Process Analytical Technology (PAT) : Use from development through implementation in the pharmaceutical industry

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In development of new chemical processes, there are many opportunities in applying various tools for process understanding and control – be it the chemical reaction progression and kinetics, API crystallization, isolation and drying, as well as in formulation development. As industry faces increasingly aggressive development timelines, and demands higher quality products, the application of in-situ analytical tools during development becomes more widespread. Process analytical technology (PAT) is being applied earlier in the development cycle of products as its benefits in providing increased process understanding are exploited.

PAT is defined as the use of rapid on-line, off-line or at-line analyzers to obtain analytical data in real or near-real time for a process, to enable to follow a process with higher precision. By being able to obtain data more often, one can get a pulse of the process, which provides an increased understanding and the possibility for greater control of a process. PAT is not just the application of various analytical tools to the measurement, but also includes the integration of these tools into a process; including the data analysis and trending which may be part of a process control system.

We will discuss some of the spectroscopic tools (UV-Vis, FTIR, NIR, Raman, headspace mass spectroscopy) that can be used to gain better insight into processes. Application of PAT early in the development process provides insights that aid in identifying critical quality attributes and process parameters, and provide a measure of process variability. Examples of how PAT has contributed to increased process understanding will be provided. Beyond providing process understanding, one can apply PAT to ensure real-time assurance of products and processes by implementing these tools on production scale.

Beyond the systematic scientific understanding that underlies the application of PAT, implementation on scale entails a multidisciplinary team to ensure success and bring value to the process. We will discuss key aspects of PAT implementation in industry for assuring product quality during the manufacturing process. One key point when initiating a PAT project is that clear project goals and objectives be set. The effort that goes into a project must be aligned with the final project goals. If the objective is to have a measurement that provides information on how a process progresses, than it may not require the development of the most elaborate and eloquent chemometric model from the data. The additional effort required to develop sophisticated models is not always justified to meet project objectives.

The use of PAT adds business value by providing improved process understanding. This translates into shortened product and process development cycle times, and enables the

optimization of processes. Application of PAT can potentially reduce costs by shortening the start-up and/or transition times of a process. With PAT tools in place, one has the capability to detect and correct process oscillations, hence reducing process variability. Costs reductions can also be the results of higher throughput and product quality (fewer rejections). Process risks can also be reduced with the use of PAT, as having on-line sensors provides real-time monitoring , hence reducing off-line sampling which exposes operators to potential hazards. PAT can provide early fault detections, and help avoid possible process runaways.

There are many benefits from using PAT. The data generated from on-line analyzers can be used for many different uses. If applying PAT for in-coming material inspection, it can provide a means to identify and qualify raw materials, avoiding quarantine times before material are tested and verified by laboratory methods. PAT can be used for process control, with an open-loop or closed-loop operations. In a closed loop configuration, the PAT data can be used for feed-forward or feedback control. The continuous data collected by PAT can be used to develop an increased process understanding, and lead to process improvements. With the PAT data, kinetic models can be developed, which can then be used as a process signature.

Many tools exist for PAT, including univariate and multivariate sensors. Univariate sensors including temperature, pressure, level, flow and density have been used broadly in industry for many decades. [1] Electrodes for pH, oxygen monitoring, and specific ions are also used, and can be interfaced to a process to provide closed-loop control – as can more sophisticated multivariate sensors. For the measurement of turbidity, color, or moisture, filter photometers, which measure absorbance at discrete wavelengths, offer a lower cost option to a full range spectrometer. Spectroscopic tools, which we will be focusing on in this presentation, include vibrational spectroscopy such as infrared and near-infrared spectroscopy, molecular spectroscopy, including UV-Vis spectroscopy and NMR and X-ray fluorescence, and Raman spectroscopy.

Within the pharmaceutical industry PAT is being applied to many processes, and providing increased process understanding and control. The use of spectroscopic tools enables one to follow the progression of a process, and establish the kinetics, from which one can define a process signature. It can be used to show the scale effects on the kinetics of a reaction. With on-line analysis, one has a tool for continuous process verification. Such tools can be used to aid in formulation development by providing monitoring during granulation, blending, tabletting and coating. Spectroscopic tools such as NIR have been used for the real-time measurement of tablet content uniformity, a non-destructive, rapid test.

In this talk we will present several examples of PAT applications in the pharmaceutical industry.

- FTIR for controlling the iodination of a napthyridine compound
- MS for increase understanding of the drying process
- NIR for monitoring solvent distillation and solvent swap
- UV-Vis for reaction monitoring, and showing scale independence of a process

- NIR for form conversion

From these examples we will demonstrate the following about the application of PAT in development:

- FTIR provides increased process understanding during the development process
- MS for drier monitoring can be used for end-point detection without the necessity of quantitation
- Distillation monitoring by NIR in the distillate is effective in monitoring this process
- The scale independence of a reaction was verified by UV-Vis reaction monitoring; continued reaction monitoring provides real-time quality assurance
- NIR applied to a form conversion process provided increased process understanding and provides real-time quality assurance of the manufacturing process

Regardless of the application being developed, there are numerous challenges in the implementation of PAT. As previously mentioned, it is important to have well-defined project objectives, with detailed plans, and buy-in from the team and especially the end-users. But even when these points have been defined, there are challenges in developing an appropriate sampling interface. The interface must consider the sample form, and that the sampling point will enable a measurement that is representative of the process. Likewise collecting samples for off-line analysis for calibration development must also follow the theory of sampling, to ensure representative sampling.[2] PAT projects involve cooperation of people from diverse functional areas, which can be challenging, requiring coordination of efforts across numerous groups.

Some steps that can be taken to increase the likelihood of success of a PAT project are to undertake projects with clear, convincing purposes that are aligned with the business. Open and frequent communication across the multifunctional team and with end-users and stakeholders will help maintain the teamwork, and address issues as they arise. A technology transfer plan should be followed, and work should be documented throughout, so that information will be available throughout the life of the PAT implementation.

References

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2. L. Petersen and K.H. Esbensen, *J. Chemometrics* 2005, **19**: 625-647. "Representative process sampling for reliable data analysis – a tutorial"