In-line monitoring of particle size and shape from image-based measurements

J. Cardona[1,2], C. Ferreira[3,4], J. McGinty[3,4], A. Hamilton[1], O.S. Agimelen[2,3], A. Cleary[1,2], Y.C. Chen[3], J. Sefcik[2,3], C. Michie[1,2], R. Atkinson[1], I. Andonovic[1,2], and C. Tachtatzis[1]
[1]*Department of Electronic & Electrical Engineering, Centre for Intelligent Dynamic Communications, University of Strathclyde, Glasgow, United Kingdom*
[2]*EPSRC Intelligent Decision Support and Control Technologies for Continuous Manufacturing of Pharmaceuticals and Fine Chemicals, University of Strathclyde, Glasgow, United Kingdom*
[3]*Department of Chemical and Process Engineering, University of Strathclyde, Glasgow, United Kingdom*
[4]*Doctoral Training Centre in Continuous Manufacturing and Crystallisation, University of Strathclyde, Glasgow, United Kingdom*

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Introduction

Within the pharmaceutical industry, particle size and shape distributions are crucial properties of crystalline particles produced in crystallisation processes. They determine the success or otherwise of processes such as granulation, suspension treatment and drying, all involved in the manufacture of the final pharmaceutical product. Some properties of the final pharmaceutical product such as dissolution behaviour are also influenced by the particle size and shape distribution of its ingredients. Therefore, crystallisation processes need to be controlled in order to produce particles with the desired attributes (size and shape). This in turn requires an accurate characterisation of the particle attributes during the crystallisation processes.

Traditionally, particle size and shape are determined by means of off-line measurements. However, these techniques only provide information on the final state of the process and involve intermediate processing steps (e.g. sampling, dissolution, drying) that can alter the properties of the particles before the measurement. In recent years, a range of in-line techniques has been developed to obtain in-situ and real-time information on the state of the process in a non-disruptive manner.

Among these in-line techniques, imaging technologies are increasingly gaining importance in the characterisation of particulate systems. Nevertheless, while off-line image-based measurements are used nowadays to acquire both qualitative and quantitative information, in-line imaging techniques, particularly Particle Vision and Measurement (PVM), have mostly been used for qualitative purposes. The monitoring and control of continuous processes introduces additional challenges since it requires the acquisition of in situ quantitative information. An important issue to consider is that in-line measurements involve a fraction of particles that are out of focus, as opposed to off-line techniques where all objects are always in focus.

In this context, this work presents a tool developed by the authors with the aim of extracting reliable in-line quantitative information on particle size and shape from image-based measurements. The results provided by this tool have been validated using particles of standard size and shape. It is shown how accurate particle attributes (size and shape) distributions can be obtained from PVM images. In recent work, this method has allowed a more robust inversion of Chord Length Distributions (CLD) obtained through Focused Beam Reflectance Measurement (FBRM) into Particle Size Distributions (PSD) using quantitative morphological information obtained from PVM images [1]. Here, we also explore the limitations of this type of measurement and emphasise the importance of considering only particles in focus for the analysis.

Methodology

The performance of the in-line image analysis tool is evaluated against NIST standard polystyrene microspheres of different known nominal sizes (150, 300, 400, 500 μm). These systems are characterised by very narrow size distributions and are expressly developed for the calibration of size measuring instruments. The effect of particle size and concentration is tested in order to establish the confidence window for quantitative data extracted from in-line images. Additionally, standard silicon particles of elongated shape (20x20x160 μm) are used to study the results obtained for non-spherical particles. The in-line images were acquired using the PVM V819 probe from Mettler Toledo. In the case of spherical particles, the projection of the 3D sphere on the 2D plane captured by the image results in a circle with the same diameter as the sphere. However, for non-spherical particles, the shape of the projection is not known a priori. Therefore, the expected projected size and shape distributions were obtained through simulations of the projection of randomly oriented 3D cuboids on a 2D plane.

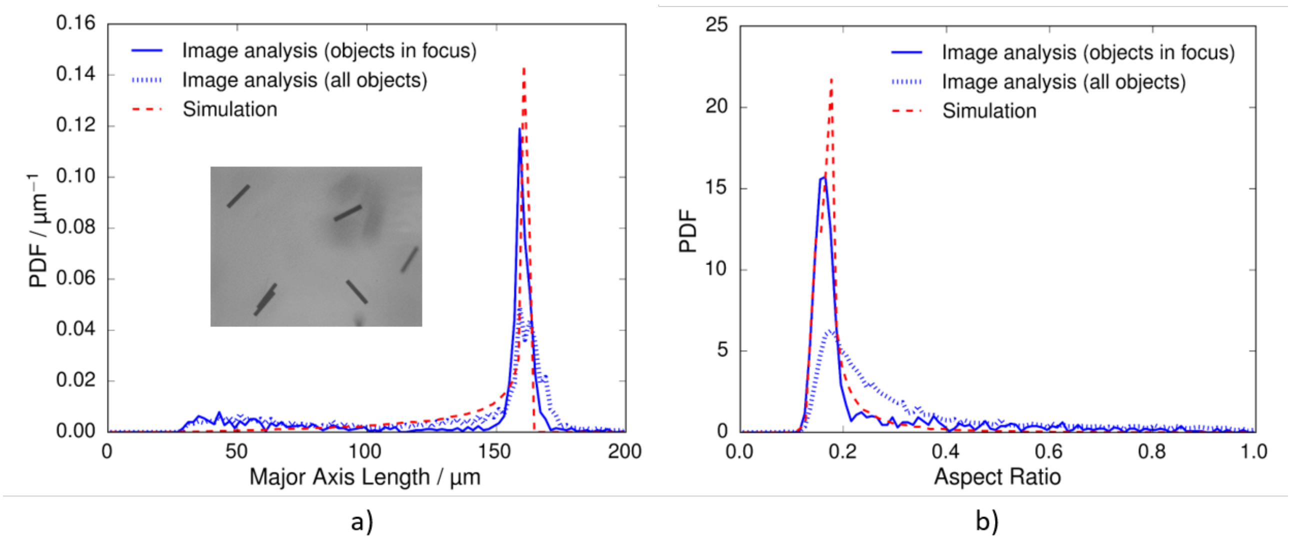

Figure 1 - Particle size and aspect ratio distributions of elongated silicon particles (20 x 20 x 160 µm). Particle size is expressed as the major axis length of the particle. The distributions shown in the figure correspond to number-based probability density functions.

Results

Results show a generally good prediction of particle size and shape attributes for both spherical and elongated particles. Figures 1. a) and 1. b) show the particle size (as the major axis length of the objects) and shape (quantified as aspect ratio) distributions of elongated silicon particles. The expected distributions obtained from simulations of the projections of 3D cuboids on a 2D plane (red dashed line) are successfully reproduced by the results obtained with the image analysis tool (solid blue line). Figure 1 also shows the importance of only considering particles in focus for the analysis. The focus threshold feature included in our tool allows to narrow down the distributions around the expected result (solid vs dotted blue lines) by avoiding the presence of blurred objects whose characteristics are different from those of the original particles. Similar results have been obtained for polystyrene microspheres. In this case, the effect of particle concentration and size is studied to establish the confidence limits of results obtained from PVM images. In denser systems, the probability of particle overlaps increases, which has an effect on particle size and shape distributions. Additionally, larger particles have more chances to fall on the edge of the image frame. Since it is not possible to establish the characteristics of the invisible side of these objects, these particles are not considered in the study and, therefore, the resulting distributions are biased towards smaller sizes.

Conclusion

A tool has been developed to extract quantitative information from in-line image-based measurements in crystallisation processes. Initial results show how reliable data on particle size and shape distributions can be obtained from in-line images. However, a good understanding of the limitations of this method is essential to build up confidence on the results provided by the image analysis tool.

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