MULTI-SENSOR MEASUREMENTS OF QUANTITATIVE PARTICLE SIZE AND SHAPE INFORMATION

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Particle size and shape are critical physical attributes for active pharmaceutical ingredients (API) as they have direct impact on downstream processing, as well as on the performance of the finished product such as bioavailability, dissolution rate and toxicity. Obtaining a reliable and robust quantitative information of these particle attributes in real-time remains a great challenge across the multiple manufacturing steps. None of the current process analytical technologies (PAT), although capable of providing an indication on these key attributes, measures particle size directly. Particle sizing technologies are often misused due to a lack of understanding of their underlying principles and a single instrument cannot provide direct in-line measurement of particle size and shape quantitatively.

We aim to establish a physical model-based approach which fuses multiple optical measurements for monitoring particle size/shape in crystallisation process [1]. An innovative spatially and angularly-resolved diffuse reflectance measurement (SAR-DRM) system was developed for in-line monitoring in a variety of chemical manufacturing applications. The SAR-DRM technology relies on multiple scattering of particles and collects multi-wavelength (UV-visible-NIR) diffuse reflectance spectra from optical fibres of multi-angle multi-space arrangements. The novel design provides a signal differentiation and consequently, more detailed information about the overall system.

Polystyrene beads are used as a model system to investigate the effect of particle size and solid loading. All conditions were continuously monitored at real-time using FBRM, PVM and SAR- DRM. Mathematical algorithms were applied to FBRM and PVM data to extract particle size distribution (PSD) and aspect ratio [2, 3]. These results were compared with the PSD and aspect ratio obtained from off-line technologies (laser diffraction and imaging). Characterisation of the particles attributes served as an input to validate SAR-DRM's sensitivity, accuracy and capability to track the differences in size, shape and concentration observed by the commercial methods. Multivariate analysis was applied to establish a performance matrix for all probes and combined methods.

The results indicate that SAR-DRM could be a complementary technique to the current in-line particle analysis methods to achieve process robustness and optimization of crystallisation processes.

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