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Structural aspects of hydrates – insight into phase transformations using nanomechanical sensors

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PURPOSE

Pharmaceutical compounds have the ability to form different solid-state forms that can impact the physical, chemical and mechanical properties of a drug. It is vital that there is sufficient knowledge regarding the solid-state forms and their mechanisms under different environmental conditions, in a manufacturing environment. Currently there exists a knowledge gap in uncontrolled solid phase transformations caused by dehydration of hydrates. It is critical to fill this gap because uncontrolled solid phase transformations have been shown to be a root-cause of many product withdrawals.¹ Consequently, this can have an impact of when the patient gets the medication. Therefore, the aim is to obtain molecular level understanding of the nature of hydrate-anhydrate transformations using state of the art non-destructive Raman and single crystals as resonators.

METHODS

Single crystals of theophylline monohydrate (TP MH) were crystallized. The MH form of theophylline was identified using differential scanning calorimetry (DSC), thermal gravimetric analysis (TGA), X-ray powder diffraction literature from Cambridge Structural Database. Single crystal dehydration of TP MH was monitored using a Linkam hotstage (10°C/minute) and an in house Raman microscope based on a line-focus method (256 pixels, 2 cm⁻¹ resolution). Nanomechanical sensor based technologies plan to be used simultaneously in order to obtain more detailed mechanical properties of hydrates.

RESULTS

All solid-state analysis confirming TP MH (CSD ref code: THEOPH01) form were in agreement with literature from CSD. Raman maps from line-focus method showed homogenous thermal distribution along TP MH single crystal with a dehydration phase transition around 55-70°C. Raman spectra showed well-defined peaks of TP MH with two new peaks at around 65°C, 1000-1200 cm⁻¹ indicating the metastable phase of TP MH. Three structures were identified in the Raman maps.

CONCLUSION

Raman measurements were in agreement with literature, which shows the potential for explaining molecular level dehydration behaviour of single crystals of API. Future work includes; establishing robust measurement principles for single crystal dehydration with Raman, FT-IR for monitoring phase transformations and coupling with nanomechanical sensors.

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