Multi-sensor measurements of quantitative particle size and shape information in crystal slurries

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Introduction

Particle size and shape are critical quality attributes for active pharmaceutical ingredients (API) as they have direct impact on downstream processing, as well as on the performance behaviour of the finished product. Obtaining a reliable and robust quantitative information of these particle attributes in real-time remains a great challenge across the multiple manufacturing steps and cannot be achieved by just using a single sensor.

In-line particle sizing technologies, such as Focus Beam Reflectance Measurement (FBRM) and Particle Vision and Measurement (PVM), measure the optical response of single particle (single scattering) to a single wavelength light source and measurable size ranges are limited by the optical resolution of the light source and the optics. The increase of turbidity in the medium leads to an increase of scattering effects and absorption contributions. When photons encounter several particles, they undergo multiple scattering, changing the direction during each scattering event. In these cases, it is very challenging to obtain reliable results from either FBRM or PVM. Spatially and angularly-resolved diffuse reflectance measurement (SAR-DRM) is a spectroscopic-based approach for in-line monitoring.[1] SAR-DRM collects multi-wavelength (UV-visible-NIR) diffuse reflectance spectra from optical fibres of multi-angle multi-space arrangements. Absorption of light occurs at specific wavelengths for different particles, which can be used to identify samples composition; and different particle sizes and shape will have a different scattering pattern. SAR-DRM spectrum from each angular and spatial arrangement yields differences responses to the changes in the scattering and absorption properties of the sample. The technology requires multiple scattering on the incident light, therefore, it could complement other single particle based measurement technologies for in-line process monitoring.

In this work, crystal slurries are quantitatively characterised by using an in-line multi-sensor approach. Multivariate regression analysis is employed to establish calibration models for estimating particle size and solid loading. The knowledge acquired is then applied to a wet milling process, which is commonly used in pharmaceutical industries to improve the solubility and bioavailability of poorly water-soluble drugs by causing the breakdown of coarse particles into finer ones through mechanical forces.

Methodology

1. Characterisation of particle attributes, evaluation of the optical probes and modelling strategies

The investigation was carried out on crystal slurries of metformin HCL of different particle size ranges (<53, 53-90, 90-125, 150-180, 180-250 and 250-355 µm) and solid loadings (from 1 up to 40 wt.%). The samples were monitored 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]. Prior to each experiment, samples were analysed using off-line technologies such as laser diffraction and imaging.

Characterisation of the particles attributes served as an input to validate SAR-DRM sensitivity, accuracy and capability to track the differences in size and solid loading in crystal slurries.

Multivariate analysis was applied to establish a performance matrix for all probes and combined methods in order to acquire a reliable and robust model to estimate particle size and concentration.

2. Application of the strategy to a wet milling process

A wet mill was coupled to the 250ml vessel via a recycle-loop configuration in gently suspended conditions in order to perform measurement and extract samples for off-line measurements. Breakage of metformin crystals through this wet milling method produced a range of end sizes from different starting particle sizes and concentrations. The significant change in particle attributes undergoing this system was then continuously monitored by FBRM, PVM and SAR-DRM. The same multivariate analysis was applied to assess the robustness of the model to this complex system.

Conclusions

The results show that FBRM and PVM are valuable tools to monitor particle size and shape distributions in low dense mediums. Increasing the solid loading, regardless of the particle size used, particles start overlapping and pictures lose their resolution which leads to ambiguous results in both FBRM and PVM. Larger particles are more likely to be overlapping or touching the picture frame and consequently, more likely will be discarded by the PVM imaging algorithm. In case of FBRM, large particles generate chords split, shifting the CLD towards smaller lengths.

SAR-DRM is capable of handling high solid loadings and relatively large particle sizes and is sensitivity to both particle size and solid concentrations, performing better than FBRM and PVM for such suspensions. SAR-DRM can be a complementary technique to the current in-line particle analysis to achieve robust process monitoring and enable improved control & optimisation of crystallisation processes.

References:

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