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# Investigation of hydrate-anhydrate transformations in pharmaceutically relevant small organic compounds

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## INTRODUCTION

Compounds of pharmaceutical interest have the ability to form different solid forms that can influence the physical, chemical and mechanical properties of a drug. It is vital that there is sufficient knowledge regarding the thermodynamic landscape of these forms and their transformation mechanisms in different conditions, because uncontrolled solid form transformations can compromise patient safety and have been shown to be a root-cause of many product withdrawals.[1] Therefore, the aim of this study was to obtain molecular level understanding of the nature of hydrate-anhydrate transformations using a chemical mapping method based on Raman line mapping.

## METHODS

Individual crystals of theophylline monohydrate (TP MH) were used as a model system. The MH form of TP was identified using differential scanning calorimetry (DSC), thermal gravimetric analysis (TGA), and X-ray powder diffraction (XRPD). XRPD data was compared to the Cambridge Structural Database (CSD). Single crystal dehydration of TP MH was monitored using a Linkam hotstage (heating rate, 10°C/minute) and an in-house Raman microscope based on a line-focus method (256 pixels, 2cm$^{-1}$ resolution).[2]

## RESULTS

All solid-state analytical methods used confirmed TP MH (CSD ref code: THEOPH01) as the starting material. Raman maps indicated the presence of three forms of TP between 55-70°C using an individual crystal of TP MH.[3] Raman spectra showed well-defined features of the three forms of TP. Notable differences in density, unit cell parameters and cell volume were evaluated.[3,4] The chemical concentration maps showed with a high spatial distribution (10x objective) the appearance of the metastable form throughout the crystal during the dehydration processes. This highlighted the complex nature of these dehydration processes.

## CONCLUSION

Raman measurements provided fast insight into multiple solid forms during dehydration, which shows the potential for explaining dehydration mechanisms using individual crystals of active pharmaceutical ingredient (API). Future work includes; using FT-IR for monitoring phase transformations and the coupling of these methods with different nanomechanical sensors.

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