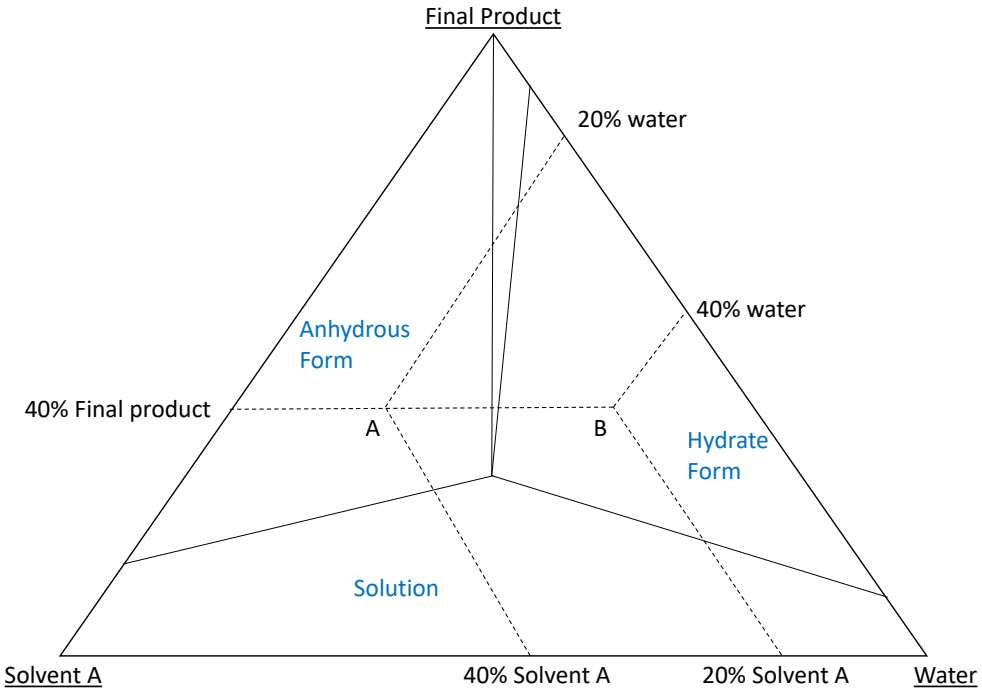


Figure 14. Schematic of a typical final product-hydrate phase diagram

Prediction and modelling

Modern modelling and predictive tools can speed up the development of crystallisation processes enormously, and numerous crystallisation parameters can be modelled at the same time. Parameters such as nucleation, crystal growth, and agglomeration/attrition, can be included in models, but these often involve significant approximations, so care is needed in interpreting data. The prediction of crystal structures (CSP - Computational Crystal structure prediction) has evolved significantly over the last 30 years and can be used alongside modelling of the actual crystallisation process to provide a rationale of final product morphology and other crystal parameters. Modelling alone cannot replace an experimental approach, but it can provide valuable insight into the process and reduce the number and scope of the experiments to be carried out. Virtual DoE type experiments can be carried out, which can then be validated with an experimental design. This often greatly reduces the number of practical experiments that need to be performed.

Design of Experiments (DoE) and Quality by Design (QbD)

DoE (Design of Experiments) is a valuable tool for optimising a variety of chemical processes, including crystallisations and is best used after a thorough understanding of the system has been acquired and, in most cases, to determine boundaries for the crystallisation process or to verify any modelling predictions that have been previously carried out. In DoE, selecting the correct factors, levels and responses for any experiment is crucial. Virtual DoE experiments can help in this regard by narrowing down the factors and hence the number of experiments that are actually performed.

Control of crystallisation parameters

Precise control of the factors during any DoE is also critical, and often, repeating the “identical” centre point experiment multiple times shows significant variation in the chosen responses due to the factors not being accurately and reproducibly controlled. As well as good control of the experimental parameters, being able to carry out experiments in a parallel manner and under process like conditions, so that the responses observed in the DoE are representative of the larger scale, is an important factor in DoE. Another important factor is being able to monitor the experiments in real time with accurate data logging to determine what the actual parameters were during the experimental run. The Mya 4 (Figure 15) and Radleys range of parallel equipment, including the Carousel 6 and Carousel 12, allow chemists to run unattended processes with confidence that none of the factors are changing during an experiment, such as solvent loss.

Figure 15. Mya 4 Reaction Station

A typical DoE is shown in Figure 16, giving an idea of some of the factors to be investigated and the corresponding parameters to be measured.

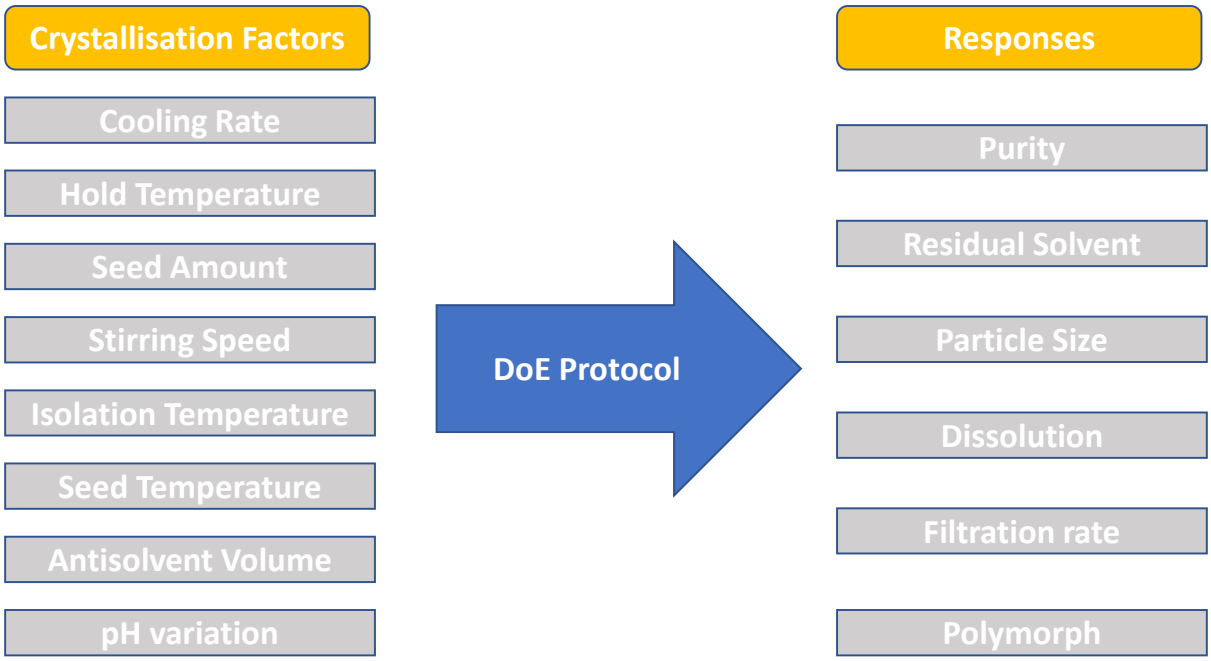


Figure 16. Typical DoE protocol for crystallisation development

QbD (Quality by Design) is the ultimate goal of any manufacturing crystallisation process that guarantees that quality and repeatability are designed into the process. Regulatory authorities (ICH guideline Q8 on pharmaceutical development and ICH Q10 on Pharmaceutical Quality Systems) have been driving a QbD approach to process development,

demanding a rigorous understanding of the links between the CQAs (Critical Quality Attributes) of the pharmaceutical product (i.e., those that influence its clinical efficacy), the CMAs (Critical Material Attributes) of the raw materials, and the CPPs (Critical Processing Parameters) applied during manufacture.

To ensure the quality of the crystallisation process, knowing the CPPs is vital prior to embarking on an extensive DoE. The CMAs are generally determined by the crude final product material and are often related to the purity of the final product material going into the crystallisation process. For the majority of crystallisation processes, these critical process parameters are scale-dependent, and the region where the crystallisation process can operate reproducibly shifts as the scale of production is increased towards commercialisation. This indicates why the crystallisation process, once developed, needs to be monitored on scale-up to ensure the commercial process still provides the quality final product.

There are a number of other guidelines that describe quality attributes of the final product, such as residual solvent levels, but it is important to remember that these are guidelines and not rules. In terms of residual solvent, a number of final product-solvates have been approved, Darunavir ethanolate and sodium warfarin IPA clathrate being examples, which are not compatible with the ICH residual solvent guidelines.

Conclusion

Crystallisation is still the industry standard method for the final processing of drug substances and will remain so for the foreseeable future. The process has evolved significantly over the years with the development of new techniques such as PAT, modelling and the development of improved temperature control. As crystallisation scientists know, every final product is different and brings its own challenges to crystallisation and scale-up, but throughout the process, there are general steps to understanding the crystallization process. The **4S** strategy is the starting point – **S**olubility, **S**upersaturation, **S**eeding and **S**olvent. After these have been established, the critical process parameters can be determined - these will generally be similar, but not the same for all final products. Crystallisation development requires a multidisciplinary approach, and as such, no one technique should be prioritised over the others. Rather, the most appropriate methodology should be used to solve a particular problem.

When a final product has reached its final crystallisation step, it has normally gone through numerous development stages. Despite the advances in data-sharing and cloud computing, information is lost along the way, and this information can be vital for crystallisation scientists. Some of this information can be anecdotal, but often, solid form screening and early development studies give a lot of clues towards how a robust, commercial crystallisation process can be developed. This means that, despite the advances in modelling, prediction and PAT, the experience of crystallisation scientists in this field is invaluable to developing a process.

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