Application Note AN N504

Monitoring a Process Critical Control Parameter for Crystallization

Crystallization is an important step in the manufacture of pharmaceutical ingredients.

An important FDA initiative that encourages the use of modern process analytical technologies (PATs) in pharmaceutical production and quality control is starting to move the industry away from empirical and towards 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.

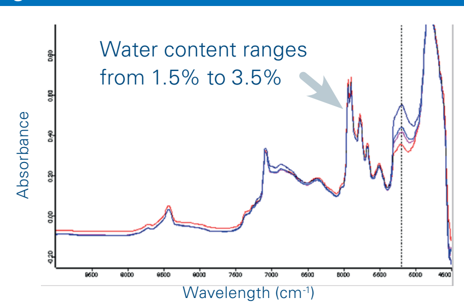
Process Analytical Technologies are systems for the analysis and control of manufacturing processes to assure acceptable end point quality at the completion of the process. This is based on timely measurements of critical quality parameters and performance attributes of raw and in-process materials and processes.

Very often crystallization process requires the crystallization mixture and conditions to be tightly controlled in order to precipitate the correct crystalline form. An example of this was at one of the world's leading pharmaceutical companies, which had a requirement to tightly control the water content in an IPA / drug mixture in a glass-lined reactor such that the water content was controlled to be just above 2.5%.

Experimental

Bruker Optics supplied a MATRIX™-F fiber optic based process Fourier transform NIR spectrometer and two 100m lengths of low OH fused silica fiber optic cable along with a custom designed transmission probe contained in a two-meter hastelloy C22 DIP Pipe. The DIP pipe was a requirement for the glass-line reactor because no side ports were available for a standard probe. The DIP pipe was designed to go into the reactor through a flange at the top. The design and realization of this DIP pipe was performed by a team of engineers who used sophisticated Computer Aided Design software to optimize the product. The initial calibration development was performed in a pilot plant and then transferred to the reactor once the MATRIX™-F had

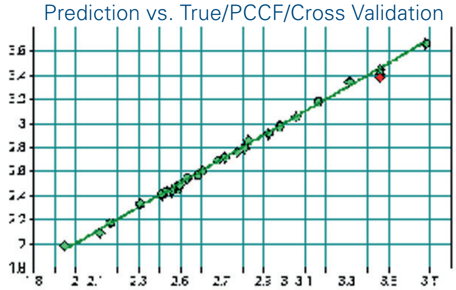
Figure 1



FT-NIR absorption spectra of the pilot plant mixture collected throughout the course of the reaction. Significant differences are clearly observed which correlate to changes in the water content.

been installed in the plant. Spectra (32 scans (~15s) at a resolution of 8 cm^{-1}) were continuously measured over several batches. Spectra collected throughout the process with different water contents are shown in Figure 1.

Figure 2



Cross validation results of a PLS based model for prediction of the water content, which show a very high correlation coefficient (99.76) and a low error (0.02 absolute).

Time stamped samples were collected and analysed off-line before the water content was correlated to the appropriate time stamped in-line NIR spectrum. The resulting calibration model for water content is shown in Figure 2 where a prediction accuracy of 0.02% is achieved over a water content range of 1.9-3.7%.

Quantitative analysis

Near-infrared spectra result from combination and overtone bands of C-H, N-H, O-H... vibrations. Since most reaction mixtures contain some organic components with these bonds, they are ideal for near-infrared analysis.

The OPUS/QUANT quantitative analysis software package uses partial lease squares (PLS) to develop quantitative models. Typically the development of a model requires measuring samples that contain a range of concentrations of the components of interest. The unique Quant self-optimisation routine is then applied to develop the calibration model. In this example, NIR spectra of the reaction mixture were collected continuously in a pilot plant and correlated via their time stamp to samples pulled from the reactor and analyzed off-line.

Measurement options

Bruker Optics offers a wide variety of instrumentation to meet your specific needs. For process applications we recommend the MATRIX™-F It's multiplexing capability; ruggedness and easy serviceability make it the perfect process system. A wide variety of process measurement accessories are available for in-line and on-line measurements of liquids, solids and slurries.

The MATRIX™-F can also be used in an at-line application with the addition of a simple fiber coupled vial holder using disposable glass vials. This can be an alternative solution for developing calibration models prior to going on-line.

Near-infrared spectra can be collected directly from liquid streams using in-line flow cells or transmission probes with no sample preparation. The use of fiber optics makes it possible to locate the instrument in a distant control room or in an enclosure in a hazardous location close to the measurement site. High quality spectra can generally be collected in less than a minute and the quantitative analysis of multiple components performed. All of these factors make NIR spectroscopy a quick, reliable in-line tool for monitoring processes.

Figure 3

MATRIX™ - F individually enclosed modules designed to easily fit into standard 19 inch racks and enclosures. The spectrometer for this experiment was housed in an environmental enclosure 100 m from the sample point along with a touch-screen computer. The results are transmitted to the Process Control system via a 4-20mA interface and the water content is controlled by a closed loop based on the NIR result.

Implementation

In a process environment the MATRIX™-F can be used, along with our process software ADIO, to measure and analyse the sample and send the results to a DCS via a variety of I/O options (4-20mA, Modbus, Profibus, Industrial Ethernet etc).

Bruker Scientific LLC
Billerica, MA · USA
Phone +1 (978) 439-9899
info.bopt.us@bruker.com

Bruker Optics GmbH & Co. KG
Ettlingen · Germany
Phone +49 (7243) 504-2000
info.bopt.de@bruker.com

Bruker Shanghai Ltd.
Shanghai · China
Tel.: +86 21 51720-890
info.bopt.cn@bruker.com

www.bruker.com/optics