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Real-time image-based investigation of spheronization and drying phenomena using different pellet formulations

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Abstract

Extrusion-spheronization (ES) is a frequently used agglomeration process in the pharmaceutical industry to manufacture spherical solid units or pellets with a narrow size and shape distribution. In this study, photometric stereo imaging was applied in real-time during the final steps of the ES process, being spheronization and drying. In addition to the pellet size distribution of undispersed (wet) samples, the imaging technique captures visual information on pellet shape and surface brightness. Pellet samples were taken at 20 time points during *spheronization* and were imaged at-line (during spheronization) and off-line (after spheronization). Particle size distributions and visual image information were both used to characterize the spheronization behaviour of different formulations. Next, particle size distributions and surface brightness values calculated from the at-line obtained images during *fluid bed drying* of pellets were analysed. The particle size distribution and brightness value changes occurring during pellet drying were explained both by the reduction in residual moisture content and drug solid-state transition. Due to the rapidness of the technique with regard to sample preparation, sample measurement and the acquisition of results in combination with the possibility to measure undispersed (wet) samples, valuable information on spheronization and drying characteristics of different formulations was obtained in real-time.

Keywords

Photometric stereo imaging – extrusion-spheronization – fluid bed drying – particle size and shape (distribution) – brightness – visualization

1. Introduction

Extrusion-spheronization (ES) is a frequently used agglomeration process in the pharmaceutical industry to manufacture spherical solid units or pellets with a narrow size and shape distribution. It is a multi-step process consisting of four consecutive stages: dry blending, preparation of the wet mass (granulation), shaping of the wet mass into cylinders (extrusion) and rounding of the cylinders into spheres (spheronization) (Reynolds, 1970). Afterwards, fluid bed drying is usually applied to effectively remove water (or solvent) from the wet pellets. Pellets produced by ES offer several technological advantages (e.g., optimal packing and flow properties, ideal shape for coating, low friability) and therapeutic advantages (e.g., less irritation of the gastro-intestinal tract and a lowered risk of side effects due to dose dumping) compared to conventional drug delivery systems.

The influence of process and formulation variables upon the quality (e.g., size, shape, drug release rate) of produced pellets has extensively been investigated (Bashaiwoldu et al., 2004; Hasznos et al., 1992; Hellén and Yliruusi, 1993; Hellén et al., 1993a; Hellén et al., 1993b; Newton et al., 1995; Sonaglio et al., 1995; Sousa et al., 1996; Vervaet and Remon, 1996; Wan et al., 1993). Due to the large amount of liquid in the granulated mass, the interaction with water can induce phase transformations altering the pharmaceutical and biopharmaceutical performance of the drug. Hence, research on *real-time* monitoring of ES has mainly focused on the detection of process-induced transformations of the API throughout the different ES process steps. Sandler et al. investigated the phase transitions in nitrofurantoin and theophylline formulations during pelletization (Sandler et al., 2005). An at-line process analytical technology (PAT) approach consisting of Raman spectroscopy, near-infrared spectroscopy (NIRS) and X-ray powder diffraction (XRPD) was used to increase the understanding of the solid-state behaviour of the APIs during pelletization. More recently, Römer et al. applied at-line NIRS and XRPD to better understand process-induced transformations of erythromycin dihydrate during pellet manufacturing (ES and oven tray drying) (Römer et al., 2007). The same group reported on the use of in-line NIR spectroscopy to monitor phase transformations of erythromycin dihydrate during a miniaturized fluid bed drying process (Römer et al., 2008). The amount of granulation liquid also influences extrusion and spheronization behaviour of the granulated mass. Extrudates must possess an optimal level of strength, brittleness and plasticity to obtain pellets with a desired size and shape. The most applied techniques to determine pellet size distributions include sieving, laser diffraction and image analysis. These methods can be time consuming (sample preparation and analysis) and require large amounts of sample. Moreover, the cohesiveness of wet materials often impedes the measurement. In this study, particle size and shape information were obtained in real-time by applying a photometric stereo imaging technique (FlashSizer 3D, FS3D) (Sandler, 2011). The tool consists of 2 white light sources, positioned 180° from each other in a horizontal plane. By illumination of the sample surface, 2 images are captured and are reconstructed to a 3D image from which the particle size can be calculated. In addition to PSD, the photometric approach also provides information on particle shape and particle surface roughness and brightness. Different roughness or brightness parameters, based on the change in grey scale values of the surface images can be computed. The FS3D is a very fast technique with regard to sample preparation, sample measurement and the acquisition of results. Moreover, the cohesiveness of samples is not problematic as measurements do not require sample dispersion.

In this study, photometric stereo imaging was applied during the final steps of the ES process, being spheronization and drying. Samples were taken from the spheronizing mass at different time points and imaged at-line (i.e., during spheronization) and off-line (i.e., after spheronization) with the instrument. Visual image information and particle size distributions were both used to characterize the spheronization behaviour of different formulations. Next, particle size distributions and surface brightness values calculated from the at-line obtained images during fluid bed drying of pellets were analysed. Residual moisture content and solid-state information were used to explain the particle size distribution and brightness value changes occurring during pellet drying.

Taking images during spheronization has been reported previously by Fielden et al. using high speed photography (Fielden et al., 1992; 1993). Insight into the spheronization process was in first instance obtained by off-line measurements, and confirmed by use of a photographic technique. Pictures of the spheronizing mass, taken from a distance, at 1 minute and 5 minutes of spheronization are shown. Our results are based on images taken more frequently during the spheronization process (i.e., during the first 5 minutes, samples were taken every 20 seconds from the pellet bed. Subsequently, pellets were obtained every minute until a 10 minutes spheronization time was reached.). The FS3D images provided a clear view of spheronized samples in which the dimensions of individual pellets can be distinguished. This was not the case for the photographs shown in the work by Fielden et al. Moreover, the photometric approach allowed to derive instantaneously size information from the obtained images, without the need to disperse the wet sample. In the work presented by Fielden et al. drying was performed prior to the determination of size and shape via sieving and image analysis.

2. Materials and methods

2.1. Materials

The pellet formulation consisted of 50% (w/w) anhydrous theophylline (TP, BASF Aktiengesellschaft, Ludwigshafen, Germany) and 50% (w/w) microcrystalline cellulose (MCC, Avicel PH101, FMC Biopolymer, Cork, Ireland). Purified water was added as a granulation liquid.

2.2. Methods

Pelletization and drying

Pellets were manufactured using the continuous Nica pelletising system (Nica System AB, Mölndal, Sweden) consisting of three units: a mixer/granulator, an extruder and a spheronizer. First, anhydrous TP and MCC were weighed and dry-mixed in a double cone mixer during 10 minutes. The blended powder mass (200 g) was added to the granulator (Nica M6L), mixing the powder blend and granulation liquid instantaneously. The powder feed rate was 35 rpm (1148 g/min) and different liquid addition rates were used. The radial screen extruder (Nica E140) shaped the granules into cylinders by rotation of the feeder and agitator in opposite directions. Feeder and agitator speed were set to 45 rpm and 28 rpm, respectively. A screen thickness of 1.2 mm was employed and the granules were forced through dies with a 1 mm diameter. At the base of the spheronizer (Nica S320) a friction plate (diameter of 32 cm) with crosshatched pattern was inserted. The spheronizer friction plate rotated at 900 rpm during a total residence time of 10 minutes. Pellets with 3 levels of moisturizing liquid were prepared for the spheronization study. Liquid addition rates of 750, 870 and 990 g/min resulted into pellets with 40% (w/w) **batch I**; 43% (w/w) **batch II**; and 46% (w/w) **batch III**

on the basis of the wet mass. Batches I, II and III were each manufactured 3 times (total of 9 batches) by the continuous ES technique (table 1).

Pellets with a moisture level of 41% (w/w) (**batch A**) and 45% (w/w) (**batch B**) were prepared for the fluid bed drying experiments (Strea-1, Aeromatic-Fielder AG, Switzerland). A liquid addition rate of 810 g/min (batch A) and 930 g/min (batch B) respectively was therefore used during granulation. Extrudates were spheronized during a total process time of 5 min. Other granulation, extrusion and spheronization settings were identical to those stated above. Drying was performed using inlet air temperatures of 50°C and 59°C (table 1).

Sampling

The extrudates of formulations I, II and III were spheronized for a total process time of 10 minutes. During the first 5 min, samples (4 g) were manually taken from the pellet bed every 20 s using a small sample cup, while the spheronizer plate continued running at 900 rpm. Subsequently, pellets were obtained every minute until a 10 min spheronization time was reached (i.e., 20 samples in total per batch). The samples inside the cup were poured into a petridish and imaged at-line (i.e., during spheronization, 1 measurement) and off-line (i.e., after spheronization, 5 measurements).

Following spheronization of formulations A and B, the wet pellets were fluid-bed dried at 50°C and 59°C (table 1). After removal of free surface water (corresponding to a product temperature of approximately 50°C), samples were taken from the pellet bed every 20 min and measured at-line with photometric stereo imaging and Raman spectroscopy and off-line via loss-on-drying. Drying continued until no significant changes in residual moisture content were measured.

Photometric stereo imaging

The imaging unit (FlashSizer 3D, FS3D, Intelligent Pharmaceuticals Ltd, Finland) consists of a monochrome CCD camera connected to a metal cuvette with a glass window and a computer. A variant of photometric stereo (Woodham, 1980) with two white light sources, placed 180° from each other in a horizontal plane, was used. All measured samples were filled into a petridish (layer thickness 5 mm) and positioned on top of the imaging instrument's glass window. Two digital images were captured during each measurement and recombined to extract PSD information. For a detailed description of the working principle of this imaging technique, readers are referred to references (Sandler, 2011; Soppela et al., 2011).

The grey-scale values of the digital images of sample surfaces correspond to the brightness of the surfaces and is characterised by a number in the range from 0 – 255 where 0 is totally black and 255 is completely white. The pellet surface brightness index is then calculated and is based on differences in these grey scale values. The calculations are derived from roughness measurements and accordingly different parameters can be calculated in a similar way using the grey scale profiles. In this study, the arithmetic average of the brightness profile (Ba) of the digital images' grey scale values was used. The average Ba parameter is calculated from the height data according to equation (1):

$$Ba = \sum_{n=1}^N \frac{|Z_n - Z|}{N} \quad (1)$$

where Z_n is the individual height (brightness) value of one measurement point and $\bar{Z}$ the mean value of all the height data points. N is the number of measurement points. B_a measures the average brightness of the profile points to the average line.

Raman spectroscopy

Pellets sampled during fluid bed drying were measured at-line using Raman spectroscopy. Three Raman spectra of each sample were collected with a Raman Rxn 1 spectrometer (Kaiser Optical Systems, Ann Arbor, MI, USA), equipped with an air-cooled CCD detector and a fiber-optically coupled P^hAT probe head. The laser wavelength was the 785 nm line from a 785 nm Invictus NIR diode laser. The spectra were recorded over the 0 – 1900 cm⁻¹ range with a resolution of 4 cm⁻¹ and an exposure time of 5 s. Data collection and analysis were performed with the HoloGRAMSTM data collection software, the HoloREACTTM reaction analysis and profiling software and the Matlab software (version 2007b). Spectra were preprocessed by normalization and analyzed using multivariate curve resolution (MCR).

Moisture analysis

Pellet samples taken during fluid bed drying were measured off-line with an infrared dryer (Sartorius MA100, Sartorius, Göttingen, Germany). Pellets were heated to a temperature of 105°C and dried until the weight loss rate was 0.1% in 50 s. Average moisture levels were calculated based on 3 measurements per sample.

3. Results and discussion

3.1. Photometric stereo imaging during spheronization

The at-line application of FS3D imaging during *spheronization* was first studied. The imaging equipment expresses the particle size distribution of a measured sample as sieve fractions and on the basis of this distribution computes D_{10} , D_{50} and D_{90} percentiles. Figure 1 displays the PSDs of batches I, II and III measured at-line after 10 min of spheronization. With increasing amount of granulation liquid, the distribution shifted towards larger sizes. The use of MCC as an extrusion and spheronization aid, even in small quantities, requires a minimum presence of water as granulating fluid (Wan et al., 1993). Below the required moisture level of the granulated mass, the plasticity of the extrudates is insufficient resulting in a larger fraction of fines during spheronization. Above the specific moisture range, extrudates are soft and easy to deform, resulting into large and round shaped particles. Hence, the high yield of pellets sized < 500 μm for batch I indicated that the amount of granulation liquid was close to this lower limit. The moisture level of batch III probably corresponded to the upper level of the specific water content range as the batch yielded a large fraction of oversized pellets (size >1500 μm).

Batches I, II and III were each manufactured in threefold to compare batch-to-batch reproducibility. Figure 2 displays the corresponding average D_{10} , D_{50} and D_{90} percentiles and standard deviations for the three replicates per batch. The particle size variation between the replicates decreased with increasing amount of granulating liquid. The decrease in standard deviation was more pronounced for the smallest and median sized particles (D_{10} and D_{50}). At the low liquid content of batch I, extrudates were brittle and shattered upon spheronization creating a large quantity of fines. Hence, particles of various sizes were spheronized causing the increased size variability between the replicates of batch I.

Besides at-line FlashSizer imaging, five off-line FS3D measurements of each sample were performed. Figures 3a and 3b display the at-line and off-line particle size distributions for batches I and III respectively at different time points during the spheronization process. For batch I, most at-line determined PSs lay within the standard deviation intervals of the average off-line sizes. Hence, the good correspondence between at-line and off-line sizes for batch I, indicates that the single image captured during spheronization provides equal PSD results as the off-line (reference) images. In addition to the between-replicate-batch variation observed in figure 2, a large within-batch variation for the lowest water amount is visible in figure 3a. The large standard deviations at each time point depict the size differences between the five off-line measurements. For the increased water level experiments (batch III, figure 3b), all five off-line FS3D measurements corresponded to each other resulting in smaller standard deviations. Figure 3b also shows that during the initial stages of spheronization of batch III, the at-line determined sizes were smaller than the average off-line PSs. As more moisture could migrate to the surface of the pellets during spheronization, the obtained images were slightly blurred and displayed a lower contrast at the edges of the particles. This affected the particle size calculation and lead to smaller somewhat underestimated at-line sizes compared to results of the off-line measured samples, where the moisture is partially readsorbed by the MCC core of the pellets or possibly evaporated from the surface.

Next to the numerical values of the particle size distribution, the imaging technique also provided visual information about the samples. By comparing the images collected at 20 different time points during spheronization, a visual record of the evolution of the granule shape in function of time was obtained. In figure 4 the at-line obtained images for batches I, II and III after 0, 1, 5 and 10 minutes of spheronization are shown. The amount of granulation liquid clearly influenced the surface texture and length of the extrudates (sampling time point 0). The batch I extrudates were short, brittle and rough. The higher liquid amount in batches II and III yielded longer extrudates with smoother surfaces. After 1 min of spheronization, most wet granules of batches I and II had an irregular shape. Frictional forces during the remainder of the spheronization period resulted in spherical particles at the end of the process. The water present in the extruded mass of batch III provided the necessary plasticizing and lubricating properties to produce spheroids after 1 min of spheronization. Additional spheronization caused further smoothing of spheroid surfaces. By comparing the FS3D images for the three batches, it is clear that the deformation rate increased by increasing the amount of granulation liquid. The mixture of small and larger sized pellets shown during spheronization of batch I (images in row 1 of figure 4) explain the large standard deviations plotted in figure 3a. The small standard deviations of batch III resulted from the uniform size distributions shown in the images in row 3 of figure 4.

Recently, Koester et al. (Koester and Thommes, 2010), reported an extension to the traditional pelletization mechanisms suggested by Rowe (Rowe, 1985) and Baert (Baert and Remon, 1993). Their study showed that next to the plastic deformation of the initially fractured extrudates, material transfer between the pellet particles should also be considered in the spheronization mechanism. The particle size distribution profile during spheronization of batch I (figure 5a) demonstrates that in the beginning of the process, the decrease in fines (size < 500 μm) was accompanied by an increase of pellets in the size fraction 500 – 1500 μm . Analysis of the corresponding FS3D images showed the loss of fine fragments during the initial 100 s of spheronization. In the images corresponding to the next stages of spheronization, small defects on the surfaces of pellets were observed. The areas encircled in figures 5b - 5d exemplify this phenomenon. After approximately 480 s of plastic

deformation during processing in the spheronizer, completely smooth surfaces were obtained (figure 5e). Hence, combining size and visual information suggests the adhesion of fine particles to larger sized pellets as reported by Koester et al. After 100 s the amount of fines stayed constant during the remainder of the spheronization process. Due to the low amount of granulation liquid, further agglomeration of these small particles to the pellet surface of larger granules was not possible.

3.2. Photometric stereo imaging during pellet fluid bed drying

A spheronization process is always followed by a drying step to complete the formation of the pellet matrix structure. Drying affects pellet characteristics such as size, density and tensile strength. At the same time, micro-structural properties change due to the densification of pellets, and solid-state transformations may occur which both influence the drug release rate.

3.2.1. Particle size distribution

FS3D measurements

Figures 6a and 7a display the D_{10} , D_{50} and D_{90} trajectories during fluid bed drying of batches A and B respectively. The PSD profiles for both batches are shown during drying at 2 inlet air temperature levels (50°C and 59°C). For both formulations, a decrease in PSD during the initial drying minutes (i.e., between the first and second measured sample) was observed. The shrinkage of pellet size was most prominent for the D_{90} percentile. Throughout the further drying process, no relevant size changes occurred. For both batches, the size of the pellets measured at the second sampling time point was similar for the 2 inlet air temperatures (50°C and 59°C). Hence, the size shrinkage did not depend on the drying temperature in this temperature interval. Due to the lack of size data between the first and second time point, no information was available on the rate of pellet shrinkage at the two temperature levels.

Moisture analysis

Figures 6b and 7b display the corresponding decrease in residual moisture content during fluid bed drying of batches A and B at the 2 examined drying temperature levels. The total moisture content of batch B at sampling time point 1 was approximately 3.4% (w/w) higher than the water content of batch A. A large drop in water content was observed between the first and second measured sample. Although the difference in granulation liquid between batches A and B clearly influenced the plasticity of the wet mass and the size of the pellets, similar moisture levels were obtained at sampling time point 2. From time point 2 onwards, the moisture content profiles of the two batches at the same temperature level did not distinctively differ. Both formulations demonstrated that the granulation liquid was removed faster when a higher drying temperature was used. When dried for an extensive time period (more than 2 times longer), the 50°C-dried batches reached the same residual moisture level as the 59°C-dried batches.

Raman spectroscopy

Theophylline is known to exist in both the (stable and metastable) anhydrous and hydrous crystalline form. The monohydrous crystallite is a channel hydrate characterized by a crystal structure in which every water molecule is located next to other water molecules along an axis of the lattice. It has been reported that theophylline undergoes polymorphic changes during wet granulation (Räsänen et al., 2001) and during subsequent drying (Airaksinen et al., 2004). Transitions between these solid

forms depend on kinetic and thermodynamic factors. Raman spectroscopy is a technique sensitive to alterations in intra- and intermolecular bonding and hence solid-state transformations. Unlike NIR spectroscopy, it does not provide information on the presence of free water molecules as water is a weak Raman scatterer. Figure 8 displays the Raman spectra ($1500 - 1800 \text{ cm}^{-1}$) of batch A pellets captured during fluid bed drying using an inlet air temperature of 50°C . Differences between the spectra correspond to the TP monohydrate to anhydrate transformation. The 1688 cm^{-1} Raman band of TP monohydrate was splitted into two bands in the TP anhydrate spectrum (1666 cm^{-1} and 1707 cm^{-1} respectively). Multivariate curve resolution (MCR) was performed on the $1500 - 1800 \text{ cm}^{-1}$ region of all Raman spectra of batch A and B pellets collected at-line during drying at 50°C and 59°C . By decomposition of this data matrix, the true underlying sources responsible of the spectral variation were identified. The 2 resolved underlying factors contributing to the spectral variation corresponded to the pure spectra of theophylline anhydrate and monohydrate respectively. The estimated concentration profiles shown in figures 6c and 7c display the contributions of the second factor (i.e. TP monohydrate) to the Raman spectra collected during fluid bed drying of batches A and B. At sampling time point 1, all batches showed a maximum contribution of component 2, corresponding to a complete TP monohydrous state. The large drop in moisture content observed for all batches between time points 1 and 2 in figures 6b and 7b corresponded to a small estimated concentration decrease in figures 6c and 7c. This demonstrates that only the evaporation of free water occurred between sampling time points 1 and 2. The similar MCR weights of the first 2 time points, indicate that almost no dehydration via the theophylline monohydrate water channels had occurred before time point 2. From time point 2 onwards, the contribution decrease corresponds to the solid-state transformation from monohydrous theophylline to the anhydrous state. The dehydration of monohydrous water molecules continued until no more water could be removed from the structure (no change in contribution at the end of drying). A clear difference between the contribution trajectories of experiments performed at different drying temperatures was noticed. The dehydration rate increased at a higher temperature. After an extended drying period, the same level of anhydrate was reached for the batches dried at the lowest temperature. As previously observed for the residual moisture content trajectories, the amount of granulation liquid did not distinctively differentiate the dehydration profiles of the two batches at the same temperate level. Airaksinen et al., reported on the presence of an anhydrous metastable form during the fluid bed drying of theophylline granules (Airaksinen et al., 2004). The characteristic peak of metastable anhydrous theophylline was not detected during drying of the pellets.

Combining PSD information from FS3D measurements (figures 6a and 7a) with moisture content (figures 6b and 7b) and solid-state trajectories (figures 6c and 7c) showed that the size shrinkage during the initial drying was caused by the evaporation of free water. The dehydration of TP monohydrate to TP anhydrate did not influence the pellet size distribution.

3.2.2. Surface brightness and visualization

Next to the particle size distribution, the FS3D tool also provided information on surface reflective properties. Based on the change in grey scale values in the surface images, several brightness parameters were calculated. In this study, the arithmetic average of the brightness profile (Ba) was used to describe the surface of dried pellets. Figures 6d and 7d represent the at-line measured Ba profiles (expressed as arbitrary units based on variations in pixel grey scale) of batches A and B respectively during fluid bed drying at 2 temperature levels. Both plots demonstrate a gradual

increase in surface Ba values during drying until a maximum (plateau) was reached. The rate of increase was dependent of the applied drying temperature. The maximum value was reached faster when a higher drying temperature was used. The moisture level profiles (figures 6b and 7b) showed that at sampling time point 1 the pellets were at the highest water state. This corresponded to a minimum brightness value in figures 6d and 7d. Combining moisture content and solid-state information with brightness profiles learned that the evaporation of free water and the successive polymorph transformation was accompanied by an increase in surface reflective properties and therefore Ba values. Maximum values were reached when the TP monohydrate to anhydrate conversion was completed. A ranking of the FS3D images, on the basis of which brightness values were calculated, explained the increasing Ba numbers. Moving from figures 6e towards 6i, a grey scale gradient appears. As long as water was removed from the pellet matrix, light reflection changed. The presence of surface water and a monohydrous state caused a different reflection of the light compared to a completely anhydrous system.

4. Conclusions

In this study, the at-line use of photometric stereo imaging during spheronization and fluid bed drying was examined. Data showed that one single at-line measurement provided equal pellet size information as the average of 5 off-line measurements. Based on the captured images and computed particle size distributions, the necessary information was provided to characterize the spheronization behaviour of different formulations. The comparison of images obtained at different time points during spheronization, allowed a visual record of the change in granule shape and size. During pellet fluid bed drying, the FS3D technique measured an initial decrease of pellet size and increase of surface brightness. Comparing size, brightness, moisture content and solid-state trajectories showed that the size shrinkage was due to the evaporation of free water. The increase of surface Ba values resulted from both the removal of free and crystal water.

Due to the rapidity of the technique and the possibility to measure undispersed wet samples, valuable information about spheronization and drying features of different formulations can be obtained. Hence, insight into the spheronization and drying step is provided, which allows the fast and effective development of a pelletization process. Particle size (distribution), density, sphericity, flowability, porosity, surface roughness, friability and drug release are the important physical properties of pellets prepared via extrusion-spheronization (Trivedi et al., 2007). This study showed that several of these properties can be obtained in real-time by a single measurement.

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Figure 1. Particle size distributions of batches I (40% w/w), II (43% w/w) and III (46% w/w) measured after spheronization.

Figure 2. Average *D*10, *D*50 and *D*90 percentiles of batches I (40% w/w), II (43% w/w) and III (46% w/w) measured after spheronization. Averages and standard deviations are based on the measurement of 3 replicate batches.

Figure 3. At-line and average off-line (with standard deviation) *D*10, *D*50 and *D*90 percentiles based on FS3D images of batches I (40% w/w) (a) and III (46% w/w) (b) in function of spheronization time.

Figure 4. At-line obtained FS3D images of batches I (40% w/w), II (43% w/w) and III (46% w/w) after 0, 1, 5 and 10 minutes spheronization.

Figure 5. FS3D particle size distribution profile and images during spheronization of batch I (40% w/w). The images obtained after 160 s (b), 220 s (c), 260 s (d) and 480 s (e) are displayed.

Figure 6. Data obtained during fluid bed drying of batch A (41% w/w) at 50°C and 59°C. (a) *D*10, *D*50 and *D*90 profiles, (b) moisture content, (c) MCR estimated concentration profile, (d) brightness. FS3D images at sampling time points 2 (e), 3 (f), 6 (g), 11 (h) and 17 (i). The brightness values at these time points are indicated by red rectangles in 6d.

Figure 7. Data obtained during fluid bed drying of batch B (45% w/w) at 50°C and 59°C. (a) *D*10, *D*50 and *D*90 profiles, (b) moisture content, (c) MCR estimated concentration profile, (d) brightness.

Figure 8. Raman spectra ($1500 - 1800 \text{ cm}^{-1}$) of batch A (41% w/w) pellets collected during fluid bed drying using an inlet air temperature of 50°C . (TP AH = theophylline anhydrate, TP MH = theophylline monohydrate)

Table 1. Overview of performed experiments

	Batch	Water (%w/w)	# Batches	Drying T (°C)	Sampling during spheronization	Sampling during fluid bed drying	Measurement
Spheronization	I	40	3	/	0 s, 20 s, 40 s, ...	/	At-line FS3D (1x) Off-line FS3D (5x)
	II	43	3		5 min, 6 min, ...		
	III	46	3		10 min		
Fluid bed drying	A	41	2	50	/	Every 20 min	At-line FS3D At-line Raman spectroscopy Off-line moisture analysis
				59			
	B	45	2	50			
				59			