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Industry Perspectives on Process Analytical Technology: Tools and Applications in API Development

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ABSTRACT: The IQ Consortium reports on the current state of process analytical technology (PAT) for active pharmaceutical ingredient (API) development in branded pharmaceutical companies. The article uses an API process workflow (process steps from raw material identification through to finished API) to provide representative examples, including why and how the pharmaceutical industry uses PAT tools in API development. The use of PAT can improve R&D efficiency and minimize personnel hazards associated with sampling hazardous materials for in-process testing. Although not all steps or chemical processes are readily amenable to the use of the PAT toolbox, when appropriate, PAT enables reliable and rapid (real or near time) analyses of processes that may contain materials that are highly hazardous, transient, or heterogeneous. These measurements can provide significant data for developing process chemistry understanding, and they may include the detection of previously unknown reaction intermediates, mechanisms, or relationships between process variables. As the process becomes defined and understanding is gained through these measurements, the number of parameters suspected to be critical is reduced. As the process approaches the commercial manufacturing stage and the process design space is established, a simplification of the monitoring and control technology, as much as is practical, is desired. In many cases, this results in controls being either off-line, or if in situ control is required, the results from PAT are correlated with simple manufacturing measurements such as temperature and pressure.

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1. INTRODUCTION

This is a review of the state of process analytical technologies (PAT) in the pharmaceutical industry from the perspective of members of the International Consortium for Innovation & Quality in Pharmaceutical Development (IQ Consortium; http://iqconsortium.org/; a group composed of representatives from 35 branded pharmaceutical companies). PAT (also referred to as in situ analytics) tools are heavily applied in pharmaceutical workflows that underpin drug substance and dosage form development, scale-up, and manufacture.[1−4] Even in this current state, industry has not attained the FDA's full vision of PAT, described 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"[5] for a significant number of products on the market or in development. The need for industry to attain this PAT vision is heartily discussed and debated within companies, conferences, and social media. Nevertheless, to ensure product quality, industry identifies and implements controls [often, using a Quality by Design (QbD)[6] approach to identify and mitigate risks], irrespective of the type or location of the analytics and controls, or whether additional cost benefits could be achieved using in situ analytics and real time control.

Internal and external impediments can be encountered when considering and recommending the use of in situ analytics for control purposes in commercial manufacturing.[7,8] Internal barriers include uncertainty related to return on investment (equipment and employee efforts), staff skills, and capabilities, hardware equivalence between the development and manufacturing sites, and integration of PAT equipment into the manufacturing site's quality management system. External barriers include vendor incompatibilities (e.g., challenges of integrating, into a single PAT system, hardware and software from different suppliers), and regulatory challenges (such as the country or region specific expectations and guidances).[9] Many products are developed and filed for global markets, and these differing regulations and requirements can result in inefficiencies such as having to test the same product to multiple standards (specifications) using multiple test procedures, along with the development of conventional off-line reference methods.

The goal of this paper is to communicate as a cross-pharmaceutical industry consortium (rather than from the perspective of a single company) about how PAT is used and implemented across the industry. Further, we strive to increase discussion, acceptance, and adoption of PAT tools in drug development and manufacturing (as appropriate). We also hope to influence vendors, regulators, and pharma by illustrating how, when, and why we use PAT, its value, and its importance by sharing our approaches and experience. The IQ Consortium has organized sessions at the IFPAC conference as one avenue toward our goals. In this work, via representative examples demonstrating the use of PAT and the value of the approach, we hope to communicate how, when, and, most importantly, why PAT is used during the pharmaceutical development.

The focus of this paper will be primarily on sharing current experiences of the use of PAT tools for active ingredients (API) development. A subsequent paper will focus on the application of PAT tools for process control in a GMP manufacturing environment and will include the life cycle aspects of spectroscopy methods (e.g., development of chemometric models, validation, diagnostics, and model maintenance).

1.1. What Is PAT? In the FDA's PAT definition, "analyzing" equates to in situ analytical tools, and it includes many measurement and instrument types, e.g., thermocouple, pH probe, vibrational spectroscopy (mid-infrared, near-infrared, Raman, ultraviolet), mass spectrometry, chromatography, focused beam reflectance measurement, and nuclear magnetic resonance. Just as there is no single off-line analytical tool that meets all process development understanding or control strategy needs for a product, there is no one in situ analytical tool that will work for all applications. Indeed, for some types of chemistry, in situ tool use is challenging at best, and sampling and off-line testing may be desired. As such, PAT tools are just one set of analytical technique to consider when determining which analytics are appropriate for process and product understanding, monitoring, and control. The appropriate analytical techniques for the process or product are determined based upon chemistry, stage of development, technique availability (in development and at the manufacturing site), process equipment accessibility, and configuration, personnel skill sets in the technique, and regulatory acceptability.

PAT data may measure chemical or physical aspects. It may be univariate, multivariate, raw, or mathematically preprocessed. Temperature, pressure, and flow measurements are often not considered PAT tools (as these measurements have been routinely made for decades). However, through process understanding, such fundamental measurements may be directly correlated with a critical quality attribute (CQA)[6] and used as a parametric control measurement for process control purposes. Table 1 describes high level differences between PAT used in development (used to develop process understanding) and manufacturing (based upon process understanding and used as a control strategy).

Table 1. Basic Contrast between PAT in Development and Manufacturing

	Development	Manufacturing
Overall Purpose	Understand	Control, trend analysis
Desired Technology	Multicomponent analyzers	Targeted analyzers
Data Complexity	Multivariate	Univariate or multivariate[a]
Support Requirements	High level expertise—continuous support	Robust and automated—minimal support
Quality System	Development mode	GMP
PAT Expertise	Method design and development	Operation and maintenance

[a]While univariate analysis is preferred for simplicity, PAT tools such as spectrometers will often require multivariate analysis.

1.2. Why Use PAT? Many process parameters may be measured by standard off-line techniques. However, PAT provides more frequent and automated measurements, enabling the study of kinetic processes as well as expanding capabilities for automated, real time process control. More importantly, the technology can provide measurements of parameters that are

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difficult or undesirable to measure with standard off-line techniques (e.g., highly hazardous materials, high pressure systems, high or low temperature systems, transient intermediates, and heterogeneous systems). One of the greatest challenges to understanding complex physical and chemical processes is the ability to measure process components with a minimum of perturbation (for both the measurement and the process). The foundation of PAT, whether it be applied in R&D or manufacturing, is the measurement.

In R&D, reliable measurements can reveal previously unknown process components, mechanisms, and relationships between variables, leading to the development of predictive models—both mechanistic and chemometric. These predictive models can be both qualitative and quantitative in nature, and the desired goal is to predict process outcomes. As development progresses, the cumulative information is used to map the process design space and to develop a control strategy for maintaining the process within that space. Thus, PAT is used during every phase of development (preclinical through commercial manufacturing) and is a valuable set of analytical tools for the pharmaceutical scientist to interrogate processes.

In the early phases of development, the analytics needed for developing an understanding and definition of the process may be complex. Analyzers may be multivariate, allowing the researcher to monitor the formation and fate of multiple process components. As the process is defined and understanding is gained through these measurements, the number of parameters suspected to be critical can be reduced. As the process approaches manufacturing readiness and the process parameter control limits are established, the desire is to simplify the monitoring and control technology as much as is practical. In the ideal case, the results from advanced PAT are correlated with simple manufacturing measurements (e.g., time, temperature, pressure, and flow) to control the process. Even in these instances, PAT may be installed in the manufacturing process to obtain information for process scale-up, optimization, transfer, fault detection, and building a process fingerprint for advanced trending and controls or to understand unexpected process deviation events *post mortem*, and it may be included in regulatory submission documentation. Key benefits of QbD and PAT use during development include improved process understanding,and identification of critical process parameters and critical product quality attributes (and their relationships with each other). Further, to ensure product quality, this knowledge can be used for process control (in real time, if required, using advanced PAT or simple manufacturing measurements). The PAT measurement may be quantitative or qualitative in nature, and it will depend upon the application. This is a key point on how industry practically develops, analyzes, and controls processes.

1.2.1. Process Understanding and Control. A more thorough understanding of the chemistry and process via PAT use results in the creation of more robust chemical processes while more efficiently utilizing critical resources such as research staff and equipment. Additionally, PAT tools are useful for bridging different reaction scales and understanding the reaction in real time. Scale-up to pilot and commercial scale may experience mixing differences compared to lab scale. Especially for heterogeneous processes, mass transfer and heat transfer can play a vital role in process safety and performance. Processes that behave well at laboratory scales may unexpectedly generate much different results—they may even fail—at larger scales due to differences in mixing. Simple awareness of these effects can initiate the development of tests so that conditions can be appropriately adjusted. A general precept for risk-based process development is that thermodynamically controlled processes tend to scale-up consistently, while kinetically controlled processes need deeper evaluation during scale-up. Further, processes that are mass transfer or heat transfer rate-limited are candidates for extra scrutiny. When PAT is transferred to manufacturing, it may be utilized in two different ways: (1) process control and (2) continued process understanding. The "process control" designation implies that the technology and methodology will be used in a decision making role and, therefore, must be GMP compliant (the focus of the current work is on process understanding; a follow up work on the application of PAT tools for process control in a GMP manufacturing environment will be prepared).

PAT is simply another set of analytical techniques: techniques that are in contact with the process via a probe. The materials of probe construction must be considered when being used to generate process information from development mode samples (to ensure the probe is not damaged during use or does not negatively impact the process).

1.2.2. Safety. PAT tools are highly important for improved product and process safety. In situ analysis can be used to provide timely process measurements to help ensure the reaction progresses within specified limits, thus contributing to product safety. Further, these same tools are also used to minimize sampling and worker exposure to hazardous materials. A primary goal of any industrial manufacturing organization is to avoid process hazards that may adversely affect employees, the community, and process equipment. In the pharmaceutical industry, many process hazards are avoided by obtaining time varying measurements of potentially hazardous materials and events, and then applying sound reaction engineering principles to mitigate the risk. The measurements are traditionally performed in the laboratory and the information gained, along with process models, is applied to estimating worse case scenarios. The process conditions for safe operation of the process are generated, and then a strategy is developed to ensure that the process remains in that operating space. The PAT measurements that provide detailed understanding in the lab may be replaced by simpler technologies that have been demonstrated to provide information that is indicative of the parameters to be controlled. However, depending on the risk, more advanced PAT may be installed for real time measurements in the manufacturing process.

PAT provides a very good approach to ensuring chemical reactions are well controlled and progress within specifications, and it also provides the benefit of eliminating hazards to personnel who may have to sample hazardous materials for in-process testing. Samples that are at high temperatures, are at high pressures, are sensitive to oxygen, or contain chemicals that pose health hazards (e.g., corrosive substances, carcinogens, mutagens, acute toxins, allergens, and lachrymators) can oftentimes be safely monitored with PAT.

1.2.3. Throughput in Process Development. Process development efficiency gains can be achieved with in situ analysis. Although PAT data is generated in real time, data analysis can be time-consuming depending upon the measurement needs. In most cases, the use of PAT provides the required information faster than off-line testing. Additionally, the use of PAT in process development can result in an increased understanding of chemical processes, due to the use of nonperturbing reaction sampling techniques (e.g., spectrometer

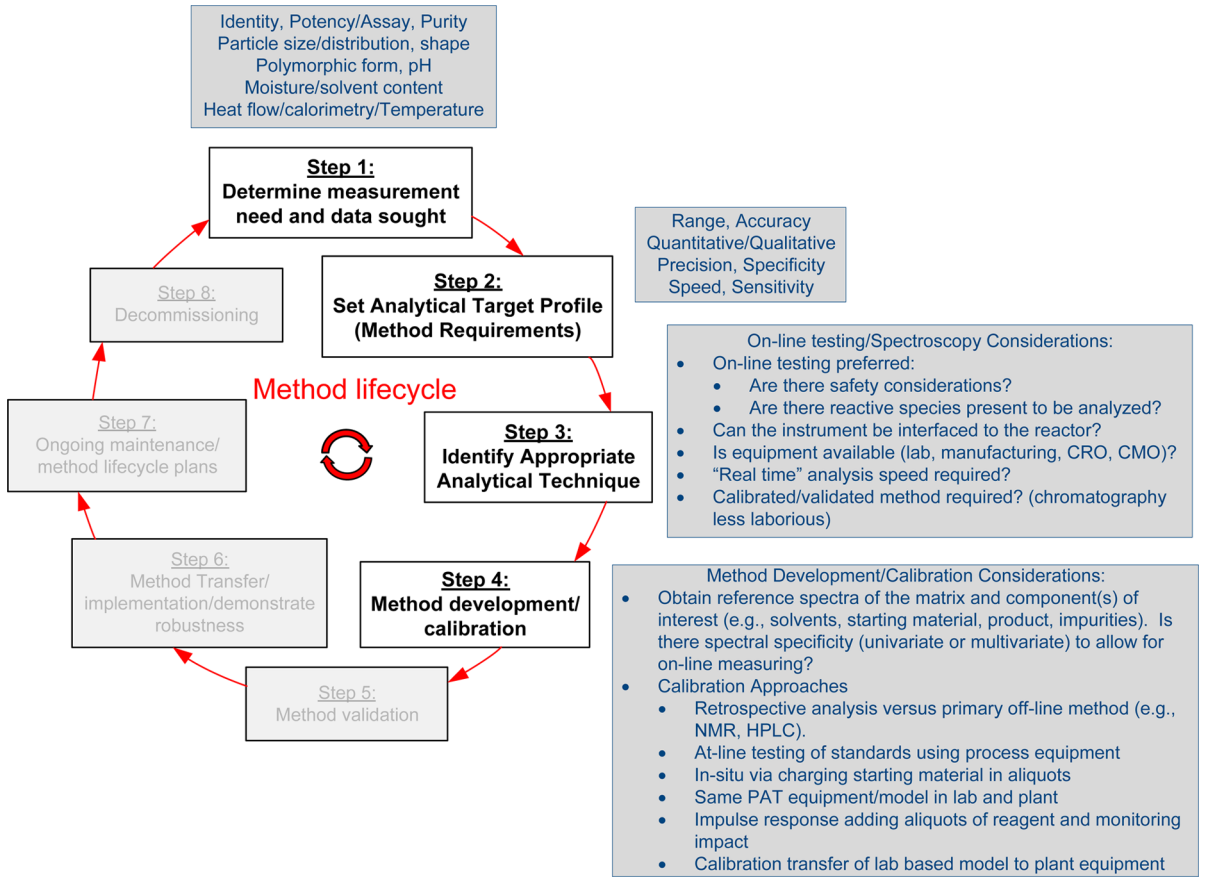

Figure 1. Method lifecycle workflow.

probes), an increased reaction sampling and analysis frequency (in many cases), and potential to monitor transient or reactive species. The end result is a more thorough understanding of the chemical process (obtained in a fashion which more efficiently utilizes equipment and scientific staff resources) which facilitates the creation of a more robust processes.

Employing PAT can result in a shorter chemical process development time, thanks to a faster turnaround of results from each process condition change made during process development. Additionally, during clinical development drug substance preparation, understanding the process kinetics of each unit operation can lead to maximizing yield and throughput, and minimizing process related impurity formation and process material holding times. PAT in these instances may be used as the in-process control (IPC) method, as an indicator that the off-line IPC testing will pass, thus ensuring consistent batch cycle time or for understanding the process at a larger scale.

1.3. When To Use PAT. In situ analytics may be used throughout the pharmaceutical development lifecycle.[10−13] These tools are regularly used during discovery, preclinical, and early clinical phases for process development and process understanding. The value of applying the tools and how the tools are used can vary significantly as the program develops through the clinical phases and to commercial manufacturing, as detailed in the previous section.

A large number of pharmaceutical manufacturing processes are physically heterogeneous. Sampling of a heterogeneous mixture from a reaction vessel or flowing stream for off-line analysis can introduce inherent inconsistency from batch to batch (proportion of phases in the sample can vary). These effects can result in an over- or under-reaction condition because a decision was made to stop or continue processing based on an erroneous measurement. Use of in situ analytics, in cases such as this, is of paramount value.

Pharmaceutical organizations are rapidly embracing continuous processing technologies. The benefit of continuous processing includes the ability to safely run energetic chemistries, rapid progression of discovery chemistries for supplying initial toxicology studies, scale-up advantages versus batch, as well as potentially faster process development timing. The faster development timing is due to the ability to rapidly change process parameters (versus running another batch for each process change) and evaluating the impact of the changes on the resultant material. The use of PAT in these processes is of importance to demonstrate the process is in steady state, for use as an in-process control, or potentially for use as a parametric release method.

1.4. How To Develop a PAT Method: The PAT Workflow. The development of an in situ analytical method progresses in a logical stepwise sequence (Figure 1).[14] As this work is focused on development activities, the workflow only progresses through step 4 (a subsequent work will discuss the remainder of the workflow). The first step is to understand what information is sought from the measurement (i.e., the design intent for the method). This should be understood and agreed to before embarking on application development. Subsequently, what method performance is required (e.g., accuracy, precision, range, specificity, sensitivity, response time, in situ or off-line, qualitative or quantitative) can be described in an analytical target profile (ATP).

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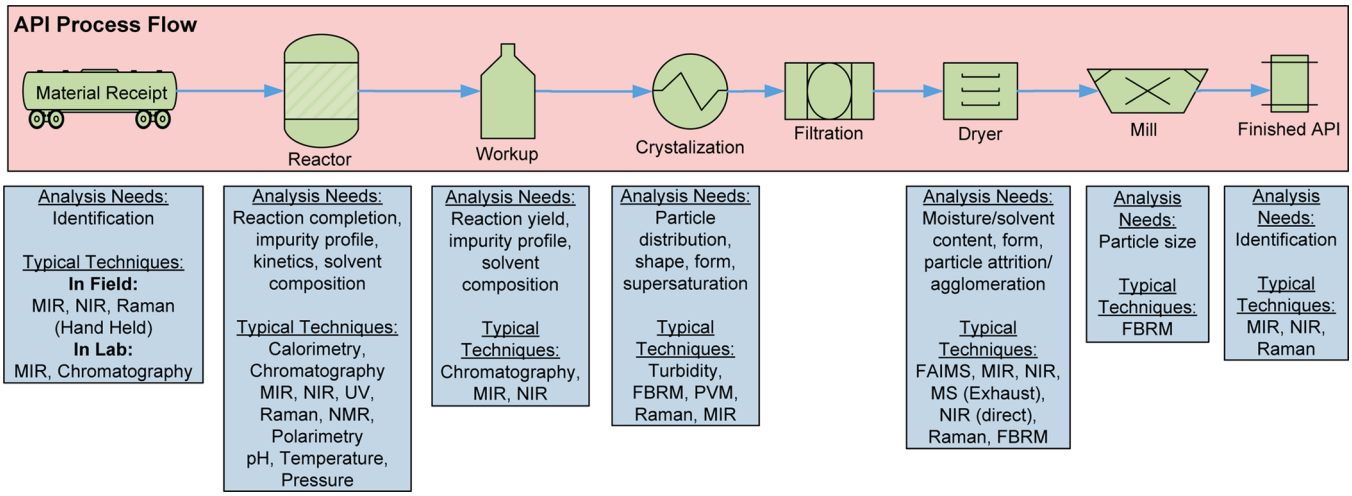

Figure 2. API process workflow and typical analytical tools to provide the desired data. Modified from ref 10.

Appropriate techniques that satisfy these criteria are identified and assessed. Some examples of key factors to be considered when identifying the appropriate PAT tool are included in Figure 1, Step 3. A wide range of PAT tools are available (e.g., all with different capabilities, strengths, and weaknesses). The tools identified should be assessed in a feasibility study, ensuring that the measurement is well understood and can be scientifically correlated to the property of interest.

Once an appropriate analytical tool is identified, its capabilities are evaluated (method development) and conformance to the analytical target profile (ATP) confirmed. The methods discussed in this current manuscript are targeted for process development and understanding, and may be qualitative, a limit test, or quantitative in nature.

1.5. API Process Workflow. Many in situ tools are commercially available for process monitoring, measurement, or control. Common tools that are routinely used in manufacturing include thermocouples and pressure sensors. Spectroscopic tools (e.g., near-infrared,[15−21] mid-infrared,[22−48] Raman,[49−54] UV[55−58] and NMR)[59−63] are utilized for increased analytical specificity (ability to monitor for the presence or disappearance of functional groups during the synthesis). By monitoring these specific functional groups, qualitative trending or quantitative assessment of the reaction component(s) levels is achieved. In situ chromatography,[64,65] mass spectrometry,[66−74] reflectance,[75−77] and calorimetry[78] also have precedence as process monitoring tools.

Figure 2 illustrates typical API unit operations, measurement needs, and precedented PAT tools. Many of these applications will be elaborated on in this paper.

2. CASE STUDIES: PAT APPLICATIONS PERFORMED DURING DEVELOPMENT

The main part of this paper will describe typical examples of how industry applies the PAT toolbox starting from confirmation of material identification and progressing through a typical process workflow (Figure 2).

2.1. Raw Material Identification. The identity of raw materials should be confirmed upon receipt and prior to their use in a manufacturing process. Traditionally, this identification is performed in the laboratory using spectroscopic methods (e.g., IR) and comparison to a standard. While effective, this method can be time and resource intensive. In recent years, advances in the quality and performance of miniaturized spectrometers have facilitated the development of hand-held instruments that can execute identity testing in the warehouse. Many of these hand-held instruments can collect good quality spectra (without sampling of the material) through transparent containers (e.g., glass, polyethylene). The sample spectrum is compared to a standard (library) spectrum built and stored within the instrument for conformance of identity assessment. These instruments are also in widespread use for pharmaceutical counterfeit detection. Raman spectroscopy is the most common technique due to its high specificity and ease of sample presentation, although NIR and MIR instruments are also available and appropriate for certain applications (e.g., drug product excipients). Recent more detailed articles have been published on this topic.[79−81]

2.2. Reaction Monitoring. Process analytical technologies are among the most valuable tools for understanding chemical reactions and the parameters that impact them. By their nature, reaction mixtures change with time and may contain transient species, making it challenging to representatively sample and analyze using off-line analytics. Many reactions involve multiple phases and are both physically and chemically unstable. In these cases, in situ analysis of each phase can provide a wealth of information and opportunities for understanding, optimization, and control which will lead to the establishment of process models, operating space, and a control strategy.

The repeatability and robustness of chemical reaction steps within API processes are affected by many different variables, including raw materials and process parameters. Variability in the performance of reaction steps has a significant potential impact on the quality and yield of the API or intermediate. Thus, good understanding, monitoring, and control of chemical reactions can be critical to the efficient operation of a process. In traditional reaction analysis, the mixture is sampled at defined time intervals; the samples are then manipulated and analyzed by an off-line method which is typically chromatography based. This approach does give some insight into the profile of the reaction but does not give a real time profile. Numerous PAT techniques are applicable to real time reaction monitoring, and the choice of the appropriate technology will depend on many factors. In this section we will describe examples of a selection of different reaction monitoring technologies.

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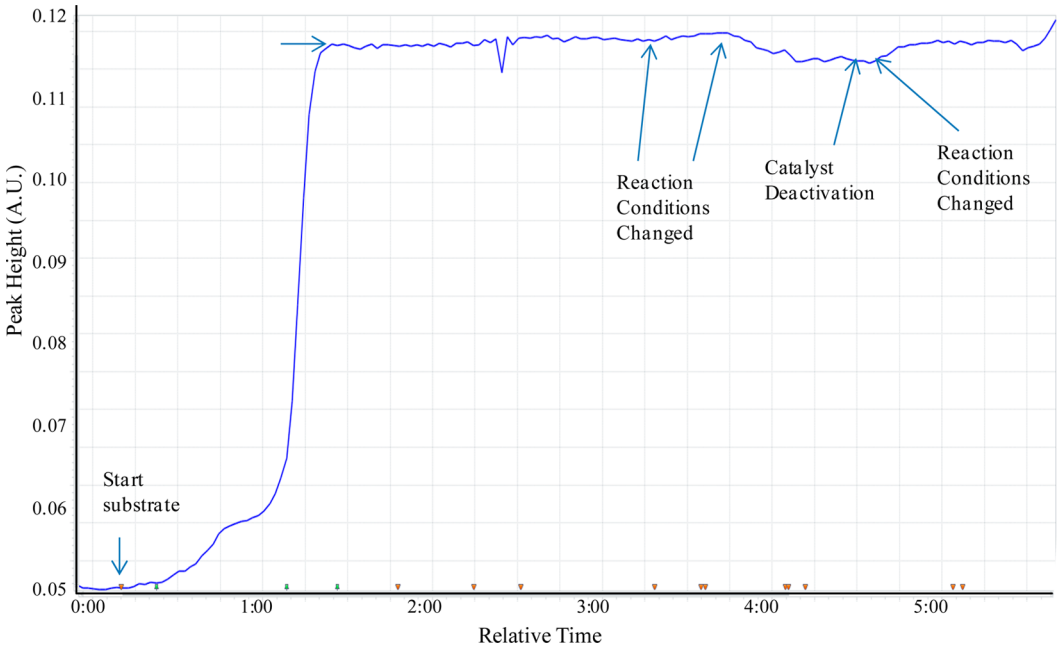

Figure 3. Flow reaction Trend Plot (Product Formation) for screening reaction conditions.

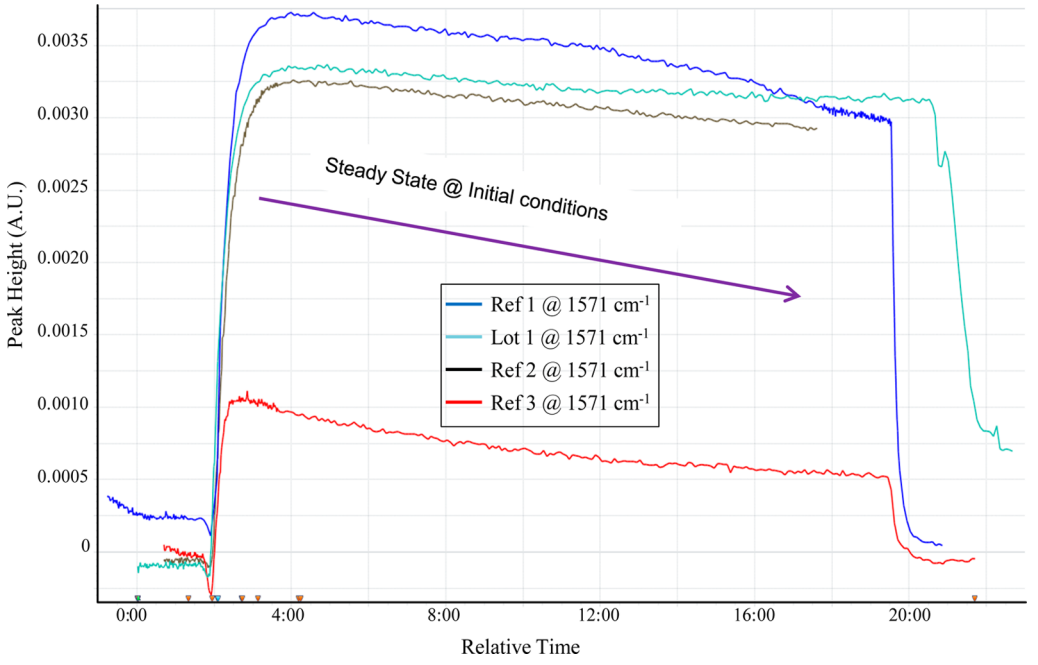

Figure 4. Flow reaction trend plots. Comparison of reaction conditions and catalyst decay kinetics under different reaction conditions.

2.2.1. In Situ Flow Chemistry Reaction Monitoring by FTIR Spectroscopy. Mid-infrared (MIR) spectroscopy is the prime PAT technique used for monitoring chemical reactions and a mainstay in chemistry laboratories, industrywide. An in situ analytical method was utilized to monitor the screening and optimization of reaction conditions, to identify the reaction steady state, and to evaluate catalyst deactivation kinetics in order to expedite development of a flow chemistry process. A MIR spectrometer was chosen based upon the chemistry, and was interfaced to the liquid outlet of a gas liquid flow reactor. Product formation was monitored univariately at 1570 cm^{-1}, and simple peak height trending analysis sufficed to meet process development needs. Samples taken at critical points in the process were analyzed off-line to confirm the MIR results and were available, if needed, for MIR calibration for semiquantitative or quantitative model creation. The flow reaction steady state was achieved at approximately 96% conversion (product formation) under the initial reaction conditions (Figure 3). The impact on conversion to subsequent changes in reaction conditions was rapidly evaluated in situ. The first change to the process parameters resulted in an increased conversion to product while a second change decreased the conversion.

Figure 4 shows an overlay of four successive reactions. This data facilitated the rapid evaluation of run to run conversion and catalyst deactivation. Work completed in the lab reactor facilitated rapid implementation of this process in a kilo lab.

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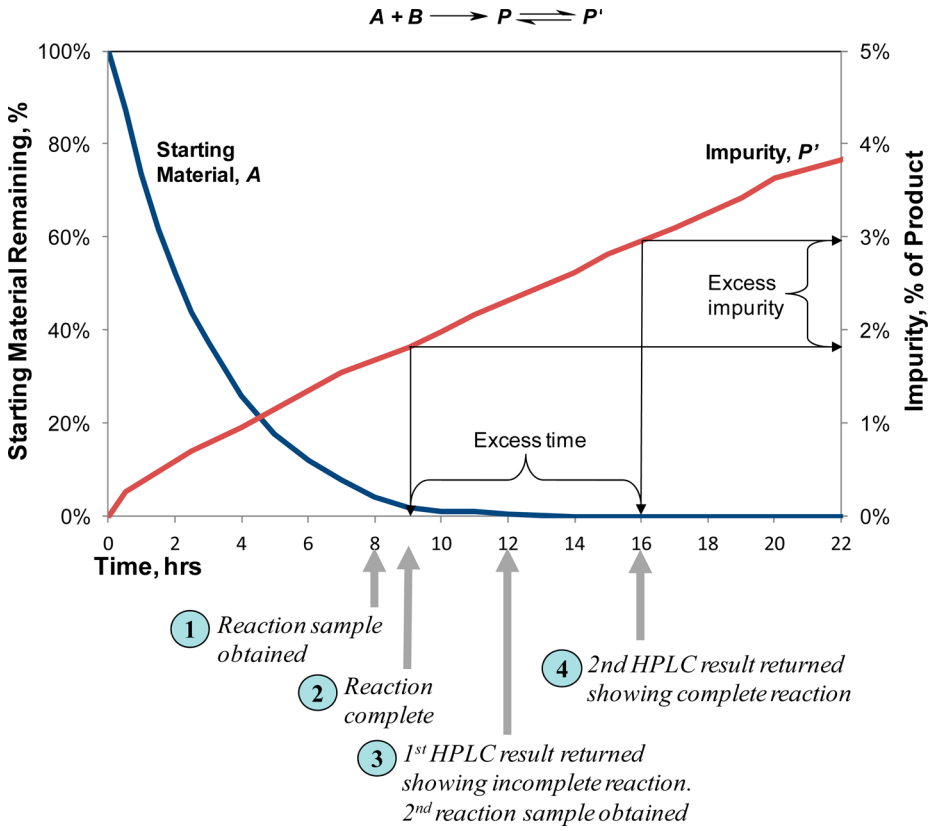

Figure 5. Reaction and analysis of a process that generates a desired product and an undesired enantiomer in stepwise reactions. The starting material, A, curve was generated with in situ FTIR data while the impurity, P′, curve was generated from HPLC results.

The use of MIR spectroscopy for this continuous flow chemistry example allowed the team to optimize process and reaction conditions and understand catalyst deactivation kinetics in real time. The overall process development and scale-up times were reduced, while simultaneously, process understanding increased. The MIR trend plot correlated well with the off-line HPLC results.

2.2.2. FTIR for Improved Product Quality and Increased throughput in Batch Process. In many batch processes, the product of an intermediate step is unstable and can decompose. It can be important to progress forward the product mixture into the next chemical step as quickly as possible following completion of the reaction (i.e., no hold time). In some cases, consumption of the starting material is important to final product quality, but this must be balanced against the quality risks due to formation of degradants of the product due to hold time. Control of the reaction may be required to ensure both product conversion targets are met and process related impurity levels are controlled. An example of this is demonstrated with the reaction of an enantiomerically pure starting material to form an enantiomerically pure product. The product's stereogenic center is relatively unstable and subsequently epimerizes. The challenge is to ensure that both the consumption of starting material and the formation of undesired enantiomer are simultaneously controlled so that neither exceeds specified targets. For a typical off-line (HPLC) IPC in a GMP environment, a minimum 4 h turnaround time from sampling to results in hand is typical. Therefore, a minimum 4 h hold time is built into the process before progression to the next step. This delay poses risks, as epimerization is occurring during the hold time and the undesired enantiomer is accumulating.

Figure 5 illustrates the importance of real time or near real time measurements. The reaction reaches the conversion target within 8−12 h. Based on the ability to eliminate the undesired enantiomer, the specification is set at 3.0%. An IPC sample (**1**) is obtained (at 8 h) for off-line analysis. The IPC result is obtained at 12 h (**3**), showing incomplete conversion (as this IPC sample was from the 8 h time point). Another IPC is immediately obtained to ensure reaction completion. Note: Using in situ analytics, it was determined that the reaction met its completion target at 9 h (**2**), 1 h after the (8 h) IPC sample was pulled. At 16 h (**4**), the off-line analytical result is released, showing the reaction is complete, and the next step may proceed. Although this 12 h IPC met the starting material target and the undesired enantiomer specification, the enantiomer has continued to accumulate and is now at a higher level than the analysis indicates—approaching a level where it is inefficiently removed in downstream processing.

Real time or near real time monitoring of this process would provide much more efficient control of undesired materials by revealing their levels as a function of reaction time. In addition to providing an example of the impact PAT can provide for quality assurance, this example also illustrates the process throughput gains that could be achieved with real time analysis. In the scenario shown, the processing time was reduced by several hours (a minimum of four) by replacing the sampling and off-line testing with PAT.

2.2.3. UV−Vis Spectroscopy. An in situ method for monitoring reaction completion was sought to prevent exposure and handling of a potentially explosive reaction mixture (a risk if the sample solution precipitated and dried). The product (a diazonium salt) has a strong absorbance band at ∼310 nm and

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was used to monitor the progression and completion of the reaction. Figure 6 shows the UV−vis spectra for a typical reaction.

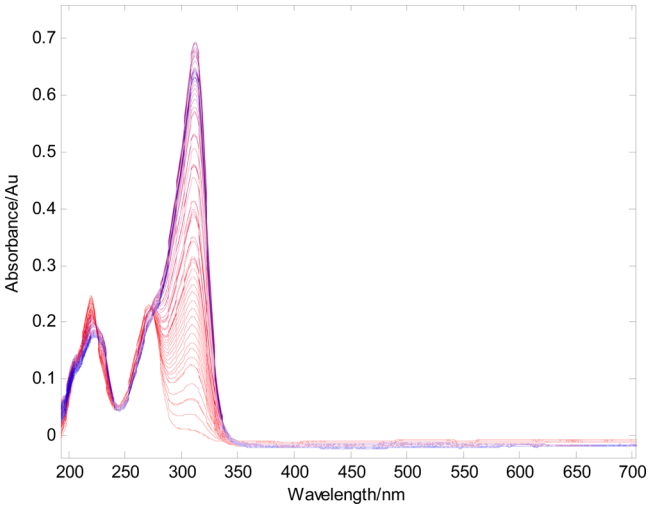

Figure 6. UV−vis spectra for the reaction forming a diazonium salt product, colored red to blue with time.

A quantitative method for reaction monitoring was developed. During method development, a PLS calibration was preferred over simple univariate peak height trending for increased method robustness. A calibration was generated using limited data points, by performing multivariate curve resolution on reactions to obtain estimated product profiles (Figure 7a) and then converting these to quantitative profiles (Figure 7b) with off-line samples. The PLS calibration was then implemented to analyze in real time.

The use of in situ UV−vis spectroscopy to monitor the formation of the product minimized potential worker exposure to the product and minimized the safety concerns associated with sampling and off-line testing. Multivariate curve resolution was used to generate reference values to build a PLS calibration, by scaling the product profile (green trend in Figure 7a) using off-line analysis of the reaction end point. This allowed a "fit for purpose" PLS calibration to be built with one off-line reference point. The UV PLS profile data from this calibration (Figure 7b) was in excellent agreement with off-line end point data and hydrogen uptake for several subsequent batches. The use of in situ analytics facilitated the spotting of a potential reagent charging problem in real time for one batch.

2.2.4. Raman Spectroscopy for Online Monitoring of a Heterogeneous Reaction. A process was developed using sodium hypochlorite for an oxidation reaction. The reaction medium was aqueous, and both the starting material and product were insoluble during the reaction (slurry). The reaction was carried out at a high starting material concentration, and representative sampling of the mixture for off-line analysis was challenging. An in situ method for reaction monitoring was sought. Raman spectroscopy was evaluated and determined to be applicable (and subsequently demonstrated capable of monitoring additional steps in the process). Figure 8 shows Raman spectra and trend plots of the spectra for several batches. The methods were transferred to a manufacturing site, in which a Raman spectrometer was installed in large scale equipment.

The ability of a commercial Raman instrument to be multiplexed with each probe located a significant distance (>50 m) from the spectrometer facilitated this installation and implementation. The process data generated was invaluable for optimization and control of the process.

2.2.5. Mass Spectrometry. Carbon dioxide was formed during an amine deprotection step, and in order to understand and optimize the process, monitoring CO_2 levels in situ was sought. The process (Figure 9) involved the removal of a *tert*-butyloxycarbonyl (*t*-BOC) amine protecting group from a substrate molecule, followed by a coupling reaction with (*S*)-2-hydroxyisovaleric acid (HOVal). The hydroxybenzotriazole sodium salt (NaOBt) catalyzes the coupling step. A symmetrical urea impurity is generated from the reaction of the deprotected intermediate with CO_2 in the presence of EDCI and is difficult to remove from the product.

The approach to minimize the formation of the urea impurity was to eliminate the CO_2 from the reactor prior to the coupling step. FTIR-ATR spectroscopy (O−C−O asymmetric stretch band at 2340 cm^{-1}) was employed for monitoring the liquid phase, and mass spectrometry (MS) (molecular ion at m/z 44) was used for monitoring the gas phase.

For development of the model, the following key assumptions were made:

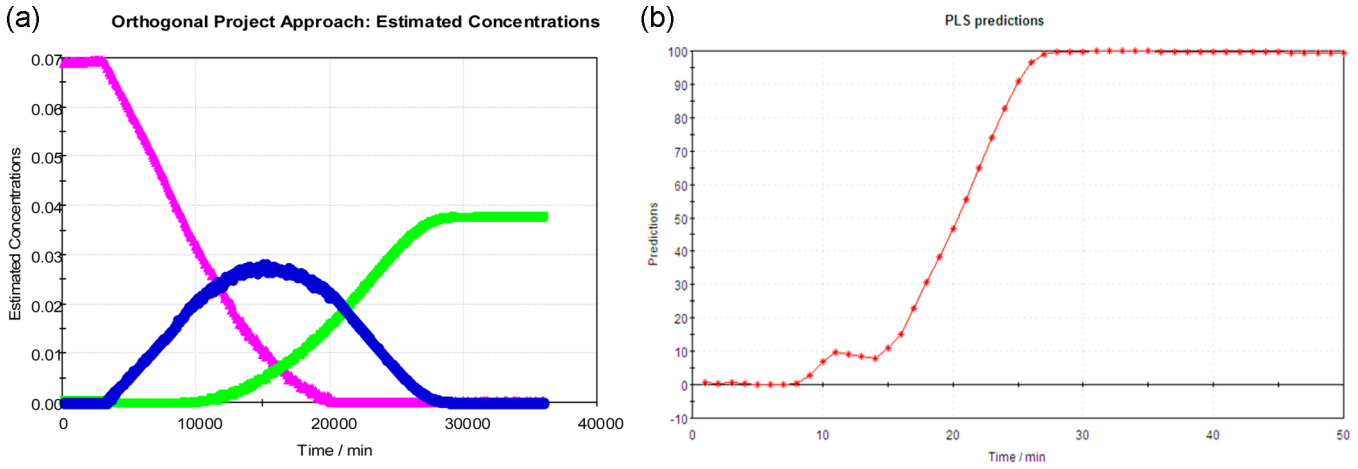

Figure 7. (a; left). Estimated relative concentrations of the reactant (purple), product (green), and transient species (blue) over time. (b; right). Quantitative profile (percent conversion) of the product formation with time for one manufacturing batch.

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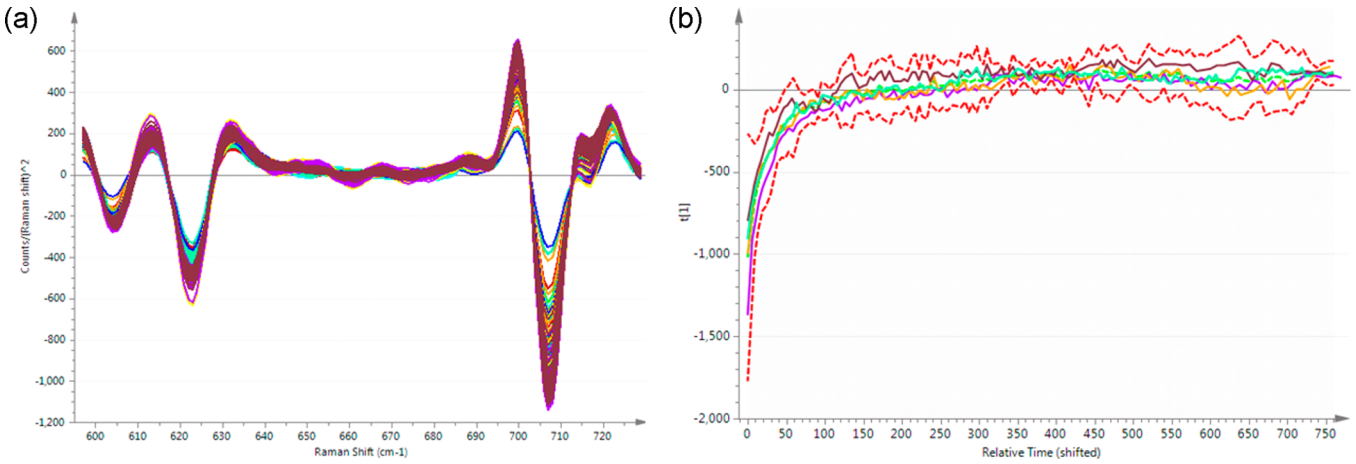

Figure 8. (a; left). Second derivative Raman spectra showing spectral changes as the reaction progresses. (b; right). Batch trends of the first principle component (PC) from batch PC analysis of the spectral data.

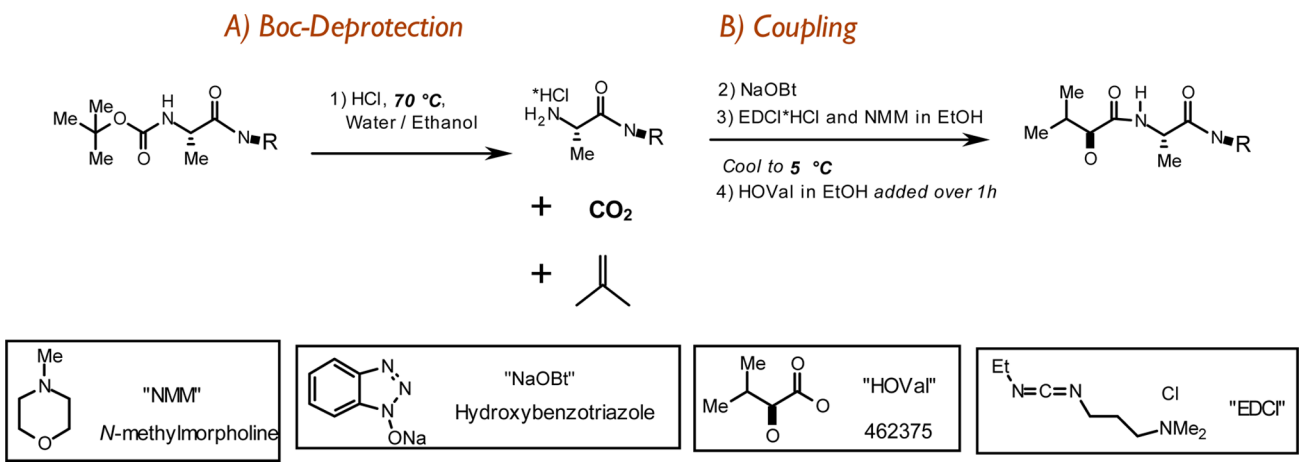

Figure 9. Reaction scheme for generating active pharmaceutical ingredient.[82]

The gas and liquid achieve an equilibrium condition described by the Henry's law relation

$$p_{CO2} = HC_{CO2}$$

The volume of the liquid phase does not change, so the mass transfer can be described by the Fick's law relation:

$$\left(\frac{dC_{CO_2}}{dt}\right)_L = -k_L a\left(C_{CO_2} - \frac{p_{CO_2}}{H}\right)$$

The rate of change in partial pressure is given by the rate of removal by the sweep gas and the rate of desorption from the liquid into the gas.

$$\left(\frac{dp_{CO_2}}{dt}\right)_g = -\frac{F_g}{V_g}p_{CO_2} + k_L a(HC_{CO_2} - p_{CO_2})$$

The total gas flow rate, F_g is the sum of the purge gas flow and the volumetric flow of CO_2 desorbed from the liquid phase, given by

$$F_g = \frac{dV_g}{dt} = F_{purge} + \frac{RT}{P}V_L k_L a\left(C_{CO_2} - \frac{p_{CO_2}}{H}\right)$$

The CO_2 partial pressure and concentration values were simultaneously measured in the gas and liquid phases, respectively, using the online measurement techniques. Henry's law constants were obtained under equilibrium conditions with nominally pure CO_2 in the headspace at atmospheric pressure.

The headspace was purged with argon at a known flow rate while measuring the CO_2 partial pressure and concentration values with mass spectrometry and FTIR, respectively, with respect to time. Results of the analyses and the model are shown in Figure 10, and the measured and modeled results matched well.

CO_2 will purge from the reactor more readily at higher temperatures where solubility in the solvent is reduced and the mass transfer rate is increased. However, there were practical and environmental considerations. Sparging the reaction mixture with an inert gas was an impractical option because the process was operated at the minimum stir volume, with the agitator barely submerged. With the deprotection carried out near the solvent boiling point, environmental considerations of solvent use, process efficiency, and simplification of process operability made it preferable to minimize lost solvent through the reactor vent due to entrainment.

Additional studies revealed a quality consideration. At the 70 °C deprotection temperatures, progressive decomposition of the product was observed, making it imperative to cool the reactor as soon as practical following completion of the deprotection reaction. However, cooling the reactor to 5 °C for the coupling reaction resulted in enhanced partitioning of CO_2 from the large

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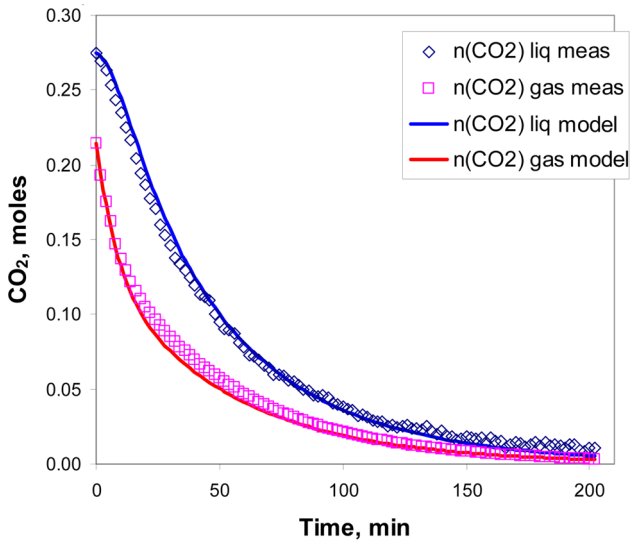

Figure 10. Data and model results for determining a k_La parameter for mass transfer from the liquid phase to the gas phase in a 10-L reactor.

headspace into the reaction mixture (resulting in a higher urea level).

Both van't Hoff and Arrhenius relationships were obtained to understand the temperature dependence on solubility and mass transfer rates, respectively. Based on fundamental principles and experimental data, the design space was constructed (Figure 11).

This design space set the target for the PAT technique(s) that might be employed. The lowest control limit concentration in this space occurs at the minimum stir volume where this particular process was designed to operate, and at 40 °C (indicated by the arrow). This point in the parameter space fixes the lower limit of detection requirement for any PAT to be used to control the process within this space. While the design space in Figure 12 appears to be large, providing large variability in temperature and reactor fill volume, the control concentration, $(C_{CO_2})_{control}$, is at a trace level quantity and pushes the limits of standard measurement capabilities.

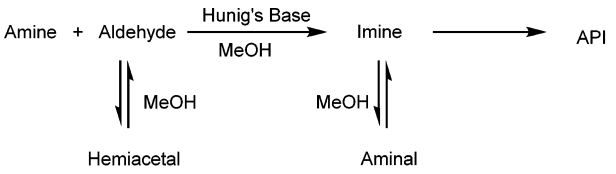

Figure 12. Reaction of an amine and aldehyde to form an imine.

With the assessment that CO_2 had to be monitored/controlled at a trace level, focus centered on identifying the appropriate technology for the analysis. A CO_2 monitor can monitor either the gas phase or the liquid phase. Because removal from the liquid is rate limiting, measurement of this phase was the desired option. However, the sensitivity of known technologies was not adequate. By understanding the distribution of CO_2 between the liquid and gas phases via the process model, the option of controlling the impurity formation through monitoring the gas phase became an option. Mass spectrometry provided sufficient sensitivity (LOD = 0.006% mol/mol) for measuring the gas phase CO_2 down to the control limit of 0.5%. A simpler approach was preferred, and a nondispersive IR (NDIR) CO_2 sensor was evaluated. Preliminary results showed adequate sensitivity (LOD = 0.01%) and a linear dynamic range that matched the mass spectrometer over the concentration region of interest. Before these applications could be fully implemented in a commercial manufacturing process, the project was terminated. As clinical projects do not always progress to commercial medicines, a fit for purpose balance must be struck in the precommercial landscape for in situ monitoring and control methods. In this case, use of PAT led to fundamental understanding on formation and control of a process impurity, while taking into account significant gas liquid mass transfer influence on the process.

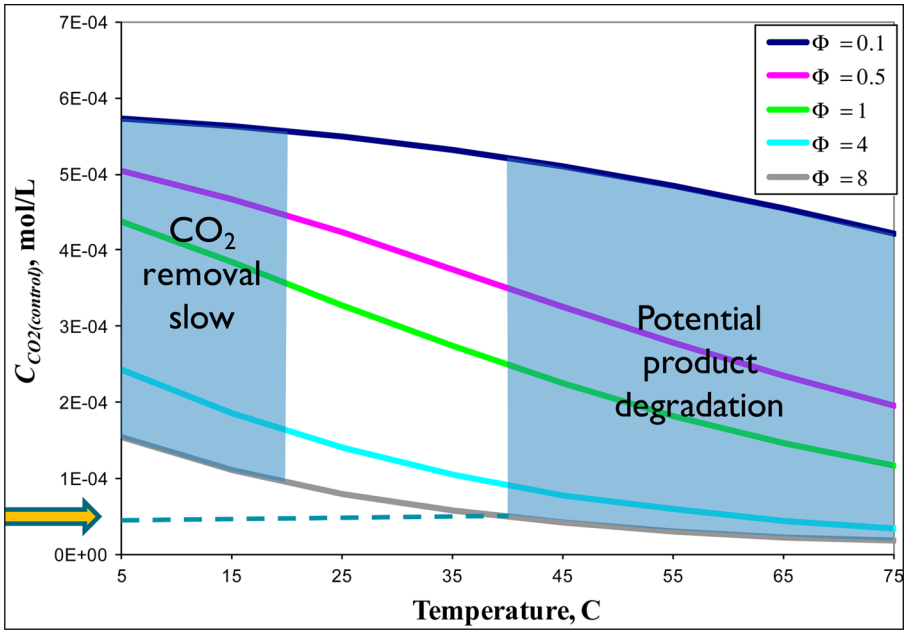

Figure 11. Design Space: Control limit for dissolved CO_2 as a function of temperature and reactor fill volume, designated by the gas liquid volume ratio, Φ. The arrow shows the lowest control limit required to measure CO_2 for the entire design space.

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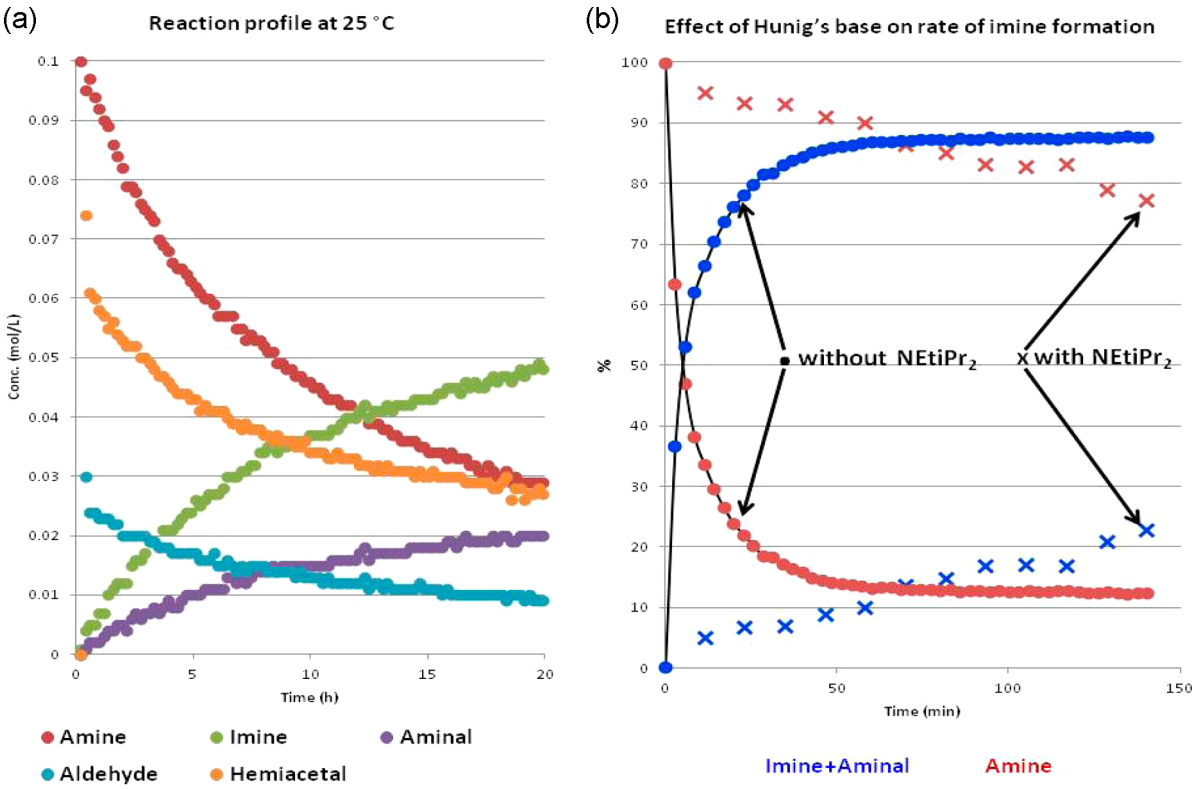

Figure 13. (a; left) Representative reaction profile generated using online NMR analysis. (b; right) Rate of formation of imine with and without Hünig's base.

2.2.6. Online Nuclear Magnetic Resonance Spectroscopy. Online NMR (nuclear magnetic resonance) spectroscopy involves flowing a continuous recirculating stream of reaction mixture from a reaction vessel to the NMR. NMR spectra are then recorded at regular intervals to monitor the progress of the reaction. Advantages to this technique include the following: the inherent quantitative nature of NMR, no sample isolation or manipulation, and in situ structural characterization of intermediates that may not survive isolation from the reaction mixture.

In this example, online NMR was used to investigate the reaction of an aldehyde and amine to form an imine intermediate (Figure 12), which was telescoped through to the API in a two-step procedure. The purpose of the investigation was to generate a kinetic profile of this reaction, which could then be used to predict the performance of the process at the elevated temperature required for scale-up. The reaction was conducted in methanol in the presence of Hünig's base (required to maintain the solubility of the final API). Online NMR was used to provide detailed process understanding, and it uncovered that a number of complex equilibrating processes were present in the reaction mixture.

A representative reaction profile is shown in Figure 13a. Each of the components were monitored by tracking the integral of a unique characteristic ^{1}H NMR resonance. Apart from the aldehyde and amine starting material and imine product, other species were also observed, These were identified as the hemiacetal and aminal, which result from reaction of methanol with the aldehyde and imine, respectively. The results of the experiments were used to calculate rate and equilibrium constants for the processes taking place in the reaction. Online NMR was not only advantageous in tracking multiple labile species in the reaction matrix, but also provided valuable in situ structural information. The quantitative data generated using online NMR was inputted into kinetic modeling software to predict the outcome at elevated temperature on scale-up.

Additional experiments conducted using online NMR demonstrated that a substantial increase in reaction rate occurred when Hünig's base was removed from the reaction. As is shown in Figure 13b, reaction completion occurred in approximately 100 min without Hünig's base, while at the same time point under the equivalent conditions with Hünig's base in the reaction mixture, conversion to imine was only 18%. This observation meant that the imine intermediate could now be generated at ambient conditions in less than 2 h, and Hünig's base could be added prior to conversion to the final API, without impacting the outcome of the process or the quality of the product obtained.

2.2.7. Online HPLC To Monitor and Control a Continuous Process. A multiple step continuous API process was developed and optimized. In situ spectroscopy was implemented to monitor for reaction steady state at several synthetic steps. However, the spectroscopic method was not specific or sensitive enough to monitor for the presence of low level impurities formed during the chemical syntheses. Chromatography was selected as the appropriate technique for the low level analysis need.

A sampling device was developed and was used to representatively sample the process flow and to interface the reactor to the HPLC. The online HPLC was implemented to track impurities postreaction for process understanding and control. Figure 15 shows process monitoring data from one chemical step. multivariate statistical process control (MSPC) was performed on the HPLC data to monitor deviations from steady state. When a deviation from steady state is observed, HPLC chromatograms can be visualized and an impurity less polar than the API is shown to be growing (lower right of Figure

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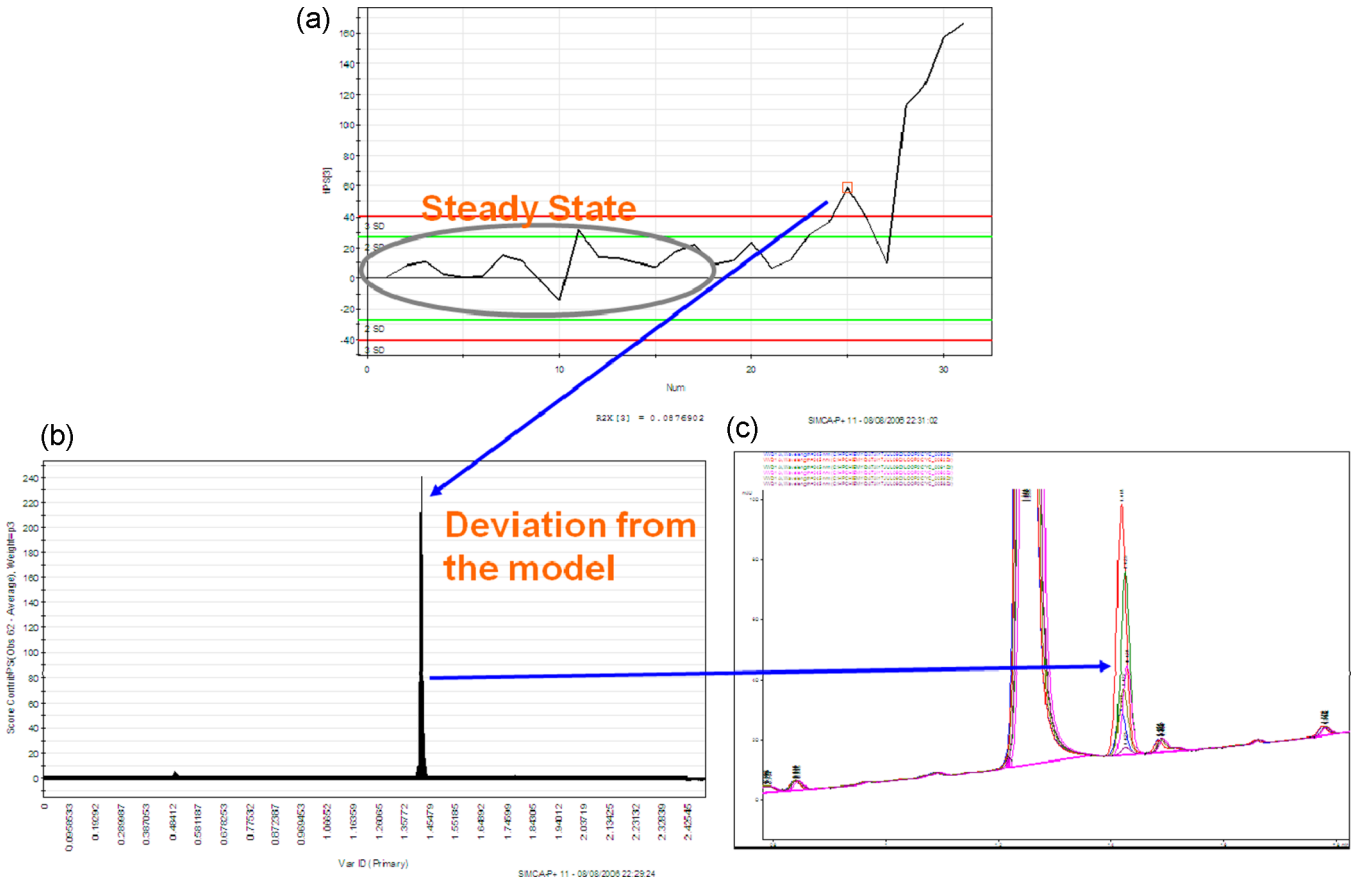

Figure 14. (a; top). Statistical control chart from MSPC analysis in real time. (b; bottom left) Loadings plot. (c; bottom right) Chromatogram for the process deviation from steady state using online HPLC.

14). The conditions are subsequently updated to return the process to steady state.

The development and implementation on an online chromatographic solution enabled rapid purity analysis at multiple sample points in near real time. The data analysis and process monitoring strategies were successfully developed and implemented to process the large amount of data generated by disparate analytical tools.

2.2.8. Multiple PAT Tools To Interrogate a Process. By simultaneously employing multiple in situ analyzers to study a process, multiple phases and multiple species can be studied to determine their interactions.[83,84] This "multidimensional" approach to understanding the process is an aid to fully defining the parameter space in which the process can be operated. It also provides an opportunity to evaluate and select the best technique and phase to measure for potential implementation of a control technology (if required).

2.2.8.1. Multiple PAT Techniques: Example 1. Silylation of cytosine demonstrates an example of using multiple PAT tools to interrogate a process. Figure 15 illustrates some high value information available when multiple PAT techniques are appropriately selected and applied. The use of multiple PAT tools to interrogate a process is an often used approach early in the development of the synthetic process, when the project team has not yet identified the critical quality attributes or process parameters. Via the application of fit for a purpose PAT, a good understanding of the process and parameters that should be monitored in subsequent reactions is developed.

The waterfall plot in Figure 16 shows the MIR analysis of this process, demonstrating good selectivity for the reagent and product. The cytosine was not observed in this (solution) phase because it was insoluble and not detected by MIR.

With these capabilities in place, various catalysts were evaluated and it was determined that the reaction could be performed below the boiling point of the HMDS (~100 °C). Using multiple PAT tools, a more complete understanding of the process was obtained (in a shorter amount of time) than would have been possible with a single analyzer. The data was used to determine reaction pathways and kinetics, material balance, and safety hazards. In addition, several options were identified for real time process control (if necessary).

(1) Monitoring of the gas phase (MS or a simpler analyzer, such as a spectrophotometer with a gas cell). Monitoring pressure change from rapidly evolved NH_3 gas was a possibility that could lead to the most desired control system.

(2) The liquid phase could be monitored by FTIR. With the separation of reactant and product absorbance bands, the possibility of a simple, single wavelength IR sensor was considered.

(3) The slurried solids were readily detected with the FBRM and a step change in turbulence was observed at the reaction end point. A turbulence sensor might be recommended for this application.

(4) The reactor temperature (grey line in graph in Figure 15) was not particularly useful, but the heat flow curve (magenta line) indicated a sharp change at the reaction

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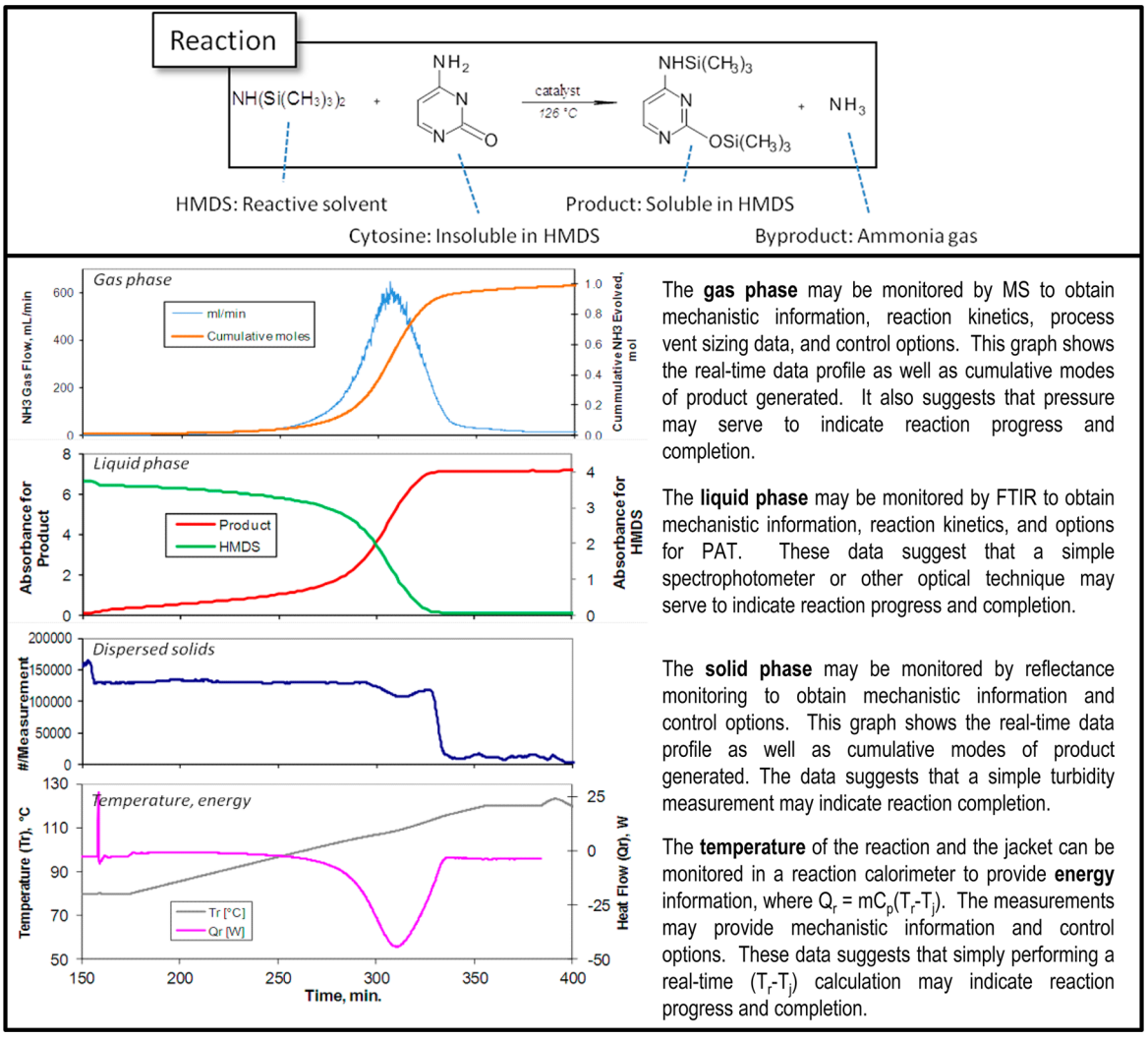

Figure 15. Monitoring of a reaction in early phase development with multiple PAT tools (MS, FTIR, FBRM, temperature).

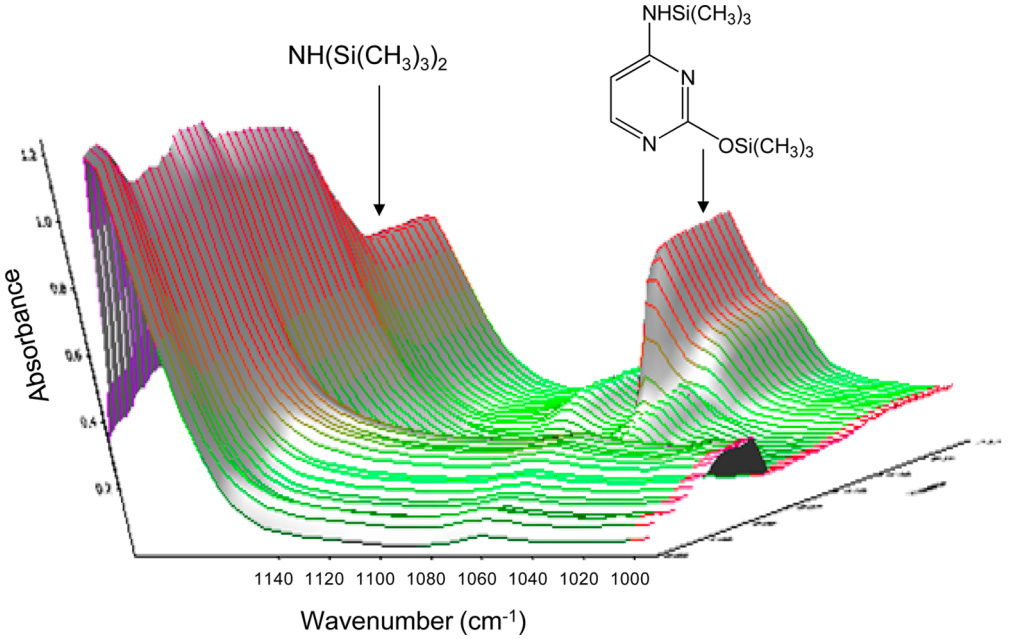

Figure 16. Waterfall plot demonstrating excellent selectivity for monitoring the reaction progress.

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end point. The heat flow is obtained from the difference between the temperatures in the reaction mixture and the reactor jacket, or ΔT. These temperatures are measured in commercial processes; therefore, the most straightforward control strategy may be some nonroutine utilization of these data, such as a variation of monitoring ΔT to determine the reaction end point. (See also the example below.)

2.2.8.2. Multiple PAT Techniques: Example 2. A sulfonamide is prepared by charging excess aqueous ammonia to a sulfonyl chloride dissolved in isopropyl acetate (IPAc) (Figure 17). In a subsequent distillative crystallization process, the product was isolated by removing components of the biphasic reaction mixture until the product precipitated.

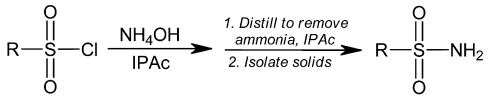


Figure 17. Reaction scheme for preparing a sulfonamide.

The heterogeneous process was irreproducible when attempting control based on time and temperature. The product was also found to be unstable at the final distillation temperature; therefore, it was important that the hold time following precipitation be minimized. An in situ method for process end point determination was sought.

To maximize the generation of information per experiment, the process was performed in a reaction calorimeter equipped with an FTIR (to monitor the liquid phase), a MS (to monitor the headspace gases), and a FBRM (to monitor the formation of solids). The trend plots for each of these analyzers (Figure 18) illustrate how the various technologies produce valuable information and might lead to the detection of the reaction end point (indicated on the plots by an asterisk).

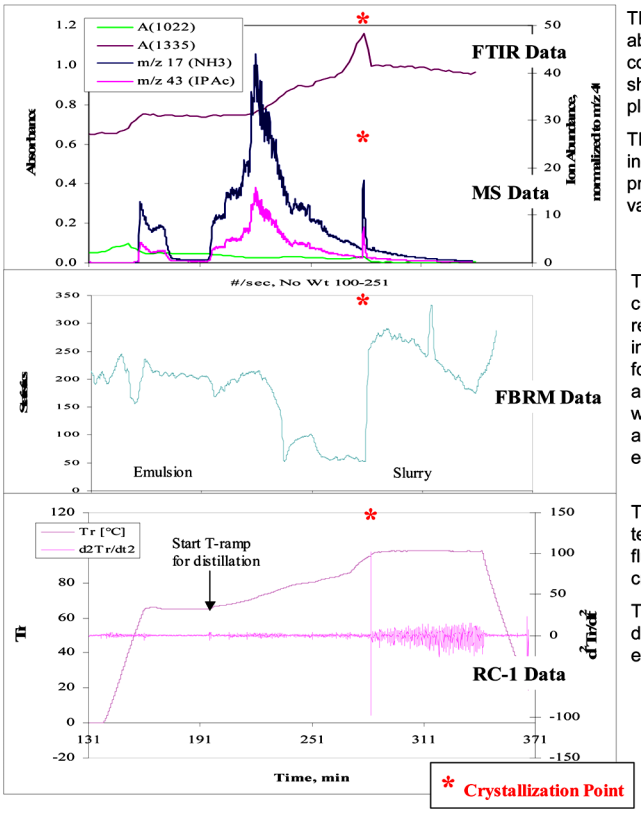
A great deal of fundamental information can be extracted from each of these PAT tools. With the immediate objective of enabling the process to supply clinical trial materials, evaluation of the data focused on the process control strategy. The use of multiple analyzers in parallel not only provided a more comprehensive understanding of the process (revealing information not provided by off-line or single in situ analyzers), it also confirmed the process control strategy that using a simple univariate measurement was valid. Several control options were presented to the manufacturing team.

(1) The FTIR demonstrated the capability to monitor the increase and sudden drop in concentration of the product. A simple spectrophotometer might be the technology of choice. In parallel, the mass spectrometer appears to have demonstrated that the detection of a pressure spike or a spike in the vent line flow rate might suffice.

(2) In the case of the formation of solids, the reflectance monitor results indicate that an inexpensive turbidity sensor might suffice.

(3) The second derivative treatment of the temperature data provided a precise indication of the end point and would require a very simple algorithm to be applied to the continuously generated raw temperature data.

2.3. Work Up. The unit operations downstream of reaction play an important role in quenching unreacted reagents and in removing byproducts and impurities. While in most cases, the API crystallization affords impurity clearance, the extent of



The **liquid phase** is monitored by FTIR shows an increase in absorbance as the reaction proceeds and the product is concentrated in the solution. When the product precipitates, a sharp drop (in solution concentration) is observed in the trend plot.

The **gas phase** is monitored by MS provides trends that indicates the purging of ammonia and isopropyl acetate. The precipitation event is marked by a "spike" in headspace vapors due to an exothermic event.

The **solid phase** data is monitored by FBRM, displayed as cumulative response vs. time. The trend reveals an unstable reflectance signal due to the emulsion's multiple refractive indices (generated during the stirred distillation). This is followed by several minutes of relatively stable reflectance as ammonia bubbles and the dispersed isopropyl acetate phase were removed. A sharp increase in reflectance is observed at the end of the process and corresponds to the precipitation event.

The **temperature** is plotted and monitored. One plot displays temperature as measured in the reaction medium. A small fluctuation in temperature can be detected due to the crystallization exotherm.

This **temperature** data was processed by taking the second derivative as a function of time (second plot), thereby greatly enhancing the detection of the endpoint.

Figure 18. Reaction and analysis of a process with multiple tools (MS, FTIR, FBRM, temperature).

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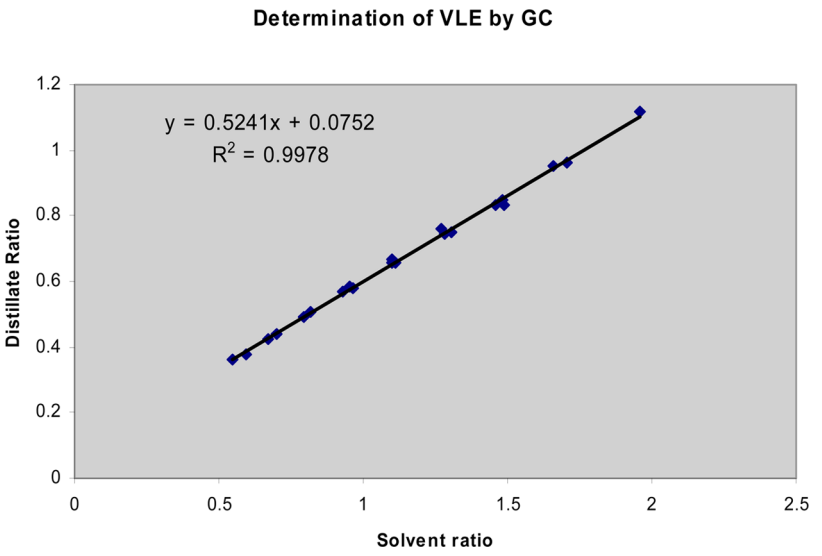

Figure 19. Determination of vapor liquid equilibrium by GC.

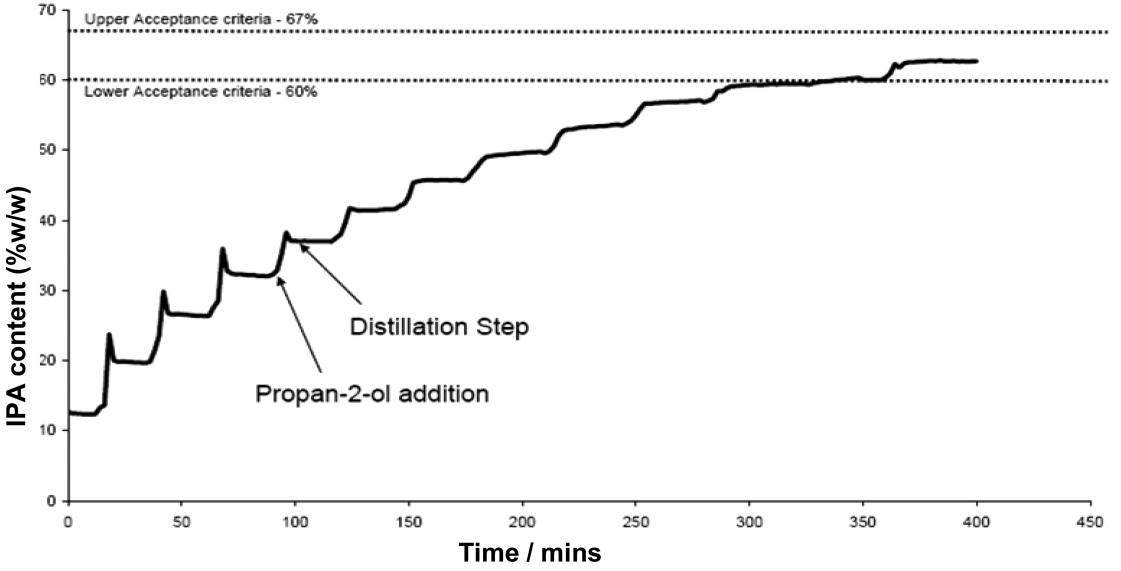

Figure 20. Distillation and solvent swap profile showing the change in composition over time.

removal and the types of impurities present in the system may require work up of the process stream dedicated to removing certain impurities that either have limited clearance in crystallization or can impact the crystallization itself in terms of API physical properties. The process stream also goes through needed solvent changes and filtrations prior to API isolation. The use of PAT can be extremely beneficial in work up operations where determination of process parameters is either critical to control API CQAs or important to ensure consistent performance and yield of the process.

2.3.1. Near IR for Solvent Composition. A quantitative measurement of solvent composition during a "put and take" stepwise solvent exchange process was sought in real time. Off-line sampling of a supersaturated solution at high temperature is difficult, could cause processing issues, could bias results, and could impact worker safety. Therefore, a measurement of solvent composition was desired using in situ analysis. In this process, the ethyl acetate reaction solvent is distilled off and replaced by isopropyl alcohol (IPA). The final concentration of IPA was defined as a critical process parameter (CPP).

NIR was selected as the PAT technique based upon the chemistry, and a method was developed for measuring the solvent composition of the distillate. This approach was favored over direct measurement, as the NIR calibration could be developed using experimental design for the solvent mixtures without the impact of API in the calibration. The composition in the vessel could be inferred from the vapor liquid equilibrium (VLE), which was determined experimentally using GC (Figure 19).

The method was developed and transferred to a manufacturing site where it was validated. A typical profile from the solvent exchange is shown below in Figure 20.

The method was included in regulatory filing as an alternative method to control the solvent composition, and it has been used to control the process.

Several important benefits were demonstrated from this work. The NIR method reduced the crystallization time by approximately 3 h per batch. This eliminated the need for sampling and off-line GC analysis and the associated resources and instrument use/costs. The in situ method also provided

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improved process control. The regulatory submission included PAT for process control, in line with FDA expectations, and was accepted by all regulatory authorities.

2.3.2. Conductivity Measurement for Salt Content. In the development of an API crystallization involving addition of aqueous NaCl as the antisolvent, the product cake is washed with water multiple times to remove residual NaCl. Excessive cake washing was avoided, as it caused significant yield loss. The validated method for determining the salt content was measuring sodium or chloride by inductively coupled plasma (ICP) or ion chromatography (IC) techniques in the dried product. For the development work, the team sought a quicker approach to determine residual salt content by monitoring in the API wet cake. As experimental designs around filtration to robustly remove residual salt were being investigated, a large number of samples were anticipated, and would result in significant analytical resources to analyze. To improve the turnaround time and reduce resources required for this analysis, a conductivity probe was evaluated as a PAT tool to determine NaCl concentration in the spent wash. Using a mass balance for NaCl across the streams, the expected salt content in the final API was computed. A calibration data set was generated at varying aqueous NaCl concentrations as shown in Figure 21.

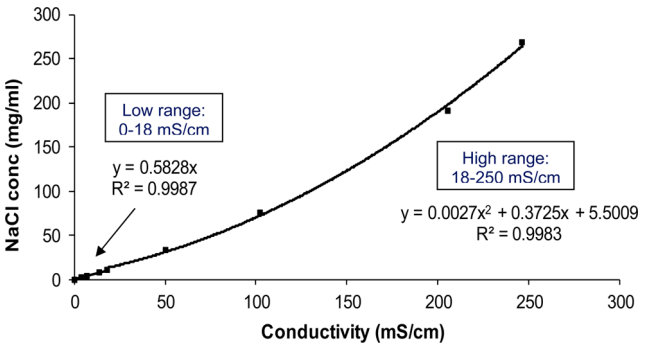


Figure 21. Determination of NaCl concentration as a function of conductivity.

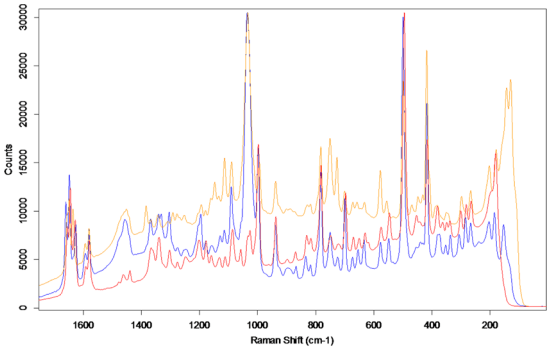
Two calibration models were used (one for the low (0−18 mS/cm) and the other for the high (18−250 mS/cm) conductivity range), as a single calibration curve over the entire NaCl concentration range biased the low concentration prediction. These models provided a reasonably accurate prediction of residual salt in the API for these development samples. Thus, the use of a simple PAT saved the development team many hours of analysis time where a reasonably accurate quantitation was sufficient. While a conductivity probe is a useful PAT during process development, one could envisage use of such technology in a continuous extraction scenario for in situ monitoring of spent wash composition.

2.4. Crystallization and Polymorph Monitoring. Crystallization is one of the most critical steps toward successful isolation of API. A controlled crystallization process can have a great influence on the ability to meet critical quality attributes requirements such as desired polymorph, particle size distribution, crystal morphology, as well as target purity. A variety of in situ and in-line techniques, including focused beam reflectance measurement (FBRM), Raman spectroscopy, turbidity measurement, and particle vision measurement (PVM), are used to develop, optimize, and control crystallization processes.[85,86] FBRM is a high speed scanning laser beam-based particle characterization tool that directly provides chord length data, which in turn provide particle size data and population trends of particles in suspension in real time.

2.4.1. FBRM. During the initial stage of process development for an API, the filtration step for the isolation of the final material was found to be very slow. For a 60 L reaction mixture, approximately 10 h of filtration time was required. Off-line particle size measurement showed that the API had small particle size (D90 ∼ 10 μm) but, more importantly, contained a significant amount (>3%) of fine particles (smaller than 1 μm). This was identified as the root cause for the slow filtration rate. From a clinical point of view, this program was categorized as a potentially high dose program. This required us to have a good control on solid density to achieve high strength capsule filling.

To control particle size during crystallization, three different approaches were tested—cooling rate variation along with stepwise cooling, effect of seeding, and heat cycling to promote crystal growth. In each case, particle size distribution (PSD) was evaluated using FBRM in real time, and an off-line laser diffraction technique was used for isolated material.

After initial screening, heat cycling studies provided the most promising results. An increase in particle size through a heat cycling technique is known as Ostwald ripening. In this thermodynamically driven process, larger particles grow in size at the expense of smaller particles. In this case, temperature was



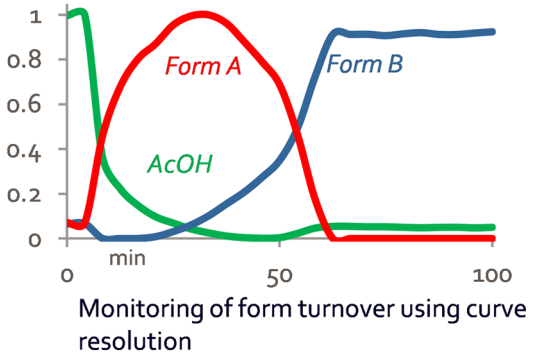


Figure 22. (a; left). Raman spectra of the three polymorphic forms. (b; right). Monitoring of form turnover using multivariate curve resolution (profiles scaled 0 to 1).

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cycled between 20 and 60 °C three times. Using real time FBRM analysis, it was observed that finer particles decreased as heat cycles continued.

Further optimization studies indicated that three (3) heat cycling between 20 and 60 °C with slow cooling (20−30 °C/h) and hold at lower temperature (0.5−1 h) would provide a larger particle size for API (D90 ~ 20 μm) with significantly reduced amount (~0.4%) of fine particles (smaller than 1 μm).

This heat cycling process was then successfully implemented in pilot plant runs for several batches, which resolved the filtration issue. Approximately 450 L of reaction mixture was filtered in less than 1 h in most cases. Off-line analysis of final API showed consistent particle size (D90 ~ 20 μm) with reduced fine particles (~0.3%) and met the required bulk density and tapped density targets.

2.4.2. Polymorph Monitoring. Three different crystalline forms of an API were identified through screening. Form A (needle-like) is the desired form for formulation, whereas form B (prismlike) is the most thermodynamically stable form. The predominance of each crystalline form depends on the conditions of the crystallization process. Form C has only been observed under specific and extreme conditions.

In the final step of the API process, a reverse addition of the potassium salt of the Intermediate grade (IG) API is added to a MeOH/AcOH mixture to crystallize final grade API, form A (as a free base). AcOH quenches the potassium to form potassium acetate during the crystallization. Depending on factors such as the purity of the IG or the temperature of the crystallization, form B can also nucleate, leading to undesired turnover of form A to B.

Raman spectroscopy (Figure 22) was used to monitor the form turnover in situ on a wide range of experiments during process design and optimization:

Various solvents were spiked into the crystallization process to determine their inhibitory effects on the rate of conversion of form A into form B. Beginning with form A, the formation of form B was monitored. As shown in Figure 23, the form A to form B conversion rate was reduced in the presence of these two solvents.

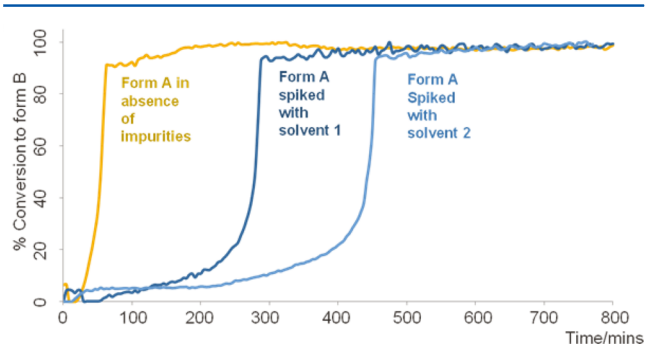

Figure 23. Relative rates of conversion of form A to form B in the presence of solvents 1 and 2 (all 3 profiles were scaled 0 to 100).

A quantitative model (PLS) was built to measure levels of form B at the end of the turnover. In the crystallization conditions where turnover did not go to completion, the quantitative Raman method allowed the quantification of Form B in the absence of other suitable in situ quantitative methods (confirmation by off-line XRPD).

Raman spectroscopy coupled with suitable chemometric tools allowed the successful monitoring of the rate of turnover between crystalline forms, enabling better understanding and control of the crystallization step of an API to maintain the desired form A. This also allowed in situ quantification of one form in the other. This method will be transferred to Pilot Plant scale in the future to monitor the impact of scale-up.

2.5. Drying. The drying step can be complex and needs to be well understood and controlled, as the material properties can be a critical quality attribute (CQA) (especially for the API). For example, solvent content, form, flowability, and particle size and distribution are all likely to be impacted by the process of drying. In addition to the control of CQAs, there is the desire to minimize drying time to conserve energy and reduce cycle time (drying can be a bottleneck in the synthetic scheme). There is also a risk of overdrying, which can cause particle attrition.

PAT can be used during the development phase to understand and optimize the drying process. During scale-up, it can be used to show the same drying kinetics are observed, to identify when to take an off-line sample at the drying end point, or to control the drying end point.

The three main approaches for implementation of PAT to monitor drying are (1) use of an in situ probe to measure the API directly, (2) use of PAT to monitor the headspace to infer bulk properties of API from exhaust gas, and (3) noncontact systems for measurement of material drying through a process window.

The following examples show where PAT has successfully been used in the drying step.

2.5.1. Process Understanding for Removal of Water from an API. During the development of a drying process, in situ monitoring was used to understand and optimize the drying process for an API which could exist in various hydration states. As NIR spectroscopy is highly selective for water, NIR using a diffuse reflectance probe was selected for this application. Figure 24 shows the spectra of various API hydration states (water content).

Figure 25 shows examples of the drying and rehydration of API monitored using NIR, where the height of the water band is trended against time.

This study demonstrated that diffuse reflectance NIR can be used to monitor the water content during the drying process. The use of PAT enabled enhanced process understanding during the optimization of the drying conditions (changing pressure and temperature)

2.5.2. Monitoring Form Turnover during an API Drying Process. An API converts from an undesired form to a preferred form during an agitated drying process. The form is controlled by processing conditions (allowing sufficient time for the conversion to occur during the processing step), and analysis of the API by off-line powder XRD. Cycle times could be reduced, making more efficient use of the dryer by monitoring this form conversion in situ.

A NIR method was developed with a diffuse reflectance probe positioned in the dryer for direct measurement of the API. The NIR spectra of the API were used to determine when the turnover was complete. A chemometric model (PLS-DA) was applied to estimate the level of turnover (conversion to the preferred form). Figure 26 plots the conversion of the API to the preferred form for several API lots.

The variation in conversion time was thought to be caused by varying amounts of leftover material in the reactor heel between batches. The NIR method was successfully used to monitor form turnover, and the proposed control strategy of a fixed drying time was verified.

2.5.3. High Shear Wet Milling. The final crystallization step of an API process produced crystal agglomerates which must be

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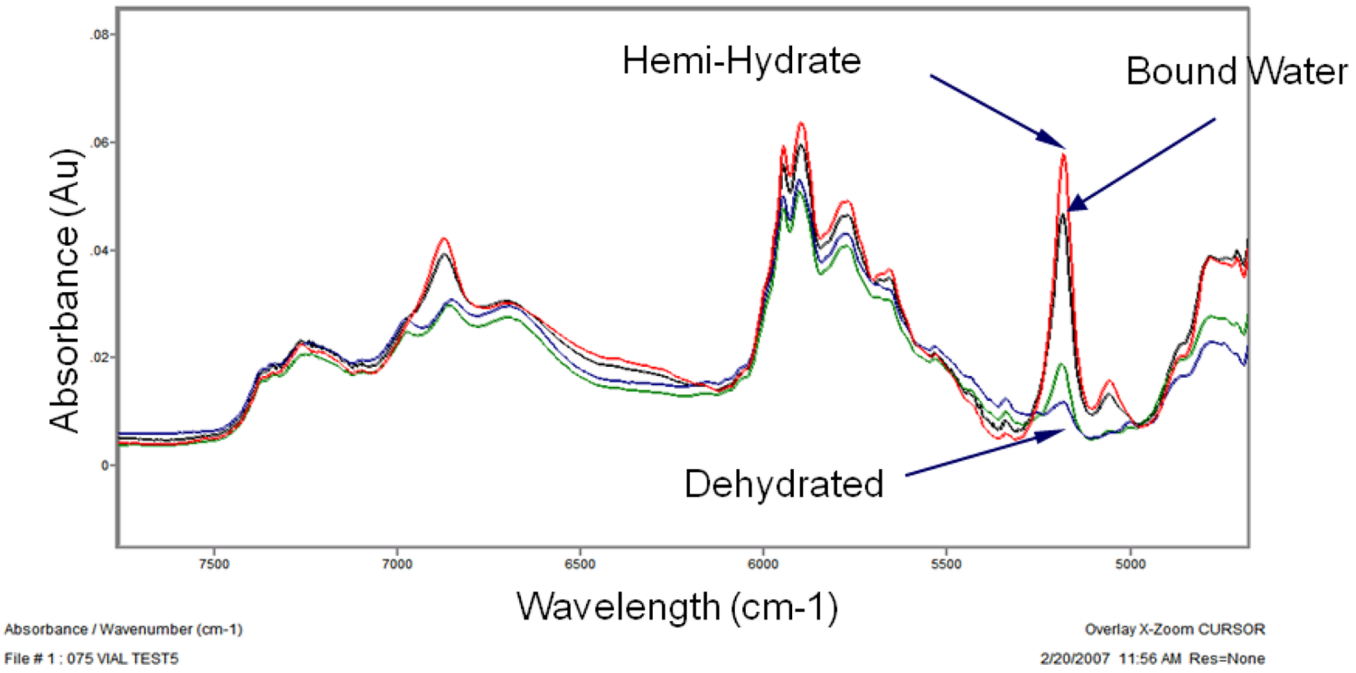

Figure 24. Spectra of API with differing hydration states.

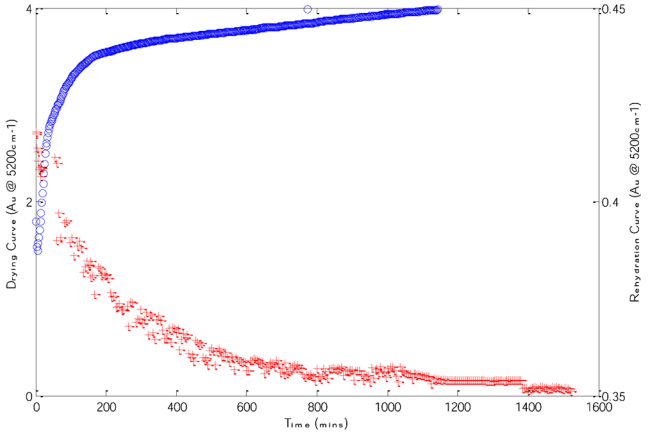

Figure 25. Trend plots for the dehydration and rehydration of the API under atmospheric conditions (red and blue traces, respectively).

broken up prior to use in drug product. Initially this deagglomeration was carried out by dry milling the API using a hammer mill. Due to potential worker exposure of this high potency compound, it had to be milled in a contained milling suite. A wet milling process was developed to remove the need for dry milling of the material. The product slurry is recirculated from the crystallizer through a high shear wet mill and back into the crystallizer. The high shear wet mill breaks up the agglomerates, and a FBRM instrument gives an in-line measurement of chord length (particle size) (Figure 27). The material is then filtered and dried as before and shipped to the drug product site for formulation.

Figure 28 shows, for each batch, the change in mean chord length of the particles as the wet milling progressed. The wet milling was carried out for a 12 h period for each batch. In this time, the entire batch passed through the wet mill approximately 100 times. In future campaigns the time required for milling could potentially be shortened by using the FBRM to determine the end point rather than continuing for a set length of time.

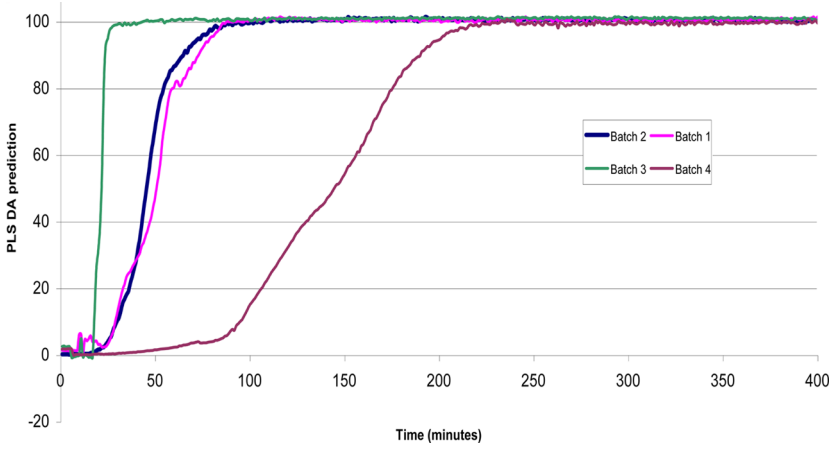

Figure 26. Conversion of form vs time for several API batches.

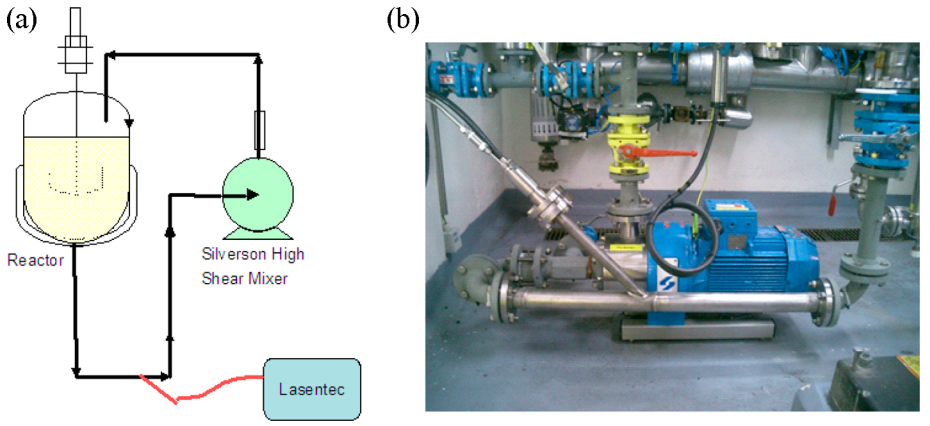

Figure 27. (a; left) Experimental setup for wet milling. (b; right) High shear mixer with FBRM probe in-line.

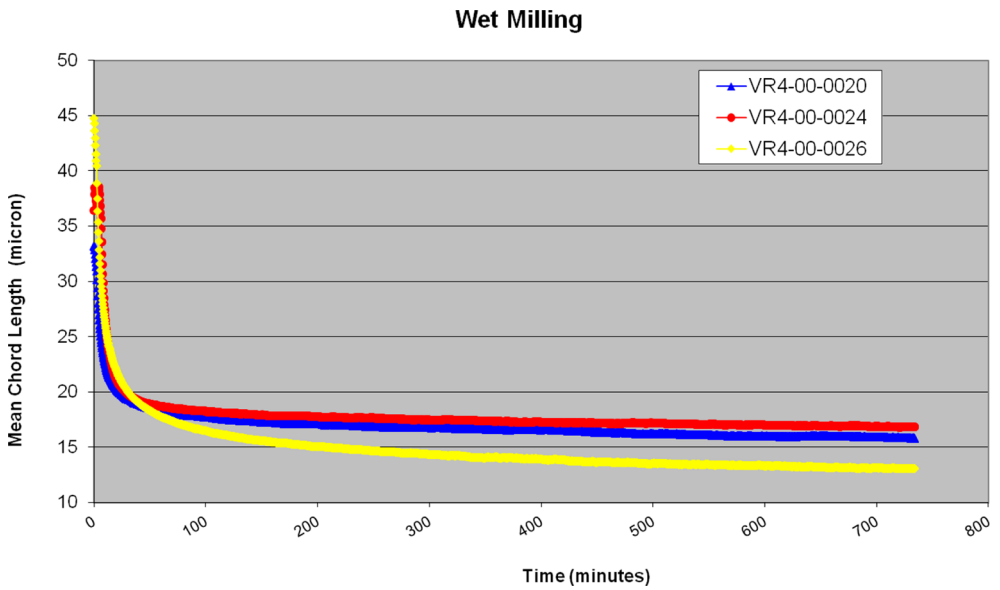

Figure 28. Reduction in mean chord length of the particles during wet milling.

3. CONCLUSIONS

The goal of this paper was to communicate as a cross pharmaceutical industry consortium about how PAT (e.g., online analysis, in situ analytics) is used and implemented across the industry. The authors strived to ensure typical and representative examples within the API process workflow were provided and would raise the awareness and inform and influence vendors, regulators, and pharma by illustrating how, when, and why PAT is used, its value, and its importance to pharma. A subsequent paper will focus on the application of PAT tools for process control in a GMP manufacturing environment.

In the examples provided in this work, PAT tools simply represent another set of analytical tools to be applied when and where it makes sense (and sunsetted when no longer required). The ability to monitor a process in real time, without the hazards associated with sampling, is one key benefit to the use of in situ tools. The application of PAT can differ as the project progresses through development. During use in discovery and early development, multiple PAT tools may be used simultaneously to aid the development and understanding of the process. As the drug development program progresses and the synthetic route and process are defined, the use of PAT tools aids in the development of in depth understanding of the process, including determining the presence of transient species difficult to sample and analyze off-line, process components, mechanisms, and relationships between variables. Through process understanding, critical parameters are identified and process parameter control limits are established. Via the development of processes using QbD principles, the number of process steps requiring real time control is low, and there is a desire to simplify the monitoring and control technology as much as is practical. This may result in controls being either off-line, or if in situ control is required, the results from PAT are correlated with simple manufacturing measurements such as temperature and pressure.

A gap does exist in terms of human capabilities. Industry does require more experienced users in PAT. New university graduates, having the right skills and training, are essential in ensuring PAT tools continue to be effectively utilized. The successful PAT subject matter expert and practitioner requires multiple skill sets that are still not fully prevalent in the industry. The desired skills include understanding of and proficiency in engineering, sampling, process interfacing, chemistry, multiple spectroscopic tools, mathematics, and chemometrics.

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Notes

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