Facilitating enhanced process understanding

The FDA has defined PAT as "a system for designing, analysing, 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". Real-time PAT monitoring has been extensively applied to all stages of pharmaceutical processing. The PAT methodologies should be based on direct measurements of process variables, rather than pre-defined process parameters, such as processing times (e.g., addition times, granulation times, etc.), or predefined consumption of materials (e.g., during film coating).

When adequate levels of PAT data have been generated, on-line/at-line PAT process monitoring can evolve into real-time release testing (RTRT), whereby at least some of the analytical testing is no longer
required or necessary to demonstrate product quality, since the real-time information that has been generated provides an assurance that product quality is acceptable. This is sometimes termed parametric release. Indeed, in an ideal world, RTRT could potentially allow process intervention to address real-time issues and realign the system to the desired state. The key concepts of PAT are multivariate data acquisition using process sensors and analysers, process monitoring and subsequent control and supporting information management tools.

PAT can either monitor one unit operation, two interconnecting unit operations or, ideally, the entire process. This article will provide a brief overview of some of the applications of PAT and RTTR.

Active pharmaceutical ingredient applications
The last stage of API manufacturing is typically crystallisation. However, this stage can often be challenging since there are numerous variables to be optimised, i.e., yield, control of impurities, residual solvents arising from the crystallisation process, crystallinity, version (salt, co-crystal, etc.), form (polymorph, solvate, hydrate, etc.), habit, particle size, shape and distribution. In turn these input variables can affect filtration rates, drying rates (particularly in agitated drying systems), particle fragility, particle surface roughness and overall API processing times. Some of the factors can significantly impact on secondary processing, particularly particle size and shape, powder flow and powder compaction. PAT is commonly used in the monitoring and controlling of crystallisation processes due to its ability to provide real-time data leading to real-time control.

The FDA has advocated the usage of PAT during crystallisation and identified some in-line and on-line monitoring tools. The habit and growth of crystals during crystallisation can be monitored in real time within the reactor using in-process visualisation techniques, such as particle vision monitoring (PVM) and other related in situ imaging approaches. In addition, the developing crystal size and related crystal size distribution can be monitored using focussed beam reflectance measurements (FBRM), as well as in-line spectroscopic tools such as attenuated total reflectance ultraviolet/visible (ATR-UVV) and ATR Fourier transformation infrared (ATR-FTIR) for real-time solute concentration measurements. In parallel, polymorph form control can also be monitored using FBRM and PVM.

Drug product applications
Blending
The preparation of a homogeneous blend of API and excipients is an important step in the manufacturing process of solid oral dosage forms, such as tablets or capsules. This is particularly true for low-strength and highly potent drugs. However, sampling using classical approaches allied with off-line analysis of the sample blend is inefficient, can introduce sampling errors and can necessitate long processing times. For these reasons, there are opportunities for PAT methods to provide a more rapid and consistent approach towards the assessment of blend homogeneity.

Non-invasive monitoring of powder blends using near-infrared (NIR) spectroscopy has been extensively reported. Calibration-free approaches based on the mean spectral residual standard deviation (RSD) as a function of time have also been developed. This approach assesses the convergence of the expected cumulative NIR spectra, based on a predefined, statically-based endpoint, i.e., ≤ 1% RSD, to establish blend homogeneity. The major advantage of this approach is that there is no requirement for pre-existing data. In contrast, the major disadvantage is that although differences between spectra from a single blend are measured, allowing qualitative decisions to be made with respect to the homogeneity of the blend, quantitative measurements will still be required using off-line testing. This can be addressed by using a limited number of off-line samples to develop a model that can accurately predict content, in addition to homogeneity.

Another downside is that NIR produces a weak signal (except with water), and consequently there are inherent limitations to the sensitivity of these methods for high potency drug formulations, where drug loading may be ≤1% in the blend. To address these sensitivity concerns, other analytical approaches have been investigated. Lai et al. developed a laser-induced fluorescence (LIF) method to monitor blend homogeneity. LIF involves irradiating blend samples at a suitable wavelength for excitation and assessing the emission at a second wavelength. The method is rapid, sensitive (API loadings as low as 0.05% w/w have been measured), accurate and homogeneity is established when the LIF response at steady state is the same between two successive sampling points.

Tableting
Blend homogeneity is intrinsically interrelated with content uniformity of the resultant drug product and the latter is defined by all of the major pharmacopoeias as well as being a required attribute for release testing of all drug products. Both reflectance and transmittance NIR have been used in content uniformity testing with encouraging results. NIR has been used for real-time monitoring of content uniformity of a tablet product in a production environment using partial least squares (PLS) modelling and the real-time monitoring of both API and excipient content uniformity of a tablet product, again using PLS. In addition, Raman, terahertz and chemical imaging analysis (CIS) have been applied, but the quantities of data can be enormous and are often difficult to interpret, necessitating multivariate chemometric approaches. Interestingly, by adopting multivariate methodologies, the user can monitor and control both API and excipients. Indeed, for certain dosage forms, the role of these key excipients can often be as important as the API itself in controlling the performance of the product, e.g., controlled-release products.

Tablet film coating
Film coating is extensively utilised within the pharmaceutical industry. Film coats can be applied as non-functional, immediate-release coatings, to address poor chemical stability in gastric media (delayed release via enteric coating) or to modify the in vitro release profile (controlled release via osmotic

Real-time PAT monitoring has been applied to all stages of pharmaceutical processing
controlled release oral delivery system; OROS). Traditionally, the film coat thickness is monitored and controlled by the average weight gain of the tablets, e.g., ca. 3% w/w target for non-functional film coats. This requires sampling and off-line or at-line analysis which is inherently inefficient.

NIR in the reflectance mode can be used as an off-line\(^a\), on-line\(^b\), or in-line\(^A\)\(^t\) PAT tool by monitoring the linear reduction in the absorbance signal of the tablet core, whilst in parallel monitoring the linear increase in the absorbance signal of the coating materials. In-line monitoring has been applied to both fluid bed\(^A\) and pan coating\(^b\) operations. NIR models can determine film coat thicknesses much more cheaply and rapidly than either scanning electron microscopy (SEM) or imaging\(^a\) and the method gives good comparability with the classical weight gain methodology\(^b\). NIR has been used in conjunction with terahertz pulsed imaging (THz) and multi-variate modeling to monitor tablet coating\(^A\)\(^t\). THz was also utilised to assess the coating requirements of a push-pull OROS system to provide off-line PAT control and correlate the effect of coating thickness with in vitro release performance\(^A\)\(^t\).

Raman has also been used as a PAT tool for film coating, offering advantages in terms of enhanced selectivity, good robustness and reduced interference from water signals (a significant deficiency for NIR), allowing calibration models to be developed based on limited batch data. A multi-variate model was developed to assess both the amount and the uniformity of an active coat of the drug diprophylinline\(^a\). Real-time monitoring using in-line and off-line Raman spectroscopy was applied to the active coating process of an OROS dosage form. Wriges et al.\(^a\) were able to demonstrate that their in-line calibration model gave better accuracy than the off-line calibration model and the former correlated well with the off-line reference HPLC assay. The authors indicated that this was the first time in-line Raman calibration models had been applied to complex dosage forms or high coating levels, i.e., coat thickness of up to 400µm.

**Real-time release testing**

The principles of RTTR may be applied during any stages of the manufacture of synthetic or biological products resulting in the exclusion some, or all, specified tests on the specifications of the finished API or the finished drug product\(^A\). However, the most obvious and well documented example of RTTR is terminal heat sterilisation of parenteral products. Here a review of the documentation obtained during process monitoring, e.g., pressure, temperature and time for the autoclave cycle by the quality assurance group, together with ongoing good manufacturing practice (GMP) compliance, will provide the necessary assurance of the quality of the process and thereby the product\(^A\). It is worth noting that although QbD is not directly linked with RTTR, it would be unlikely to envisage RTTR without both a science\(^A\) and risk-based\(^A\) approach. Additionally, not all PAT approaches lead to RTTR and a design space is not needed for RTTR. However, a product specification is still required\(^A\).

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**IN-DEPTH FOCUS: PAT**
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Conclusion

PAT plays a fundamental role within the QbD paradigm, but it is not a new approach, since process analysis and control have been used in API reactors for several decades. PAT needs to be part of an integrated control system. There are deemed to be three levels of process control, one or all of which can be used inter-changeably within a designated process:

- Real-time, automated testing and flexible normal operating process ranges, with the ability of the control system to respond interactively to input variability;
- Reduced end-product specification testing, flexible CMA and CPPs within a designated design space, and
- End product testing together with constrained material attributes and process parameters.

It is also important to differentiate between those PAT tools required to develop in-depth process understanding and those systems used for day-to-day production/process monitoring, which can be very simple analytical tools for measuring fundamental variables, such as weight, pressure or temperature. There is also a balance between on- and off-line process monitoring. In addition, current regulatory interpretation necessitates retention of all historical spectral data; for which a fully PAT-aligned, data-rich system could be a significant undertaking. This is a technical burden that other industries do not share. A recent equipment, analytical and academic symposium on continuous manufacturing highlighted some of the major PAT challenges.

- Standardisation of analytical data formats allowing unified data treatment between various instrument vendors;
- Enhanced robustness of in-line sensors aligned with continuous monitoring;
- Rapid maintenance and repair of in-line monitors;
- In situ cleaning of sensors (this is particularly relevant for solution-based processes, such as crystallisation);
- Costs of sensor and monitoring devices;
- Enhanced analytical sensitivity for RTRT; and
- Enhanced quality and ease of data interpretation by non-experts.

In summary, there is a requirement to provide confidence that the proposed PAT is robust and will operate consistently, that there is an adequate return on investment and that regulators will accept the proposal.

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