ARDENA

Application Note

Precision Polymorph Screening with Electron Diffraction

POLYMORPH SCREENING

Polymorph screening plays a critical role in pharmaceutical drug development as it identifies different crystalline forms (polymorphs) that a drug substance can adopt. Polymorphism can significantly affect the physicochemical properties of a drug, including solubility, dissolution rate, stability, and bioavailability, all of which are key factors in the drug's effectiveness, safety, and manufacturability. Identifying and selecting the most suitable polymorph early in the development process ensures optimal therapeutic performance and compliance with regulatory standards.

SUCCESS THROUGH DIVERSITY

Diversity in polymorph screening is essential because it increases the likelihood of discovering and understanding the various crystalline forms of a drug compound, ensuring that the optimal polymorph is identified for development. The greater the diversity in the screening process—by varying conditions like solvents, temperatures, and crystallization methods—the more polymorphs are likely to be discovered. For instance, testing a wide range of solvents during polymorph screening increases chances of identifying different solvates and hydrates.

In addition, diverse screening conditions allow for the identification of both thermodynamically stable polymorphs and kinetically favored, metastable ones. While stable forms may be preferable for long-term stability, metastable forms might have superior solubility and bioavailability, offering a potential advantage in early-stage drug performance.

By embracing diversity in the polymorph screening process, pharmaceutical companies can ensure that no potentially beneficial polymorph is overlooked, optimizing the drug's performance and reliability throughout its lifecycle.

SUCCESS THROUGH DIVERSITY

Once the solid form landscape of a compound has been identified through polymorph screening, solid form identification and quantification of manufactured batches becomes possible. Solid form quantification is critical in pharmaceutical development and manufacturing as the solid form composition directly influences the drug's efficacy, stability, and manufacturability. Different solid forms can exhibit varying solubility, bioavailability, and stability profiles. Accurate quantification ensures that the desired solid form is present in the required proportions, preventing unintended effects on drug performance. Key benefits of solid form quantification include quality control, stability assessment, optimized bioavailability and regulatory compliance.

Techniques such as XRPD and thermal analysis are often employed to achieve accurate solid phase quantification, provided that all solid forms present in the material are known. Electron diffraction has the unique property of identifying even minute amounts of solid phases, which allows for a more thorough characterization of minor forms, impurities, or decomposition products.

SUCCESS THROUGH DIVERSITY

Electron diffraction has the potential to identify novel forms in a mixture of a powder using the crystal mapping method. The ELDICO ED-1 from ELDICO Scientific is optimized for this purpose due to its unique design:

- Low distortions, yielding accurate unit cell parameters.
- Dedicated goniometer, enabling to analyze every particle on the sample holder.
- STEM mode to locate particles on the grid
- Automation of the software

Case Study: Polymorphism of Aripiprazole

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 ELDICO, Ardena has effortless access to a cutting-edge electron diffractometer, the ED-1. In the current case study, the benefit of electron diffraction is described in the polymorph screening and solid phase quantification of Aripiprazole. Aripiprazole is an atypical antipsychotic medication primarily used to treat schizophrenia, bipolar disorder, and as an adjunct for major depressive disorder.

POLYMORPH SCREEN SETUP

The polymorph screen at Ardena was initiated by converting the crystalline Aripiprazole into an amorphous material. Based on a solubility study involving 30 solvents, a polymorph screen was designed which consisted of 9 crystallization methods. >200 experiments were performed, and the solids were measured by XRPD. After that, the 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, DVS, LCMS and NMR.

POLYMORPH SCREEN OUTCOME

Aripiprazole was highly polymorphic as 15 unique forms were identified. Seven anhydrous forms were identified which were physically stable. Five solvated forms were identified in combination with several solvents. Three unstable forms were identified that converted to anhydrous forms upon thorough drying. Overall, the polymorphism of Aripiprazole poses a challenge for production as multiple forms may be obtained as the final solid product. Salt formation may be used to overcome the polymorphic behavior.

FORM IDENTIFICATION BY ELECTRON DIFFRACTION

An Aripiprazole sample from production was analyzed and found to consist of ~93% of Form III using Rietveld analysis. The ~7% of unknown crystalline phases could not be identified by XRPD alone, yet it was required to fully quantify the solid phases to mitigate risks. For that reason, electron diffraction at ELDICO was used to elucidate the unknown phases. Crystal mapping was performed to find single-crystalline particles and short continuous rotation series were recorded to determine unit cells. Based on this, most particles were identified as triclinic Form III, while some particles showed a monoclinic lattice. The refined unit cell parameters of those particles matched Form IV. By taking Form IV into account, an improved fit could be achieved which enabled association of the remaining diffraction peaks to Form II. The identification of all forms then allowed full quantification of the Aripiprazole sample: 93% Form III, 5% of Form IV and 2% of Form II.

CONCLUSIONS

Ardena's extensive solid form screening on Aripiprazole yielded >400 XRPD patterns from which 15 unique solid forms were classified. From those forms, 7 anhydrous, 5 solvated and 3 unstable forms were identified.

Solid form quantification by XRPD of an Aripiprazole batch initially led to an estimated content of 93% Form III, where the remaining 7% could not be resolved. Electron diffraction at ELDICO successfully led to identification of the missing forms, allowing full quantification including the minor polymorphs.