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Photometric imaging in particle size measurement and surface visualization

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ABSTRACT

The aim of this paper is to give an insight into photometric particle sizing approaches, which differ from the typical particle size measurement of dispersed particles. These approaches can often be advantageous especially for samples that are moist or cohesive, when dispersion of particles is difficult or sometimes impossible. The main focus of this paper is in the use of photometric stereo imaging. The technique allows the reconstruction of three-dimensional images of objects using multiple light sources in illumination. The use of photometric techniques is demonstrated in at-line measurement of granules and on-line measurement during granulation and dry milling. Also, surface visualization and roughness measurements are briefly discussed.

1. Introduction

There is a constant aspiration towards deeper understanding of material properties in solid dosage form design and late phase development stages during different manufacturing steps of medicines. Through increased understanding of materials and the relative importance of the phenomena and interactions on all levels, i.e. molecular > particle > powder > product, we are able to control the manufacturing of our dosage forms to meet target end-product specifications. The characterization of powders, granular materials and different surfaces is of great interest within the pharmaceutical sciences (Brittain, 1995). As approximately 80% of all drug products are solids, e.g. tablets or capsules, the understanding of the physical characteristics of powders and granules is essential (Hlinak et al., 2006). The physical characteristics of solid particulates have to be considered and studied throughout the development process of a product, from the preformulation stage to large-scale manufacturing. In development and manufacturing many powder handling steps are involved, often including crystallisation, blending, granulation and compaction. Thus, different kind of interactions between particles and between particles and process equipment occur. All these interactions together with specific behavior bulk materials in certain unit operations may give rise to challenges. Efficient analytical tools are needed for characterization of the different manufacturing steps. In this context, the characterization of powders, granular materials and different surface properties with different imaging tools are of great interest.

Image-based characterization of pharmaceutical solids has grown vastly over the last decade with the advent of various techniques producing highly useful and descriptive information such as atomic force microscopy (AFM), spectroscopic imaging, and dynamic image analysis tools for particle sizing. Examples of the use of AFM include characterization of tablet surfaces (Seitavuopio et al., 2003) and inhalation particles (Young et al., 2003; Begat et al., 2004). Within spectroscopic imaging there has been a lot of activity using, e.g. near infrared (NIR) imaging (O'Donnella et al., 2008), Raman spectroscopic imaging (Brown et al., 2010) and terahertz pulse imaging in terms of quality of modified release coated tablets (Ho et al., 2007, 2008) to mention a few examples. Moreover, for instance 2D- and 3D-imaging approaches have been used in monitoring of particle size and shape in crystallisation processes (Wang et al., 2008).

Particle size measurement by imaging is most commonly carried out with microscopy or other optical camera-based systems by measuring single particles, which are dispersed in air or a suitable liquid. Such examples are numerous, but the most interesting are the recent advances in image-based dynamic particle sizing that have taken image-based sizing to a new level enabling mea-

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surement of a large number (up to several millions) of particles using automated systems (e.g. Yu and Hancock, 2008; Patchigolla and Wilkinson, 2009; Sandler and Wilson, 2010). The area of utilisation of image information of bulk materials without dispersing particles has attracted some interest over the past years. Bonifazi (1997), Bonifazi et al. (2002) and Novales et al. (1998) have discussed the perspectives in the field of particulate solids control of bulk or collection of particles instead of single particles. Also Huang and Esbensen (2000, 2001) introduced a method of image analysis (IA) that omits the dealing with individual particles and acquires images directly from in situ powders. They showed that this type of images of the entire field-of-view of powders, also contain information, which relates to individual particles, but mainly the bulk powder. The study concluded that this information is the reflection of complex bulk properties, such as flowability and fluidization velocity. Earlier we have introduced a photometirc concept of calculating the particle size from undispersed powder surfaces under controlled illumination conditions (Laitinen et al., 2002).

The aim of this paper is to give an insight into photometric particle sizing approaches, which differ from the typical particle size measurement of dispersed particles. These approaches can often be advantageous especially for samples that are moist or cohesive, when dispersion of particles is difficult or sometimes impossible. The main focus of this paper is in the use of photometric stereo imaging. The technique allows the reconstruction of three-dimensional images of objects using multiple light sources in illumination. The use of photometric techniques is demonstrated in at-line measurement of granules and on-line measurement during granulation and dry milling. Also, surface visualization and roughness measurements are briefly discussed.

1.1. Technique description

In this section a brief introduction to digital image information and three-dimensionality in images is given, then two different methods, namely “grey scale difference matrix” and “photometric stereo”, that can be used to extract particle information from undispersed surface images are described.

1.2. Digital image information

Digital images consist of picture elements called pixels. Pixels contain information about the brightness of a certain location in the image. The term monochrome image or a black and white image refers to a two-dimensional matrix of pixels with particular levels of brightness. Only monochrome images are covered in this section since the main applications here are based on black and white images. The concept of digital images is thoroughly described in textbooks (Sonka et al., 1998; Gonzalez and Woods, 2001). The image and its two-dimensional pixel matrix may be presented as a light intensity function $f(x,y)$, where x and y are discrete valued

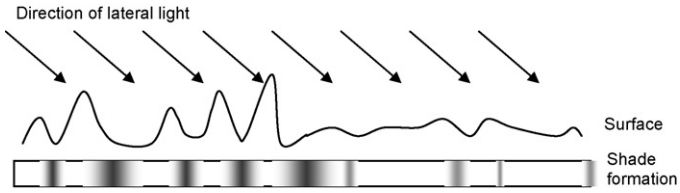

Fig. 2. Shade formation using lateral illumination.
Modified from Laitinen et al. (2002).

spatial coordinates and f at the point (x,y) is proportional to the brightness of the image at that given point. Depending on the application and imaging resolution, the size of the images, i.e. size of its brightness matrix can vary. In monochrome images the grey level that corresponds to the average transmitted beam from the surface of the object, is typically characterised by a number in the range 0–255, where 0 is totally black and 255 completely white. Fig. 1 illustrates the concept of pixels and grey level values in an image.

1.3. Three-dimensionality in image information

In two-dimensional images the three-dimensional (3D) reality is projected on a plane. 3D characteristics are often required in order to get quantitative information about particle morphology. To acquire three-dimensionality in images, viewing under different angles is possible (Russ, 1999). Moreover, depending how the picture is produced different amount of 3D features can be distinguished. For example, optical microscopy provides a poorer depth-of-field than SEM (scanning electron microscopy) techniques. 3D features can also be revealed using lateral illumination as described by Pons et al. (1999, 2002). These features are connected to shading effects that expose the topography or the visual texture of an object or a surface (Fig. 2). A rough structure produces an image with large grey scale variations and smoother structures generate images with smaller grey scale variations. In this context, if we consider particulate and powder analysis it is possible to make comparisons between materials if controlled illumination conditions are used. The challenge is to find, extract and quantify the image information that is generated.

1.4. Grey scale difference matrix

A parameter called the grey scale difference matrix (GSDM) for calculations of the particle size from surface images was developed (Laitinen et al., 2002, 2003). This is one approach taking advantage of the shading effects with controlled illumination. The subsequent steps are taken in the creation of the GSDM. Two light sources are used to illuminate the sample from opposite sides of a sample surface and consequently two images of a sample surface are taken by alternating light sources. Thus, two digital images are received and

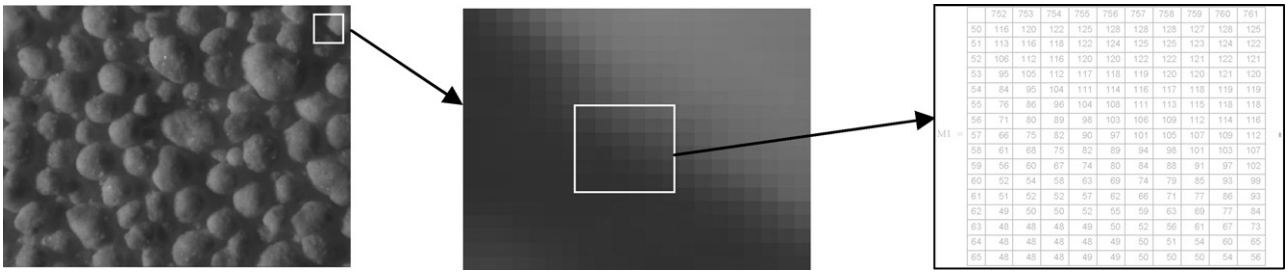

Fig. 1. The concept of a digital image. *Left*: original digital image (resolution 800 × 600), *middle*: top right corner of the original image with visible pixels, *right*: grey level values of the white rectangular area from the previous image.
Modified from Laitinen et al. (2003).

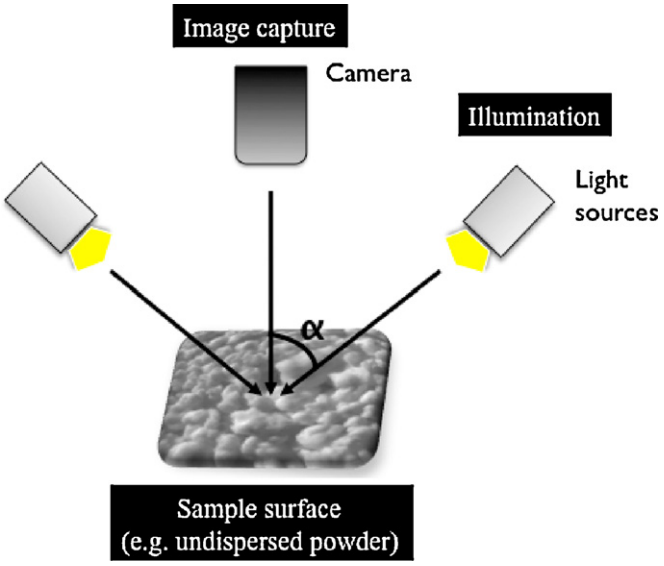

Fig. 3. Imaging setup for photometric stereo. The direction of the incident illumination is varied and the viewing direction is kept constant.

two matrices of their grey scale values can be formed. The difference of these two matrices can then be calculated. The operation of matrix subtraction is explained by Eq. (1) using a 2×2 example matrix.

$$GSDM = M1 - M2 = \begin{bmatrix} 4 & 6 \\ 9 & 5 \end{bmatrix} - \begin{bmatrix} 8 & 6 \\ 5 & 11 \end{bmatrix} = \begin{bmatrix} -4 & 0 \\ 4 & -6 \end{bmatrix}, \quad (1)$$

where $M1$ is the grey scale matrix of image 1 and $M2$ is the grey scale matrix of image 2. The difference is thus calculated for each corresponding pixel in $M1$ and $M2$.

For an ideal totally smooth surface the difference of the two matrices consist of zeros. For a real surface the difference matrix gets values between −255 and +255. In the next step a distribution of the difference matrix is formed. This concept has been used in some of the studies explained below.

1.5. Photometric stereo imaging

In photometric stereo the idea is to vary the direction of incident illumination between successive images while the viewing direction is held constant (Fig. 3). The technique was first introduced by Woodham (1980). In our research we have developed a variant of photometric stereo with two white-light sources that allows the creation of 3D surface of a sample (Fig. 4). In the method light sources have been placed 180° from each other in a horizontal plane. Samples are imaged through a glass window and two images are taken. The resulting gradient fields obtained with this setup contain direct information about surface normal in *xz* plane and indirect information about surface normal in *yz* plane. Line integration is used in the horizontal direction to obtain a three-dimensional surface. The cumulative error that is typical for line integration-based methods is removed with a high pass filter. It is assumed that the sample surface is approximately straight on larger scale, due to the fact that samples lay against a straight glass surface of the cuvette glass window. The high pass filter is constructed from a moving average low pass filter. Peaks on the 3D surface are assumed to be particles. The volume (V) based particle size is then calculated from the area of the peaks in *xy* direction:

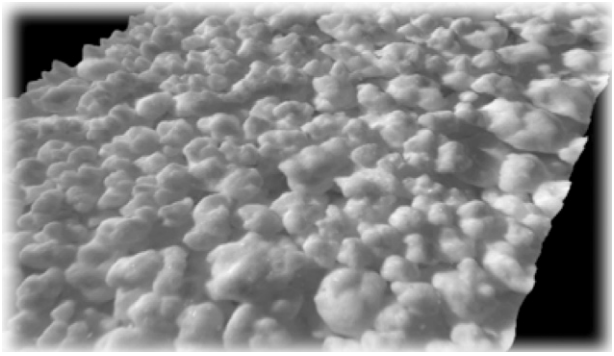

Fig. 5. A typical surface image of undisperesed granules from on-line measurements during fluid-bed granulations visualized in 3D and created with the photometric stereo approach.

$$d = \sqrt{(a)} \times c \quad (2)$$

$$V = d^3 \quad (3)$$

where a in Eq. (2) is the area of the of the peaks, d is the diameter of the particle, c in Eq. (1) is calibration constant, calibrated with cellets (Syntapharm, Mülheim an der Ruhr, Germany (6 different size fractions of spherical cellulose particles, between 100 and 1400 μm)). Previous work in the area related to the GSDM parameter mentioned above has investigated the sample preparation procedure, optimal illumination angles and imaging conditions in general for an imaging system (Laitinen et al., 2002, 2003, 2004) used for photometric stereo imaging. A typical reconstruction of a three-dimensional image of objects using two light sources is shown in Fig. 5. The size of the field-of-view will vary depending on the optical solution. In our laboratory, depending on the application and the objects to be imaged, a typical size of an image is from a few millimeters up to few centimeters, and the optical solutions give pixel resolutions between approximately 2 and 11 μm.

2. Applications in pharmaceutics

2.1. Particle size and shape measurement

2.1.1. GSDM in particle sizing

In studies employing the GSDM algorithm a variety of granule pilot scale batches (Pharmaceutical Technology Division, Uni-

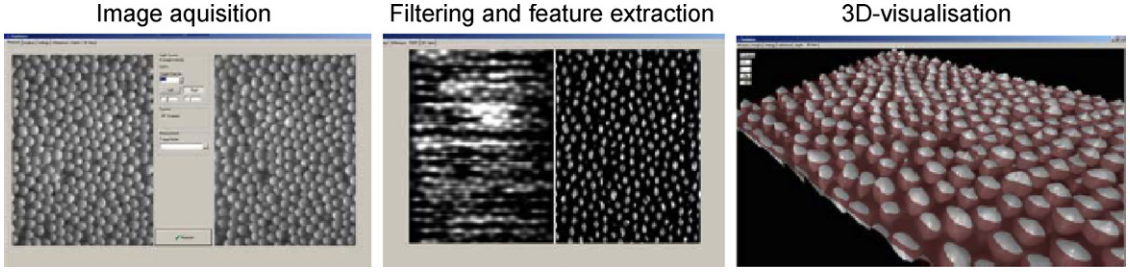

Fig. 4. Example of image acquisition and filtering and 3D-visualization.

versity of Helsinki, Finland) with varying particle sizes and compositions prepared with fluidized bed granulation were used (Laitinen et al., 2002, 2003). Models between surface image information of granules and their respective particle size distributions were formed and the results clearly showed that the GSDM feature can be used in particle size measurements for particles between 50 and 3000 μm. The correlation coefficient between the median particle size of the results from the optical measurements and sieve analysis was 0.82 ($p < 0.0001$). Slightly better models were created for laser diffraction data, the correlation coefficient between the median particle size of the results from the optical measurements and laser diffraction being 0.92 ($p < 0.0001$). An improved model between the GSDM features and sieve analysis was created later using a larger set of material and optimised imaging conditions (Laitinen et al., 2004). The Pearson correlation coefficient between the mean sizes measured from surface images and the mean size measured by sieving was 0.97. The PLS model that was created had a R^2 value of 0.91 and Q^2 value of 0.87. In addition to the use of the GSDM Antikainen et al. (2007) introduced a novel neural network approach related to mammalian visual cortex models called pulse-coupled neural network (PCNN) in particle sizing from bulk images. The PCNN was evaluated with regard to image feature extraction and the PCNN was used to create image signatures that are one-dimensional feature vectors. These functioned as fingerprints for images of different fractionated and unfractionated granules produced with fluidized bed granulation. The image signature vectors obtained were then linked successfully to size distribution data by employing multivariate modeling. The PCNN time-signal has also been used to classify different particle shapes (unpublished data) shown in Fig. 6.

2.1.2. Process analytical applications

2.1.2.1. At-line measurements. The GSDM based model was employed at-line in a pilot-scale fluidized bed granulator (Glatt WSG 5, Glatt GmbH, Binzen, Germany) by Laitinen et al. (2004). The granulation setup has been described in detail by Rantanen et al. (2000). The process conditions followed an experimental design using three process variables were altered on three levels: inlet air temperature (30, 40, 50 °C), nozzle spraying pressure (1, 1.5, 2 bar) and granulation liquid flow rate (160, 175 and 190 g/min). The study indicated that the method used was suitable in the measurement of granule samples during all process phases, i.e. it was possible to measure wet/moist and dry samples with a wide particle size range. The particle size measured from the image information also allowed the prediction of weight variation behavior of batches upon tablet compression. The recent use of the photometric stereo algorithm has indicated that the method allows the generation of high quality topographical 3D images (Fig. 4) which allow the particle size analysis both at-line and on-line during a granulation process (for on-line measurement see below). Fig. 7 shows the comparison of the D50 particle size of a selection of at-line determined granules with the developed photometric stereo 3D algorithm and Spatial Filter Velocimetry sizing technique.

2.1.2.2. On-line measurements during granulation and dry milling. One of the greatest challenges with regard to process monitoring is the interface of the measurement equipment with the process.

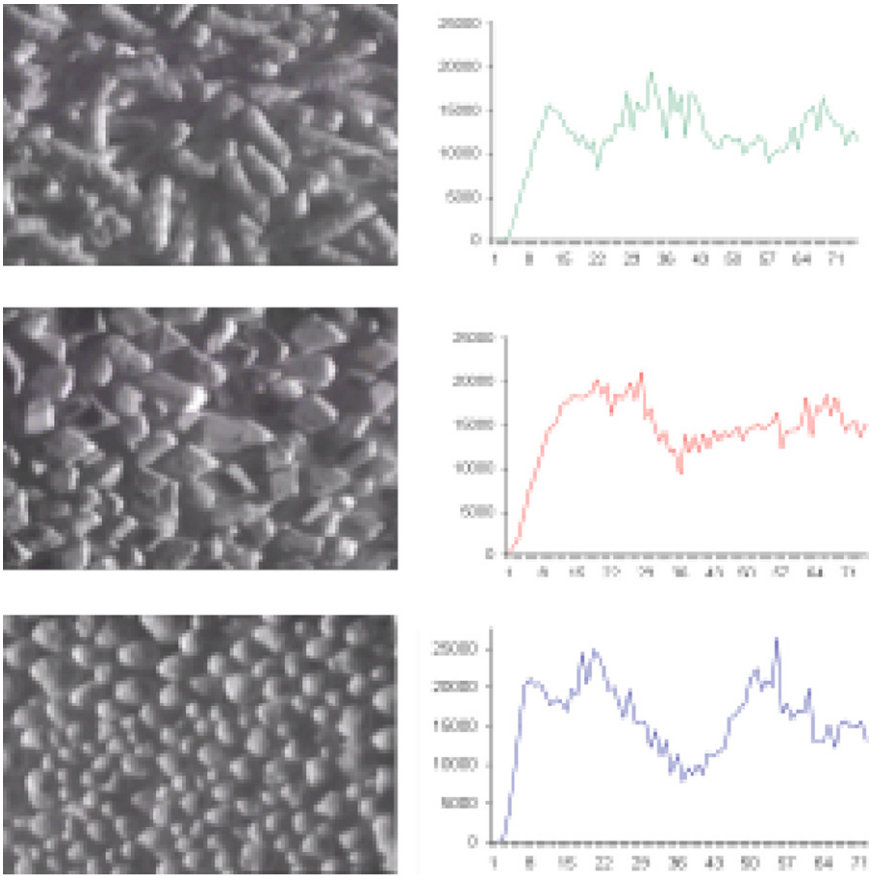

Fig. 6. Examples of surface images of differently shaped particles and their respective PCNN time-signals. The signals can be used for shape classification purposes.

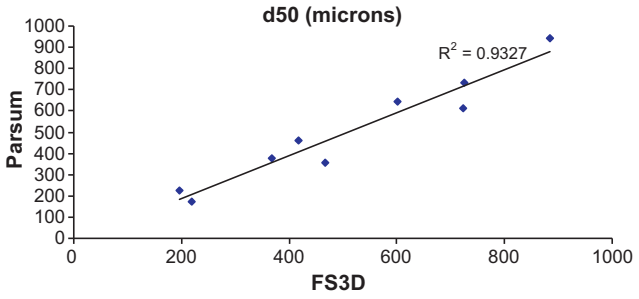

Fig. 7. Comparison of the used 3D particle size algorithm (FS3D) versus Parsum (Spatial Filter Velocimetry sizing technique) with granule samples.

In granulators, solutions, which make an effort to monitor moving powder beds have been tried, but the measurements turn out to be very difficult due to the dynamic nature of the powder behavior in the process. However, successful examples exist, e.g. by using spatial filter velocimetry (Burggraeve et al., 2010). Närvänen et al. (2008a) have approached the process interfacing with the creation of a on-line double-cuvette measuring system (SAY Group Ltd., Helsinki, Finland), where the sample under measurement is made static for the duration of the measurement. Whereafter, the sample is returned back to the process without any loss in material during monitoring. This sampling unit consists of special frame by which can be mounted in the process chamber, e.g. in a fluidized-bed granulator or drier (Fig. 8). The sampler frame has been described earlier by Närvänen et al. (2008a, 2008b). The cuvette is designed in the manner that packing of the material is similar every time. The emptying is accomplished by the use of a highly turbulent air-jet pulse. Short air pulse cleans the walls of the cuvette and prevents the sticking of the particles into the walls. Närvänen et al. (2008a) also showed the use of a method that is capable of forming a three-dimensional topographic image of a undispersed sample surface from a digital image with the automatic sampler (shown in Fig. 8).

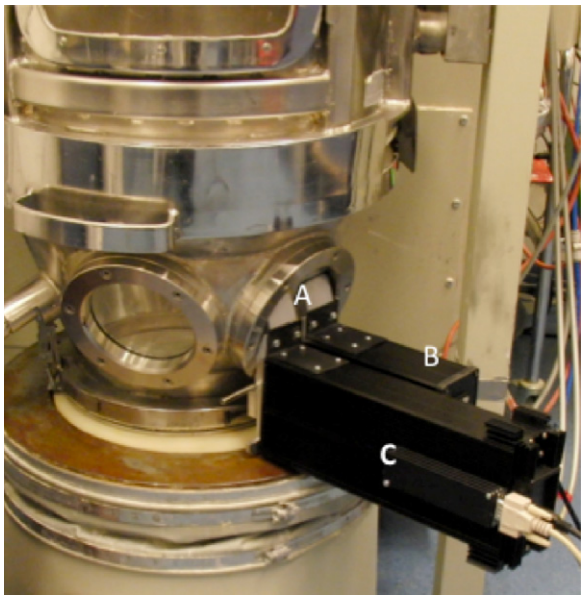

Fig. 8. An on-line sampling system designed for a fluid-bed granulator. *Key*: sampling cuvettes (A), near-infrared probe (B), and photometric stereo camera system (C).

In their method, a flat granule bed surface is illuminated from three different directions, using three primary colors (red, green, and blue). One color picture was taken by a digital camera, after which a topographic image of the object surface was constructed using the color information. This is similar to the photometric approach with monochrome images explained above.

The monochromatic photometric stereo approach has been recently employed in fluid-bed granulation and dry milling (Sandler et al., 2009). The above-mentioned double-cuvette system allowed the simultaneous measurement of particle size with

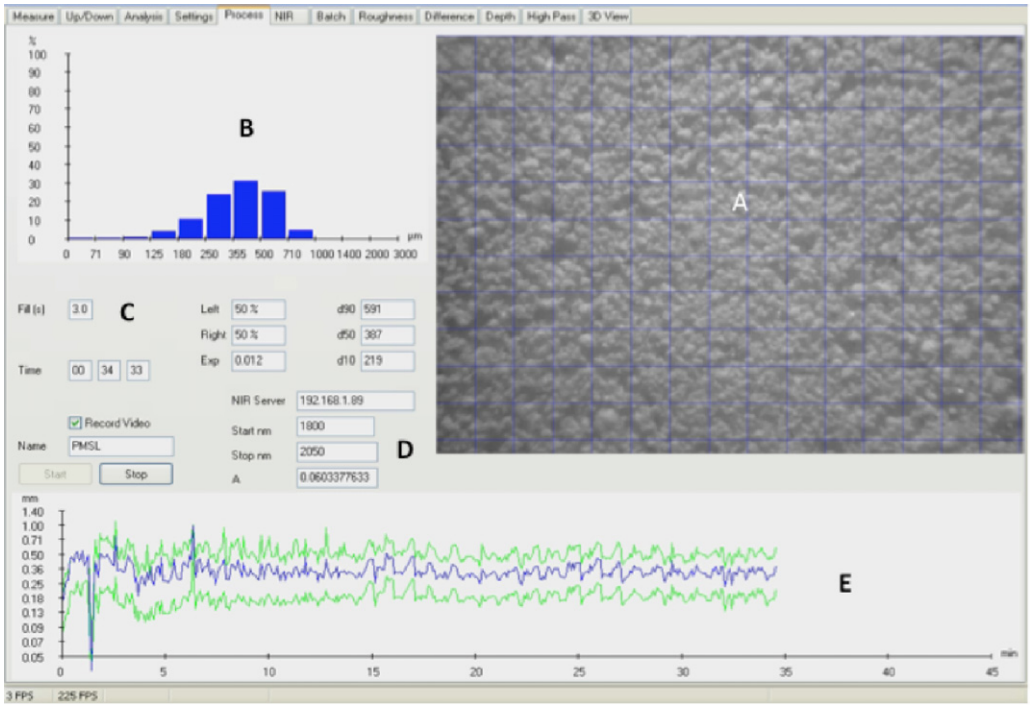

Fig. 9. Examples of a possible process control screen at t34 min of the fluid-bed granulation process. Different features are shown with text and arrows on screen. (A) View of the sample being measured, (B) particles size distribution of the sample under analysis, (C) powder flow (cuvette fill), (D) NIR measurement integration, and (E) real time particle size monitoring ($d100$, $d50$, $d90$).

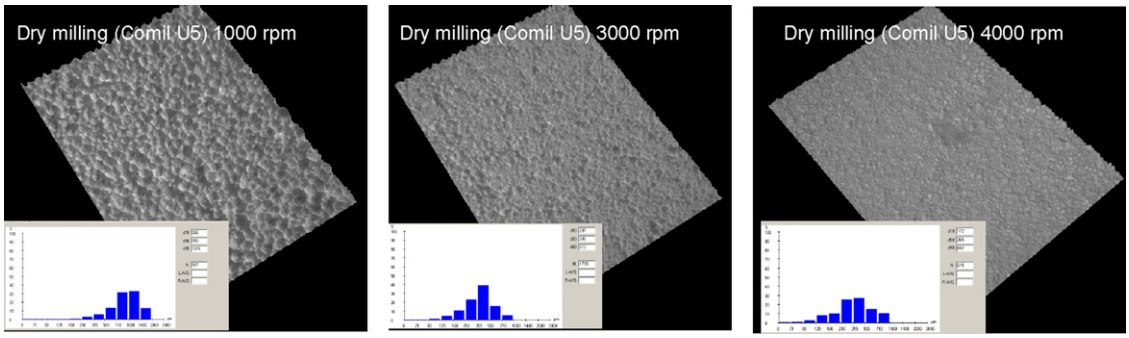

Fig. 10. Surface visualization and particle size distributions of granules samples after dry milling with different rpm (rotations per minute) settings.

imaging and near-infrared monitoring of moisture content samples during the entire process runs. The used 3D imaging technology proved to be powerful in measurement of granule samples during all process phases including analysis of dry and wet samples. The system allows dynamic measurement of on-line particle size and also powder flowability due to the design of the cuvette showing visually how the sample is entering/filling the cuvette. The utilisation of the double-cuvette system made NIR measurement integration possible. This opens perspectives for simultaneous imaging of size data and its use in NIR baseline correction. In essence, when NIR spectra are measured simultaneously with particle size data through the cuvette window the NIR baseline shift due to particle size effect can be removed, if found appropriate. Fig. 9 shows an example of how a process control window could look like with the features that can be studied from the process in real-time. In general, the particle size measurement during processing is similar to the at-line approach described in Laitinen et al. (2003). The main difference is the speed of imaging, higher image resolution and quality, together with automated sampling, which allows the rapid imaging to be performed. Due to this, the challenge is in the data handling and extraction. For instance, during a 5 kg pilot scale granulation process images can be taken every 100 ms, then a typical granulation of a batch might produce approximately 20,000 images. However, current possibilities in multivariate data processing and data storage capabilities provide solutions for this.

In addition to fluid-bed granulation the effects of the dry milling process on granule particle size was also studied and monitored with the photometric camera technology (Sandler et al., 2009) and a modified cuvette system. For the dry milling of granules the image analysis setup consists of a camera connected to steel cuvette with a glass window. The samples are fed into a cuvette through a hopper with an orifice diameter 2.5 cm and the particle size is recorded with 3-s intervals. A high-shear granulator was used to make paracetamol formulations and consequently dry-milled with

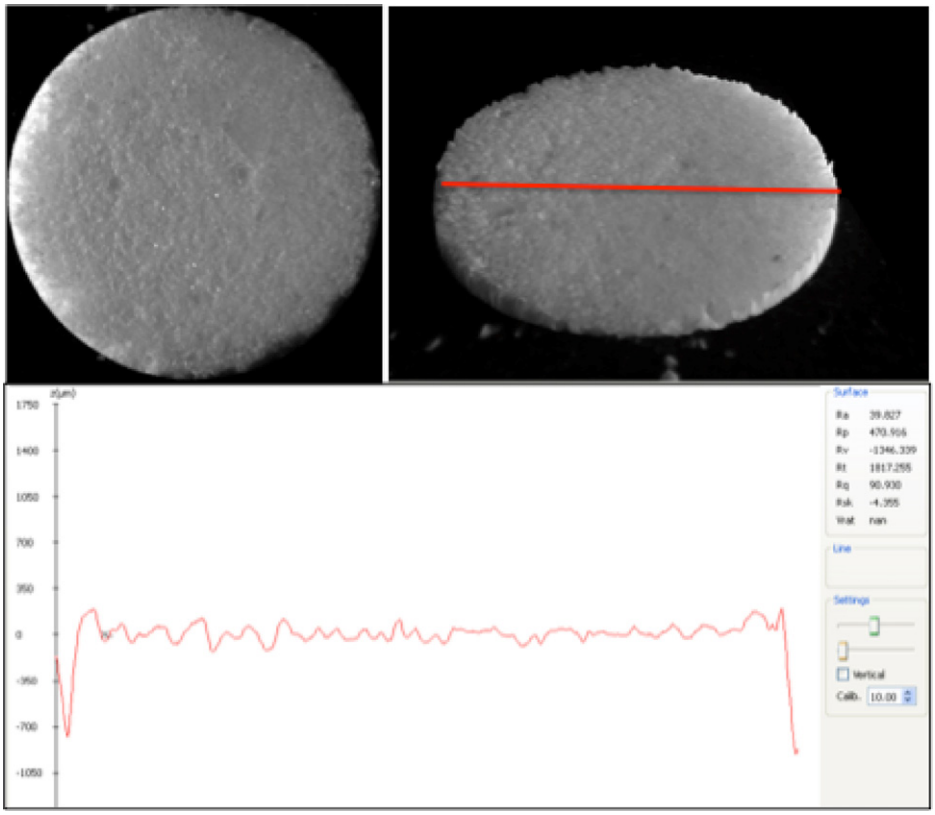

Fig. 11. An example of a surface roughness profile measurement from a relatively rough tablet surface, visualized in 3D, using photometric stereo imaging. *Top left*: 2D image of the tablet sample, *Top right*: 3D reconstruction of the tablet surface with a red line indicating a roughness profiling measurement location, *Below*: a roughness profile and various roughness parameters calculated from the 3D-surface.

three different mill speeds. Granule images with particle size distributions calculated from the images from the process monitoring are presented in Fig. 10. It could clearly be seen that higher mill speed decreased the particle size of the granules as expected. Real-time monitoring of the size during the dry milling stage opens up new possibilities in feed-back and feed-forward control and prospects for process analysis of unit and continuous processes. Hence, if for instance an image-based measurement solution is integrated to the dry milling process, it does not only enable real-time visual monitoring of particle size, but also gives understanding of the mechanical properties (i.e. friability of granules) of the material. Therefore, this allows the building of feed-back loops to change mill settings or feed-forward loops to change tablet compression parameters before the material that has passed the measurement point will reach the next process phase. With the advent of continuous processing in pharmaceutical manufacturing the possibility to monitor entire material flows in this way will benefit material and product control.

2.1.2.3. Surface roughness measurements and visualization. Apart from the applications described above that concentrate on particle size measurement, a photometric approach has natural applicability in surface roughness measurement and 3D-visualization various surfaces. Earlier similar imaging setups have been used for tablet coating roughness evaluation (Ruotsalainen et al., 2003; Krogars et al., 2002). Roughness values, such as R_a, which is the arithmetic average of the roughness profile, or the S_a, the arithmetic average of the 3D roughness among a multitude of other roughness parameters can be calculated from the digital image information and are based on the change in grey scale values in the surface images. This also opens possibilities in real time control of granule roughness during similar process measurements during granulation. Fig. 11 depicts an example of 3D surface visualization surface roughness profiling using photometric stereo on a tablet surface.

When applying this photometric approach to concentrated dispersion or surfaces with a collection of particles the user has to be careful with interpretation of the results. As with any technique one has to be careful with sampling and sample preparation if using an at-line approach to avoid unrepresentative samples and to make sure that a statistical number of particles is measured. One of the main causes for careful analysis of size data using undispersed surfaces with the photometric approach is the interpretation of agglomerates versus single particles. Due to the nature of measurement very rough agglomerate structures can be regarded as multiple particles if the shading effects are large on a surface.

3. Conclusions

There is an enormous unused potential in the optical and other image sources produced in various steps of drug development. Consequently, the development of this discipline creates a challenge within the characterization pharmaceutical solid systems. The attempts in developing image-based particle, agglomerate and surface analysis tools for pharmaceutical powders should strive for reliable, fast, and easily usable methods with possibilities of intelligent image feature extraction and feedback control mechanisms for process monitoring situations. Photometric stereo imaging combined with feature extraction can give solutions to some of these challenges as demonstrated in this paper. The recent increased availability of high-resolution cameras, automated imaging systems and high-performance computing enables advances in the development of high-throughput image-based analysis of phenomena during various steps of drug product development. Automated image processing algorithms for feature segmentation and extraction offer the ability to extract objective measurements of the multidimensional image contents, and are particularly useful for the analysis of image data sets that are very large, or of features that are too subtle, for reliable human evaluation. In the future comparisons of measurements obtained from particle and other solid pharmaceutical systems created under different experimental conditions can be used to derive profiles that summarize, e.g. differences in the physical characteristics of these systems much more efficiently using image-based characterization than is the norm today.

Disclosure statement

NS owns shares in Intelligent Pharmaceutics Ltd., which is a university spin-off company that aims to commercialize imaging products that are based on the photometric concept.

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