PAT – A European Academic's Perspective

Tony Moffat

The School of Pharmacy, University of London, 29-39 Brunswick Square, London WC1N 1AX, UK
E-mail: tony.moffat@ulsop.ac.uk

Although industries such as the petrochemical and food industries have had continuous process control for decades, the pharmaceutical industry has lagged behind due to the regulatory environment in which it operates. The Food and Drug Administration in the USA has taken steps to change this by their Process Analytical Technology (PAT) initiative: to understand and control the manufacturing process.

Near-infrared spectroscopy (NIRS) is an ideal tool for process monitoring as it is can be used in-line or at-line for timely measurements. The conventional bench-top instruments have now been modified so that they are small, robust instruments for use in real-life process applications. For example, they are well suited to monitor synthetic reactions for the production of actives to ensure optimum yields.

Conformance is a concept that can be used for the identification and qualification of raw materials by NIRS in the warehouse or dispensary. As well as chemical identification, materials can also be checked for polymorphism and have their particle sizes measured at the same time. Even herbal materials can be checked to ensure that they are from the correct species.

On-line blending can be measured by the use of small NIR spectrometers fixed to the blender. They can monitor not only the mixing of the active, but also the excipients whose complete mixing and homogeneity in the final blend may be crucial to the manufacture of a successful product.

Moisture determination is relatively easy by NIRS because of the strong absorption of the OH-bond at 1940 nm. For example, the discrimination of anhydrous lactose from lactose monohydrate and wet lactose monohydrate is a simple matter. The on-line monitoring of drying after wet granulation is also simple and effective.

Some manufacturers of NIRS equipment have designed their instruments to be used at the end of the production line to confirm that the correct drug and dosage are being dispensed in applications such as filling injection vials.

Perhaps one of the most exiting new methods of using NIRS information is in examining the conformity of products. A conformity plot of the product over time shows any variation in the product and can be used to monitor quality. Quality may be described by many parameters and NIRS can measure them simultaneously. Similarly, NIRS can be used in Hotelling's Control Plots to

examine the deviation from normality of a product from batch to batch.

Physical parameters of tablets may also be examined such as compression, hardness and dissolution. These are all interrelated and NIRS can predict these properties.

The usual assays for the active and content uniformity can also be accomplished by NIRS. Preparations containing a low amount of active (< 10 % w/w) can be assayed by transmission NIRS with good accuracy. However, there is still the problem of transferring the calibration from one instrument to another. This is still not a trivial matter, especially if the transfer is between instruments from different manufacturers and from linear wavelength to linear wavenumber calibrations.

The identification of the site of manufacture of tablets made by the same company can be important when trying to identify the origin of parallel imports. NIRS can do this easily.

NIRS imaging techniques have the advantage that they can look at small areas of the surface of a tablet (routinely 25μm x 25 μm). The use of this form of NIRS can assist in root cause analysis procedures. For example, it can be used to determine the reason for the failure of tablets due to chipping (where the difference between good and poor batches was due to the particle sizes of the components). A second example is where batches of blend were sticking to the tablet dies when the different homogeneities of the blends were seen to be very different.

In conclusion, NIRS is an excellent tool for PAT. It can assist in monitoring manufacturing processes to: assist in designing, analysing and controlling manufacture; make timely measurements; be applicable to the analysis of raw materials, process monitoring and the analysis of products. The ultimate goal is for real-time release.