

SEARCHING FOR NEW POLYMORPHS BY PARALLEL CRYSTALLIZATION AND HIGH-THROUGHPUT X-RAY DIFFRACTION SCREENING

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The importance for polymorph screens has been recognized by the pharmaceutical industry and regulatory bodies world wide. The multivariate nature of crystallization screens requires a corresponding number of tries. Parameters like solvent (pure or as binary or possibly ternary mixtures) or temperature have to be varied over a wide range. Hence polymorph screens offer themselves particularly well for parallelization.

An integrated high throughput approach must however include analytical methods for detecting different polymorphs in a time efficient manner. Among the different analytical tools for detecting polymorphs, like i.r.- and Raman-spectroscopy or a variety of thermal methods X-ray diffraction offers potentially the most unambiguous way for the identification of polymorphs. Unfortunately X-ray powder diffraction analysis of large numbers of samples is very time consuming and labor intensive.

This paper describes the development and implementation of a combined high-throughput crystallization and X-ray diffraction method. The new method comprises i) a multi-well plate for setting up crystallization tests, the plate featuring simultaneously as sample holder for subsequent X-ray diffraction analysis, ii) a modified, commercially available micro-diffractometer equipped with a sample translation stage and iii) software for interpreting and managing the polymorph screens.

The multi-well plate is a sandwich construction, whereby an X-ray transparent polymer film is attached to a 96-hole mask. The resulting plate is used to carry out a polymorph screen with different crystallization techniques (evaporation, cooling, vapor diffusion). The precipitated crystalline product forms a deposit on the polymer film, which is detached from the 96-hole plate and transferred to the micro-diffractometer. The diffractometer then operates a fully automated procedure for measuring X-ray powder diffractograms for each of the 96 array points.

The method has been applied successfully to reconstitute a number of polymorphs for test compounds.