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The Role of In-line Image Analysis in the Transition to Continuous Manufacturing in the Pharmaceutical Industry

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Abstract. In recent years, the pharmaceutical industry is seeing a movement towards the implementation of more efficient continuous manufacturing. This shift requires the development of in-line process analytical technologies to monitor and control the process at any given time. However, extracting reliable information from these sensors is a challenge. Among the available technologies, in-line image analysis is quickly gaining importance. This work presents an image analysis framework developed to address one of the main challenges of in-line image analysis: the presence of out-of-focus particles. Through two relevant examples such as the characterisation of a system of microparticles of mixed shapes and the monitoring of a common operation in the pharmaceutical industry such as the wet milling process, the benefits of incorporating this technique are assessed. The real-time analysis of imaging data in combination with other simultaneously-acquired quantitative data streams enables the user to make informed decisions and implement enhanced control strategies.

Keywords. Continuous manufacturing, digitisation, in-line imaging.

1. Introduction

The digitisation of manufacturing processes has seen widespread uptake across numerous industries in recent years. One such case is the pharmaceutical industry which has traditionally operated in batch and where the product specification is generally only tested through off-line measurements at the ending point of the process. The development of in-line Process Analytical Technologies (PAT) offers the
possibility to extract in situ information and enables near real-time monitoring and control of the process [1,2]. In addition, the risk of sample alteration during the analysis is significantly reduced with respect to off-line measurements.

In particular, in continuous manufacturing environments the pharmaceutical and other similar industries are tending to implement in-line PAT [3,4]. This is essential to enable automation and optimisation of manufacturing processes. However, extracting reliable in-line quantitative information has proven to be challenging. In the particular context of particle technology – one of the pillars of pharmaceutical manufacturing – obtaining reliable information on particle size and shape distributions is essential to assess the state of the process.

Several optical-based techniques have been used in the past for in-line monitoring. For example, measurements based on backscattering such as Focused Beam Reflectance Measurement are well-established [5,6] although they do not provide direct information on particle size distributions. Complex algorithms, which often depend on particle shape assumptions that are not always appropriate, are required to extract this information [7]. Additionally, the range of operation of the different techniques is limited, particularly in terms of the concentration of particles in the system.

One data stream with increasing potential due to improved computer processing power is in-line imaging. Instruments such as the Particle Vision and Measurement (PVM) probe are frequently used to obtain qualitative information of the process [8-10]. Our group has developed an interactive tool to enhance the potential of such technology through the extraction of vital quantitative information from in-line images in the form of particle size and shape attributes [11]. The tool addresses one of the main challenges of in-line imaging which is the presence of particles out-of-focus that significantly alter the measured particle characteristics. In this paper, we present two examples of the application and added-value of this tool: the characterisation of a system of polystyrene microparticles of mixed shapes and the in-line monitoring of a common process in the pharmaceutical industry such as the wet milling operation.

2. The image analysis framework

The image analysis algorithm used in this work [11] combines standard image processing steps such as median filtering for noise removal and Laplacian of Gaussian filtering and thresholding for edge detection with a novel focus evaluation feature that enables the rejection of partially detected objects. This feature is essential to obtain representative results from in-line imaging measurements since out-of-focus particles have a significant influence on the final results. For every detected particle, the image analysis framework provides size and shape attributes such as area, length, width, equivalent circular diameter, circularity, solidity and aspect ratio – calculated as the ratio of width to length. These properties dictate the performance of downstream processes and being able to monitor them reliably offers the possibility to implement control strategies to ensure they meet the desired specifications.

3. Results

In this section, the image analysis framework is evaluated in two different scenarios. First, it is used for in situ characterisation of a system of polystyrene microparticles of
mixed spherical and ellipsoidal shapes. Then, it is applied to the monitoring of a process that involves changes of particle size with time such as the wet milling of benzoic acid, paracetamol and metformin. In both cases, the results are compared with those provided by common off-line characterisation techniques and the main advantages and drawbacks of using in-line imaging methods are analysed.

3.1. Characterisation of polystyrene microparticles

Polystyrene beads of three different sieved fractions (i.e. 0-90, 180-250 and 300-500 \( \mu m \)) were suspended in water at a solid loading of 10 wt.% and analysed using the in-line Particle Vision and Measurement (PVM) V819 probe from Mettler Toledo. Additionally, off-line particle sizing analysis was carried out using one of the most established methods for this purpose: laser diffraction using Malvern’s Mastersizer 3000. The system is formed by a mixture of spherical and ellipsoidal particles as shown in the sample images in Figure 1. These same images also show a tendency of smaller particles to be more elongated while larger particles tend to be more spherical.

In this work, particle size and shape distributions are represented as volume-based discrete Probability Density Functions (PDF). In this particular case, the particle width is believed to be more representative of the nominal size achieved through sieving since it will be the limiting dimension. Figure 1a shows the effect of the focus evaluation feature included in the image analysis framework on the width distribution of polystyrene particles of 300-500 \( \mu m \). Although the initial results without focus filtering are reasonable (dotted line), the rejection of out-of-focus objects (solid line) provides a significant improvement and practically eliminates the contribution of artifacts of small sizes that bias the distribution. These artifacts are generally pieces of particles that are partially out-of-focus as shown in the inset image of Figure 1a.

![Figure 1. Polystyrene microparticles. (a) Effect of focus evaluation on particle width distribution for polystyrene ellipsoids of 300-500 \( \mu m \), (b) Comparison of particle width distributions obtained through in-line PVM imaging and equivalent spherical diameter distributions obtained through Mastersizer measurements for polystyrene ellipsoids of different sizes (inset: aspect ratio distributions extracted from PVM images).](image)

Figure 1b presents the results obtained for the three different sieved fractions after applying focus evaluation (solid lines). Generally, a good prediction of the expected
size range is observed for the in-line measurements from PVM images. Figure 1b also shows the off-line laser diffraction measurements for the same samples (dashed lines). In this case, the results correspond to the distribution of spheres that have the same scattering pattern as the sample and are represented as equivalent spherical diameter (ESD) distributions. This translates into broader distributions that tend to exceed the expected size range.

An important add-on when using imaging techniques is the possibility to extract information on particle shape distributions. The inset of Figure 1b shows the aspect ratio distribution obtained from PVM images for the three sieve fractions studied in this work. As expected, the larger the particles the more spherical they become (i.e. aspect ratio closer to 1). This information, which can be essential for the performance of pharmaceutical processes, is lost in laser diffraction measurements due to the assumption that all the particles in the suspension behave as spheres.

3.2. In-line monitoring of wet milling processes

After characterising a relatively well-behaved system such as the one formed by polystyrene microparticles described in Section 3.1, a more realistic system is studied in this section. Wet milling processes are common in the pharmaceutical industry. They are mainly used with the objective of homogenising the size and shape of particles generated by crystallisation processes and as a way to obtain a product that is easier to handle in downstream operations.

In this work, three different active pharmaceutical ingredients (i.e. benzoic acid, paracetamol and metformin) undergo a wet milling operation. The procedure consists of five consecutive periods of increasing milling speed: $T_1$ where the mill is not active, $T_2$ with a milling speed of 6,000 rpm, $T_3$ at 10,000 rpm, $T_4$ at 14,000 rpm and $T_5$ at 18,000 rpm. The process is monitored in-line using a PVM V819 probe and two samples taken at the start and the end of the milling process are analysed through off-line imaging with Malvern’s Morphologi G3 equipment.

Figure 2a compares the volume-based particle length distributions obtained through in-line and off-line imaging techniques at the starting and ending point of the wet milling process of benzoic acid. A good agreement is reached between both methods and explains the transition from the large particles observed initially to the final slurry of small particles obtained after milling (see inset images).

![Figure 2. In-line monitoring of wet milling processes. (a) Particle size distribution of benzoic acid before and after the wet milling process as monitored by in-line PVM and off-line Morphologi G3, (b) Evolution of particle size distribution of benzoic acid with increasing milling speed (inset: evolution of the volumetric size mean $D_{4,3}$ with increasing milling speed for paracetamol, metformin and benzoic acid).](image-url)
While it is not possible to track the evolution of the milling process reliably through offline techniques, due to very probable alterations of samples taken during the process (e.g. agglomeration, further breakage, temperature change), in-line image analysis offers this possibility. Figure 2b shows a continuous decrease in particle size as the milling process evolves for benzoic acid. The inset of this figure shows the effect of the milling speed on the volumetric mean size obtained through in-line imaging for the three APIs used in this work, and compares it to the results obtained through offline imaging at the start and the end of the process. As expected, in all three cases the mean size decreases as the milling speed increases, although the breakage rate appears to be significantly faster for metformin compared with benzoic acid and paracetamol. In general, the results for benzoic acid agree with offline measurements as shown before in Figure 2a. However, for both paracetamol and metformin, the initial size is clearly underestimated by in-line measurements. The finite size of the PVM frame (i.e. 1075 x 825 µm) is at the origin of this discrepancy since particles larger than approximately 500 µm have significant difficulties to fully fit within the frame. Additionally, the resolution limits of the PVM probe do not allow to detect the small particles obtained at the end of the milling process for metformin. More details regarding this work can be found in [12].

Although some limitations exist, important conclusions can be extracted within the range of validity of the results obtained through in-line analysis. The ability to observe the slow evolution of the particle size distribution towards smaller sizes for increasing milling speeds opens the window to use this variable to control the final particle size distribution of the product and set it to the desired specifications.

4. Conclusions

This work discusses the contribution of in-line image analysis to the evolution of the pharmaceutical industry towards continuous manufacturing. The development of an image analysis algorithm that addresses one of the most important challenges for in-line imaging such as the presence of particles out-of-focus enables the extraction of reliable information using this technique. The advantages and limitations of this method are discussed through two particular examples: the characterisation of a system of polystyrene microparticles of mixed ellipsoidal and spherical shapes and the monitoring of the wet milling process of benzoic acid, paracetamol and metformin.

In-line analysis methods have the significant advantage of being able to monitor the process at any given time while minimizing sample alteration (e.g. dilution, breakage, agglomeration) common in off-line analysis. Furthermore, in-line imaging adds very valuable information regarding particle shape, which is not accessible through other methods.

Although some limitations exist in terms of handling high solid loadings or the finite size and resolution of the images, in-line imaging is a powerful tool for the understanding, monitoring and control of processes in the pharmaceutical and fine chemical industries.
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