PAT at work: the determination of a process critical control parameter in pharmaceutical manufacture by NIR

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Introduction

An important FDA initiative that encourages the use of modern process analytical technologies (PATs) in pharmaceutical production and quality control is helping drive industry away from empirical to science-based standards for manufacturing control. It is also an effort to facilitate the introduction of new technologies to the manufacturing sector of the pharmaceutical industry. Process analytical technologies are systems for analysis and control of manufacturing processes based on timely measurements of critical quality parameters and performance attributes of raw and in-process materials and processes to assure acceptable end point quality at the completion of the process. They involve optimal applications of process analytical chemistry tools, feedback process control strategies and information management tools applied to pharmaceutical manufacturing.

Bruker Optics Limited has supplied many systems for PAT implementation based on near infrared (NIR) spectroscopy. An example of this implementation is at one of the world's leading Pharmaceutical companies, who have a requirement to measure a process critical control parameter (PCCP) in a glass-lined reactor. This PCCP is important in a crystallization process and is critical in assuring the quality of the pharmaceutical product.

Installation

Bruker Optics supplied a Matrix-F fibre-optic based Fourier transform NIR spectrometer with 200 meters of low OH fused silica fibre-optic cable and a custom designed transmission probe contained in a two-meter hastelloy C22 DIP Pipe. The DIP pipe was a requirement because the reactor is glass-lined and there are no ports available for a standard probe. The DIP pipe is designed to go into the reactor through a flange at the top. A team of engineers based in Coventry, who used sophisticated computer aided design software to optimise the product, performed the design and realisation of this DIP pipe.

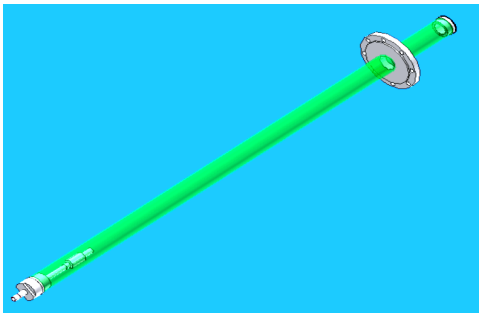

Figure 1. CAD design of fibre-optic dip pipe

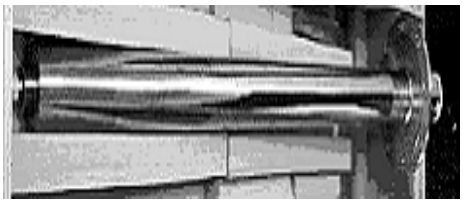

Figure 2. Manufactured fibre-optic dip pipe

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Calibration

Initial calibration for the PCCP was performed in a pilot plant and then transferred to the reactor once the Matrix-F had been installed in the plant. The spectrometer was housed in an environmental enclosure 100 m from the sample point. The NIR spectra show significant differences, which correlate with changes in the PCCP. The unique self-optimise function in the OPUS software was used to develop and validate the model. OPUS uses partial least squares (PLS) as the algorithm for quantitative analysis and the validation method used in this application was full cross validation. The OPUS software is fully compliant with 21 CFR Part 11 and fits the customers ERES requirements. The calibration model shows a very high correlation coefficient (99.76) and a low root mean square error of cross validation (*RMSECV*) of 0.02 absolute. Once validated, this model has been successfully implemented on the plant for a number of months and is now a vital part of the process control strategy.

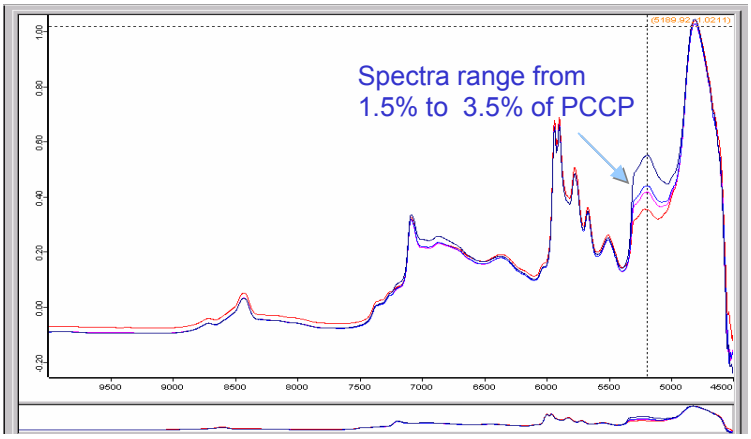

Figure 3. Calibration using OPUS self-optimising software.

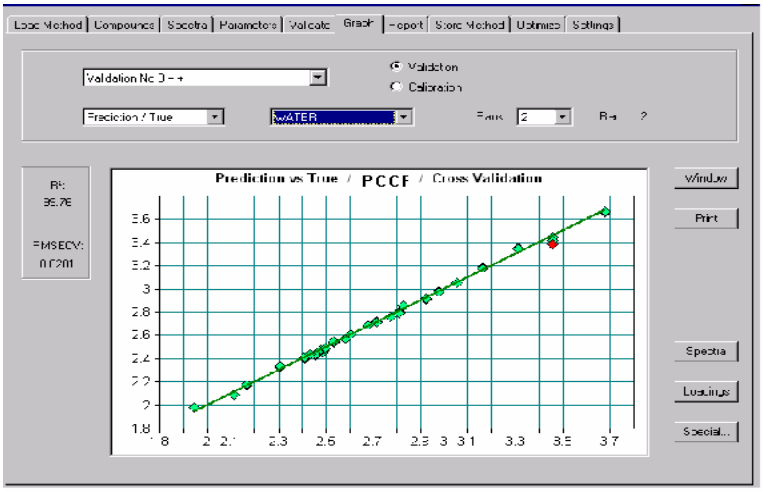

Figure 4. Spectra from calibration set.

The results are transmitted to the process control system via a 4–20 mA interface and the PCCP is controlled by a closed loop based on the NIR result. If the PCCP is out of specification, automatic dosing of the component is performed to bring it back into specification. A second 4–20 mA output transmits the Mahalanobis distance, which is used to highlight any potential manufacturing problems and to provide useful information on calibration maintenance.

Conclusions

This PAT implementation has ensured "right first time" manufacturing with all batches produced in specification. It has also reduced the need for taking samples from the reactor to the IPC laboratory for testing, one of the benefits of this being a reduction in a potential health and safety hazard. As this installation produces real-time results, it also means that the product can be released earlier, resulting in reduced cycle times and higher production capacity.

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