Polymorphism Investigations and Structure Elucidation of Pharmaceuticals in Development

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Characterization and monitoring of solid state properties of the active ingredients and excipients are fundamental elements of the pharmaceutical development since batch to batch inconsistency can cause crucial problems in the manufacturing of the pharmaceutical dosage form, the quality of the formulation, the bioavailability and drug stability.

Extensive research is required to characterize a new chemical entity. An example from pharmaceutical industry with difficult polymorphic behaviour will be presented. Typical methods for the solid state characterization are X-ray powder diffraction, thermal analysis, solubility and dissolution measurements, water sorption and desorption behaviour and IR or Raman spectroscopy.
Three crystalline forms were detected whereas one turned out to be chemically modified compound. The process of characterization and identification of the different crystalline forms and their thermodynamical relationship has been supported by a combination of experimental and computational work. All solid state properties of a substance are based on their molecular packing and molecular interactions in their single crystal structure. The determination of single crystal X-ray structures and their computational analysis is therefore of great value for the identification of the new crystalline forms and for the analysis of crucial causes and reasons for certain properties.
Since only for one polymorphic form, single crystals suitable for a structure analysis were obtained, new methods were applied. The structure of the second polymorph has been solved from high resolution powder diffraction data measured at the synchrotron source. Based on the obtained results the mechanism of the solid-solid transition could be explained and a controlled chemical and pharmaceutical manufacturing process finally achieved.

Reference
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