

COMPLEMENTARY TECHNIQUES FOR THE CHARACTERIZATION OF PHARMACEUTICAL SYSTEMS

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Comprehensive physical characterization of pharmaceutical solids often requires a multidisciplinary approach. X-ray diffractometry and thermoanalytical techniques (specifically differentially scanning calorimetry (DSC) and thermogravimetric analysis) are often the first techniques of choice to characterize raw materials. Dehydration of theophylline monohydrate yielded a metastable anhydrous phase, which could be detected by variable temperature XRD but not by DSC.

Aminophylline monohydrate (**I**) decomposed to anhydrous theophylline (**III**) either directly or through an intermediate phase (anhydrous aminophylline; **II**). By measuring intensities of the XRD peaks unique to **I**, **II** and **III**, it was possible to simultaneously quantify the three phases during the entire reaction, and study the reaction kinetics. The DSC profile was complex due to overlapping thermal events. As a result it was not suitable to separate the reaction steps and study them individually. However, the XRD results were confirmed by isothermal thermogravimetry.

XRD and DSC are also complementary techniques to (i) characterize the phase transitions in a multicomponent system during the various stages of the freeze-drying process, and (ii) evaluate the crystallization behavior in frozen aqueous solutions and during freeze-drying. By attaching a vacuum pump to the low temperature stage of the diffractometer, it was possible to simulate the freeze-drying process *in situ* in the sample chamber of the XRD. This enabled real time monitoring of the solid-state of the solutes during the process. Several drugs and excipients, both alone and as mixtures, including cefazolin sodium, mannitol and glycine have been characterized. Finally, while atomic force microscopy revealed surface crystallization in amorphous trehalose particles exposed to water vapor, XRD did not.