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Chemical mapping of hydrate-anhydrate transformations at a single particle level using Raman line focusing

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PURPOSE

The aim of this study was to investigate the distribution of hydrated and dehydrated species in a single crystal / single particle chemical mapping method based on Raman line mapping that provides rapid, non-destructive and high spatial resolution imaging of dehydration processes.

INTRODUCTION

The majority of pharmaceuticals are marketed as solid dosage forms. In order to ensure the quality of a drug product it is paramount that processing and environment induced stresses (temperature, humidity and pressure) are controlled during manufacturing. This means that a thorough understanding of the physiochemical and mechanical properties of these solid dosage forms is vital in order to preserve the performance of a drug product.

It has been well documented that the hydrate status influences the stability, solubility and bioavailability of drug products. [1, 2] Hydrates are known to occur in approximately one-third of the organic molecules listed in the pharmacopoeias. [2] There is an increasing interest in understanding the dehydration processes of hydrates because of their key importance to processability and storage. Whilst a macroscopic level understanding of the dehydration mechanism of hydrates exists, molecular level insight into hydrate-anhydrate transformations is still limited.

Currently the standard methods used to study solvated species include: differential scanning calorimetry (DSC), moisture sorption analysis, x-ray powder diffraction (XRD) and optical microscopy. Although useful, these instruments do have their limitations such as the need to use bulk material in order to carry out analysis, as well as their limited sensitivity. [3]

Non-destructive spectroscopic methods such as Raman, FT-IR and NIR spectroscopy are used at different stages of the drug discovery and development process, and are particularly well suited to monitor hydrate formation and dehydration during processing, however; they too have their limitations such as long measurement times. [4]

In this study, a novel method for understanding the dehydration mechanism of hydrates using a Raman line-focus method is introduced. The developed Raman instrument has two modes of operation: laser point- and laser line-focus (Figure 1).

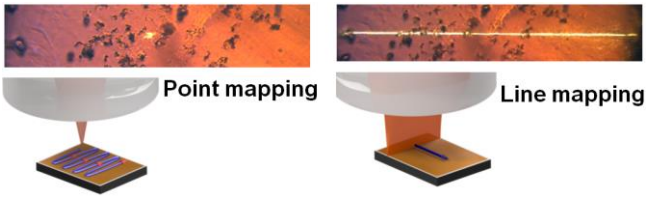

Figure 1. Point- and line-focus laser illumination modes in Raman microscope.

Therefore, the aim of this study is to obtain molecular level understanding of the nature of hydrate-anhydrate transformations from theophylline monohydrate (TP MH) to theophylline anhydrate (TP AH) at the single crystal particle level.

METHOD

Single crystals of TP MH were used as a model particles. The MH form of TP was identified using differential scanning calorimetry (DSC), thermal gravimetric analysis (TGA), X-ray powder diffraction (XRPD), and compared to the Cambridge Structural Database (CSD). Single crystal of monocrystalline 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). A high power (500 mW) laser with the 785 nm laser illumination wavelength was selected as a light source. The line-focus method with line size of 256 pixels enables measurements 256 times faster than traditional point illumination Raman microscopy. The total time needed to obtain a spectral map with spatial dimensions 2200×1000 µm considering 2 seconds exposure time will be around 15 minutes in line-focus mode versus 180 hours in traditional point illumination mode. Multivariate curve resolution (MCR) of the spectral data was performed to estimate the concentration profiles of hydrated and dehydrated species of TP.

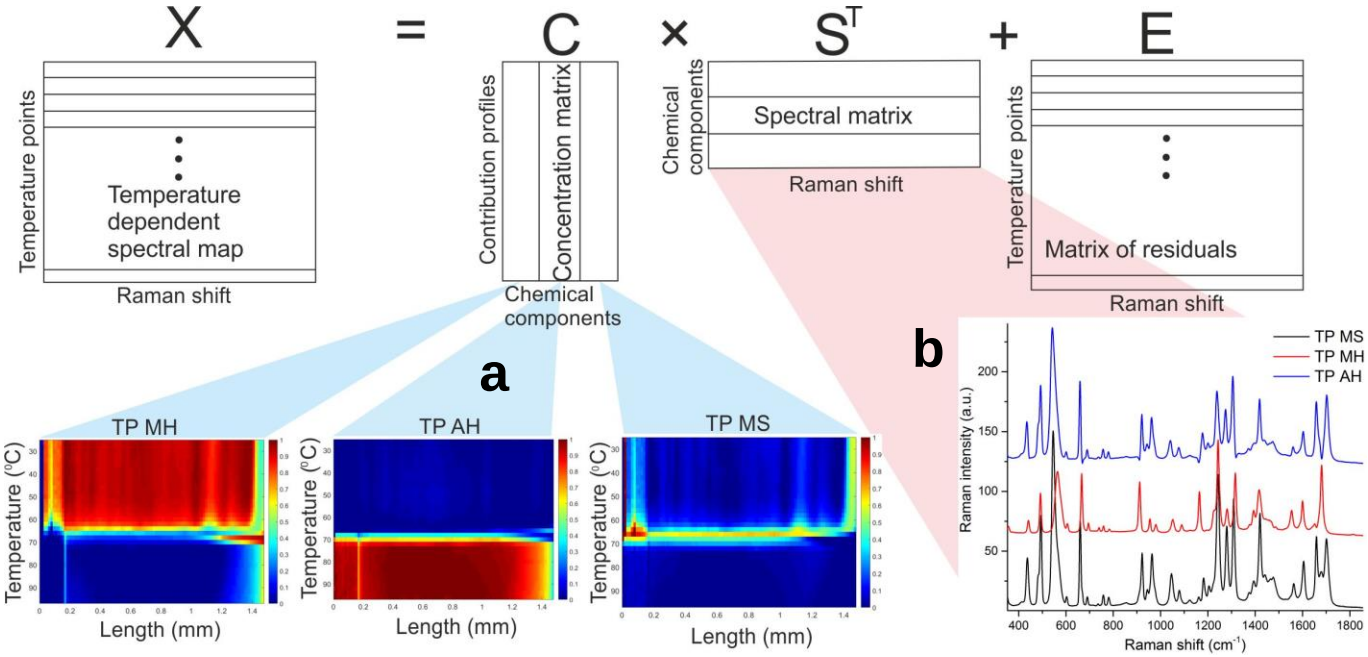

Figure 2. MCR data analysis. a) Chemical concentration maps of TP MH, TP AH and TP Metastable (TP MS) b) Raman spectral reference.

RESULTS AND DISCUSSION

All solid-state analytical methods used confirmed the solid-state form of TP to be TP MH (CSD ref code: THEOPH01). Optical microscopy images confirmed that dehydration is occurring mainly at the end of the needle shaped TP MH crystal (Figure 3), as previously reported. [4,5] Raman chemical maps using the line-focus method enabled fast identification of solid form species at the TP MH single crystal level during the dehydration occurring at around 55-70°C. The Raman spectra showed well-defined features of TP MH and the AH phase, as well as indication of the metastable phase of TP MH. Using MCR three components were realised, which indicated the presence of TP MH, theophylline metastable (TP MS) and TP AH (Figure 2). The metastable form of TP has structural similarities with the monohydrate phase and thus, a very similar Raman spectrum when compared with the TP MH phase. The Raman line focusing method provides a possibility for fast chemical mapping during thermally induced solid form transformations and additionally, a possibility to localize the different solid forms occurring during thermal cycling. This approach can also be used to experimentally investigate the computationally (molecular dynamics based) observed crystal face-specific dehydration phenomena. [6]

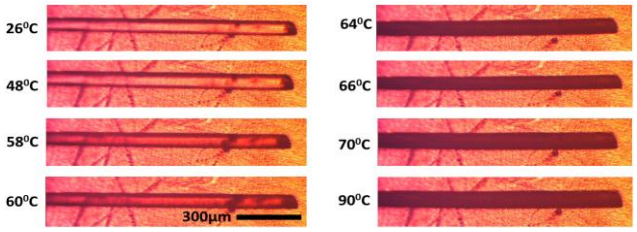

Figure 3. Optical microscopy showing the dehydration of TP MH.

CONCLUSION

The Raman line-focus method provided a novel, fast, and high spatial resolution way for chemical mapping of dehydration processes of solvated species during thermal stressing and indicated the potential for explaining molecular level dehydration behavior using single crystals of an API.

ACKNOWLEDGEMENT

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