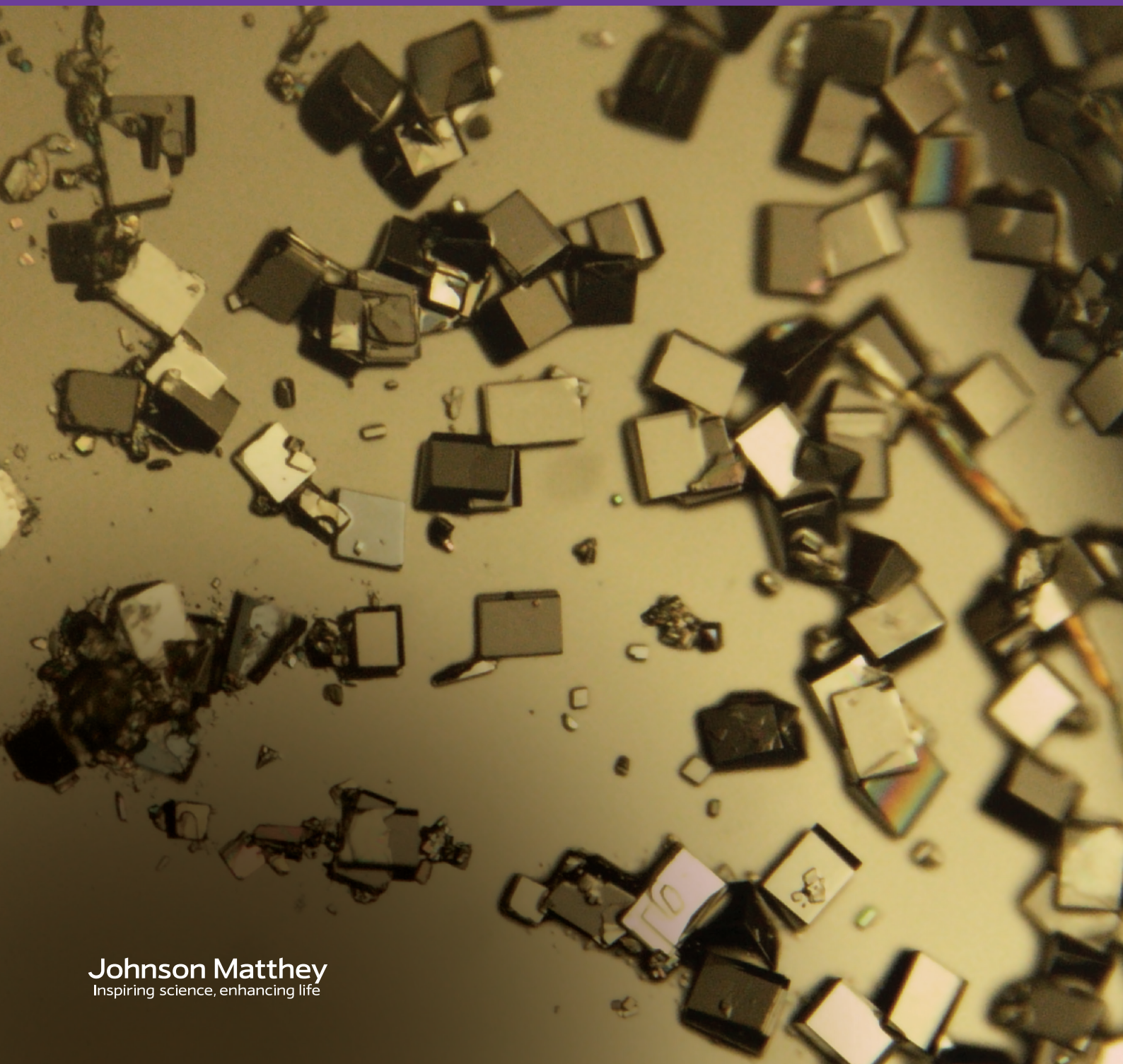
JM

# White paper

## Crystallisation process development



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## Dr Joe Harris

**Senior scientist - Crystallisation development, Johnson Matthey**

Since joining JM at the start of 2018, Joe has led and worked on projects developing controlled crystallisations for numerous APIs. Joe has a PhD from the University of Bristol. He undertook postdoctoral research at Friedrich Alexander University Erlangen Nürnberg studying biomimetic crystallisation. His work at JM focuses on combining state-of-the-art process analytical technology with modelling and solid form understanding to optimise crystallisation processes.

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## Providing a first-choice opportunity

In the manufacture of active pharmaceutical ingredients (APIs), crystallisation is a key unit operation. The importance of designing the solid state and particle form of a given API is well-appreciated in the industry as it can impact the downstream processability of the isolated material and can be used to maximise the efficacy of the final drug. Crystallisation provides the first-choice opportunity to achieve this designed particle, however, historically time and cost pressures have inhibited developing the understanding required for robust and reliable processes at an early stage. Consequently, issues such as oiling out, solvent and impurity entrapment, multimodal particle size distributions and previously unseen polymorph transitions have been all too common to first be seen upon process scale-up, often requiring significant quantities of additional time and investment to circumvent.

With improved process analytical technologies (PAT) and more accessible computational modelling, it is now viable to quickly perform meaningful studies that scale with modest quantities of material. This allows crystallisation process development to be incorporated into phase appropriate development and avoids the mistakes of the past. Crystallisation development now becomes an additional tool for the development scientist to improve the API synthesis or downstream processing (Figure 1). Additionally, unoptimised commercial processes are also coming back for crystallisation development to improve reproducibility or to explore the cost benefits of streamlined procedures.

Governed by both thermodynamics and kinetics, crystallisation is an interdisciplinary science which sits at the interface of physics, engineering and chemistry. For robust design, both the kinetics and thermodynamics of the process must be understood and exploited to devise a method by which growth of material from solution can be navigated along the desired free energy pathway. The shape, size and crystal form of the particles generated heavily impact downstream manufacturing and formulation processes, and when not appropriately controlled can result in hurdles for manufacturing and regulatory approval. Because of their importance, the particle forms of an API are already tightly regulated and as quality by design becomes increasingly expected by regulatory bodies, the need to understand and control crystallisation processes is becoming ever more pertinent.

Herein, we demonstrate how an approach combining in-process measurements and crystallisation modelling, underpinned by expertise in solid form science can identify and side-step pitfalls encountered during API crystallisation.

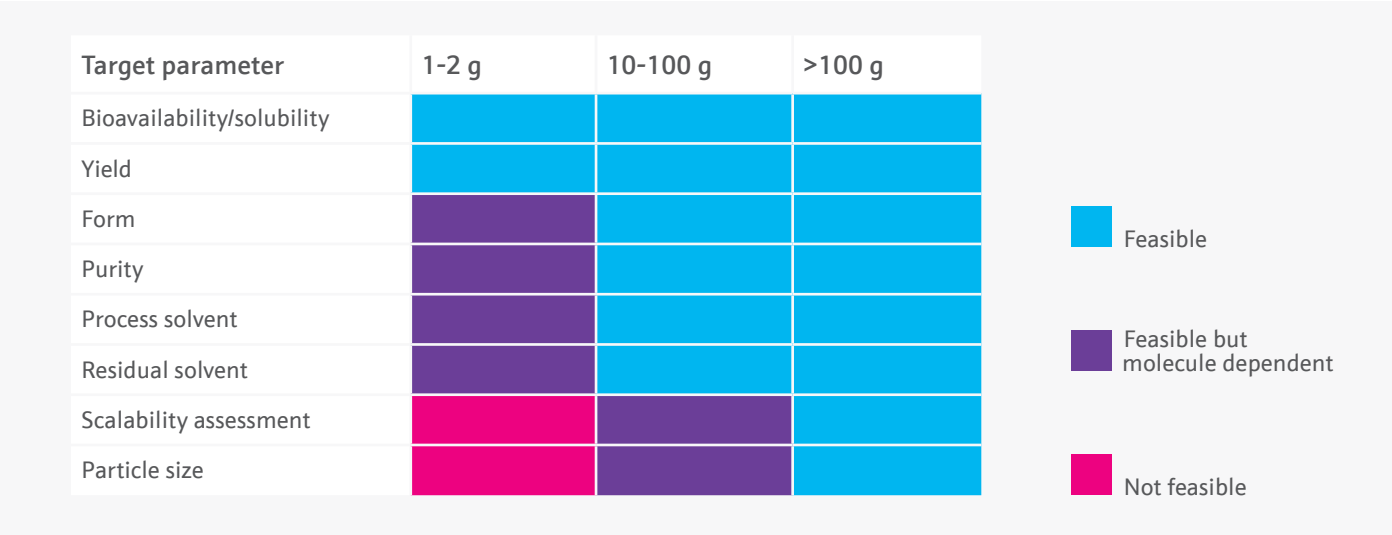



*Figure 1. Quantities of material required to design a process to fulfil key quality criteria.*

## Adopting crystallisation development at an early stage

Preconceptions that processes can only be developed on a larger scale, or that attempts to anticipate large-scale problems requires some prescience are now being challenged. The advent of in-process measurement tools of increased sensitivity means that complex transient phase behaviour can be observed in situ. Furthermore, detailed models of both complex fluid dynamics and crystallisation kinetics mean that robust, scalable processes can now be developed on the small gram-scale. These advances allow steps to be implemented at an early stage to avoid costly, unforeseen late phase process development.

Vital information which requires extensive experimentation to obtain during crystallisation process development at late-stage is commonly recorded during small scale polymorph screening experiments. This includes solubility data and indications of solvent-dependent crystallisation kinetics and potential transient forms. Process transfer commonly means that these observations and data can be lost as synthetic routes evolve over the years from medchem to commercialisation. A simplified crystallisation development can therefore be efficiently coupled with polymorphism studies that might be carried out when only a few grams of material are available. This simplified study will develop a controlled process appropriate for toxicology and early GMP batches. Furthermore, valuable process insights will then be captured at this stage which expediates fuller crystallisation development studies when clinical trials are appropriately progressed, and more material is available. The product from controlled crystallisation processes will typically be of higher crystallinity than that obtained from unoptimised processes. The solubility of the amorphous form of any given API may easily be an order of magnitude greater than that of its crystalline forms. This means that the highly crystalline material generated from controlled crystallisations are more representative of the final commercial drug substance and therefore appropriate for early stage in vivo tests.

### Solvent selection

Selecting an appropriate solvent is a pivotal step in crystallisation design. Early phase process development allows for communication between the crystallisation scientists and synthetic chemists to occur, and an optimal solvent for both synthesis and crystallisation to be selected. Furthermore, information about solid form boundaries and the capacity of certain solvents to form solvates can be fed in from solid form screening studies.

As the molecular weights and complexities of APIs have increased over recent years their solubility in commonly used solvents has decreased. To combat this, binary and ternary solvent mixtures are often required to provide adequate solubility of the molecule so that a volume-efficient scalable process can be developed. The search for such solvent combinations is therefore paramount. Where this search would once be reliant upon a mix of intuition and extensive experimentation, advances in computational predictions have reduced this experimental burden. Software packages such as DynoChem™, Cosmoquick™ and Hansen Solubility Parameter (HSPiP™), can now be employed to accelerate solvent selection based on predictions of solubility from molecular structure and limited solubility measurements. Not only do these software packages suggest novel solvent combinations which are not obvious but, once solubility curves of the required solvent/antisolvent combinations are obtained, non-linear solvent landscapes can be identified and precise solvent/antisolvent ratios required for desired yields determined. As an example, DynoChem™ modelling was employed at JM when optimising the crystallisation of an API which showed limited solubility in the majority of process solvents. The API did not exhibit sufficient solubility in single solvent systems for a volume efficient crystallisation to be performed. A solvent mixture was identified in which solubility of the API was achieved in process relevant volumes (Figure 2), and crystallisation of the material was achieved in a yield of >90% as predicted by the model.

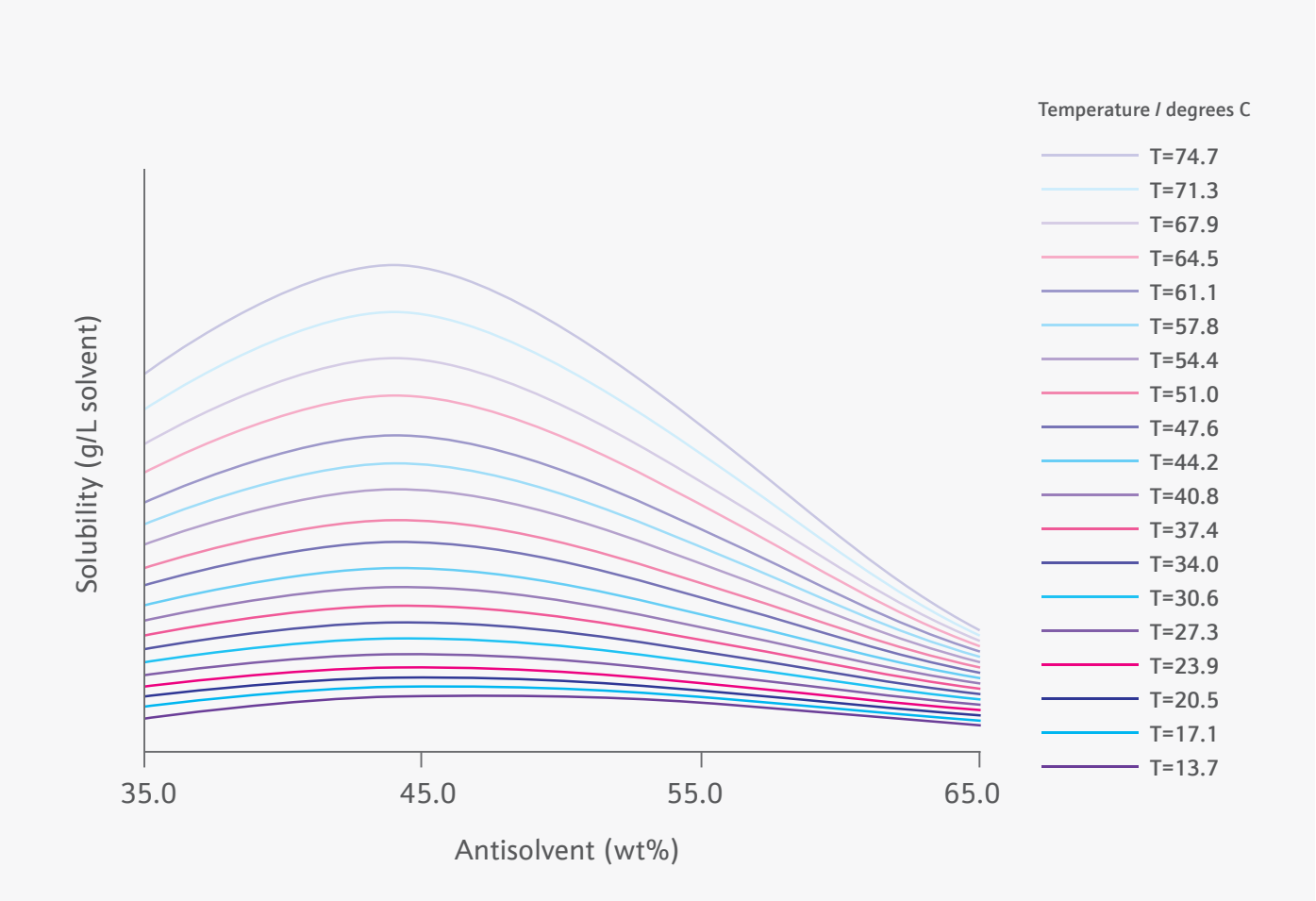



*Figure 2. Temperature variable solubility of an API as a function of solvent composition.*

**Not too fast, not too slow, but just right**

Crystallisation is governed by both thermodynamics and kinetics. The thermodynamic solubility of a material in a specific solvent is simple to measure and allows for theoretical yield to be easily calculated from the solvent composition and temperature profile of the process. It is, however, the kinetic aspects of the crystallisation process that dictate the trajectory of the crystallisation. The rate of crystal growth is both system and solvent dependent, and unlike thermodynamic solubility is non-trivial to measure. In Figure 3, the three possible scenarios for a cooling crystallisation are shown. In the first scenario, demonstrated by the blue line labelled 1, seeds are added, and the crystalliser is cooled rapidly. The rate of the cool exceeds that of crystal growth, and the supersaturation of the system gradually increases until the labile zone is entered. At this point, spontaneous nucleation of material occurs, and a multimodal particle size distribution is obtained. Uncontrolled nucleation events such as this can also lead to entrapment of solvent and impurities, and potentially the spontaneous formation of an undesired polymorph. In the second scenario, demonstrated by the black line labelled 3, after seed addition the solution is cooled very slowly so that the solution concentration adheres to that of the solubility of the material in solution. In this scenario the labile zone is avoided, but the batch time is excessively long, and the probability of problems such as attrition and solution degradation are increased. In the third scenario, demonstrated by the purple line labelled 2, the solution is initially cooled to a point at which the system becomes metastable whereupon seeds of the desired form are added. The rate of cooling is then balanced with the rate of crystal growth so that constant growth on the seeds occurs, and a product of predetermined size can be isolated. As the rate of crystal growth is system dependent, the problem faced when deciding the rates at which a crystalliser must be cooled is clear; how fast is too fast, and how slow is too slow? If the kinetics of crystal growth are understood, the optimum crystallisation trajectory can be followed, and the particle size distribution of the final product controlled simply by manipulating the quantity and particle size distribution of the seed. Measurement and prediction of crystal growth kinetics have previously been difficult and experimentally challenging. Furthermore, changes in input energy and mixing when transferring between scales and the impact of these on the kinetics of the system have been difficult to quantify. Improvements to the sensitivity of PAT tools such as the ReactIR™ used for the measurement of solution concentration, and more robust software for quantifying and modelling crystal growth (DynoChem™ and gCrystal™), mean that measurement and prediction of crystal growth are both easier to measure and predict than ever before. Skilled teams can rapidly screen solvents and disregard those in which crystal growth is too slow as to be practicable on scale. They can then tune the rates of cooling and antisolvent addition to be balanced with that of crystal growth. Reproducible, robust crystallisation processes following optimal trajectories can then be designed, validated and transferred between scales with reduced experimental burden. For example, at JM, in situ solution concentration experiments were employed to optimise the crystallisation of an API which exhibited slow growth kinetics. Solvents which afforded sufficient solubility were screened at low-gram scale and a solvent was identified in which the rate of growth exceeded that identified previously. The improved crystal growth kinetics allowed for halving of the processing time without inducing primary nucleation.

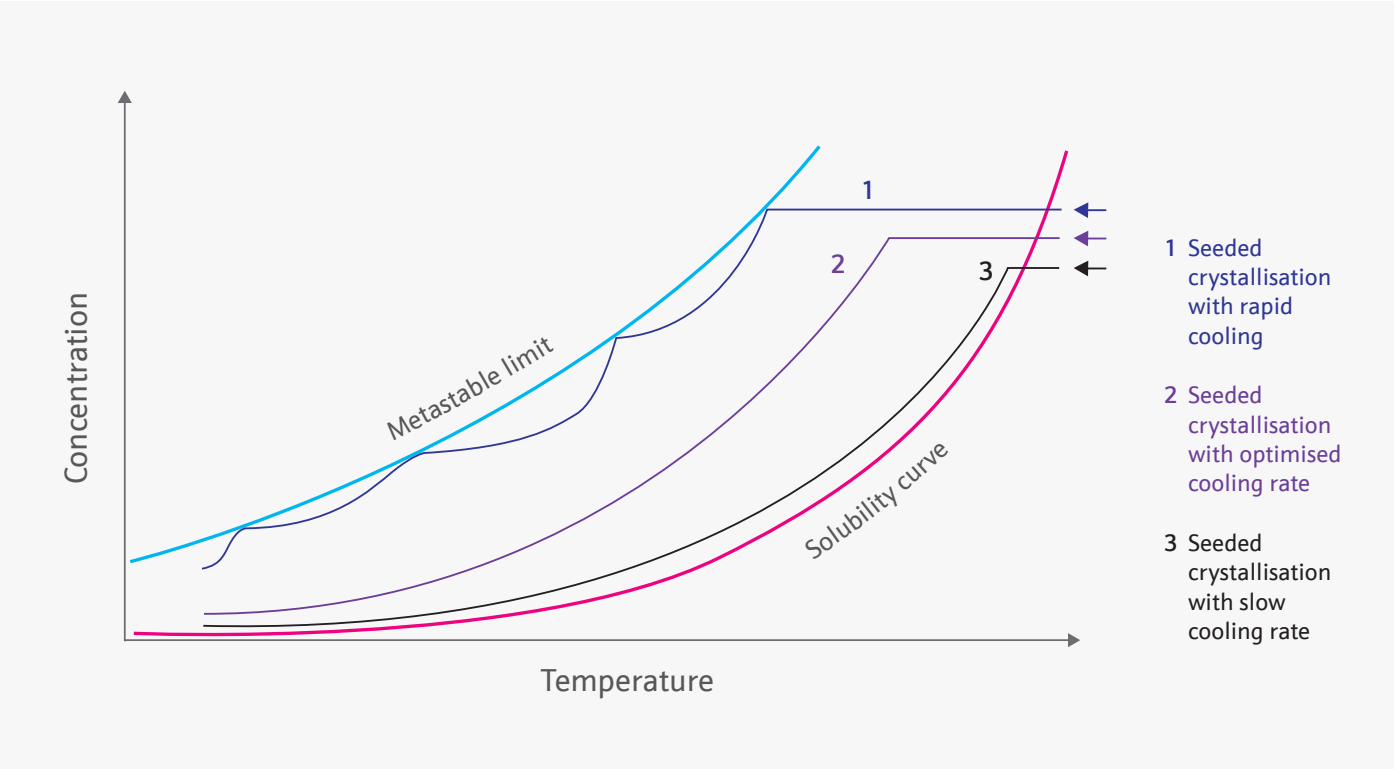
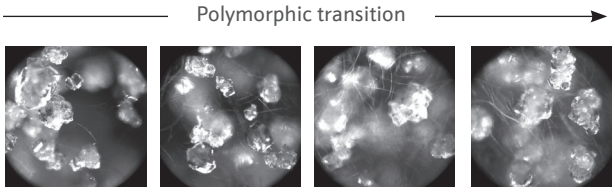



*Figure 3. Possible crystal growth trajectories in a cooling crystallisation.*

### Seeing is believing

The formation of transient forms and the onset of uncontrolled nucleation events can be hard to pinpoint in a crystalliser which, to the naked eye, appears to contain a turbid suspension throughout the process. The arrival of advanced high-resolution process analytical tools such as the Blaze™ Metrics probe gives hitherto unavailable insights into both existing and novel crystallisation processes. A combination of high-resolution microscopy and Raman spectroscopy allows the formation of transient forms to be both pinpointed and the materials identified in situ. In Figure 4, the exact point at which the formation of an undesired polymorph with fibrous morphology is shown, and its growth tracked in situ. Furthermore, when PAT tools are used in tandem, the precise solution concentration, temperature and solid loading at which nascent particles of an unwanted form nucleate can be identified. The crystallisation system can then be tuned to avoid the experimental space in which the formation of undesirable forms nucleate.




The advanced characterisation tools now at the disposal of scientists mean that crystallisation systems can be probed at ever reduced volumes. Chord length measurements and in situ images can be used to validate crystal growth models at a small scale. Breakage, aggregation and secondary nucleation can all be appraised throughout the scale-up process and these events factored into predictive models during method transfer from vessel to vessel.

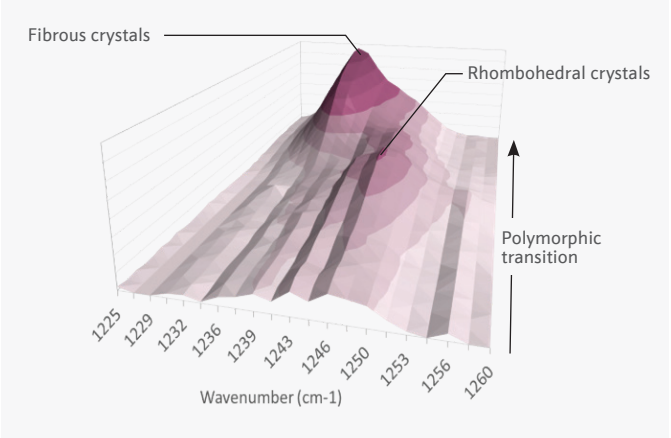



*Figure 4: In situ imaging and Raman spectroscopy of a polymorphic transition from a metastable form with rhombohedral morphology to a stable Form with fibrous morphology.*

### How robust is robust?

While the tools and software available may have advanced, critics would argue that the overall goal is unchanged, and the problems of transferring between scales still exists. So how robust are the models?

As software packages and models become more user friendly, the line between modeller and experimentalist has blurred. Complex fluid dynamics models of vessels can be generated by all, and in specialist teams the scientist performing the experiments is the same as the one building the model. All this means is that the scientist must design a model so robust that they can't break it. Once tuned and assessed on a small scale, a design of experiments approach can be adopted to find the edge of failure. Furthermore, the use of process analytical technology means that when this edge of failure is located, the events that occur such as nucleation and aggregation can be imaged and the boundaries of the process changed to prevent their reoccurrence.

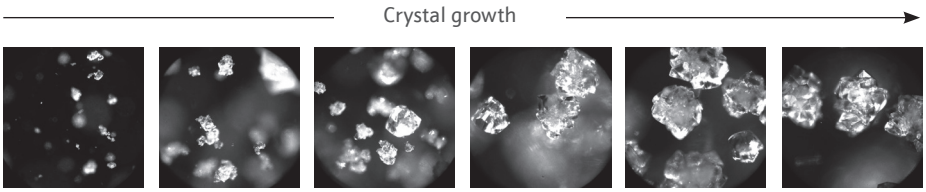



*Figure 5: In situ images of crystal growth and aggregation are observed. This data can be fed into crystal growth models to optimise and improve robustness of models.*

## Conclusion

**Crystallisation development is increasingly accessible and valuable at stages of development when very limited material is available.**

**Higher resolution process tools allow for the identification of in situ transitions that could not previously be observed on smaller volumes of material.**

**Solid state knowledge coupled with process modelling allows the development timeframes to be decreased and valuable insights to be generated that help to direct future development.**

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