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In situ monitoring of hydration and dehydration in pharmaceutical solids

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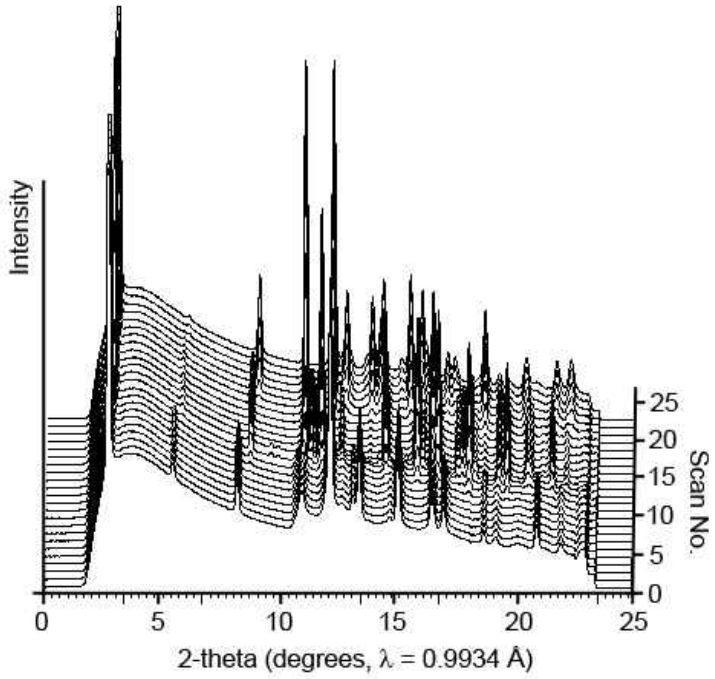
This talk will describe a multi-technique study of hydration and dehydration in pharmaceutical solids, using sodium naproxen as a case study. The aim of the work is to establish molecular-level structural understanding of the chemical changes that take place in the solid state as a function of temperature and relative humidity. Dynamic vapour sorption (DVS) analysis on the anhydrous compound carried out as a function of temperature provides a preliminary overview of the solid-form landscape and identifies static conditions to obtain four different hydrate forms [1]. Differences in the sorption and desorption cycles indicates the existence of a polymorphic dihydrate, and the two polymorphs show significant differences in their dehydration behaviour. Crystal structures are established for all phases in the system using either single-crystal or powder X-ray diffraction data, supplemented by dispersion-corrected density functional theory (DFT-D) calculations. The hydration and dehydration processes are monitored by powder X-ray diffraction (PXRD), as a function of relative humidity and temperature, and by variable-temperature solid-state 13C and 23Na NMR. Synchrotron PXRD is applied to the two dihydrate polymorphs to monitor the dehydration processes in approximately real time. The kinetic and structural details of dehydration are established by applying parametric Rietveld refinement [2] to the synchrotron data. This approach adds a structural picture to the kinetic processes. The PXRD studies indicate an essentially continuous dehydration pathway from one of the dihydrate polymorphs to the monohydrate, but a stepped dehydration pathway for the other dihydrate polymorph. The different mechanisms are linked to different degrees of structural similarity, and in particular to the existence of topotactic or non-topotactic transformations between the dihydrate polymorphs and the unique monohydrate and anhydrate phases.

[1] *D. Raijada, A. D. Bond, F. H. Larsen, et al., Pharm. Res., 2013, 30, 280-289,* ***[2]*** *G. W. Stinton, J. S. O. Evans, J. Appl. Cryst., 2007, 40, 87-95*



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