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THE RELEVANCE OF POLYMORPH SCREENING IN THE PHARMACEUTICAL INDUSTRY

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ABSTRACT

Solid form screening, the activity of discovering and characterizing different solid forms of an active pharmaceutical ingredient (API), is an essential part of drug development. This screening process needs to be designed, performed and evaluated carefully, since the decisions made based on the screening may have consequences on the whole lifecycle of a pharmaceutical product. The target solid form is chosen after screening based on different criteria such as solubility, stability, therapeutic efficacy, processing characteristics and even intellectual property (IP) considerations. This paper will discuss some basic principles about solid form screening and how we implement them at Eurofins CDMO Alphora to help our clients with this important task.

INTRODUCTION

In general, solid APIs may be in amorphous or crystalline form. A crystalline solid consists of an array of components (atoms, molecules, ions) that are repeating in all 3 dimensions (crystal lattice) while an amorphous solid has a disordered and random arrangement of these components.

Polymorphism is the ability of one substance to crystallize in more than one crystal structure. These different crystalline forms of the same API are called different polymorphs. In addition to polymorphs, one API may exhibit different solid forms that include crystallization of the API molecule with other components. Solvate/hydrate forms are obtained when solvent/water molecules are included in the crystal lattice. Co-crystals are crystalline materials composed of two or more different molecules, typically active pharmaceutical ingredient (API) and co-crystal formers ("coformers") that are not solvents, in the same crystal lattice. Lastly, salts consist of ionisable API that has been combined with a counter-ion to form a neutral complex.

For the purpose of this article, we refer to polymorphs as:

- single-component crystalline forms that have different arrangements or conformations of the molecules in the crystal lattice
- amorphous forms, and
- solvate and hydrate forms.

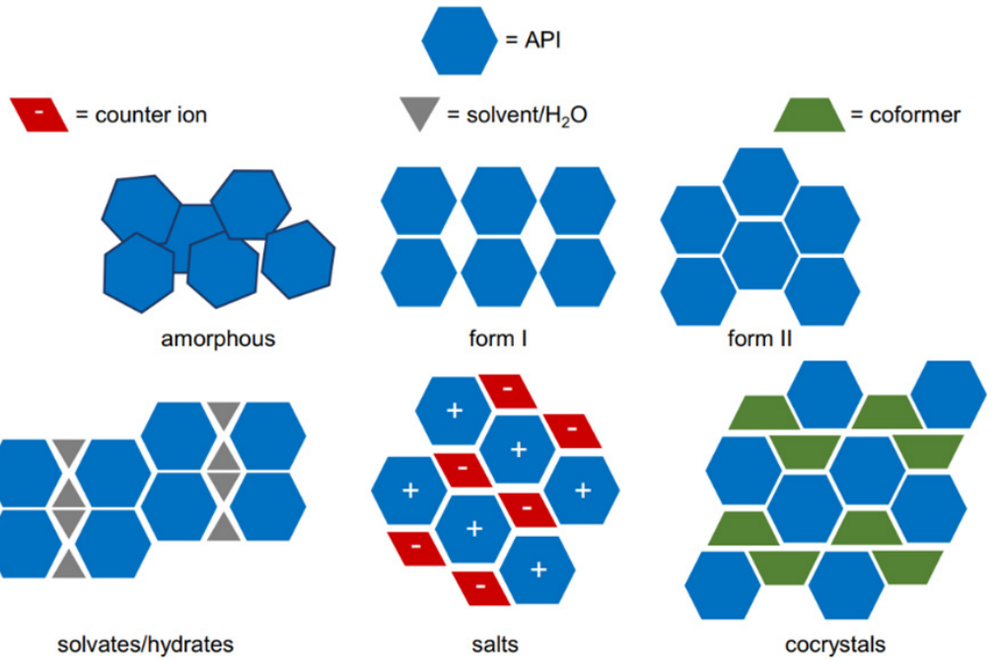

Figure 1: Different solid multicomponent pharmaceutical forms for API. From reference 1.

Polymorphism can be a major challenge in drug development. Ritonavir, the anti-HIV medication, is a famous story dealing with this challenge. Late discovery of a more stable and less soluble polymorph while the drug was released to the market, severely impacted patients, and manufacturing, costing hundreds of millions of dollars.

About 90% of APIs show polymorphism and some famous examples include Acetaminophen with 3 polymorphic forms, Atorvastatin with 60 solid forms, Ritonavir with 5 polymorphic forms and Axitinib with 60 solid forms. Polymorphism directly affects the manufacturing process and final product through differences in solubility, morphology, particle size, occlusion and inclusion of solvent and impurities, as well as hygroscopicity that has impact on stability and storage.

The aim of solid form screening is discovering possible polymorphs of the API and to select the optimal form with best characteristics for process development. Solid form screenings may be executed at different stages of drug development process and each will serve a specific purpose.

Several factors may be considered to maximize the chance of discovering different polymorphs through screening. Some of these factors include number of experiments (high-throughput experimental methods), scientist's insights and skills as well as solid form informatics and computational predictions.

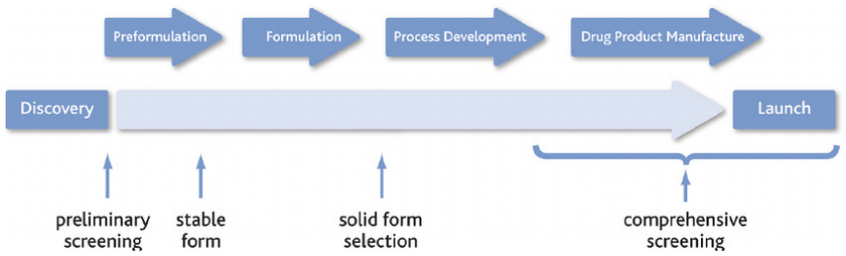

Figure 2: Form screening at various stages of development. From Reference 2

Polymorph screening can be approached experimentally and computationally. Although polymorph predictions have evolved over the last decade, we still cannot fully rely on them, and empirical experimentation is still the best tool for discovery and understanding API polymorphism.

Computational methods can be helpful in designing the experiments and to confirm whether the stable form has been found or not. Performing a comprehensive screening and discovering most of the relevant polymorphs is essential for the success of drug development and can also achieve a valuable intellectual property (IP) situation for the innovator company.

EXPERIMENTAL POLYMORPH SCREENING

Crystallization is the main tool utilized in polymorph screening and consists of two steps: nucleation and crystal growth. In order to maximize the probability of discovering all relevant polymorphs, it is important to explore different crystallization techniques and look for both kinetically and thermodynamically stable forms.

Different crystallization techniques include crystallization from solution such as cooling, evaporation, anti-solvent addition and slurry conversion as well as recrystallization from neat compound such as sublimation, thermal treatment and grinding.

Crystallization from solution is typically explored in API polymorph screening for several reasons:

- APIs are usually in contact with different solvents during production that may cause formation of solvates or a specific polymorph;
- Utilizing a variety of solvents in the screening increases the chance of discovering new solvates or polymorphs;
- Solvates & hydrates may dry to novel solid forms;
- Solvates or hydrates may provide desired characteristics and hence be selected as the target solid form for the API.

High-throughput screening (HTS) of polymorphs has been heavily utilized in the pharmaceutical industry recently since it increases the probability of discovering novel solid forms while using minimum amount of API. HTS of polymorphs is usually performed with the aid of automated instrumentation in multi-well plates and provides the possibility of performing hundreds of experiments in parallel at a short period of time. Obtained solids are usually characterized by high-throughput characterization techniques such as PXRD or Raman to identify new solid forms.

At Eurofins CDMO Alphora these experiments are usually performed in 96-well plates handled by a Junior robot and in each routine screening several solvent systems are explored using slurry, cooling, anti-solvent addition, evaporation and grinding crystallization techniques. Obtained solids are then characterized by HTS-PXRD and novel solid forms are identified by advanced data mining tools. This screening can be modified to fit different programs at different stages of development either to look for the best solid form for process development or to check the stability of the selected form at the later stages to avoid challenges related to solid form of the API.

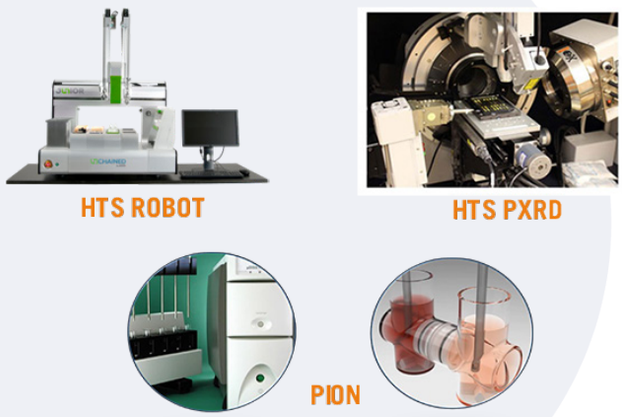

Figure 3: Instruments used at Eurofins CDMO Alphora for polymorph screening and characterization.

New discovered polymorphs need to be fully characterized. Several characterization techniques are usually used for physicochemical characterization of discovered solid forms. These characterizations may include:

- X-ray diffraction (single crystal and PXRD)
- Raman spectroscopy
- Infrared (IR) spectroscopy
- Liquid and solid-state NMR
- Differential scanning calorimetry (DSC)
- Thermogravimetric analysis (TGA)
- Microscopy (PLM, SEM)
- Dynamic vapor sorption (DVS)
- Solubility/dissolution
- Microcalorimetry
- Solution calorimetry

Based on these characterizations different solid forms may be ranked based on their crystallinity, hygroscopicity, stability and solubility. Considering all these characteristics the best solid form is selected for process development. After this selection, crystallization development of the API will be focused to control polymorphism using crystal engineering techniques. Crystal engineering aims to provide control over product purity, yield, particle size as well as polymorph.

At Eurofins CDMO Alphora, solid-state scientists work alongside process development team as well as drug product development team to ensure best solid form for the API is selected on time based on extensive screenings and characterizations. In collaboration with drug development scientists, solubility, stability, dissolution and permeability assessments are done at early stage on the selected polymorph with the aim of accelerated stability studies and PION Micro Flux instrument. With a knowledge-based crystallization development, our processes ensure high yield and purity of the API with control over polymorph and other solid-state characteristics such as particle size and morphology.

CONCLUSION

Since solid-state is the most stable form of matter, APIs are mostly prepared and stored as solid and solid dosage formulations are also very common for drug products. As a result, development of any new pharmaceutical requires extensive screenings and characterizations to provide a deep understanding of API polymorphic landscape and its solid-state characteristics. Final polymorph of the API needs to be selected carefully based on performance and characteristics of discovered solid forms and IP strategies also need to be considered.

Polymorph screening has evolved tremendously over the last decades in pharmaceutical industry. The combination of high-throughput experimentation with fast and efficient characterizations as well as computational predictions is offering screenings that were not possible before. All these new tools provide an opportunity to investigate and understand solid-state phenomena of APIs at early stages of drug development and develop a robust process based on this knowledge that will avoid unexpected challenges related to API polymorphism at later stages.

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