Lonza
Pharma & Biotech

Solid Form Screening: A Key Drug Development Step

INTRODUCTION

Bringing safe, effective medicines to market has never been more challenging. Given the changing landscape of the pharmaceutical industry—accelerated timelines to market; a shift to specialized, enhanced drugs; and pipelines filled with more-complex, highly potent molecules—each step of the drug development process hinges on efficient workflows and wise decisions. This complex process includes drug synthesis, solid-form selection and development, as well as drug product selection and development.

Selection of a solid drug form is a key decision because an estimated 90% of organic molecules have multiple forms, illustrated in Figure 1. Choosing the right solid form and identifying the interplay between solid form and drug product can save time and money and minimize risk, often making the difference between success and failure in development of new drug products.

Solid form selection involves selecting both the chemical makeup of the solid to be manufactured (e.g., polymorph) and its physical form (e.g., crystal structure). These attributes determine critical drug product properties such as stability, bioavailability, and, ultimately, the mechanical properties that determine manufacturability, as shown in Figure 2.

Lonza works with each client to define a work flow that is appropriate for the project. Here, we describe the process and provide a case study to show its application.

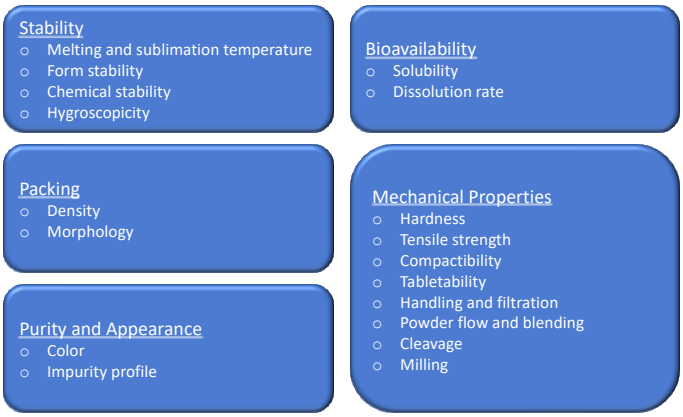

Figure 2
Drug product properties affected by solid form selection

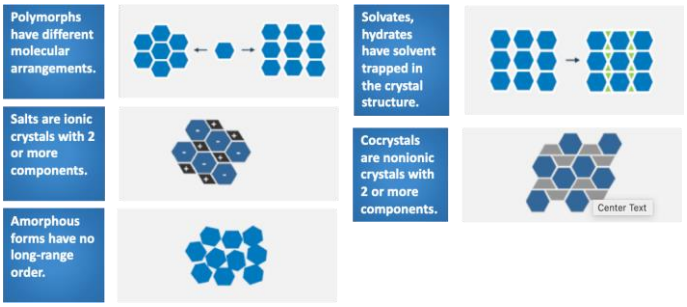

Figure 1
Characteristics of various solid forms

SOLID FORM SERVICES

Solid form services encompass the identification, preparation, and characterization of solid forms to select the preferred form, as well as design processes to isolate the preferred form. The end results provide confidence in the stability of the solid form and its ultimate manufacturability into drug product, anticipating and avoiding problems later in the drug development process.

This work must be phase-appropriate and product-specific. Drug developers advancing complex molecules will benefit from starting with an in-depth understanding of the active pharmaceutical ingredient (API) and formulation parameters impacting the target product profile, and then using that knowledge to make decisions that lead to optimized solutions for the drug product in development.

Each drug and indication may require a different approach. The earlier an experienced formulation team is involved in the decision-making process, the better the overall results will be from early pharmacokinetic testing to commercialization.

A HOLISTIC METHODOLOGY

Lonza's solid-form methodology begins with developing a thorough understanding of the drug molecule and the target product profile. It's important to develop a clear problem statement from the outset, identifying the key technical challenges to be addressed. These can include low aqueous solubility (an issue with more than 70% of compounds in drug pipelines today), low permeability, slow dissolution rate, metabolism issues, efflux, and/or site-specific release requirements in the GI tract.

This characterization work is important because (1) critical drug properties may be affected by the chemical and polymorphic form; (2) the information will be required later to satisfy regulatory requirements, and (3) choices have big ramifications on downstream processing (e.g., will there be an issue at plant scale and, if so, how and when will it be solved?).

Typically, the characterization process begins in early development with a thorough characterization of the available drug form, followed by screening processes for polymorphs, salts, and/or cocrystals, if applicable. Then other screening tests can be performed to evaluate additional technologies (e.g., for bioavailability enhancement), as needed.

The target product profile can provide more constraints and it is important to estimate dose requirements for preclinical and clinical dosing early in the process (even if that information is not fully available yet).

Lonza uses state-of-the-art analytical tools and equipment to determine solid-state properties, chemical composition, and solubility and dissolution properties. Crystallization design and scale-up may also be considered using simulation tools and automated reactors. All the data generated, along with literature and/or institutional knowledge of molecules with similar properties, are used to define the advantages and risks of different types of formulations, as well as to understand when a new formulation and/or drug substance will be required. In other words, instead of using a technology that happens to be at hand, a rational process is used to evaluate choices and choose the best solid-form approach from the onset of the development process. Lead solid forms and delivery technologies are identified, as are process parameters, scalability concerns, and testing protocols. Iterations and investigation of additional formulation or delivery approaches may be required, grounded in the knowledge gained during characterization work. In some cases, this will involve a change in the solid form, but in others, it may require only a change in drug-delivery approach.

CASE STUDY

In this case study, the methodology was used to study potential polymorph changes after spray-drying drug product using a "hot process." The problem statement for this project was focused on determining the risk and developing a control strategy for polymorph form changes during processing.

This project was undertaken during Phase 3 clinical studies, preparing for process qualification of drug product that was prepared using a "hot process."

Hot-process spray drying is used to increase the bioavailability of drug compounds that have low solubility in both water and the organic solvents that are typically used for spray-drying. In this process, a suspension of API in spray solvent is prepared and then pumped through an in-line heat exchanger immediately before the spray nozzle. By elevating the temperature of the spray solvent (sometimes to more than 100°C), API concentrations can be attained that are often more than 10 times those using conventional processes operating at room temperature. This approach improves efficiency, reduces processing time, and reduces the size of equipment needed.

In this case study, we had 8 to 12 weeks available to determine the effect of conversion of the Form A polymorph of an API to the Form B polymorph when the suspension was held for several days. The effect of the form change on dissolution of the suspension downstream in the heat exchanger was unknown. Specifically, we sought to (1) define the thermodynamic relationships between the forms, (2) determine the impact of particle-size distribution on dissolution, and (3)evaluate potential control strategies.

Figure 3 summarizes the spray-drying process and the areas of investigation. In this case, we used a simple solubility model, based on the heat of solution ($\Delta Heat_{sol}$) , and assessed relative energy and solubility as functions of temperature using solution calorimetry (see Figure 4). Knowing $\Delta Heat_{sol}$ enabled development of a solubility-versus-temperature model for both polymorphs. Thermodynamic data, particle size distribution, and dissolution data were used to develop an appropriate control strategy and minimize risk (Figure 5). Results were entered into a heat-exchanger model to do a quick verification. The case study illustrates how risk can be reduced early in development through successful use of in-depth characterization, modelling, and solid-form experience and expertise, avoiding delays and problems as formulation and process development proceeds.

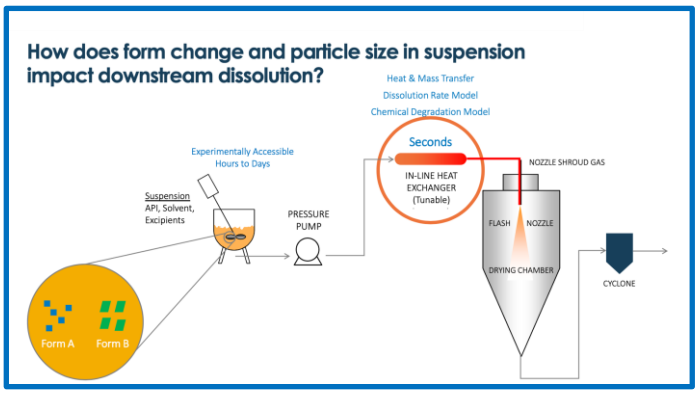

Figure 3
Spray-drying process and areas of investigation

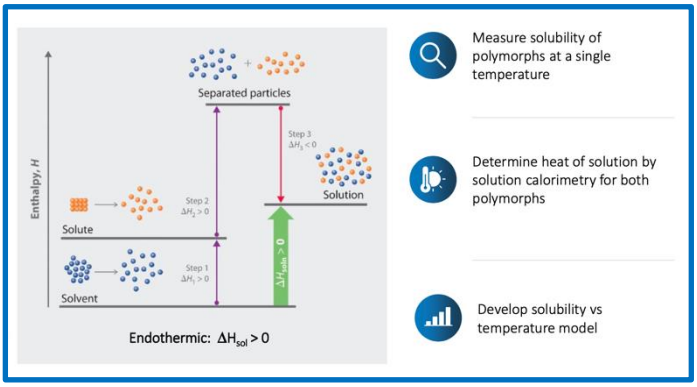

Figure 4
Illustration of analyzing relative energy and solubility as a function of temperature (T)

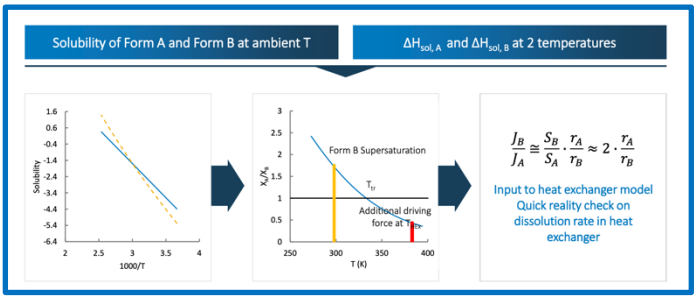

Figure 5
Basis for control strategy and risk mitigation

SUMMARY

The challenges of drug development are exacerbated by the complexity of molecules in drug development pipelines and target product profiles, as well as by accelerated timelines, which are becoming the norm. Innovative and proactive methodologies, such as the methodology described here, can help overcome these challenges. Careful solid form selection can help ensure that all options for drug product and drug substances are considered early in the development process, leading to optimized solutions, rather than defaulting to technology sources that happen to be available. Collaboration between process chemists, solid form experts, and the drug product team improves the product and mitigates risk.

Lonza has decades of experience in formulation, drug development, and engineering, including customized API development services and addressing an array of drug substance and particle engineering challenges. We also provide integrated product development, analytical method development, and manufacturing services inclusive of phase-appropriate encapsulation. To learn more, please visit our website.