

USE OF X-RAY POWDER DIFFRACTOMETRY TO MONITOR PHASE TRANSITIONS DURING PHARMACEUTICAL PROCESSING

Raj Suryanarayanan, College of Pharmacy, University of Minnesota, Minneapolis, MN 55455, USA

Conventionally, X-ray powder diffractometry (XRD) has found widespread use for the identification of crystalline solid phases. Recent advances in instrumentation and software extend the utility of the technique to the study of multi-component systems. The XRD patterns of solid dosage forms can be complex with numerous overlapping X-ray lines. Using a pattern subtraction technique, the contribution of the excipients can be selectively subtracted. This enables not only the detection, but also the quantification of phase transitions during processing. Multiple phase transitions can occur during pharmaceutical processing. For example, aqueous wet granulation of anhydrous theophylline, resulted in the formation of theophylline monohydrate. During the drying stage, the monohydrate dehydrated to form a metastable anhydrate, which then transformed to the stable anhydrate. It was possible to simultaneously monitor all these theophylline phases because of the pronounced differences in their XRD patterns. The solid-state of theophylline in the final tablet depended on the binding agent used as well as the process used for the preparation of the granules. Glancing angle XRD enables depth-profiling of phase transitions during tablet dissolution. This technique was used to study indomethacin crystallization and to profile anhydrate to hydrate transformation during dissolution of theophylline tablets. Finally, low temperature XRD enabled the physical characterization of solutes in frozen aqueous solutions. By attaching a vacuum pump to the low temperature stage of the diffractometer, it was possible to carry out the entire freeze-drying process *in situ* in the sample chamber of the XRD. This enabled real time monitoring of phase transitions during all the stages of the freeze-drying process.