Following a process-induced transformation during granulation using *in situ* techniques

Benefits at a glance
- Monitoring hydrate formation during high-shear wet granulation
- Comparison of *in situ* spectroscopies
- Optimization of wet granulation conditions

Introduction

Selection of a particular polymorphic or hydrate form of an active pharmaceutical ingredient (API) during drug substance manufacture can be critical to the safety and efficacy of the drug product.[1] However, even after successful API form generation during primary or drug substance manufacturing, monitoring the polymorphic or hydrate form continues to be important through the manufacturing of the drug product.
A widespread step in the formulation of the oral dosage unit is wet granulation. A wet granulation step is designed to yield appropriate particle size prior to tableting. An unfortunate side effect of this process can be a process-induced transformation (PIT) of the API to either a different polymorphic form or a different hydration state of the API. Both of these transformations can have a dramatic impact on the dosage form. The API form in the final drug product can directly impact the patient and thus it is critical to both monitor and control the form during manufacture. Historically, off-line x-ray diffraction (XRD) QA/QC methods have been used to identify the resulting powder to either release or reject the batch. XRD is invasive and time consuming and is susceptible to subsampling (analyzing an unrepresentative fraction of a heterogeneous mixture). The FDA's process analytical technology (PAT) initiative provides a framework for in-process testing to alleviate the inefficiencies and potential errors inherent in off-line testing and strives to improve pharmaceutical manufacturing.[2]

Near infrared (NIR) and Raman spectroscopies are recognized as spectroscopic techniques within the PAT toolbox. Both NIR and Raman have been demonstrated as applicable from studies of dry hydrate mixtures.[3] In this study, both approaches were used to monitor a wet-granulation unit operation where a solvent-mediated pusedo-polymorphic hydrate transformation of theophylline, from the anhydrate (AT) to monohydrate (MT) form occurs.

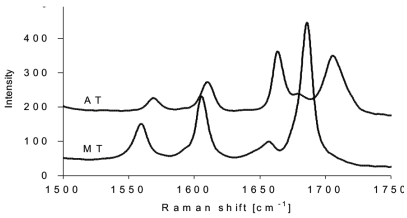

Figure 1: Raman spectra of AT and MT. (Copyright © 2004 John Wiley & Sons and the American Pharmaceutical Association. Reprinted from Ref. 4 with permission from Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)

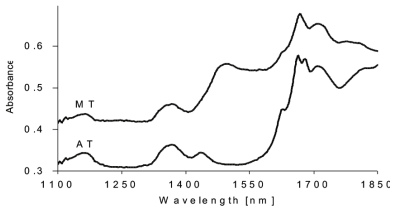

Figure 2: NIR spectra of AT and MT from 1100 to 1850 nm. (Copyright © 2004 John Wiley & Sons and the American Pharmaceutical Association. Reprinted from Ref. 4 with permission from Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)

Experimental

A Raman analyzer operating at 785 nm and an immersion optic were used for this experiment. Spectra were acquired every 15–30 seconds using 100 mW of laser power.

The NIR system used was a NIR spectrometer from Control Development, Inc., with a fiber optic probe. Spectra were collected using 5 milliseconds of integration time and 64 accumulations.

ⓘ All Raman analyzers and probes referenced in this application note are Endress+Hauser products powered by Kaiser Raman technology.

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Results

Raman spectra of samples of AT and MT are shown in Figure 1. Characteristic peaks for AT are observed at 1664 and 1707 cm^{-1} and MT at 1686 cm^{-1}. A univariate calibration model was used to determine the ratio of AT and MT in the samples. The NIR spectra are shown in Figure 2.

Waterfall plots of Raman and NIR spectra are shown in Figures 3 and 4. When Raman spectroscopy is used to monitor wet granulation, it is possible to follow the transformation. However, in the case of NIR the main differences observed arise from the presence of water. Water masking and interference resulted in an inability to monitor the transformation kinetics during wet granulation by NIR.

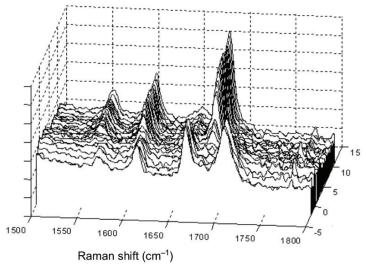

Figure 3: Waterfall plot of Raman spectra. (Copyright © 2004 John Wiley & Sons and the American Pharmaceu-tical Association. Reprinted from Ref. 4 with permission from Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)

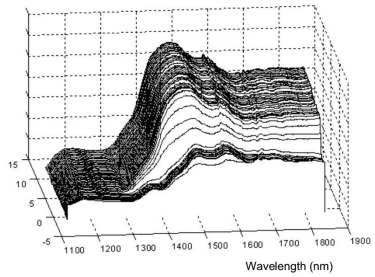

Figure 4: Waterfall plot of NIR spectra. (Copyright © 2005 John Wiley & Sons and the American Pharmaceu-tical Association. Reprinted from Ref. 4 with permission from Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)

In addition to monitoring the ratio of AT to MT following the PIT, other effects included changing the mixing speed of the granulator. In addition, the effects of surface properties and initial surface area of the API, and modifying the binder addition process were evaluated. These experiments led to process understanding of what did not affect the granulation process. For example, no effect was observed for seeding. Also, no difference in transformation rate occurred even for significantly higher API loading. Modifying the binder addition process (from adding a solid powder to adding an aqueous solution) also had no effect on the rate of transformation. Two factors that did influence the granulation were mixing speed and using ball-milled AT.

Conclusions

In this work, *in situ* Raman spectroscopy was used to monitor the high-shear wet granulation of a formulation containing theophylline. Raman was shown to be capable of following the solvent-mediated psuedo-polymorphic conversion of the API. NIR spectroscopy could not be used to monitor the PIT due to the large absorbance of bulk water that effectively hid spectral information related to the transformation. NIR data chiefly provide information concerning the water content during granulation. Transformation kinetics could be generated even though the time scale of the conversion was relatively short. The high information content of the Raman spectrum provided a means of characterizing the API and optimizing the process parameters to yield a consistent endpoint. This application highlights the capability of Raman spectroscopy as an *in situ* PAT tool for the understanding and control of process-induced solid-sate transitions.

References

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