ARDENA

Application Note

De-risking Drug Development: Informatics-Supported Solid Form Selection

INTRODUCTION

Solid form selection is a critical step in the development of solid pharmaceutical products (like tablets or capsules). It involves choosing the most suitable crystalline or amorphous form of an active pharmaceutical ingredient (API). The chosen solid form can profoundly affect the API performance, manufacturability, stability, and bioavailability.

Solid form selection is furthermore required for regulatory compliance and for securing intellectual property. A well-chosen solid form balances solubility, stability, and processability, supporting both patient efficacy and commercial viability. Selection of the best candidate requires experimental solid form screening. In addition, an informatics-based approach can be applied to further support the selection of the desired form, as outlined in this case study.

POLYMORPHIC LANDSCAPE

Experimental polymorph screening is crucial for mapping the solid-state landscape of a compound. By exposing different experimental parameters such as solvents, temperatures, and crystallization methods to a compound, researchers can increase the likelihood of discovering unique crystalline forms. Discovery and understanding novel crystalline forms, including solvates and hydrates, provide valuable insights into the stability hierarchy across polymorphs.

A diverse polymorph screening strategy not only reveals kinetically favored, metastable forms but, more importantly, facilitates the detection of the true thermodynamic minimum, corresponding to the polymorph with the greatest long-term physical and chemical stability. Although metastable forms may exhibit enhanced solubility or bioavailability, the thermodynamically stable polymorph is generally preferred from a regulatory perspective and for further drug product development due to its stability across manufacturing and storage. By adopting a comprehensive and diverse experimental polymorph screening approach, a stable solid form can be identified for further development, which derisks the development pathway of the compound.

STABLE FORM SELECTION

Once the solid-form landscape of a compound has been established, the identification of the most thermodynamically stable polymorph requires thorough characterization and stability assessment of the polymorphic forms.

Competitive slurry experiments are used to determine the most stable form in selected process conditions, while complementary thermal analyses (DSC), variable-temperature X-ray powder diffraction (VT-XRPD), and solubility measurements provide insights into phase relationships and relative thermodynamic stability.

STRUCTURAL INFORMATICS ASSESSMENT

To confirm whether the solid form selected from the experimental screen is the most stable, the solid forms can be subjected to a structural informatics assessment.

The basis of a structural informatics assessment is to analyze the structural features of a specific crystal form in comparison to features observed for similar structures in the Cambridge Structural Database (CSD), and to relate this commonality to thermodynamic stability.

The structural features that are studied typically focus on:

- the propensity and geometry of the observed intermolecular interactions,

- solid-state 3D conformation of the molecule, and properties of the overall observed crystal packing.

Case Study: Solid Form Selection through Experimental Screening and Crystal Structure Database Assessment

INTRODUCTION

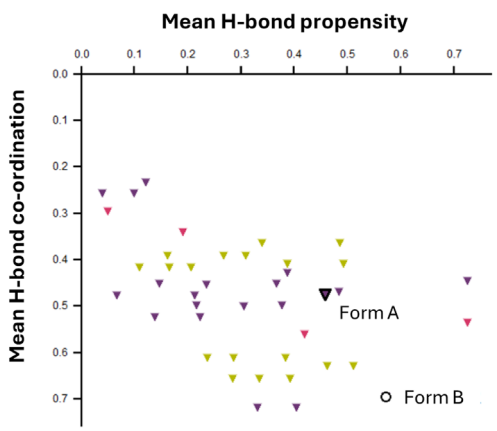
Ardena is a global CDMO with an extensive track record in solid form screening. The solid form screening capabilities at Ardena enable a fast and comprehensive understanding of the solid form landscape of a compound. Through partnership with the Cambridge Crystallographic Data Centre (CCDC), a "Solid Form Health Check" can be applied which uses structural information from the Cambridge Structural Database (CSD), the largest crystal structure database in the world. The benefit of structural informatics to experimental polymorph screening is outlined in the current case study.

POLYMORPH SCREEN SETUP

The polymorph screen on Compound X was initiated at Ardena by converting the crystalline API into an amorphous material. Based on a solubility study involving 20 solvents, a polymorph screen was designed which consisted of 6 crystallization methods. 100 experiments were performed, and the solids were measured by XRPD. After that, all solids were exposed to 40°C/75% RH (relative humidity) and were remeasured by XRPD to determine their physical stability. All new solid forms were analyzed by XRPD, DSC, TGA-MS, LCMS and NMR.

POLYMORPH SCREENING OUTCOME

Compound X was slightly polymorphic as 3 unique forms were identified. Two forms were obtained most frequently and were physically stable: Forms A and B. The single-crystal structures of both Forms A and B were determined at Ardena by single-crystal X-ray diffraction analysis. The crystal density of Form B was higher than that of Form A. Form B had a higher melting point than Form A. Both findings suggested that Form B is more thermodynamically stable than Form A.



STRUCTURAL INFORMATICS

To further assess the relative stability of Forms A and B, and to confirm that Form B is the most stable form, a Structural Informatics assessment was performed by the CCDC. Structural features including intramolecular geometry and intermolecular interactions were compared against database distributions. The hydrogen bond network was assessed against potential alternatives, and aromatic interactions were evaluated. These features from the crystal structures were compared to structures with similar functional groups in the CSD, and the observed commonalities were related to potential thermodynamic stability.

Part of the Structural Informatics assessment (bottom left figure) indicated several alternative hydrogen bond networks, most of which were likely too unstable to isolate experimentally. Crystal structures of Forms A and B were analyzed, showing that Form B had a superior hydrogen-bond network, ranking higher than Form A in mean propensity and mean coordination. No other improved networks are predicted for this molecule (points in the bottom right would indicate an improved hydrogen-bond network).

Form A ($P2_1/n$ monoclinic space group) exhibited adequate conformations and interactions, but its $Z' = 2$ structure, molecular flexibility, and hydrogen-bonding suggested the possible existence of more stable polymorphs ($Z' = 2$, meaning there are two molecules in the asymmetric unit, which is significantly less common in the CSD than $Z' = 1$ structures). Form B (P-1 triclinic space group, $Z' = 1$) displayed a distinct conformation and optimized hydrogen-bonding and aromatic interactions, indicating a more efficient packing arrangement. These results point to Form B being the energetically favored polymorph.

CONCLUSIONS

Ardena's solid form screening on Compound X yielded 340 XRPD patterns from which 3 unique solid forms were classified. From those forms, 2 anhydrous (stable) and 1 solvated (unstable) forms were isolated.

Structural Informatics further established that Form B possessed the most favorable crystal structure conformation, including an optimized hydrogen-bond network and complementary aromatic interactions. Experimental screening, supported with informatics-based structure assessment, is a powerful combination to confirm the most stable form for development.