The power of synchrotron X-ray powder diffraction

A state-of-the-art technology opening doors to new horizons for the characterisation of pharmaceuticals and other complex materials…

X-Ray Powder Diffraction (XRPD) is a powerful technique that exploits the interaction between X-rays and matter to study the structural and microstructural properties of materials. Its power lies in the **direct** and **unique** relationship between the X-ray powder diffraction pattern of a given substance and its structural order and/or disorder. The position and intensity of the peaks in a diffraction pattern (so-called Bragg peaks) reflect in fact the solid state symmetry of the substance and, in powder mixtures, XRPD can determine the percentage in weight of the components. Furthermore, the diffraction peaks' width and shape unveils further precious information on the substance microstructure.

The high brightness of synchrotron radiation sources enables X-ray characterisation of pharmaceutical products and chemical compounds with a quality much superior to that achievable with lab-based X-ray sources. The Paul Scherrer Institute is home of the Swiss Light Source (www.psi.ch/sls), providing unique facilities and services for single-crystal, powder diffraction and chemical analysis to both academic and industrial users. We have a long tradition in providing services to industry and are proud supporters of our spin-off companies Dectris, Eulitha, Expose and Excelsus Structural Solutions (ESS). With the advent of ever more sophisticated X-ray detectors with fast readout, detailed in-situ kinetic of phase transformation studies of chemical processes have become possible. It is my prediction that the volume of industrial analytical services at synchrotron radiation sources will grow significantly during the coming years.

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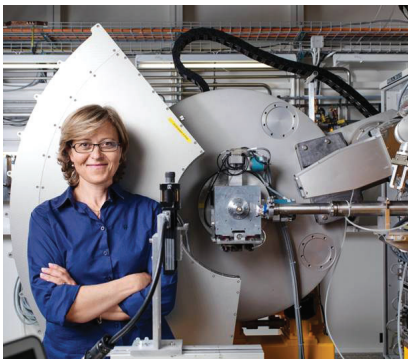

Swiss Light Source Powder Diffraction Station

In the field of pharmaceutical powders, XRPD is thus considered as the **gold standard method** for the identification and quantification of solid forms (i.e. polymorphs, solvates, hydrates, salts, co-crystals, amorphous).[1] However, it is the quality of an XRPD pattern that defines the accuracy and reliability of the technique, and therefore the wealth of information that can be extracted. When it comes to data quality, nothing competes with **Synchrotron X-Ray powder diffraction (SR-XRPD)**, which is widely superior to laboratory XRPD in terms of angular resolution, counting statistics, energy tunability and fast acquisition time.

In SR-XRPD, X-rays are generated by a synchrotron facility and are at least five orders of magnitude more intense than the best X-ray laboratory source. When combining SR-XRPD with the new generation of solid-state ultra-fast and efficient detectors,[2] level of detection (LoD) smaller than **0.05% wt** are obtainable even when only micrograms of powder are available. Such an efficient data collection with acquisition times ranging from milliseconds to few minutes allows one to control the inevitable radiation damage of organic compounds and perform kinetic studies of structural changes during chemical reactions or under temperature and pressure variations.

Synchrotron radiation facilities have traditionally been accessible only to expert scientists due to their intrinsic complexity, and are characterised by long waiting times not compatible with the speed requested by private companies. **Excelsus Structural Solutions SPRL (ESS)** is a spin-off company of the Paul Scherrer Institute founded in March 2012 with the mission of providing industry with fast and easy access to SR-XRPD, including data interpretation and design of non-standard experiments.

SR-XRPD is a key tool to support research, development, manufacturing and life cycle management activities for (bio)pharmaceuticals. Drug substances can exist in different crystalline forms (**polymorphs**), solvates/hydrated forms (**pseudo-polymorphs**) and **amorphous** forms, as a result of the manufacturing and storage conditions. These different forms can have a profound effect on the quality or performance (e.g. solubility, bioavailability, efficacy, safety) of the drug products.[3] For example, therapeutic failure has been attributed to uncontrolled hydrate formation in tablets during storage.[4] For this reason, it is now a **regulatory requirement** to conduct a detailed analysis of the polymorphism of the drug substance and drug product during technical development, including screening, characterisation, property determination and setting of acceptance criteria for the different forms. Typical

BASF has been working with Excelsus Structural Solutions (ESS) since its inception. Synchrotron X-Ray Powder Diffraction has always been an elemental part of our analytical toolbox, but in the past the effort of accessing beam time and collecting data was exorbitant. Since our collaboration with ESS, this has become as simple as a phone call. We do not have to concern ourselves with all the details of the experimental setup, which can be impressively, but also dauntingly, complex. It is a great pleasure for us to work with a company so dedicated and professional as ESS has proven to be. ESS is our first choice when it comes to accessing SR-XRPD Data.

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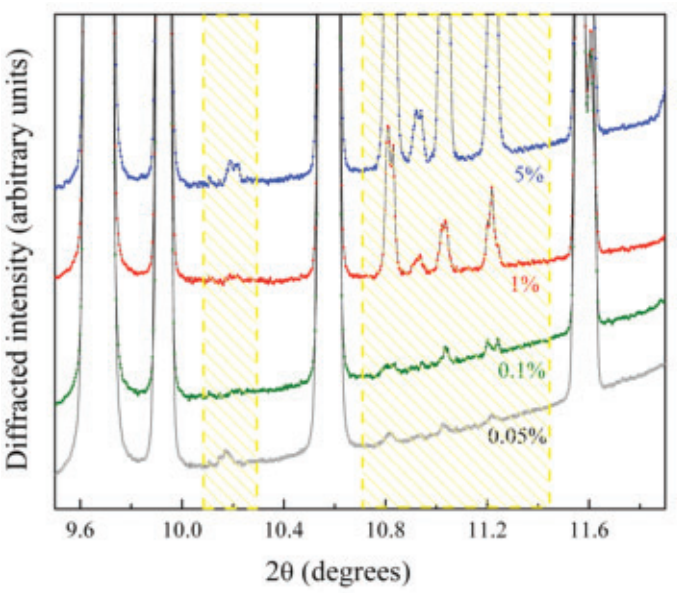

SR-XRPD patterns recorded on pharmaceutical binary mixtures of similar elemental composition ranging from 0.05% to 5% weight (wt) of the minority phase. The small XRPD signal is directly detectable down to 0.05% wt with a signal-to-noise better than 10, allowing the quantification of the minority phase

applications include:

- Structural solution of a new solid form;
- Development of formulation and screening of excipients, including co-crystals;
- Characterisation and quantification of all polymorphic forms in a drug substance and product, including in fully opaque blisters;
- Detection of impurities down to a trace level (<0.05% wt);
- Optimisation of manufacturing processes;
- In situ non-ambient kinetic studies at the millisecond scale;
- Stability studies of polymorphic forms;
- Troubleshooting activities and investigations during commercial manufacturing;
- Patent application for new materials and patent-life extension;
- Detection of counterfeits even with minute differences.

SR-XRPD data quality is appropriate for both **qualitative analyses** (e.g. structural identification, structural solution and refinement, detection of crystalline traces in amorphous, microstructural analyses) and **quantitative analyses** of complex mixtures of active pharmaceutical ingredients (APIs) and finished products.

SR-XRPD is a powerful technique in several other areas where the properties and performance of products are dependent on their crystalline structure and relative distribution of their polymorphic forms, such as: food and aroma compounds, cosmetics, pigments, catalysts, cement.

Novartis owns strong technical and scientific capabilities allowing us rapidly assess and resolve problems that might arise. Each material has the potential to present different challenges and technical features. Some may be straightforward and routine, others may be complex. We have further enhanced our analytical capability by forming a partnership with Excelsus Structural Solutions (ESS). For complex tasks requiring a creative, technical or logistical solution, a specialist service such as SR-XRPD was not available worldwide. Faced with exceptionally challenging deadlines our partnership with ESS has been very successful in improving our ability to deliver quick solutions. ESS brings energy, pride and passion on everything they do, they innovate and improve. This partnership has been found to ensure a smooth transition of products during drug product development, underpinning more conventional routes.

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