

***In Situ* XRPD of Compacts as a Potential Non-Destructive Analytical Technique for Detecting Process Induced Phase Changes**

Peter L.D. Wildfong, Nicole A. Morley and Kenneth R. Morris
Purdue University, Department of Industrial and Physical Pharmacy, West Lafayette, IN,
U.S.A.

The GMPs for the 21st century FDA initiative has provided the opportunity to establish a more rigorous scientific understanding of pharmaceutical manufacturing processes. The potential applications for numerous process analytical technologies involves methods that draw upon traditional analytical techniques to help identify and monitor process critical control points and provide controls that will ultimately expedite the manufacturing process. Implementation of these technologies particularly during the drug development phase, adds robustness to a product/process by “feeding forward” information and understanding to the eventual production campaign.

XRPD is a standard method by which crystalline phases of materials can be detected and differentiated. Its traditional use as a tool in the pharmaceutical industry has been to study different solid phases of active pharmaceutical ingredients. Our research uses a non-destructive method for *in situ* whole compact quantification of phase transformations induced during the compression process. Our investigations have fostered a better understanding of the mechanism for one type of these transformations, from which we hypothesize that the extent to which an API may undergo a mechanically activated phase transformations is limited by the extent to which that material can be deformed.

The anti-diabetic compound chlorpropamide was selected as a model compound for these experiments, in particular two enantiotropic polymorphs that are easily interconverted by the application of pressure. A non-destructive *in situ* technique for whole compact analysis using transmission-XRPD with a polycapillary optic was performed to quantify the extent of conversion induced by the applied stress state.

Our results showed that during compaction at room temperature, the low temperature phase (CPA-A) always converts to its metastable polymorph (CPA-C) even at relatively low pressures. Likewise, metastable CPA-C converts under pressure to CPA-A. The extent of both of these transformations increases with an increase in either applied pressure or dwell time, eventually reaching a plateau. Analysis of the compacts indicates that this plateau corresponds with the densification limit for each respective powder. We believe that as material deformation reaches a maximum, the shear component of the applied stress tensor is minimized, reducing the key driving force for mechanically activated conversion of either form.