

## HIGH-THROUGHPUT SCREENING IN SOLID FORM SELECTION

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Active pharmaceutical ingredients (API) are often marketed in a formulated solid form, which has to meet stringent criteria on stability, aqueous solubility, toxicity, processability *etc.* It's a complex issue to select the most appropriate form to market since in most cases various polymorphs exist of the free species and its different salts. To select the most appropriate form the total solid-state behaviour (polymorphs and salts) has to be explored. However, crystallization of the various forms depends on many experimental parameters, such as solvent, supersaturation, impurities, stirring *etc.*, demanding a huge amount of experiments.

Using high-throughput (HT) screening techniques numerous experiments are performed in parallel, accelerating the form-selection process significantly. In a standard polymorph screen at Crystallics more than one thousand crystallization experiments are performed varying solvents, concentrations and temperature profiles, using minute amounts of product. Besides these crystallization experiments in multi-well plates, automated analyses and data interpretation are key to secure a high throughput. Since for characterization of solid-state behaviour X-ray powder diffraction (XRPD) is the most appropriate technique, an in-house HT XRPD station is used to generate thousands of XRPD patterns. The measured XRPD patterns are automatically classified using various multivariate analyses techniques resulting in distinct clusters of XRPD patterns. These diverse clusters are related to different solid forms, which are further characterized using thermal analysis, spectroscopic and other analytical techniques. Finally, the classified forms are mapped to their crystallization conditions.

However, solvates often have similar conformation and packing of the molecules. Are HT-XRPD and automated classification capable to correctly classify these or are additional techniques necessary? These and other issues in automation of polymorph and salt form screening will be addressed, based on experiments and theoretical considerations.