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Process Analytical Technology: An Investment in Process Knowledge

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Abstract:

Process analytical technology (PAT) is fast becoming an integral part of many active pharmaceutical ingredient (API) production facilities. The incorporation of early PAT devices, such as pH probes for example, was shown to increase process efficiency and safety by acting on data in real time and by eliminating sampling. PAT applications, such as online redox, NIR, and sophisticated particle size analysis, increase (in real time) detailed knowledge of processes, thus affording increased robustness and greater straight-through processing (right-first-time) opportunities. Modern developments in analytical technologies provide chemical and analytical insights for all types of chemical reactions and process monitoring such as drying, distillations, crystallizations, hydrogenations, and others. This article will discuss two applications; each is very different from the other. The first application, redox monitoring, is a traditional PAT application used to monitor differences in the oxidation state of two reaction constituents. Our discussion will describe an oxidation/reduction (redox) application used to monitor the reduction of excess bromine with sodium bisulfite using an online probe. The second application is crystallization and granulation monitoring using a Lasentec Focused Beam Reflectance Measurement (FBRM) instrument for the optimization of a crystallization and granulation process in manufacturing (reference information is publicly available on this equipment; visit the Mettler-Toledo website at: http://www.lasentec.com/method_of_measurement.html).

Introduction

Pfizer is committed to continuous improvement of our manufacturing operations by the intelligent application of new technologies to promote process understanding. Our investment in the use of Process Analytical Technologies (PAT) is a good example of this commitment. By now the benefits of PAT have been well articulated elsewhere, most recently by the U.S. Federal Department of Agriculture's Dr. Ajaz S. Hussain, Deputy Director, Office of Pharmaceutical Science, CDER.[2] In a nutshell, PAT gives the manufacturing unit the ability to monitor many of the process steps of API production continuously, and in real time, and act in response to these data. Moreover, these same data can be coupled with other tools, such as statistical process control charts, or Design of Experiments among many, to continuously improve and optimize the manufacturing process.

Our first example involves reduction of excess bromine from a reaction using an online redox monitor. This example illustrates the added benefit PAT brings to productivity and safety. The second example demonstrates a different technique, the Lasentec FBRM instrument, which was used to continuously monitor the crystallization and granulation of an API intermediate. Control of physical parameters in the API manufacturing is an area of constant focus, given their impact in the formulation and pharmacokinetics of the final drug product.

Redox Reaction Monitoring

The progress of oxidation/reduction reactions, which involve the transfer of electrons, can be monitored by measuring the difference in potential throughout the process. The synthetic scheme involved in our first application is shown in Scheme 1.

The chemical reaction is simple: react 6-aminopenicillanic acid with a mole excess of bromine and sulfuric acid to result in a dibromonated intermediate, dibromopenicillanic acid. Once the reaction is complete, the excess bromine must be reduced to a point when a slight excess of bromine is present. A slight excess of bromine is needed to protect the intermediate from losing a bromine and resulting in the undesirable monobromopenicillanic acid impurity. The action of quenching the excess bromine with sodium bisulfite is secondary to the formation of the intermediate product. However, it is critical to downstream processing and product purity. The secondary redox reaction described in Scheme 1 involves sequentially charging a set amount of sodium bisulfite to the reaction as a quench followed by a series of off-line in-process control (IPC) tests to determine if the correct amount of excess bromine remains. In this processing scheme, over- and undercharges of sodium bisulfite were not uncommon. Overcharges of sodium bisulfite are particularly problematic as an excess (of sodium bisulfite) could compromise the quality of the desired product, thus requiring a repetition of the bromine charge and quench.

The redox reaction constituents described above have electronic potentials or oxidation states: bromine is −1.066

(1) Lasentec FBRM. Reference information is publicly available on this equipment; visit the Mettler-Toledo website at: http://www.lasentec.com/method_of_measurement.html.

(2) Hussain, A.; Deputy Director, Office of Pharmaceutical Science, FDA, Final Report on Process Analytical Technology (PAT) and Manufacturing Science. FDA Science Board Meeting, November 5, 2004.

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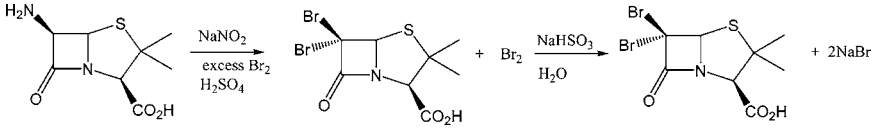
Scheme 1. **Synthesis of 6-dibromopenicillanic acid**



$E°$/V, and sodium bisulfite is +1.12 $E°$/V.[3] Cell potentials and balanced equations can be calculated from the stated oxidation number or obtained experimentally. However the availability of rugged, commercial oxidation/reduction probes eliminates almost all of the basic experimentation resulting in rapid electronic potential data reported as millivolt response. The difference in electronic potential can easily be measured on-line. In production, a Rosemount ORP-platinum, gel-filled triple junction reference cell with a "tefzel" body was installed in a recycle line of the reaction vessel (Figure 1). The platinum gel-filled electrode (anode/cathode/reference) replaces the traditional gas electrode that required hydrogen gas around the inert platinum electrode/anode and a salt bridge with a cathode to complete the circuit creating the potentiometer.[4,5] The traditional probe is constructed with glass and is not a usable on-line option in today's production environment. The redox probe was connected to a millivolt meter and then to the Distributed Control System (DCS) via an analogue signal for real-time data utilization. The corresponding millivolt response for bromine (in this reaction mixture) is approximately 750 mV, whereas the sodium bisulfite response is around 350 mV. By charting the millivolt response during the reducing agent addition, the progress of the reduction can easily be followed (Figure 2). The reduction reaction end point must be stopped at a point when a slight excess of bromine is present. The endpoint was previously verified by sampling and testing using the reaction mixture's UV absorbance, which was our traditional method. The redox endpoint data was gathered simultaneously (using physical samples) with the ORP probe and off-line testing (by the IPC laboratory).

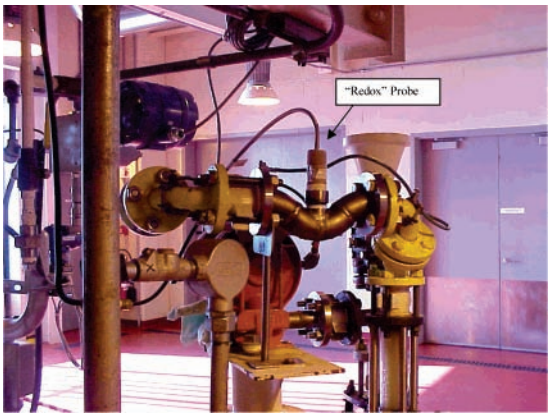


Figure 1. **Typical redox probe installation for bromine reduction monitoring.**

The results proved relatively simple to interpret; when the millivolt response from the redox probe was ~500 mV (Figure 2) the UV/vis absorbance was less than 0.100, indicating that a slight excess of bromine remained and we were at the desired endpoint.

The benefits of this technique were obvious. The optimization of the sodium bisulfite charge using on-line redox monitoring eliminated reprocessing due to over-charging the reducing agent, eliminated hazardous sampling and operator exposure, and eliminated IPC test time. Issues around reprocessing and overcharge of bisulfite were reduced by more than 10-fold after the implementation of this application.

Additional process information could be derived from continuous on-line redox reaction monitoring. Reaction data such as the amount of sodium bisulfite used from batch to batch could indicate a varying amount of bromine which provided an indication of incomplete reaction or the prevalence of other undesired side reactions. The amount and quality of the data derived from the on-line redox monitoring provided an excellent opportunity for process optimization, control, and validation.

On-Line Particle Size: Crystallization and Granulation

API production units routinely monitor particle size not only to understand filtration and drying characteristics but also to strengthen the robustness of the milling operation by providing a consistent distribution in the isolated API. It is well established that consistency has positive downstream effects in the formulation process.

This application involved a crystallization process typical of many pharmaceutical operations. A crude API intermediate is first dissolved in methanol. To optimize yield, the granulation slurry is then concentrated under reduced pressure to remove most of the methanol. The product is then crystallized by the addition of an anti-solvent, in this case isopropyl alcohol. Due to equipment constraints and in an effort to optimize productivity there was a desire to change the stripping operation from a two-step strip in a small tank to a single strip in a larger tank. To assess the impact this process change would have on the particle size of the final isolated product, we utilized a laser Focused Beam Reflectance Measurement (FBRM) instrument manufactured by Lasentec.[1]

The Lasentec instrument uses low-level laser light to measure the diameters of particles/crystals during crystallization and granulation. This technology uses a FBRM probe, which is inserted into a flowing medium of any concentration or viscosity. A laser beam is projected through the sapphire window of the FBRM probe and is highly focused just outside the window surface. This focused beam

(3) Budavari, S., Ed. *Merck Index*, 11th ed.; Merck & Co.: Rahway, NJ, 1989; pp 1382 and 8533.

(4) Holtzclaw, H.; Robinson, W.; Odom, J. *General Chemistry with Qualitative Analysis*, 9th ed.; Heath: Lexington, MA, 1991; pp 640−643 and 673−679.

(5) Kenkel, J. *Analytical Chemistry for Technicians*, 2nd ed.; CRC Press: Boca Raton, FL, 1994; pp 157−176.

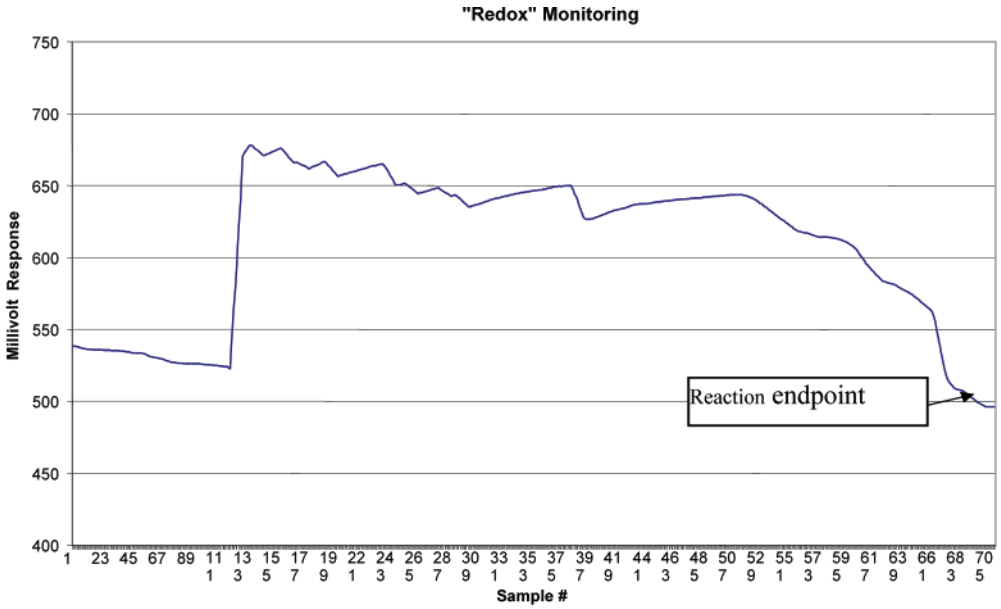


Figure 2. **Manufacturing distributed control system trend display. Bromine reduction begins at 675 mV and is complete at 500 mV (slight positive for bromine).**

is then moved so that it follows a path around the circumference of the probe window. The focused beam is moving at a high rate of speed (2−6 m/s, depending on the application) so that particle motion is insignificant to the measurement. As particles pass by the window surface, the focused beam will intersect the edge of a particle. The particle will then begin to backscatter laser light. The particle will continue to backscatter the light until the focused beam has reached the particle's opposite edge. The backscatter is collected by the FBRM optics and converted into an electronic signal that is then converted to size measurement (chord length) of the particle.

We began by running some preliminary laboratory experiments to establish some general characteristics of this crystallization process. In particular, we wanted to understand the effect, if any, that any material left over from a previous batch in the strip tank (seed) would have on the final particle size. In addition, we wished to assess the value of slow isopropyl alcohol addition times and extended granulation times given the known low solubility of the product in the isopropyl alcohol at most operating concentrations.

What we found most impressive with the use of this equipment was the ability to have a visual picture of how the different particle size populations shifted and trended through the crystallization process (Figure 3, a and b).

Lasentec time trend screen shot (Figure 3b, time vs relative particle concentrations by particle sizes) illustrates the relative consistency between the parallel lines. We can conclude the crystallization was done immediately following the IPA addition. No crystal growth is seen, as the lines illustrating particle size remain parallel. This leads to the conclusion that the granulation could be optimized (shortened) for better productivity with virtually no impact on the particle size of the slurry.

The product from the laboratory runs was isolated, dried, and subjected to Malvern testing which is the traditional method to determine particle size (the data from Lasentec and Malvern are not directly transferable); these data are shown in Table 1.

The Lasentec data helped us visualize the dynamics of the crystallization and granulation processes. The Malvern data allowed us to link what we were observing with concrete particle size distributions in the isolated material. Our conclusions from these experiments were that adding seed resulted in the isolation of significantly bigger particles, with a larger distribution of particle sizes. The addition rate of the anti-solvent did not prove to be significant.

Our next step was to move the Lasentec to the plant floor to monitor this reaction.

Production Results

The Production team identified the stripping step of the crystallization as rate limiting. The strip was done in two parts due to the (small) 2000-gal size of the stripping vessel. To eliminate the stripping step as rate limiting, a switch to a 5000-gal tank was made for the trials, therefore allowing us to complete the strip in a single pass and thus reducing processing time. The tank switch and Lasentec installation were completed prior to the campaign.

The Lasentec Process Particle Size Monitor was installed into the dip pipe of the 5000-gal tank so that the probe tip would contact the slurry at most times except the very end of the concentration. It became immediately clear, as in the laboratory pilots, that the granulation step was not adding any real value. The nucleation and crystallization occurred during and ended quickly after the addition of the IPO anti-solvent. No additional nucleation is seen after the anti-solvent addition. Lasentec monitoring of the number of particles indicated a flat trend during granulation. Lasentec also indicated the granulation hold time could cause some attrition. Figure 4 illustrates typical production particle size profile using the Lasentec FBRM.

Figure 4 left screen shot (A) illustrates the typical increase in crystals during stripping (red) through granulation (orange,

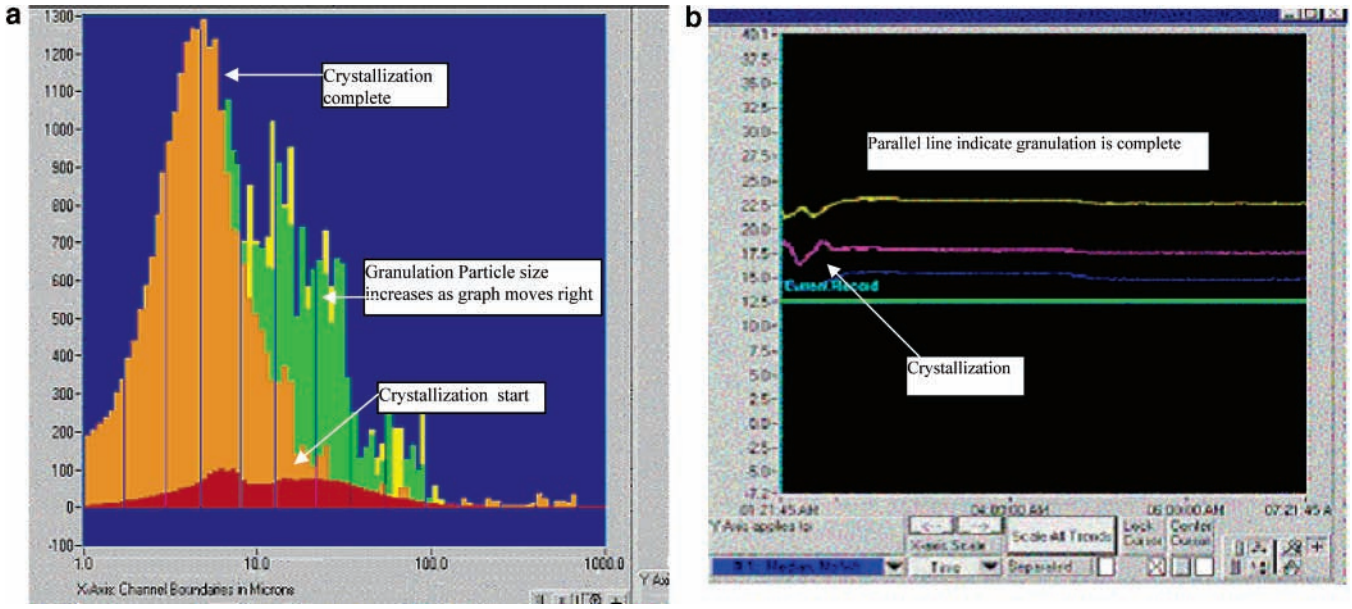


Figure 3. **(a) Lasentec screen shot: typical lab pilot. Particle size on *X*-axis, relative concentration in *Y*-axis. Red = start of strip. Orange = end of strip. Green: at end of IPO charge. Yellow: at end of granulation. As the peaks move right (green and yellow peaks), particles are growing, and less fines are present. (b) Particle size trend by discrete channel over a 6-h granulation. Channel data: dark blue: 100−250 μm; purple: overall average; yellow: 10−100 μm.**

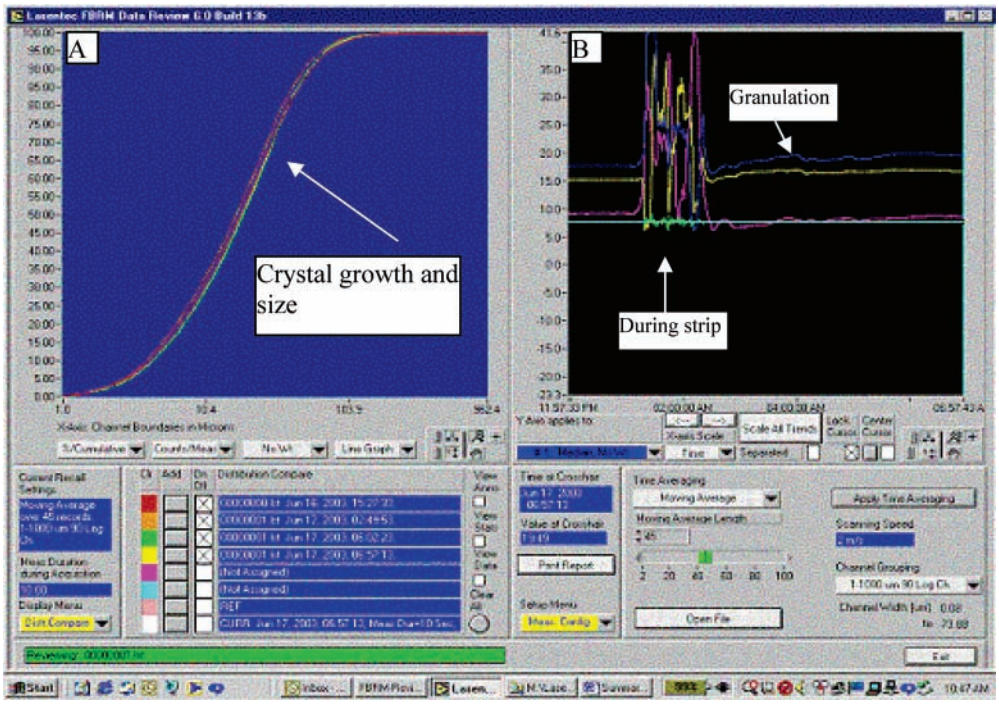


Figure 4. **Particle size trend by discrete channel over a 6 hour plant granulation. Note: Noise in trend lines (right screen) indicates a low tank level during stripping. Channel data: dark blue: 100−250 μm; purple: overall average; yellow: 10−100 μm.**

green, and yellow). The yellow line (left screen) is shifting slightly right, indicative of smaller particles illustrating some attrition over time. The right screen (B) illustrates that, once stripping and IPO (anti-solvent) addition are complete, little or no change in crystal size or population is seen and crystallization is complete. This granulation profile did not change and could be optimized at $\lesssim$2 h, saving 4 h of processing time.

Our Lasentec plant trials illustrated that granulation times were longer than needed. No additional nucleation was taking place following the anti-solvent addition as seen by the lack of increase in the number of particles recorded by the Lasentec instrument. Reducing the granulation time provided an added boost in productivity.

The ability to visually monitor the dynamics of this crystallization and granulation ultimately helped Production in implementing the desired process changes, which not only boosted productivity due to the change in tank configurations but also eliminated redundant granulation times. In addition, minimization of granulation times, which created fines due

Table 1. **Malvern data on preliminary lab crystallization experiments**

exp. no.	seeding (Y, N)	IPO addition time (min)	Malvern data			
			$D(v,0.1)$	$D(v,0.5)$	$D(v,0.9)$	$D(3,4)$
1	Y	5	24.02	320.68	686.12	335.2
2	Y	60	25.56	249.61	608.61	283.1
3	Y	120	25.63	287.98	631.4	306.58
4	N	5	40.9	153.12	496.83	215.31
5	N	60	39.61	143.97	489.58	207.7
6	N	120	34.27	96.8	276.76	132.87

to particle attrition, combined with other operational changes related to elimination of the previous batch "seed" (Table 1) helped in achieving a more consistent batch-to-batch particle size profile which in turn had positive downstream effects in filtration, drying, and milling.

Conclusions

The underlying benefits of having real-time process analytical technology (PAT) results in manufacturing operations that appear to us to be self-evident. The simple redox PAT application greatly improved process robustness and helped achieve operational objectives of once through processing (right-first-time); in addition there were global downstream quality benefits as well. The on-line particle size monitoring ultimately afforded many of the same benefits. These examples along with other successful PAT implementations have helped in driving the discussion on integrating PAT into manufacturing away from strict cost-savings arguments toward understanding the process. Nevertheless, the biggest advantages we have seen in Pfizer with the implementation of PAT applications are process knowledge and understanding, and robustness and consistency of product.

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