VERANOVA™

Crystallization Development Services

Unlock the potential of your API

First-class crystallization expertise to develop controlled, robust, and scalable routes to your API's optimal solid form.

At Veranova, through our Pharmorphix® brand, we leverage solid form, process analytical technology (PAT), and computational modeling expertise to enable our bespoke crystallization development packages.
Our industry-leading technologies and collaborative approach help to accelerate your drugs to market.

Managing complexity with confidence

We are a trusted and experienced partner with a proven track record of delivering leading solid form and particle engineering services, having completed over 2,000 customer projects on a wide range of structurally diverse and complex APIs.

Supporting innovation with collaboration

Our crystallization development services are backed by our multidisciplinary team of experts including, crystallographers, solid-state scientists, chemists, engineers and computational scientists. Uniting this diverse range of expertise, we're able to work closely with customers to understand their project's needs and goals and find the optimal solid form of their API.

Advancing science with you

Veranova has over 50 years of experience navigating the challenges of pharmaceutical development and manufacturing. Backed by our extensive knowledge, state-of-the-art facility and instrumentation capabilities, we specialize in crystallization control across scales of development, from as little as 5g upwards.

- Maximize process yields
- Improve purity
- Control form, morphology, and particle size distribution
- Create processes suitable for transfer and scale-up
- Strengthen IP

Crystallization development

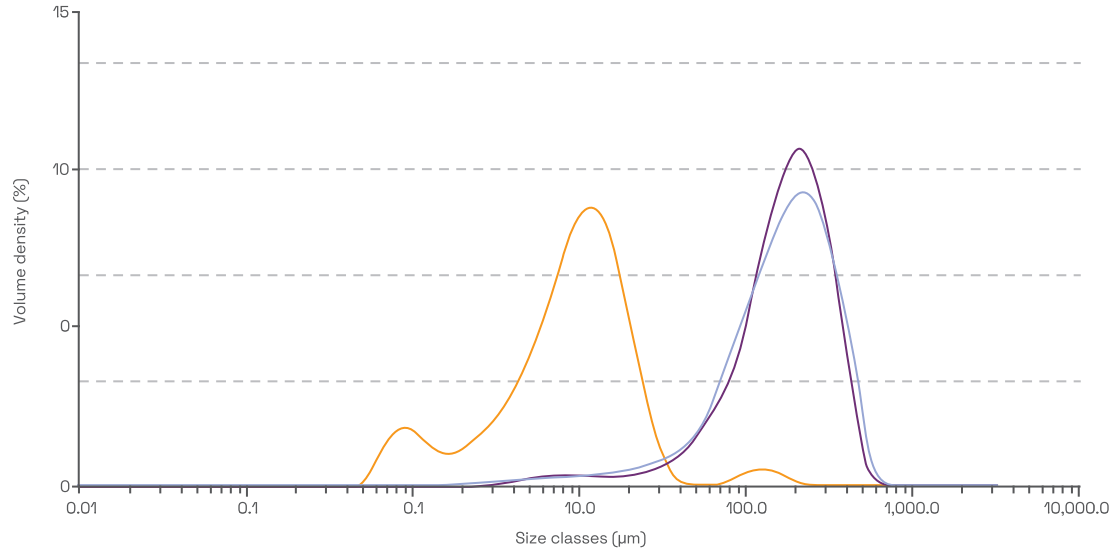
Developing a robust crystallization process to isolate the optimal solid form of an API is an essential step in pharmaceutical development to control solid form, purity, and residual solvent content.

However, for R&D teams looking to target a specific crystal habit and deliver consistent uniform particle size distribution (PSD) from a single process step, this can be a challenging stage of the developmental process.

Our long-standing expertise in solid form, PAT, and computational modelling underpin our development of crystallization processes, allowing us to deliver the best outcome at the required scale.

Our team apply highly specialized instruments to understand and control the crystallization processes, allowing us to design robust and scalable procedures as well as addressing prevalent crystallization issues such as oiling out, isolating the wrong polymorphic form, or extended filtration/drying times in existing processes.

The routine use of *in situ* probes allow for online monitoring of the crystallization process, providing invaluable insights into the crystallization kinetics and mechanisms at play.



Description	Dx (10) (µm)	Dx (50) (µm)	Dx (90) (µm)
Milled seed material	1.81	9.49	21
Small scale crystallization	66.4	180	340
Large scale crystallization	62.2	180	369

Figure 1: An example of particle size control and optimization by crystallization development and particle engineering protocols.

Early stage crystallization development enables late stage benefits

Vital information such as solubility data, indications of solvent-dependent crystallization kinetics, and potential transient forms is commonly recorded during early-stage small-scale experiments. However, process transfer often means that these vital observations and data are easily lost as synthetic routes inevitably evolve from early medicinal chemistry, to more scalable process chemistry routes, and ultimately to commercial scales. This often results in extensive reactive experimentation being required during the late-stage process development to re-acquire this data.

At Pharmorphix, we couple our extensive knowledge in both solid form science and crystallization, offering simplified crystallization development packages in combination with our polymorphism, salt and cocrystal studies that can be conducted when only a few grams of material are available. These simplified studies develop a controlled crystallization process that is appropriate for toxicology and early GMP batches. Furthermore, valuable process insights will be captured at this stage which expedites comprehensive crystallization development studies when clinical trials are appropriately progressed.

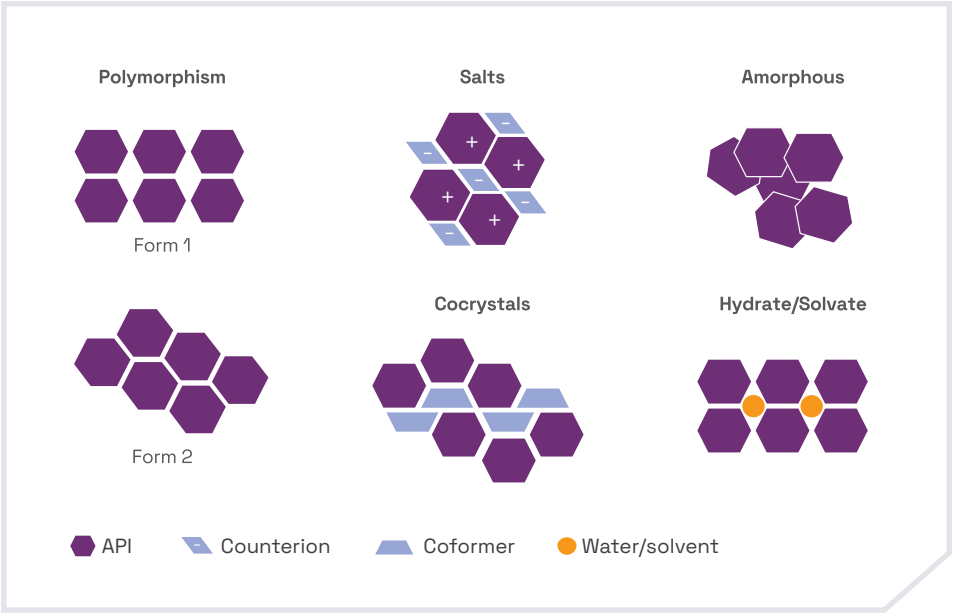


Figure 2: Different solid forms (crystalline polymorphs, salts, cocrystals and hydrates, and amorphous material).

Obtaining vital crystallization information at early stages contributes towards the design of robust and reliable processes once they are ready to be transferred from site to site, and vendor to vendor. The API product obtained from controlled crystallization processes will typically be of higher crystallinity than that obtained from unoptimized processes. The solubility of amorphous forms of any given API may easily be an order of magnitude greater than that of its crystalline forms. This means that the highly crystalline materials generated from controlled crystallizations during the early stages of development are more representative of the final commercial drug substance and therefore appropriate for early stage *in vivo* tests.

Information that is generated at early stages of development:

- Polymorphism studies/salt selection
- Suitable process solvent(s)
- Solubility measurements and metastable zone widths
- Design of crystallization processes to target high yields and low process volumes
- Global solubility models using DynoChem
- Understanding of crystallization kinetics and mechanisms with *in situ* PAT data

In addition to crystallization development, all projects have access to our in-house:

- Solid form and particle engineering services (within the UK and US)
- Single crystal X-ray diffraction (SCXRD) service
- Analytical and physiochemical services department
- Particle sizing and micronization team
- Modelling team

The key to controlled, growth-dominated crystallization is a thorough understanding of the solubility and metastable zone width (MSZW) of the system in combination with knowledge of the nucleation and growth kinetics. Once this understanding is acquired by experimental techniques, PAT and modeling, the process can be optimized to target crystal growth and avoid unwanted nucleation events (route 2).

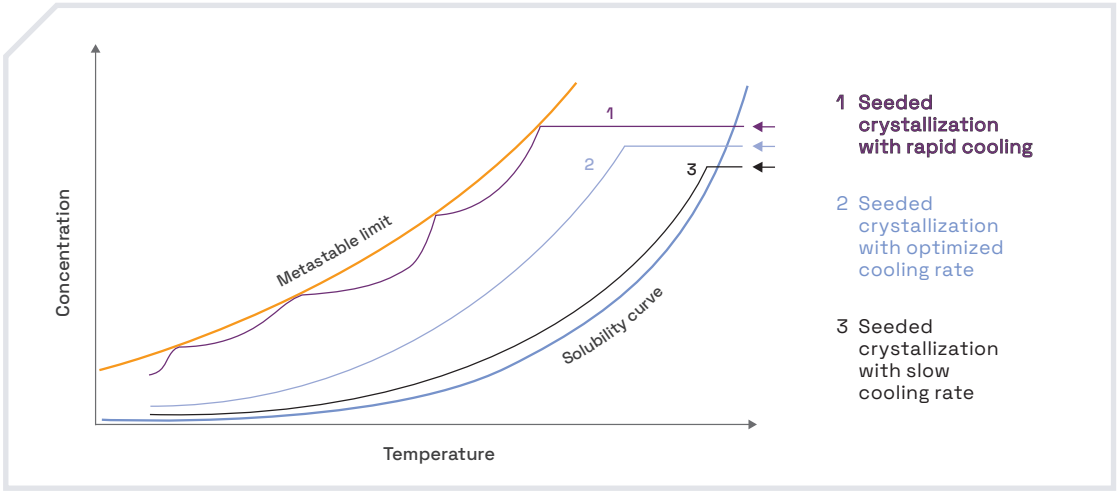


Figure 3: Pictorial representation of different crystallization pathways with respect to the solubility and MSZW.

Seeing is believing

The arrival of advanced high-resolution PAT such as the BlazeMetrics™ probe gives previously unattainable insights into both existing and novel crystallization processes. A combination of high-resolution microscopy and Raman spectroscopy allows the formation and growth of transient forms to be pinpointed and the materials identified *in situ*.

Common crystallization issues, such as oiling out, can also be easily identified at early-stage process development with the use of the BlazeMetrics™ probe. When PAT tools are used in tandem, the precise solution concentration, temperature, and solid loading at which untoward crystallization mechanisms occur can be determined. The crystallization procedure can then be tuned to avoid these conditions/parameters in which oiling occurs and/or undesirable forms nucleate.

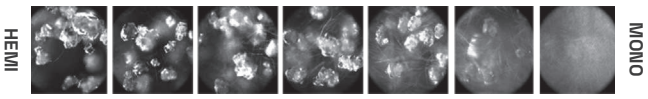


Figure 4: *In situ* imaging of a polymorphic transition from a metastable form with rhombohedral morphology to a stable form with fibrous morphology.

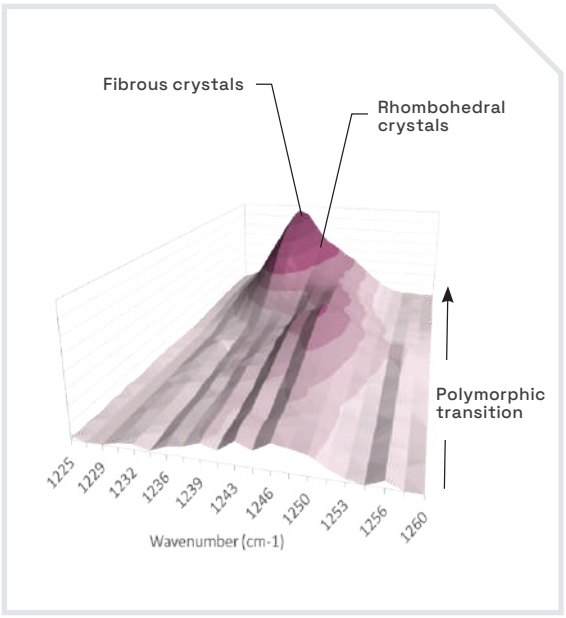


Figure 5: *In situ* Raman spectroscopy of a polymorphic transition from a metastable form with rhombohedral morphology to a stable form with fibrous morphology.

Through these advanced characterization tools, our experienced team of scientists are able to examine crystallization systems at reduced scales. 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 assessed throughout the scale-up process and these events are factored into predictive models during method transfer from vessel to vessel.

Our advantage is through the talent and expertise within Veranova's Crystallization Development Team. Our experts are trained not only in the art of crystallization, but also in solid form science, modeling, PAT, and particle sizing. Paired with readily available access to our in-house resources such as the Analytical Team and Single Crystal Diffraction Services, as well as a multitude of collaborative in-house relationships across sites globally, the service offering we provide in this space is effective, streamlined, and of the highest quality.

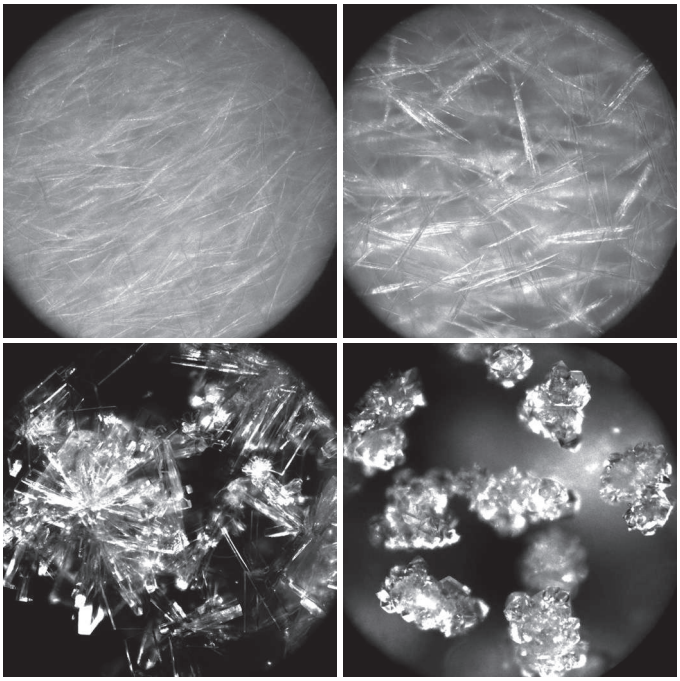


Figure 6: Example *in situ* images of various crystal morphologies using the BlazeMetrics™ Blaze900 probe.

How robust is robust?

While the tools and software available for crystallization design and in-process modeling may have advanced, critics would argue that the overall goal is unchanged and the problems of transferring between scales still exist. So how robust are the models?

As software packages and models become more user friendly, the line between modeler and experimentalist has blurred, and today, complex fluid dynamics models of vessels can be generated by all. In our specialist teams, the scientist performing the experiments is the same as the one building the model. Once tuned and assessed on a small scale, a design of experiments (DoE) approach can be adopted to find the edge of failure. Furthermore, the use of PAT 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 recurrence.

Technology transfer between Veranova sites and from non-cGMP to cGMP is common practice that ranges from simple crystallization systems to complex multicomponent crystallizations with tight specifications. The state-of-the-art kit, accompanied by the in-depth knowledge and experience from small scale to plant, means that smooth transfer is part of our offerings to our clients in small, mid-sized, and large pharma. A process transfer document will be generated based on the optimized procedure at each lab and modeling is used to move the technology and processes between vessels, guaranteeing the consistency of the outcome.

Crystallization with collaboration

At Veranova, our Pharmorphix experts specialize in generating bespoke crystallization development packages to suit our client's needs, maximizing the value of the projects whilst tailoring the scope to suit material availability, timelines and final product specifications.

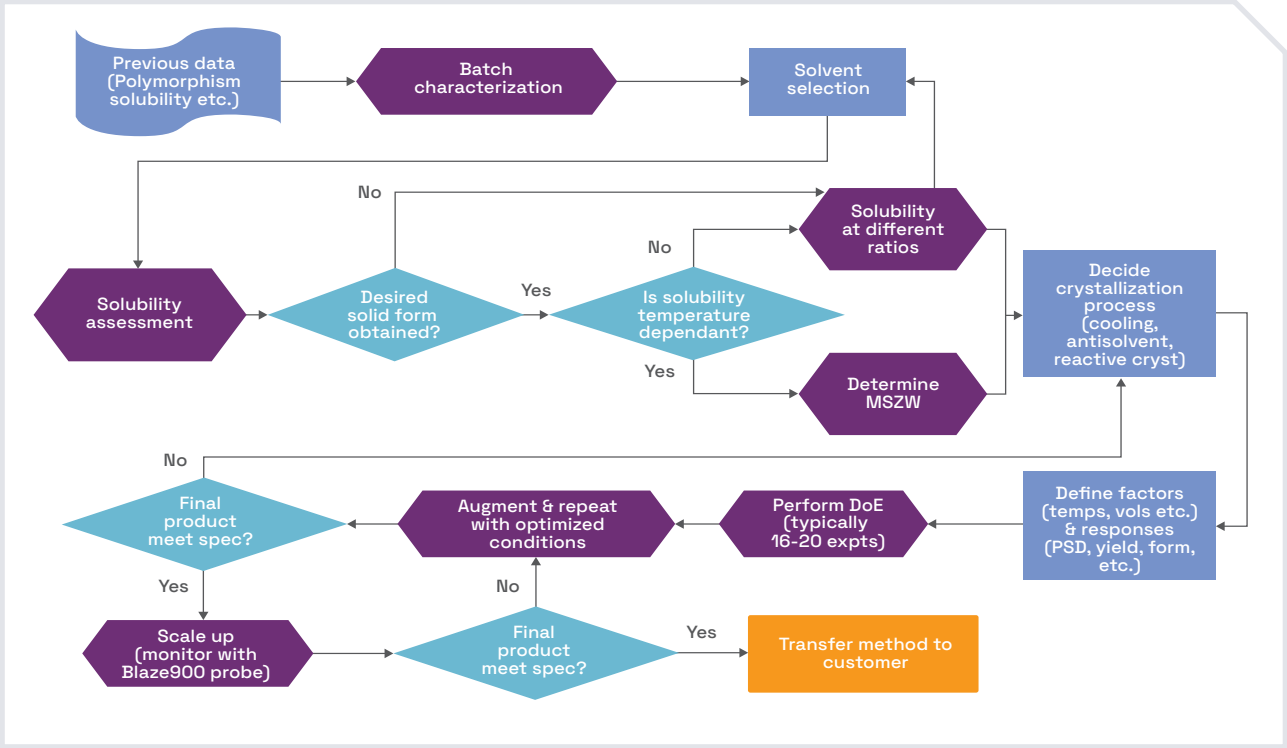


Figure 7: Flow chart representing a typical workflow used in-house at Veranova to outline and work on a crystallization development project for an API, intermediate, agrochemical, etc. to define a scalable and robust crystallization process.

Advance your science with Veranova

We employ our long-standing expertise in solid form, PAT and computational modeling, to enable our first-class approach to crystallization process development. Allowing us to deliver the best outcome at the required scale. Our extensive expertise in the area offers solutions to our in-house products, as well as to our large portfolio of clients.

How can Veranova support your project's needs?

- Providing the right mix of long-standing expertise, innovative technologies and scientific excellence to optimize processes and enhance purity and yields.
- Dynamic and tailored approach to enable full control over the final product quality and particle size.
- Early-stage crystallization development services and advanced analytical techniques to ensure on-time, on-budget projects that circumvent challenges such as oiling, bioavailability, formulation, and dosage challenges.
- Integrated process and product development approach that reinforces your intellectual property.

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