The Use of Process Analytical Technology in Active Pharmaceutical Ingredient Process Development

Zhihong Ge, Analytical Research Department, Merck Research Laboratories
Rahway, NJ 07065, USA

Introduction

Process Analytical Technology (PAT) is a system for design, analysis, and control of manufacturing processes, based on continuous monitoring/rapid measurements of critical quality and performance attributes of raw material, intermediates and products. PAT involves measurement science by using conventional process sensors such as pressure, temperature and pH probes, as well as novel analyzer technologies. Demands for improved pharmaceutical productivity and quality, as well as the encouragement of recent PAT initiatives by the FDA, have caused PAT to become increasingly recognized and embraced by pharmaceutical companies in both research and manufacturing areas. The drivers for using PAT include:

- Process Knowledge/Control
  - reaction optimization
  - process characterization
  - mechanistic/kinetic studies
- Applications that can not be done any other way
  - information which can only be obtained real-time, in/on-line (e.g. monitoring transient non-isolated intermediate)
- Process Safety and Industrial Hygiene
  - Sampling
    - potent compounds
    - hot temperature, high pressure etc.
  - Process
    - Grignard reaction initiation, borohydride reduction
- Test burden reduction
- Cycle time reduction

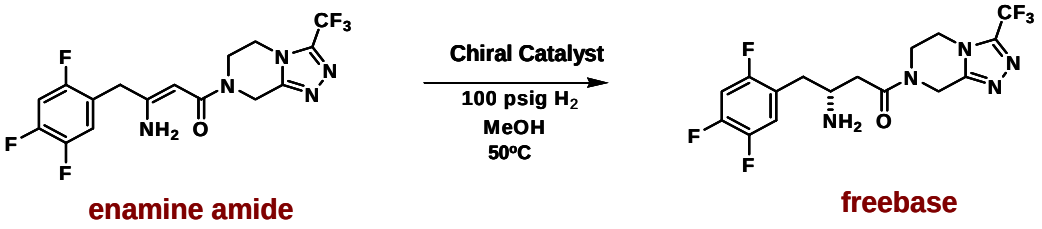
Novel analytical techniques, such as Fourier Transform Infrared (FT-IR), Near Infrared (NIR), Raman and Focused Beam Reflectance (FBRM) are popular PAT tools used to understand and control pharmaceutical processes. In this presentation, benefits of these technologies to development and manufacturing of Active Pharmaceutical Ingredient (API) processes will be demonstrated in several case studies.

In-line FT-IR for Monitoring an Asymmetric Hydrogenation Reaction

As noted in the introduction, in-line analysis and control are needed under certain circumstances to improve yield, control quality and ensure safety in the organic syntheses of intermediates or final products. An example of this is the catalytic hydrogenation reaction monitoring by in-line/on-line spectroscopy technique. Catalytic hydrogenation reactions are well known to potentially be sensitive to matrix effects. In-line analysis provides kinetic and mechanistic information which can be used to study the sensitivity of the reaction to such matrix effects.

In the asymmetric hydrogenation reaction shown in Scheme 1, the chiral catalyst is used to convert achiral starting material enamine amide to freebase product with desired chirality. This

reaction is run under 100 psig of hydrogen at 50 °C and normally takes 15-21 hours to complete. HPLC is the conventional analytical technique used to determine the end of the reaction. The HPLC method is time-consuming and requires sample removal from the vessel, which is under high pressure and temperature. In addition, it has been observed that longer reaction time leads to product degradation. Accordingly, rapid process monitoring by a PAT method would be a more desirable alternative approach.



In our facilities, in-line FT-IR technology was evaluated for real time monitoring the hydrogenation process at both lab and pilot plant scales. The FT-IR probe was inserted directly into the reaction vessel. Figure 1 shows the representative spectra collected during hydrogenation reaction. Clearly, the FT-IR can be used to distinguish between the starting material enamine amide and product freebase. By using multivariate statistical (chemometric) methods of Multiple Linear Regression and Partial Least Squares, as well as simple peak ratio data treatment, the real time reaction profiles of the enamine amide and freebase can be obtained (Figure 2). The data showed excellent agreements between the FT-IR and HPLC results and demonstrated the feasibility of using FT-IR to determine the end of reaction at pilot plant scale.

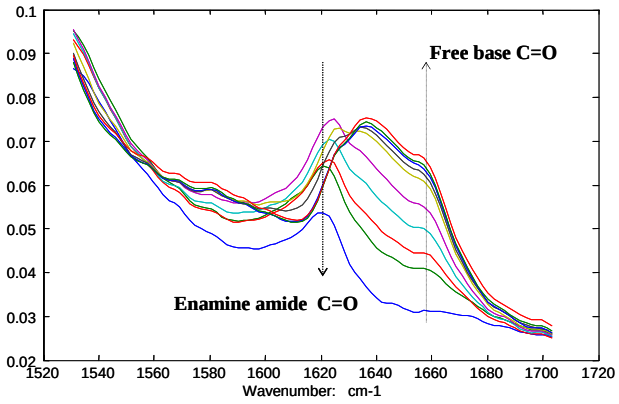


Figure 1. FT-IR Spectra of Hydrogenation Reaction

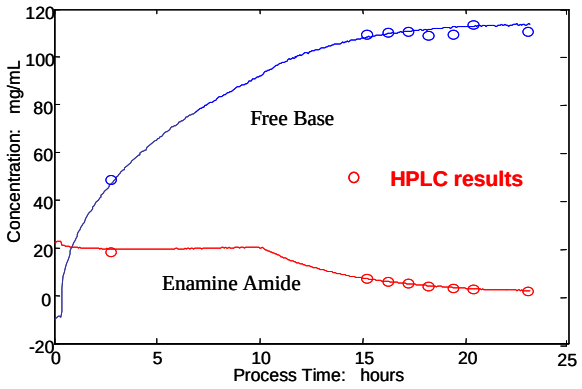


Figure 2. Reaction Profile by FT-IR

PAT for Monitoring a Crystallization Process

Crystallization of API is one of the most critical steps during pharmaceutical manufacturing processes. It improves the purity of the compound and also sets the physical properties which are determining factors for bioavailability, formulation and stability. There are three key crystal attributes that are commonly of interest: morphology (crystal shape), particle size distribution and polymorphic form (crystal form). These key attributes can be controlled during crystallization through control of supersaturation, solvent composition, temperature, seeding, etc. In order to design a robust crystallization process, it is critical to understand these key attributes and PAT is an ideal tool to accomplish this goal. In-line analysis minimizes possible data artifacts associated with sample isolation and preparation that may alter the crystal form or concentration of the supersaturated solution.

As an example, multiple in-line techniques were applied during process development of compound MK-A, which can exist as several polymorphs (A, B and C) with close thermodynamic stability. Figure 3 shows the setup of the crystallization vessel with three in-line analytical probes immersed: attenuated total reflectance-Fourier transform infrared (ATR-FTIR), Raman and Focused Beam Reflectance (FBRM).

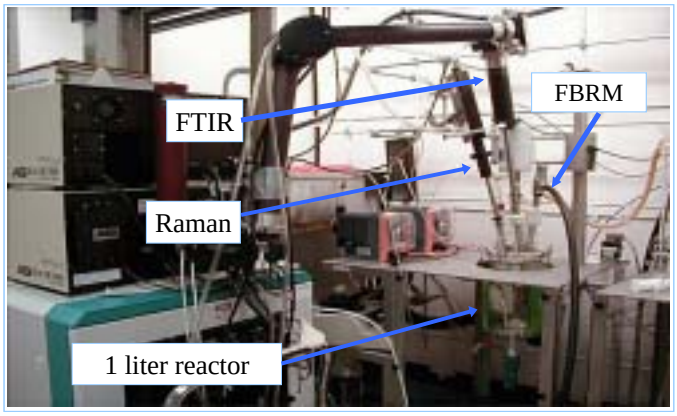


Figure 3. The 1 L Vessel with FT-IR, FBRM and Raman Probes immersed for crystallization development

ATR FT-IR was used to monitor the solution concentration of the MK-A compound during crystallization. After calibration with solutions of known concentrations at the process temperature range using partial least squares (PLS), FT-IR was applied to measure both solubility and concentration profile during crystallization. The supersaturation profile was then determined by subtracting solubility from concentration. Figure 4 shows the supersaturation profiles obtained from crystallizations under two different cooling profiles. The 2 hr linear cooling showed a rapid increase in the supersaturation followed by a gradual supersaturation relief. The sudden increase in supersaturation could result in nucleation which likely leads to the formation of undesired polymorphs and small crystals (fines). Extending the cooling time to 4 hours produced lower level and more uniform supersaturation relief throughout the cool down. Accordingly, it was decided to continue the development with 4 hr non-linear cooling as the supersaturation profile suggested a more controlled crystallization.

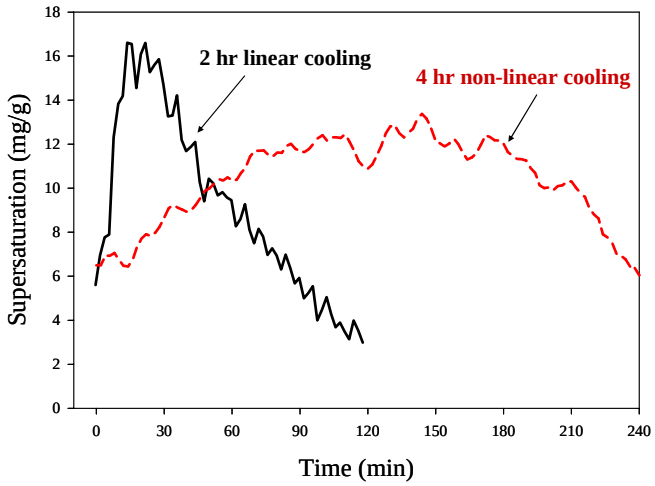


Figure 4. FT-IR for Monitoring Supersaturation Profiles

Raman spectroscopy was applied to characterize polymorphs as well as determine polymorphic transition in process slurry. As shown in Figure 5, the Raman spectra of various crystal forms of MK-A revealed distinct spectral features in terms of peak position and peak width. A calibration model was built by PLS regression for quantification of each crystal form. Figure 6 illustrates the transition kinetics of a mixture of Forms A and C in toluene at 16°C. As expected, form A converts to forms C since Form C is the most stable form at temperature below 69°C.

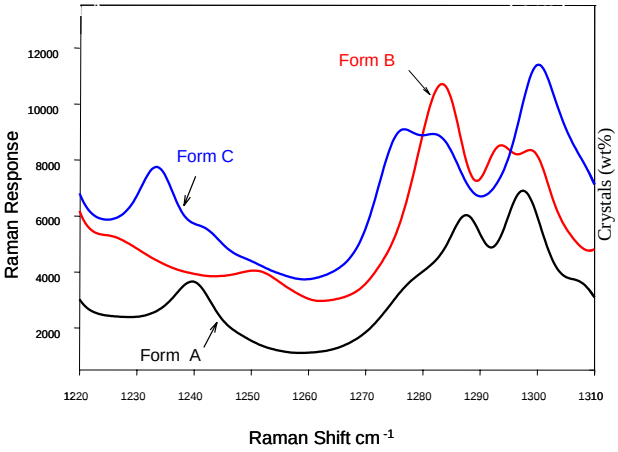


Figure 5. Raman spectra pure forms A, B and C

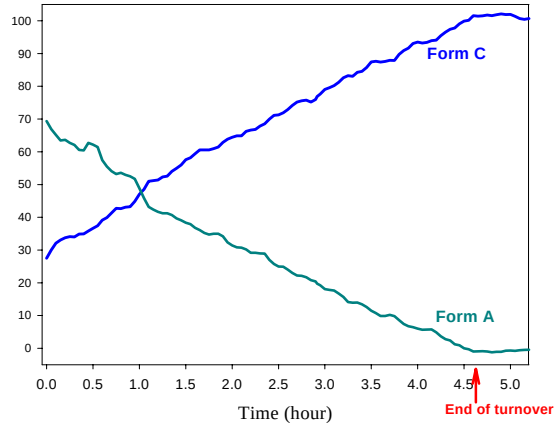


Figure 6. Predicted concentration Profiles of forms A and C at 16°C

FBRM uses time variance of reflectance to provide particle size distribution based on chord length. By monitoring crystal counts (either fines or total) in a slurry, FBRM can be used to detect the point of nucleation during crystallization. Figure 7 shows the real time profiles of fine count (1-10 microns) by FBRM during crystallization of MK-A using unmilled and milled material as seed. A much larger increase in counts of fine particles was observed using unmilled seed, indicating a much greater extent of nucleation. Based on in-line analysis, the final process was seeded with milled material.

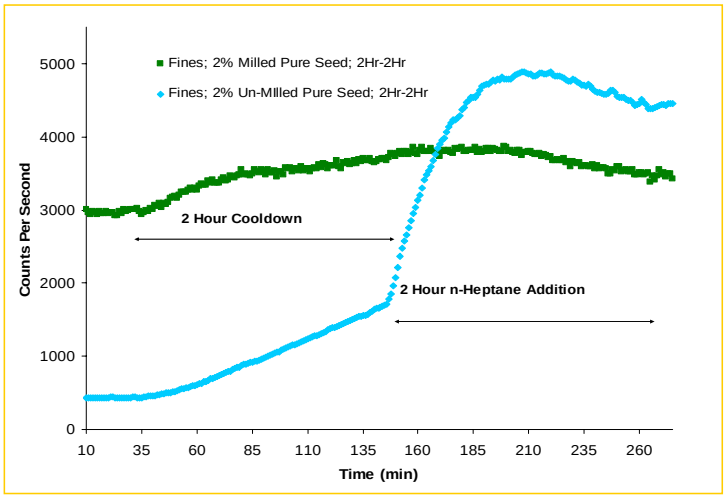


Figure 7. Profile of fine counts (chord length = 1-10 microns) by FBRM

In-line NIR for Monitoring of an API Drying Process

The final step of preparation of the novel carbapenem antibiotic Ertapenem Sodium involves a drying process, in which the wet cake is dried to target organic solvent and water level to yield the final active pharmaceutical ingredient (API). Ertapenem is hygroscopic, thermally labile and readily degrades. Accordingly, in-line Near-IR spectroscopy was implemented for monitoring this drying process at manufacturing scale to minimize the sample handling and product degradation. The residual solvent and moisture levels were determined by using a fiber-optic based Near-IR system with a diffuse reflectance probe inserted directly into the dryer. The overlapped NIR peaks necessitate the use of chemometrics for quantitative analysis. Using a calibration model developed by the Partial Least Squares method, NIR was able to reliably determine the water and residual solvent levels during Ertapenem Sodium drying. An example of the results obtained is shown in Figure 8. The data illustrate excellent correlations between NIR and reference methods Karl Fischer (KF) and Gas Chromatography (GC).

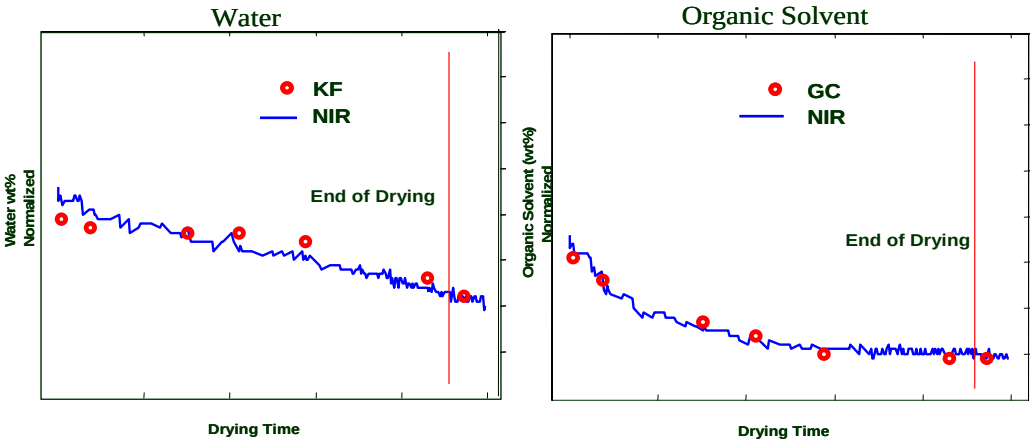


Figure 8. NIR for monitoring Ertapenem Sodium drying process

Conclusion

Process analytical technology (PAT) plays an important role in the development and manufacturing of the API. It provides insight into key factors of processes so we can better understand the kinetics and mechanisms, define critical quality attributes, and ultimately, design robust processes to ensure the delivery of consistent and high quality of pharmaceutical product.

References

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