Comparing P^hAT System™ and RamanRxn1™ Approaches for the Study of Wet Granulation

RamanRxn Systems™ Application Note Number 317

Key Issues

- *Improved statistical sampling of heterogeneous mixtures*
- *Non-invasive in-line monitoring of hydration during granulation*
- *Improved quantitation*

Introduction

Currently, the standard method for analyzing the solid-state form of pharmaceutical solids is off-line x-ray diffraction (XRD). XRD is used to accurately determine the solid-state form of a compound, but it is invasive and time consuming and is susceptible to sub-sampling—analyzing an unrepresentative fraction of a heterogeneous mixture. Spectroscopic techniques such as near-infrared (NIR) spectroscopy and Raman spectroscopy provide simplicity and amenability to on-line and in-line sampling, but the small sampling volume typical of these techniques also can present problems with sub-sampling. A method that samples from a larger area would mitigate this problem.

The *P^hAT System*™ from Kaiser Optical Systems, Inc., (KOSI) offers several advantages over traditional immersion optics for solids analysis. First, the *P^hAT System* uses a non-contact probe, so it can be used non-invasively. Second, depending on the configuration, the *P^hAT System* can acquire data from a spot approximately 3 to 6 mm in diameter, compared to about 60 µm for the immersion probe, minimizing the problem of sub-sampling. Here, a *P^hAT System* is compared to a standard KOSI RamanRxn1™ analyzer using either immersion sampling or a non-contact sampling approach.

Experimental

Two Raman sampling approaches were evaluated in these experiments: a standard RamanRxn1 analyzer and a *P^hAT System*, both from Kaiser Optical Systems, Inc., and both equipped with a 785-nm Invictus™ laser. The sample interface for the standard RamanRxn1 was an MR Probe equipped with a KOSI-developed ¼" immersion optic (IO) or a 2.5" non-contact optic (NCO). The *P^hAT System* used a proprietary probe head with a non-contact optic.

Wet granulation of theophylline was carried out in a high-shear mixer/granulator at a mixing speed of 100 rpm (Figure 1). Further experimental parameters are given below.

Figure 1. The non-contact probe of the *P^hAT System*, covered by a temporary shield, monitoring material in situ in the granulation bowl.

Results

Figure 2 contains the calibration plots for data from theophylline obtained with the RamanRxn1 with a ¼" IO and for the *P^hAT System*. The data from the *P^hAT System* is more repeatable, with $R^2 = 0.997$, compared to 0.985 for the ¼" IO. NIR spectroscopy and off-line XRD on this system gave $R^2 = 0.994$ and R^2=0.989, respectively.

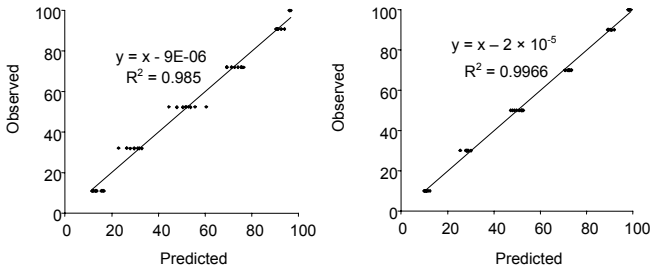

Figure 2. Calibration curves for theophylline obtained with (A) a standard system utilizing a ¼" IO and (B) the *P^hAT System*.

RamanRxn Systems
Reaction Analysis, Monitoring and Control

The transformation of theophylline anhydrate to the monohydrate by aqueous wet granulation with mannitol and microcrystalline cellulose was monitored using the **RAMANRXN1** with a ¼" IO and using the *PhAT System*. Spectra with the *PhAT System* were acquired using 1-s exposures with 4 co-additions every 10 s. By comparison, the system with a ¼" IO required 5-s exposures with 4 co-additions every 30 s, so the *PhAT System* provided a threefold sampling-time advantage.

Kinetics of Transformation

Figure 3 compares the transformation kinetics of the theophylline anhydrate during wet granulation as determined using Raman spectroscopy. The anomalous results from the ¼" are probably due to material sticking to the face of the optic. The results from the *PhAT System* and the **RAMANRXN1** equipped with the non-contact optics are similar, but the *PhAT System*, with its more representative sampling, yielded a smoother profile with less noise.[3]

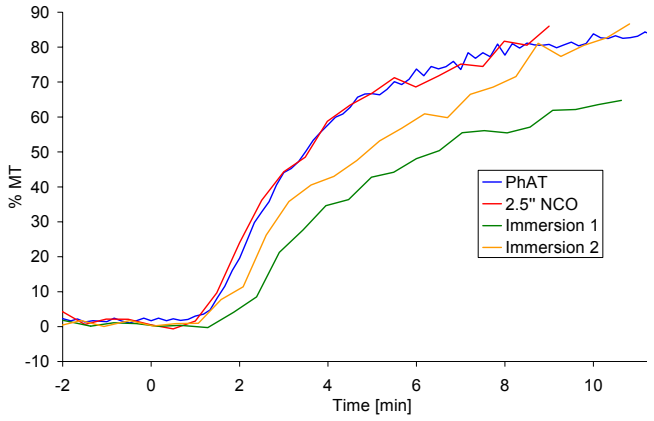

Figure 3. Transformation kinetics of theophylline anhydrate using four different optics.

Nitrofurantoin

Wet granulation of nitrofurantoin was also carried out in a high-shear mixer/granulator. Figure 4 contains the calibration plots for data from nitrofurantoin obtained with the **RAMANRXN1** with a ¼" IO and for the *PhAT System*.

These results are very similar to those for theophylline, lending credence to the following statements:

a. The *PhAT System* enjoys the benefits of representative sampling.
b. The *PhAT System* enjoys the benefits of reproducible sampling.
c. The *PhAT System* is the preferred Raman approach for analyzing both static solid-state samples[2] and solid masses during DP unit operations.[3]

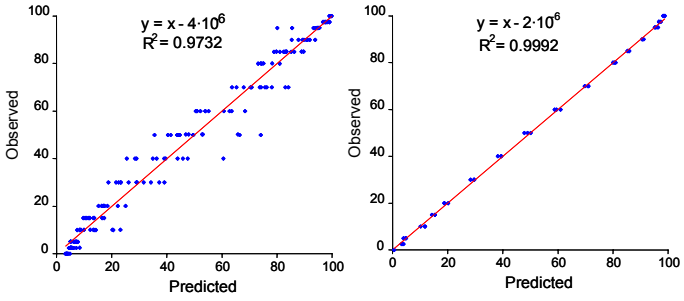

Figure 4. Calibration curves for nitrofurantoin using an IO (a) and a *PhAT System* (b).

Conclusion

For pharmaceutical solids analysis, the *PhAT System* offers significant advantages over more traditional sampling configurations. Material doesn't stick to the face of the optic and contamination of the analyte is less likely, which makes it more compatible with current regulatory requirements. The larger spot size gives better statistical sampling of heterogeneous mixtures. Additionally, the *PhAT System* is relatively insensitive to focus, facilitating alignment, enabling the monitoring of dynamic processes, and improving method robustness. Other applications that benefit from these advantages include the analysis of tablets and low-dosage formulations, blend uniformity, and product degradation.

Acknowledgement: Application data kindly provided by Purdue University.[2,3]

References:

1. Wikstrom, H.; Marsac, P.J.; Taylor, L.S; J. Pharm Sci., 94, 209-1219 (2005).
2. Rantanen, J.; Wikstrom, H.; Rhea, F.E.; Taylor, L.S.; Appl. Spectrosc., in press (2005).
3. Wikstrom, H.; Lewis, I.R.; Taylor, L.S.; Appl. Spectrosc., in press (2005).

KAISER OPTICAL SYSTEMS, INC.
A ROCKWELL COLLINS COMPANY
WWW.KOSI.COM
371 Parkland Plaza
Ann Arbor, MI 48103
phone (734)665-8083 / fax (734)665-8199