

## Monitoring API Drying Operations with NIR

**The authors describe implementation and performance of a miniaturized NIR analyzer and associated chemometric techniques applied to the monitoring of a drying process for active pharmaceutical ingredients (APIs). They also include a broader discussion of how process analytical technology (PAT) is designed to encompass total quality design concepts using on-line monitoring technology to gain a more complete understanding of pharmaceutical processes.**

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**T**here has been a significant increase in process analytical technology (PAT) activity within the pharmaceutical industry during the last 12–18 months largely due to the “Guidance for Industry on PAT” (1) issued in October of 2004 by FDA. The definition of PAT within the document is more encompassing than one might expect from the common understanding of PAT that has evolved in the chemical and petrochemical industries during the past 20 years. FDA defines PAT as:

“... a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality (1).”

The guidance goes further to explain the goal of PAT and link it to total quality systems that have been pervasive in many industries. “The goal of PAT is to enhance understanding and control the manufacturing process, ... *quality cannot be tested into products; it should be built-in or should be by design* (1).”

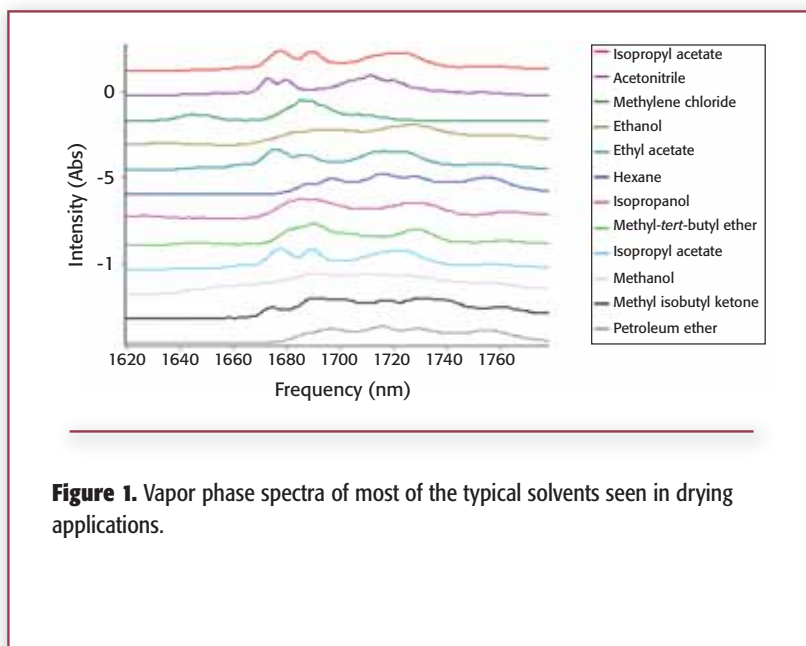
The pharmaceutical industry is incorporating PAT into pharmaceutical development through the use of near-line and on-line monitoring tools in order to obtain greater understanding and control of their processes. Though these tools can include many instrumental tech-

niques, mid- and near-infrared, Raman, UV and visible spectroscopy instruments are playing a prominent role (2–5).

In this article, the use of a miniature, chip-based NIR spectrometer will be discussed in conjunction with the development of a dryer-monitoring process, one of a number of processes comprising unit operations in the production of APIs (active pharmaceutical ingredients).

### **API Production**

In the production of APIs, once the material has been isolated from solution and washed, a critical unit operation is the drying of the material. The API material is placed into one of several types of dryers including both agitator and tray dryers. The dryer then is sealed and a vacuum is applied, the temperature is elevated and dry nitrogen make-up gas flows through the dryer. The end point for the drying of GlaxoSmithKline (GSK) production material usually is determined by a technician who samples the API manually a number of times during the process and determines the residual solvent contents by off-line analysis, such as high performance liquid chromatography (HPLC), nuclear magnetic resonance (NMR), or gravimetric analysis. On-line dryer monitoring has the potential to eliminate the need for multiple,



**Figure 1.** Vapor phase spectra of most of the typical solvents seen in drying applications.

tact of a probe with the API. Direct probe contact with the API can coat or foul the probe with a small amount of material that is not representative, causing misleading results or blocking the probe from seeing any new material. Another advantage of vapor phase monitoring is that the solvent is present in a nitrogen matrix that is inert in the NIR. This makes developing a monitoring method much less complex than it would be if there was contact with the solid, which would be complicated by having the API spectrum present as well as the solvent. Most, if not all, of the major solvents used to produce APIs have spectra that can be detected in the near-infrared spectrum and analyzed using chemometric modeling or spectral pre-processing such as first or second derivative. In Figure 1, we see a number of vapor phase solvents measured in a one-meter gas cell with an NIR spectrometer (6).

in-process sampling during drying, thus speeding up the drying process. The time savings come through eliminating the need to bring the dryer back to atmospheric pressure and ambient temperature, open the dryer oven and sample the material, then close the dryer and resume the low-pressure and high-temperature drying conditions after the sample is taken.

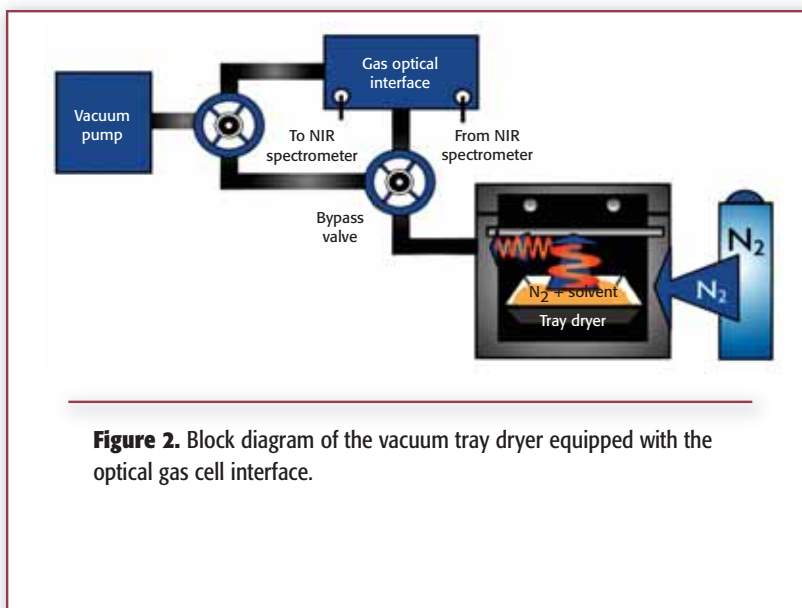
Often, drying is allowed to proceed overnight, which can result in dryer processing problems. Over-drying can cause loss of desired hydrate forms such as a monohydrate, a change in polymorphic form, as well as processing complications such as fracturing of crystals leading to smaller-than-desired particle sizes. This can arise from agitating too long after the solvent has evaporated. Establishing the actual drying end point can eliminate these problems, reduce drying and cycle times, eliminate over drying of product, lower energy costs, and minimize product sampling with its associated hazards, time, and costs — all of which ultimately improve API quality. These are all benefits derived from PAT

that also are consistent with the FDA Guideline, and that help to produce data-driven process understanding.

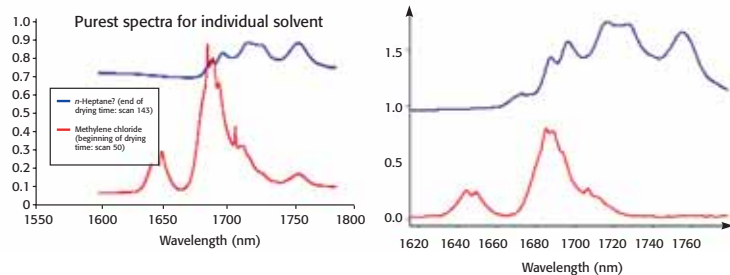
### Dryer-Monitoring Application

One approach that GSK has taken to dryer monitoring is to analyze the composition of the vapor-phase gases that are drawn from the dryer. This has several advantages to monitoring the solid phase. The primary advantages of the vapor phase approach are its universal applicability to different types of dryers used and that it does not require direct con-

The dryer monitoring application discussed here is one that can be applied to a tray dryer or agitated filter dryer. Figure 2 shows the arrangement for a tray dryer. The API powder, wetted with solvents, is placed in a pan or several pans in the dryer. The system then is heated, a vacuum is applied, and dry nitrogen is drawn through the dryer. The



**Figure 2.** Block diagram of the vacuum tray dryer equipped with the optical gas cell interface.



**Figure 3.** Vapor phase spectra of n-heptane (blue) and dichloromethane from dryer (spectrum on left) agree well with spectra of pure n-heptane and dichloromethane seen on right

vacuum can pull the gases (nitrogen plus the solvent vapor) directly to the vacuum exhaust or through the gas phase optical interface. This allows the dryer system to be operated when the interface is being serviced, allowing it to be calibrated or cleaned without interfering with drying operations. In addition to the normal particulate filters on the dryer, additional filtration is incorporated before the gas interface to prevent contamination with particulates from the API powder being dried.

### Experimental

The spectrometer used was the Axsun NIR (Axsun Technologies, Billerica, MA). This system is based upon a superluminescent diode source, MEMS Fabry-Perot tunable filter, and an InGaAs detector. The system is suitable for the process environment. The optical bench is mounted on a thermoelectric cooler, and is sealed to eliminate exposure to plant gases that may interfere with the measurement or cause a safety problem. Each scan of the spectrometer is wavelength and absorbance referenced to provide accurate and reproducible spectral measurements. Sixty-four scans were averaged routinely and the measurement time was under 3 seconds. Spectra were measured at 0.25 nm resolution. Communications

were tested using 4-20 mA, USB connection, and wireless. The wireless was found to have a range of over 200 feet in all directions.

Gas-phase analyses have long been performed using an FT-IR spectrometer in conjunction with a long path length gas cell, of the “White” design (7). A custom multi-pass gas cell (Axiom Analytical, Irvine, CA) was designed, fabricated and used for the interface to the dryer. Light was delivered to the cell via a single-mode optical fiber and a collimator, resulting in an approximate 2 mm diameter beam. This was coupled via a periscope into the cell. The optics inside the stainless-steel cell consisted of two plane, gold-coated, mirrors and provided a pathlength of 1.4 m. The light was collected by a second periscope and focused into a 600  $\mu\text{m}$  multimode optical fiber, connected back to the spectrometer. Light exiting the fiber was focused onto a 300  $\mu\text{m}$  diameter single-element extended InGaAs detector (1.9  $\mu\text{m}$  cutoff). The overall size of the gas cell was determined by the requirement to couple with a 2-inch diameter vacuum fitting from the exit line of the dryer. The gas cell was a purely “passive” device, and did not require any additional safety enclosure.

The spectra taken during the gas analysis were measured from 1390–1780 nm, a region of the near-

infrared associated with the first overtone of carbon-hydrogen stretching modes, at 0.25 nm resolution; and 64 scans were averaged. We measured the reference gas-phase spectra at 2 nm resolution and 50 scans, accumulated in less than three seconds.

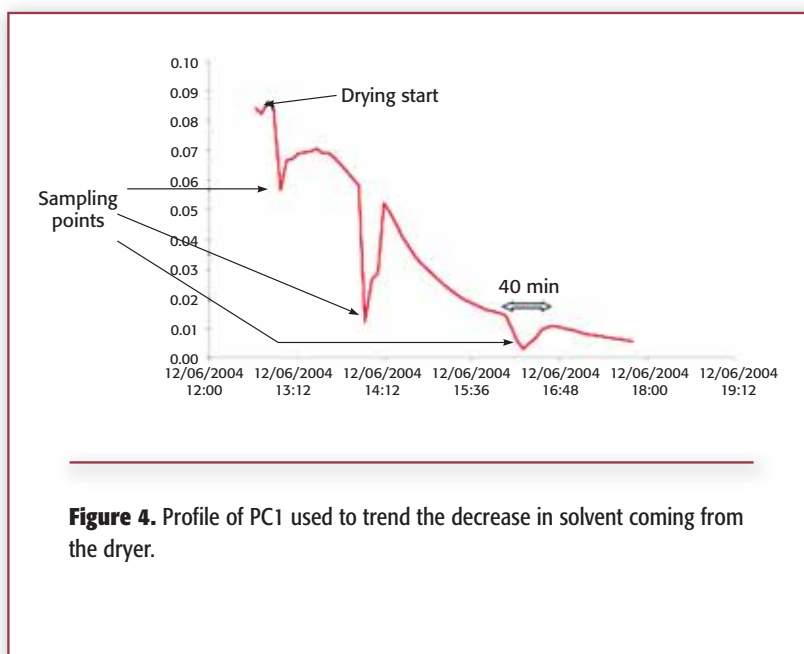
### Measurements, Results, and Process Learning

The application described here involved drying an API material that was wetted with two solvents, dichloromethane (DCM) and n-heptane. Figure 3 shows spectra of DCM and n-heptane taken on-line and off-line spectra of pure solvents in separate gas cells. Because the boiling point of DCM (39.8 °C) and heptane (98 °C) differ significantly, taking spectra early (mostly DCM) and late (mostly heptane) in the dryer run produced spectra that agree very well with the pure vapor-phase solvent spectra. This shows that solvents could be monitored individually with this NIR method.

Because the object of the analysis was to determine when the wetted API was dry, the spectra were not monitored individually. Initial efforts to monitor the decrease of solvents in the gas stream from the dryer using spectral features were complicated due to baseline shifts. A number of approaches were considered to compensate for the baseline shifting. To overcome this issue and obtain the reaction drying profile, the following data analysis was performed using SIMCA-P+ software (8). The dataset consisted of a 2-D matrix  $X$  composed of  $I$  spectra represented by  $J$  variables. The spectra were corrected for baseline shift using 1st order derivatives (5 points Savitsky & Golay coefficients). Principal component analysis (PCA) (9) then was applied to the dataset. The aim of PCA is to reduce the dimensionality of the dataset, while keeping as much information as possible. The data matrix obtained after PCA contains a reduced number of uncorrelated sets of variables, called the principal components (PCs), each of

them characterized by two sets of vectors, called the *scores* and the *loadings*. The scores relate to the evolution along time, and the loadings to the spectral dimension. The scores of the first principal component (PC1) contain the overall trend of the drying profile for the reaction studied. PC1 summarizes the evolution along time of the highly correlated spectral information contained in the NIR spectra. The PC1 scores then were plotted against time to provide the overall drying profile of the reactions.

Initially, it was estimated that the drying would take about 12 hours. Figure 4 is a plot of the PC1 scores from the reaction measured during drying. The



**Figure 4.** Profile of PC1 used to trend the decrease in solvent coming from the dryer.

## **MOST, IF NOT ALL, OF THE MAJOR SOLVENTS USED TO PRODUCE APIs HAVE SPECTRA THAT CAN BE DETECTED IN THE NEAR-INFRARED SPECTRUM AND ANALYZED USING CHEMOMETRIC MODELING OR SPECTRAL PRE-PROCESSING SUCH AS FIRST OR SECOND DERIVATIVE.**

contribution from both solvents represented by PC1 begins at about 12:30 with the solvents at their highest concentration.

Sampling points can be seen for the off-line testing, which took place at about 13:00, 14:00, and 16:00. At each of these points, the temperature was lowered and the pressure released to atmospheric to allow the sample to be taken. On average, about 40 minutes of drying time are lost at each sampling point. Finally, just before 18:00, the profile levels out, showing that the drying is complete in less than six hours.

Success at monitoring the first batches led to the elimination of sampling for off-line testing. Without the large disruptions to the profiles caused by the sampling, coupled with better understanding of the data, we saw an increase in sensitivity (Figure 5). In addition to seeing the profile decline with the solvent concentrations in the dryer gasses, we were able to see the actual

liberation of solvent from the multiple agitations that were initiated during the drying process. This allows the operators to see the effects of agitation on the drying process, enabling them to optimize drying.

### **Conclusions**

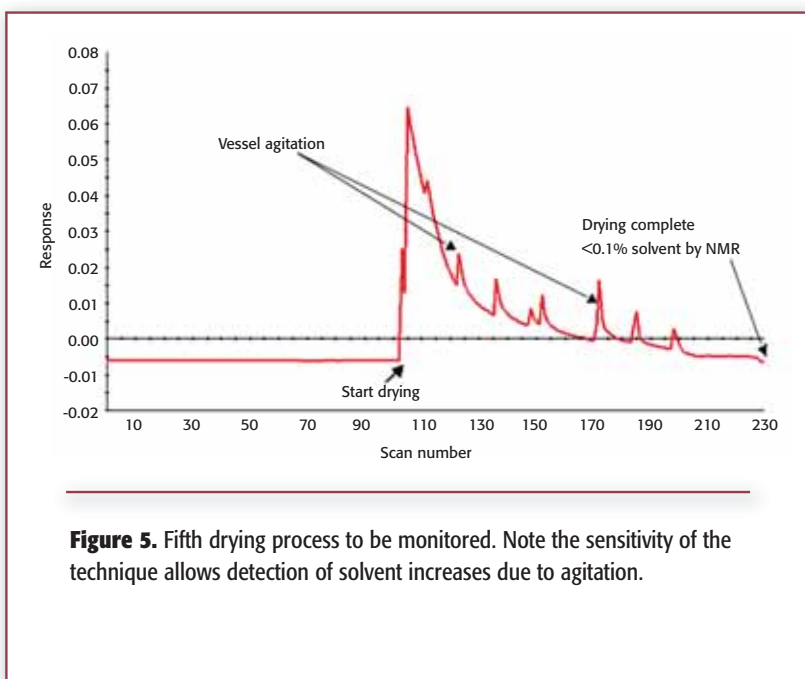
By implementing an on-line NIR tool that enables the monitoring of a critical process attribute, such as the completion of drying, we can accomplish the monitoring goal for the drying unit operation stated in the PAT Guidelines. It provides us with the data we need. However, this is only one part in developing a good PAT application. Good design of experiments needs to be coupled with monitoring to enable us to develop knowledge and understanding from the data provided from monitoring. Without the design step, all we have is data; we do not possess the understanding that is needed to implement a sound control strategy. Without further analysis of the data, we would

not know that end point detection, as we have discussed, helps to prevent adverse processing issues, and ultimately can impact the quality and performance of the drug product. By implementing PAT in this way, we can learn more about, and thus control, this key process. Further development can enable predictive modeling by correlating the on-line data with the off-line results to give even better control of drying.

In the field of process analytical technology, success begets additional success. With the experience gained from this successful implementation, we will be able to apply the advantages of this NIR technology and the PAT process to other, more challenging projects.

### **Acknowledgment**

We would like to acknowledge Edita Botonjic of Axsun Technologies for running the vapor-phase reference spectra.



**Figure 5.** Fifth drying process to be monitored. Note the sensitivity of the technique allows detection of solvent increases due to agitation.

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