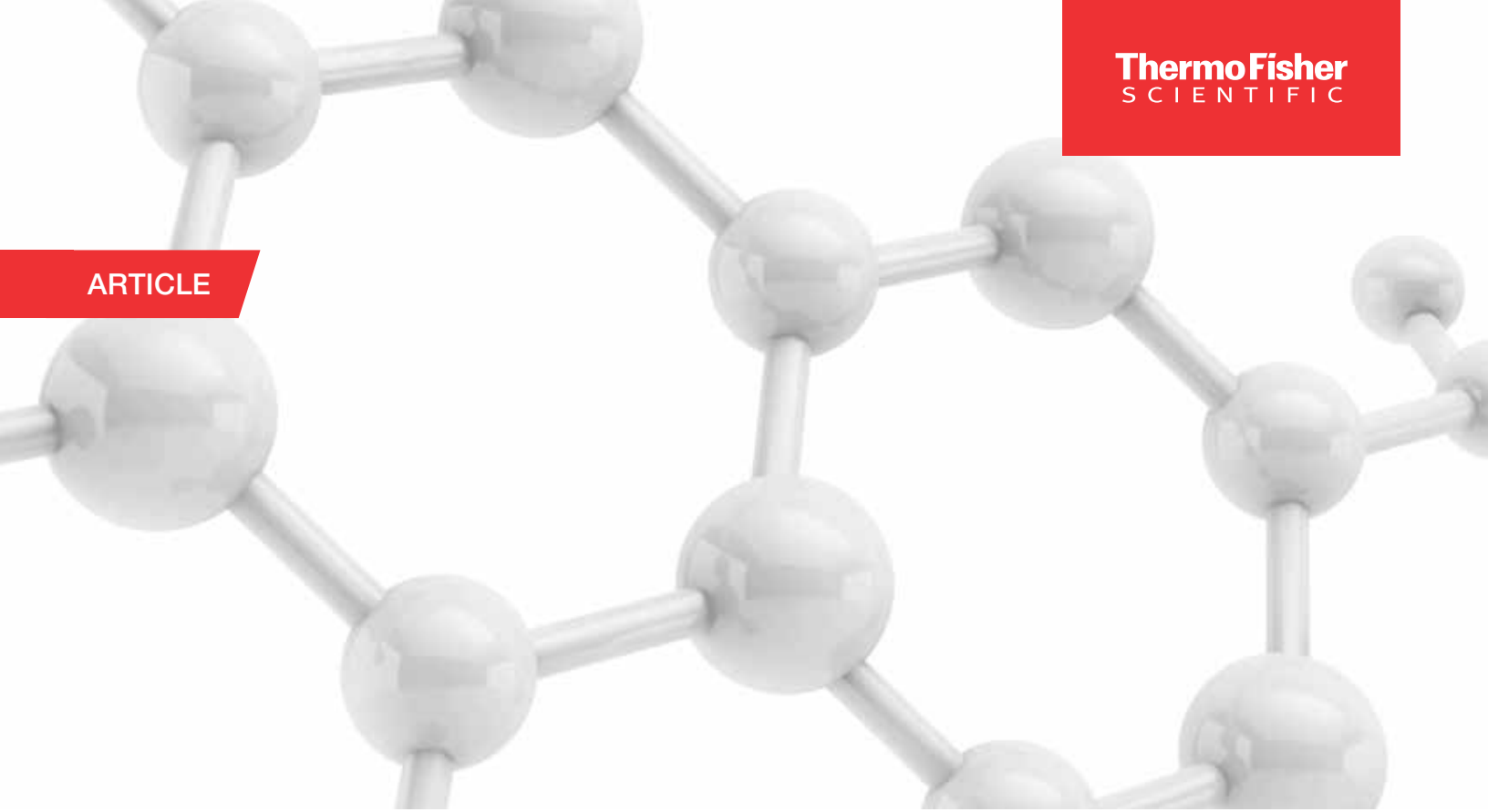


ARTICLE

Understanding the roles of solid-state characterization and crystallization within the product lifecycle

The physical properties of a solid active pharmaceutical ingredient (API) dictate the crystallization process used for isolation, purification, and form control and guide the development of an effective formulation. This article describes the role of solid-state characterization and crystallization process development throughout the product lifecycle and explains the importance of developing an early understanding of key solid-state properties for successful downstream processes. It also provides tips for working with partners and building a robust knowledge base in solid form drug development.

A successful integrated approach to smooth formulation development requires a good understanding of solid-state API properties and how to control them. Indeed, the majority of products on the market are solid form, and crystallization is the easiest way to pull solids from solution. Development of a crystallization process both *requires* and *adds* to an understanding of the physical properties of the solid-state material. Any method that contributes to an understanding of the physical properties (structural characteristics, powder properties) is needed to support the development of an effective form.

Chemical process and formulation development

Solid-state characterization, materials science, and crystallization play a role in nearly every step of the development process. At the pre-formulation stage, an assessment of molecular and solid-state physical properties of candidate APIs is performed, and these properties help define the choice of formulation. The properties you determine at the early development stage will also inform any later solid form screening activities, which in turn will inform development of the initial crystallization process. These findings then determine the process for manufacturing and can direct crystal modification, size distribution, purity, yield, and processability.

Crystallization process development

Crystallization has three functions: isolation, purification, and particle engineering. First, the process isolates the solid from the matrix that generates the API molecule. Next, the removal of by-products and solvent to a given specification must occur. Finally, a particle engineering process must match the powder properties to the formulated product requirements (e.g., shape, mean size, size distribution, and size limits).

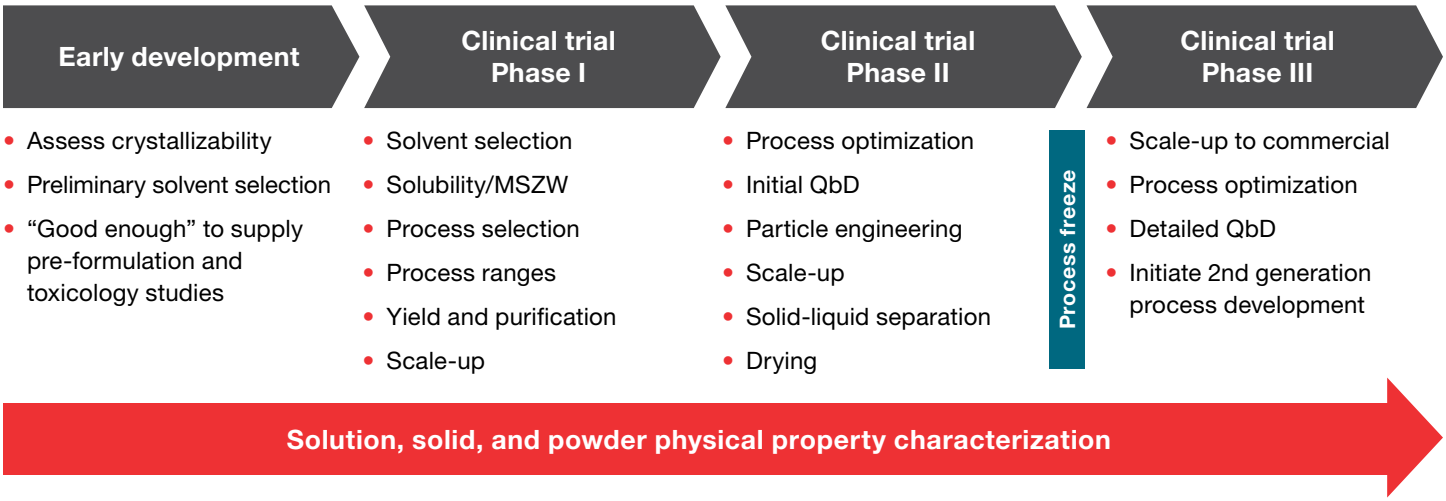
Crystallization development can occur in either a one-step or two-step process. Each process has unique advantages and disadvantages. The one-step process isolates, purifies, and produces the right powder specification and offers cost and time reductions relative to the two-step process. However, the one-step process requires a high level of process understanding and control. The two-step process first crystallizes for isolation and purification and then, in a second step, crystallizes for form giving and particle engineering, if required. One of the main advantages of this task separation approach is easier optimization, because there are fewer parameters to optimize at once. Purification before particle engineering results in a smaller chance of shape-directing or growth-inhibiting by-products, and overall, the approach offers more control along the way. Disadvantages to the two-step approach include increased costs associated with additional process steps and slower turnaround times.

The workflow associated with crystallization process development (see Figure 1) begins with Phase I, the early development and preclinical stage. This is when limited data are generated on the solid stage in order to enable early formulation development. An initial crystallizability assessment or rudimentary process for generating material in the lab at a small scale may also be developed in this phase. Preliminary solvent selection is made, and a process that is deemed acceptable to supply pre-formulation and toxicology studies is progressed.

Also in Phase I, the proper solute/solvent combination is selected, and various factors such as solubility, metastable zone width (MSZW), and yield are determined. The process is selected and process ranges are set. At this time, yield, purification, and scale-up (and any potential barriers to scale-up) are considered.

Phase II crystallization process development includes process optimization, possibly through Quality by Design (QbD)—a systematic, risk-based approach for formulation development. Also in Phase II, further consideration is given to particle engineering and scale-up. Other important activities for formulation, such as solid-liquid separation and drying, become important in Phase II as the scale of manufacturing increases. At the point of leading into Phase III, the process is frozen and any activities following the freeze are focused on scale-up to commercial, optimizing the process through a detailed QbD approach. Second-generation process development may begin during this time. Importantly, solution, solid, and powder physical property characterization takes place throughout each of these phases and at each development step.

Figure 1.



The crystallization process development workflow stretches from early development to Phase III clinical trials.

Key parameters for consideration in crystallization process development

Crystallization process determination centers on three important factors: thermodynamic solubility, nucleation kinetics, and growth kinetics. Thermodynamic solubility gives the maximum amount of material that can be dissolved at a given temperature and pressure in a given solvent, and the difference in solubility at the starting conditions and the end-point of the process determines the theoretical yield. An ideal yield for optimized process parameters is greater than 90%. Nucleation kinetics determine the number of particles (size and distribution). Growth kinetics determine the process duration for batch processing, and the equipment size and residence time for continuous processing. Each of these factors can be manipulated at least somewhat through the use of a variety of techniques and advanced technology to help achieve target parameters for both in-process analysis and downstream processing. Materials science measures specific properties that may be relevant to a given dose form and development lifecycle, including particle size, particle shape, compressibility, flow, moisture sorption, and specific surface area.

It is important to note that during clinical phases both the API and the drug product can change based on the results of clinical trials and with scale-up. As this occurs, the risk of changes in the API and subsequent downstream product becomes critical and must be understood.

Tips for success

Because solid-state characterization and crystallization process development play such key roles throughout the product lifecycle, it is critical to engage with a partner that has the expertise, experience, and capability to adequately support each step. Based on years of experience in materials science and crystallization processes, Thermo Fisher Scientific has put together a list of top tips for success:

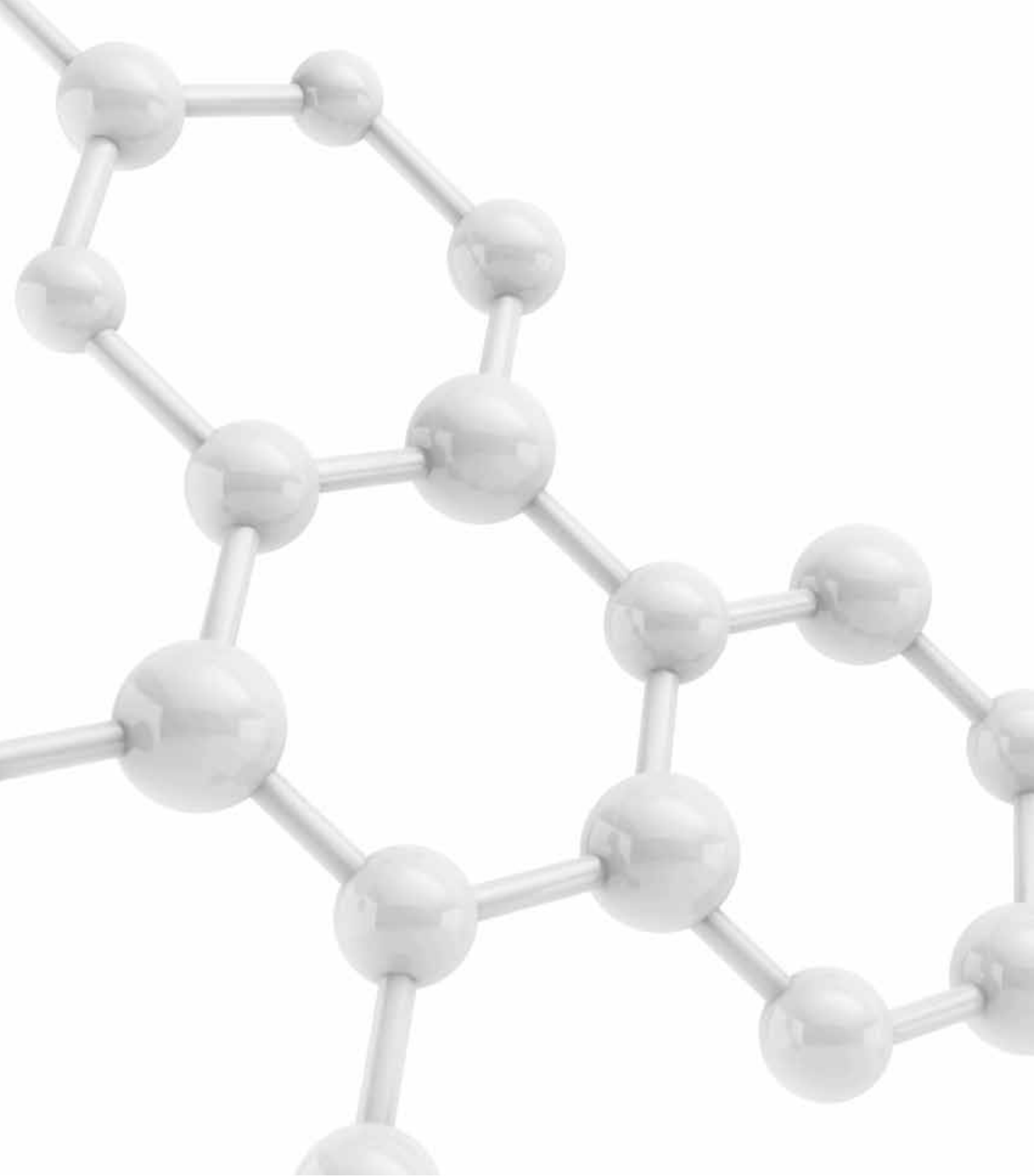
- Begin your engagement *early* with a partner that can offer solid-state characterization studies and expertise.
- Start to understand the solid-state landscape of the API early and link knowledge gained to drug product performance. (For example, many people regard first-in-human [FIH] formulations as essentially "throwaway" formulations; however, the FIH stage of formulation development provides a remarkable opportunity to characterize and track the physical and chemical properties of the API from medicinal chemistry batches to Good Laboratory Practices [GLP] traditional toxicology batches to the FIH studies. Tracking these properties provides an invaluable record of what works and what does not work.)
  - Understand polymorphism, physical properties, and crystallization.
  - Build in variability for robustness: use different lots of API and characterize them before use in drug product development batches.
  - Use an appropriate characterization strategy for the dose form.
  - Be judicious with resource allocation, remembering that most candidates do not reach Phase III.
  - Use a materials science approach to evaluate the potential impact of variability on the drug product throughout the product lifecycle.
- As the product develops through clinical phases toward commercial manufacture and the formulation changes, review the characterization strategy and use lessons learned to build a deeper knowledge base.

The importance of integrated services

Crystallization process development requires substantial input from multiple realms of expertise. Physical property characterization, analytical development, chemical process development, formulation development, downstream operations, and manufacturing needs all inform crystallization process development. A key collaboration occurs between crystallization and materials science experts and results in the correct particles and best processes, appropriate targets for API properties, smooth development and subsequent transfer to manufacturing, and a common understanding of risk.

Solid-state characterization (including changes in API and drug product throughout the lifecycle) enables efficient and robust drug product development, supports patient safety, ensures correct API therapeutic dosing and delivery to the patient, and ensures the API and drug product manufacturing sites can manufacture in a consistent, robust, and economical manner throughout the product lifecycle. API solid-state properties should guide crystallization process development, which in turn has an impact on the product lifecycle, including scale-up to commercial.

Thermo Fisher's Quick to Care™ program offers a comprehensive molecule to medicine program that integrates clinical supply services, clinical supply optimization, and transportation management through all phases. For clients looking to achieve FIH milestones, Thermo Fisher's Quick to Clinic™ program offers phase-appropriate formulation for Phase I and FIH trials, drug development, and clinical trial supply services. By adding solid-state characterization into early drug development programs, we can synthesize and make material in small amounts in a phase-appropriate state for Phase I and FIH trials, providing the opportunity to track, trend, and understand physical properties. In turn, the process establishes a firm foundation for Phase II and beyond, resulting in a robust development program informed by science and guided by knowledge-backed decisions.



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