

The Importance of Defining and Characterizing Solid State Forms



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The process of discovering and characterizing an API's various salt forms and polymorphs is a critical drug development activity. Indeed, these forms can play a major role in successful preclinical evaluation and product development. In this interview, *Pharmaceutical Technology* spoke with Pingyun (P.Y.) Chen, Ph.D., Director of Early Development at Catalent Pharma Solutions, about the importance of salt form selection and polymorphic screening as well as their potential effects on formulation development.

Pharmaceutical Technology: What is salt form selection and why is it important?

Chen: Salt screening and selection are some of the most critical activities for the successful development of small-molecule drug candidates. Salt provides the opportunity for chemists and formulators to modify the physical and chemical properties of a drug molecule, such as solubility, stability, hygroscopicity, and flow properties, to name a few. Modifying these properties can improve the API and drug product manufacturing processes, the drug's shelf life, or even the efficacy and safety of the end-product.

Approximately 50% of all small-molecule drugs on the market are developed as salt forms. For example, both Zantac® (for heartburn relief) and Zyrtec® (for allergy relief) are hydrochloric salts.

Pharmaceutical Technology: If you get a salt form, does it mean you won't need formulation development to enhance bioavailability?

Chen: Not really. As discussed, salt forms are selected to overcome various development challenges. Some of them are selected to enable the API's purification or isolation.

Salt form is a good option for formulators and can be a very effective way to improve the solubility and bioavailability of poorly soluble molecules. A salt form with good solubility and dissolution behavior can greatly simplify and accelerate formulation development. For example, you can use API powder or simple blend in capsules for clinical trials. It also allows you to use a conventional tablet or capsule formulation for the commercial product.

Salt forms make the formulator's job easier, but they do not eliminate the need for formulation development.

Pharmaceutical Technology: What unique advantages does Catalent have in terms of salt selection, polymorph screening, and automation approaches?

Chen: Catalent's technology, experienced scientists, and know-how truly differentiate us from others.

The high-throughput screening platform and associated workflows were developed and optimized by GSK. This capability was acquired by Catalent in 2010. It is a highly automated system with state-of-the-art automation, analytical capabilities, and data analysis software.

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The platform has been successfully applied to support nearly 100 compounds each year across all development phases—from drug discovery to commercialization—in all major therapeutic areas. That's more than 1,000 compounds over 15 years.

We have worked with compounds that have various solubility and chemical stability challenges or compounds that are difficult to crystallize and isolate.

The platform and workflow are also very flexible. It can be used to conduct customized screening based on material availability, budget, and the specific requirements of the program. Most of our screens are also completed within four to six weeks, which is significantly faster than typical timelines in our industry.

Most importantly, we have a team of highly educated and experienced scientists. Many of us have advanced degrees and over 15 years of industry experience.

Pharmaceutical Technology: What are polymorphs? What instruments are used for polymorph screening, and why is it important to screen for them?

Chen: Different polymorphs have different arrangements and/or confirmations of the molecules in the crystal lattice. As such, they have different physicochemical properties such as solubility and chemical stability.

So, it's important to conduct polymorph screening to identify different polymorphs, hydrates, and solvates, and to determine their thermodynamic relationship. And most importantly, one must determine the most suitable polymorph for development.

Many techniques can be used to identify and assess different polymorphs. Commonly used techniques include optical microscopy, powder x-ray diffraction (PXRD), thermal analysis, vibrational spectroscopy, and dynamic vapor sorption (DVS) to assess the moisture absorption profile.

Pharmaceutical Technology: How can polymorph screening and selection accelerate drug development? In other words, what decisions are made based on results from polymorph screening?

Chen: As discussed previously, it is critical to identify the various polymorphs that you may encounter during API

isolation and formulation, and to determine the most stable polymorph for development early in the process so the correct polymorphic form is made and formulated to support pre-clinical and clinical studies.

Otherwise, switching to a different polymorphic form at a later stage will likely require additional process development, reformulation, and possibly bridging tox and pharmacokinetic (PK) studies, which can result in significant delays and increased cost. There are a number of well-documented cases of commercial product failures caused by the late discovery of different or more stable polymorphs (e.g., Ritonavir). There are even more of such cases during drug development.

Pharmaceutical Technology: When is the best time to perform these tests?

Chen: These activities should be done early during pre-clinical phases. The timing can vary depending on the technical requirements, challenges, and development strategy of the specific programs.

For most programs, the screening and selection should be completed in time so the right salt form is used to support preclinical PK and tox studies, and the right polymorph of the selected salt is used to support first-time in-human study and onward.

This strategy will avoid a switch of salt and polymorphic forms at later stages, and also avoid any delays and cost associated with such a switch discussed previously.

Pharmaceutical Technology: Are there cost and time savings to perform these tests? Are these results required or helpful for regulatory filings?

Chen: Salt screening and selection are pursued to overcome various development challenges. They are not required for regulatory filings per se because you cannot accidentally make a different salt.

However, polymorph screening is generally required based on the ICH guidelines and for the chemistry, manufacturing, and controls section of a regulatory filing. Polymorph screening ensures that your API and drug product manufacturing processes are robust and that the drug product is stable, efficacious and safe for patients.

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