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Research paper

On-line monitoring of fluid bed granulation by photometric imaging

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ABSTRACT

This paper introduces and discusses a photometric surface imaging approach for on-line monitoring of fluid bed granulation. Five granule batches consisting of paracetamol and varying amounts of lactose and microcrystalline cellulose were manufactured with an instrumented fluid bed granulator. Photometric images and NIR spectra were continuously captured on-line and particle size information was extracted from them. Also key process parameters were recorded. The images provided direct real-time information on the growth, attrition and packing behaviour of the batches. Moreover, decreasing image brightness in the drying phase was found to indicate granule drying. The changes observed in the image data were also linked to the moisture and temperature profiles of the processes. Combined with complementary process analytical tools, photometric imaging opens up possibilities for improved real-time evaluation fluid bed granulation. Furthermore, images can give valuable insight into the behaviour of excipients or formulations during product development.

1. Introduction

Fluid bed granulation is a common unit operation in solid dosage form manufacturing. Its performance is influenced by several factors including process parameters, powder characteristics and binder properties. Granulation consists of three consecutive and partly overlapping phenomena, i.e. wetting and nucleation followed by consolidation and growth and finally breakage and attrition [1]. Controlling changes during granulation is important for achieving a smooth process and the required end-product quality. Fluid bed processes are conventionally monitored using process parameters, e.g., process air flow, volume and humidity [2]. Information on the typical behaviour of different materials can be obtained by combining temperature and humidity data obtained from the process [3]. However, to monitor the process effectively and reliably in real-time, direct measurements on key product properties such as moisture and particle size distribution can be beneficial. The endeavour of the industry to increase in-process controls and e.g. to shift from batch to continuous processing with further process automation requires reliable, continuous and automated solutions for process monitoring. In this context, on-line, in-line or at-line measurements are preferred over off-line measurements [4].

Monitoring moisture during granulation and pelletisation is important in terms of product quality and numerous methods, such as NIR and acoustic emission have been developed and studied [5–9]. Furthermore, controlling particle size during granulation is critical due to the great importance of granule size in the subsequent tabletting process. A few systematic real-time methods for measuring particle size in fluid bed granulators have been developed, including an imaging probe, spatial filtering velocimetry (SFV), acoustic emission, NIR, Focused Beam Reflectance Measurement (FBRM) and Particle Image Velocimetry (PIV) [10–15]. However, the movement of the sample, probe fouling and insufficient fluidisation close to the sampling probe make the particle size measurements challenging. An attempt to overcome these problems and to gain direct visual information on the granulation process by measuring particle size of a motionless sample with an on-line or at-line surface imaging approach have also been studied [16–19].

In addition to particle size, enormous untapped potential lies in the images collected during processing [18]. The most common problems encountered in granulation include oversized granules, excessive amount of fines, poor fluidisation and heterogeneity of the finished product [20]. Continuous imaging could help to direct the process towards optimised particle size and improved product uniformity as images provide simultaneous numerical and visual real-time information on material characteristics. The need to

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develop effective methods to monitor and control fluid bed processes in real-time can be met by well selected continuous in-line or on-line analysers that can be used in combination with process data. The combination of particle size measured by SFV and moisture information collected through NIR spectroscopy has earlier been shown to be advantageous in real-time monitoring and the control of a fluid bed granulation process [4].

This paper aims to investigate if image information together with simultaneously collected process data can visualise and provide insight into the phenomena taking place during fluid bed granulation. Specifically, the goal is to study the usefulness of the generated image information in real-time monitoring of granule formation and drying during fluid bed granulation.

2. Materials and methods

2.1. Formulation and granulation

Granules consisting of paracetamol (Mallinckrodt Inc., Raleigh, NC, USA), microcrystalline cellulose (Avicel PH101, FMC BioPolymer, Little Island, Ireland), lactose monohydrate (Pharmatose 200M, DMV Pharma, Veghel, The Netherlands) and polyvinylpyrrolidone (Plasdone K25, ISP Technologies Inc., Wayne, USA) were manufactured. The drug amount was kept constant at 5% (w/w) in all formulations and the ratios of the fillers are shown in Table 1.

Five granule batches, referred to as I–V, were manufactured with an instrumented bench-scale fluidised bed granulator (Glatt, WSG 5, Glatt Gmbh, Binzen, Germany). The batch size was 3 kg and 1500 g of 15% aqueous povidone solution was used as a binder. The aim was to produce granules with varying particle size and moisture properties. The batches and respective formulations are shown in Table 1. The spraying rate was 77 g/min, atomisation pressure was 0.15 MPa and the nozzle height 45 cm from the distributor plate. The inlet air temperature was 40 °C during mixing and spraying and 60 °C during drying. The inlet air flow rate was adjusted depending on the formulation to obtain optimal fluidisation.

The (1) inlet air flow rate, (2) inlet air humidity, (3) inlet air temperature, (4) outlet air humidity, (5) mass temperature, and (6) outlet air temperature were continuously recorded during processing of the batches. The water amounts of the inlet and outlet air were calculated from the measured relative humidity and air temperature. The total inlet water amount of each process phase was calculated for each batch by multiplying the inlet air water amount by the process time. Weight loss on drying of samples obtained at the end of the mixing, spraying and drying phase was measured by IR-drying (Sartorius Thermocontrol MA 100; Sartorius, Göttingen, Germany). The samples were measured in 105 °C and the sample weight ranged from 3 to 5 g.

2.2. Photometric imaging

Each granulation was recorded by a 3D surface imaging device prototype, consisting of a camera connected to an automated sampling double-cuvette attached to the granulator vessel (Flashsizer FS3D, Intelligent Pharmaceutics Ltd, Turku, Finland) (Fig. 1). The dimensions of the cuvette are $5 * 4 * 1.3$ cm and the size of the measurement field is 1.5×1.1 cm. The sampling interval was five seconds and 300–450 images were taken per batch depending on the length of the granulation. The number of particles per image measured ranged from 600 to 1700. In the sampling cuvette a pulsed air pressure is used to return the sample to the process between each imaging time-point. The air pulse also cleans the glass window of the cuvette, preventing window fouling. The camera is situated horizontally to the window and sample surface. The viewing direction is kept constant, but the direction of the incident illumination is varied. The resulting gradient fields contain direct information about surface normal in *xz* plane and indirect information about surface normal in *yz* plane. Line integration was used in horizontal direction to obtain a 3D surface.

The numerical particle size values were obtained from the 3D images by assuming the peaks on the 3D surface to be particles. The volume (V)-based particle size (d) is then calculated from the area of peaks (a) in *xy* direction:

$$d = \sqrt{a} * c \quad (1)$$

$$V = d^3$$

c in Eq. (1) is calibration constant, calibrated with six different-sized (100–1400 μm) spherical cellulose particles, cellets (Syntapharm, Mülheim an der Ruhr, Germany). The operating principle of the 3D imaging system has been described in more detail earlier [21]. The arithmetic average of the brightness profile from each image was extracted from the image data and used to describe the granule surface brightness during drying as described by Burggraeve and colleagues [22].

2.3. NIR spectroscopy

NIR spectra were continuously collected from each granulation process through the double-cuvette sampler with a NIR spectrophotometer over the spectral range 1081–2250 nm (Control Development, South Bend, USA). The median particle size at each granulation time point was extracted from the untreated NIR spectra by plotting the spectral height (i.e. counts) at 1288 nm against time. The spectral baseline shifts at this wavelength are attributed to particle size changes due to minimal chemical absorption. Moreover, this wavelength has been used for particle sizing earlier [23]. The particle size corresponding to each spectral height was obtained by referencing the NIR particle size curves to the image-based particle size curves.

2.4. Characterisation of the granules

The particle size distributions of the final granule batches were measured in triplicate by photometric imaging. The entire batches were fed through a hopper connected to the camera based on a

Table 1
Filler proportions in the batches.

Batch	Lactose (%)	MCC (%)
I	100	0
II	75	25
III	50	50
IV	25	75
V	0	100

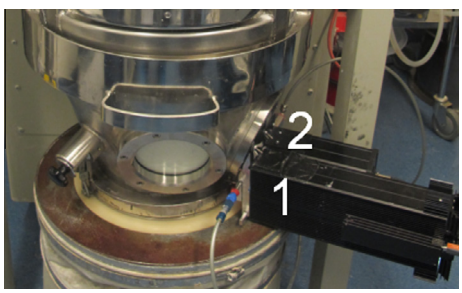

Fig. 1. The photometric imaging device (1) and NIR spectrometer (2) connected to the granulator bowl. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)