Monitoring API Crystal Breakage in Wet Milling Using Inline Imaging and Chord Length Distribution Measurements

Bilal Ahmed, Vaclav Svoboda, Okpeafoh Agimelen, Javier Cardona, Jerzy Dziewierz, Cameron Brown, Thomas McGlone, Alison Cleary, Christos Tachtatzis, Craig Michie, Alastair J. Florence, Ivan Andonovic, Anthony Mulholland and Jan Sefcik

Introduction

Particle size and shape are critical attributes that affect the performance of particulate products. The monitoring and control of particle size and shape is an ongoing challenge in the field of particle technology. Current practices for determining particle size and shape mostly rely on offline analysis, in which the measurement is carried out after the process has finished. In addition to the offline analysis being carried out at the end of the process, the particle size and shape may be altered by the filtration and drying process required to extract particles from a liquid medium. Hence, the particle size and shape determined at the end of the process may not be representative of the size and shape of the particles during the process.

The Particle Size Distribution (PSD) and shape (quantified by the aspect ratio - ratio of particle width to length) of the particles in a suspension can be monitored in situ using data from suitable instruments. The Focus Beam Reflectance Measurement (FBRM) and Particle Vision and Measurement (PVM) sensors are inline probes that can be used for this purpose. The FBRM sensor measures a chord length distribution (CLD) which depends on the PSD and aspect ratio of suspended particles. The PSD and aspect ratio of the particles can subsequently be estimated from the CLD data by solving an inverse problem [1]. The PVM sensor captures images of particles in a suspension from which the PSD and aspect ratio of the particles can be estimated using a suitable image processing algorithm [2].

In this work, we employ previously developed algorithms [1,2] for solving the inverse problem associated with CLD data and analyse images from the PVM sensor to monitor the PSD and aspect ratio of particles during wet milling of organic crystals. Wet milling is an emerging application carried out in industry to reduce the size of particles to a suitable range. Organic crystals typically undergo breakage from wet milling. However, various systems and process conditions produce different effects which pose different challenges to the CLD inversion as well as the image analysis. We study the strengths and limitations of the CLD inversion and image processing under various conditions and find that they complement each other in obtaining quantitative information about particle size and shape.

Materials and Methods

A 1L stirred tank vessel charged with different particle suspensions was connected to an IKA MagicLab Wet Mill (a rotor-stator mill) in a recycle-loop configuration. The stirred tank was equipped with temperature controller and the FBRM and PVM probes were used for data capture. The suspension was passed through the wet mill at a series of increasing rotor speeds with real time monitoring. Benzoic acid, paracetamol and metformin hydrochloride were used in three separate experiments. In each process, the CLD data at every stage was captured with the FBRM probe while images of the particles were acquired using the PVM probe. Before the start of each process, samples of each material were analysed using the Malvern Morphologi G3 instrument (offline particle imaging) for particle size and aspect ratio estimation. Similarly, samples of the filtered and dried milled particles were analysed for particle size and aspect ratio estimation at the end of each wet milling process using the Morphologi G3 instrument.

Results

Obtained results from the employed method has shown the relative sensitivities of the two modalities to changes in particle size and shape due to the wet milling. The effect of bubbles produced during the process on the two modalities has also been studied. When the particles are sufficiently large and within the resolution of the PVM instrument camera, and not too large so as to into the image frame, the inline imaging method gives PSD estimates which are closer to online estimates of similar materials. This is especially true for systems composed of long needle-like particles such as benzoic acid and metformin HCL mixed with shorter or more rounded particles. This is because the CLD method needs to find a compromise PSD which the measured CLD at an appropriate aspect ratio. In systems like these, the aspect ratio distribution estimated by the imaging method tends to be dominated by the smaller particles, while the mean aspect ratio estimated by the CLD method tends to be dominated by the long needle-like or rod-like particles. However, the inline imaging method is limited to particles of sizes above about 30μm, whereas the CLD method can go to smaller sizes. In addition, the PSD estimated by the inline imaging method becomes less representative as the sizes of the particles approach the size of the image frame. The accuracy of the PSD estimate is also affected by the proportion of objects that are captured outside the focal plane of the camera. Similarly, the PSD by the CLD method becomes less representative as the length of needle-like or rod-like particles approach the diameter of the circular trajectory of the FBRM laser spot making the chord length probability estimate 22 less accurate. Hence, in systems composed of a mixture of needle-like or rod-like particles and more rounded particles of various sizes, a combination of both the CLD and inline imaging methods (probably in a multi-objective approach) should give more robust estimates of the PSD and the aspect ratio. This will be particularly important to real-time monitoring and control of crystallisation processes where various process conditions could lead to the production of particles of various sizes and shapes and effects such as bubbles which could be very challenging to capture by a single sensor method.

Conclusions

We have employed wet milling processes of slurries of different crystalline materials to assess the strengths and limitations of two different inline particle monitoring modalities namely CLD and PVM imaging. The materials were carefully chosen as they produce crystals of different morphologies and mechanical strengths. The results from both CLD inversion and PVM image analysis demonstrate the ability of our software tools to quantitatively monitor particulate processes with respect to particle size and shape distributions. The results from the three case studies have identified a number of strengths and limitations of each method depending on the process conditions and nature of particles in each system. The CLD inversion algorithm can be applied to dense particle suspensions whose images may be difficult to analyse. However, the CLD data is affected by effects such as bubbles or particle transparency. The image processing algorithm allows the distribution of aspect ratios of particles to be estimated, but it is limited by the resolution of inline images

References:

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