Chemical Engineering Journal 164 (2010) 268–274

Contents lists available at ScienceDirect

Chemical Engineering Journal

journal homepage: www.elsevier.com/locate/cej

Labscale fluidized bed granulator instrumented with non-invasive process monitoring devices

Jari T.T. Leskinen[a,b,*], Matti-Antero H. Okkonen[c], Maunu M. Toiviainen[d], Sami Poutiainen[a], Mari Tenhunen[c], Pekka Teppola[d], Reijo Lappalainen[b], Jarkko Ketolainen[a], Kristiina Järvinen[a]

[a] School of Pharmacy, University of Eastern Finland, PL1627, FI-70211, Kuopio, Finland
[b] Department of Physics and Mathematics, University of Eastern Finland, PL1627, FI-70211, Kuopio, Finland
[c] VTT Optical Instruments, VTT Technical Research Centre of Finland, FI-90571, Oulu, Finland
[d] VTT Optical Instruments, VTT Technical Research Centre of Finland, FI-70211, Kuopio, Finland

ARTICLE INFO

Article history:
Received 30 June 2009
Received in revised form 20 August 2010
Accepted 24 August 2010

Keywords:
Fluid bed
Granulation
Particle size
Moisture
PAT

ABSTRACT

Fluidized bed granulation is a common size enlargement process in the pharmaceutical industry, in which fine powder is agglomerated using a liquid binder to obtain larger granules. However, fluidized bed granulation is a complex process by nature, being difficult to control due to the strong interactions between many process variables, such as moisture content and granule size. In order to control the process via correct pathway, one should be able to monitor the process, i.e. measure the process variables in-line.

In this study, three Process Analytical Technology (PAT) devices, i.e. an acoustic emission sensor, a flash topography particle size analyzer and multi-point NIR probes, were developed and instrumented into a labscale fluidized bed granulator for simultaneous granulation process monitoring. Parallel techniques were used for characterizing the granule size distribution and moisture content of granules during fluidization. Cellets^{R}, protease granules and caffeine formulation were used as samples. Granulation was carried out in a custom made modular top spray granulation chamber.

The granule size values obtained with the acoustic emission and flash topography particle size analyzer were in good agreement with the values measured with offline reference methods. Multi-point NIR (eight probes) and acoustic emission methods were able to detect the three granulation phases, mixing, agglomeration and drying. Single location monitoring does not reflect the heterogeneous sample during granulation, and thus, more information can be obtained by multi-point NIR. In general, the sensitivity of the multi-point NIR technique is susceptible to the fouling of probe windows whereas the acoustic emission technique is sensitive to background fluidizing air flows as well as external interference. The most informative data can be obtained when multiple PAT techniques are applied simultaneously for in-line process monitoring.

1. Introduction

There are many reasons why pharmaceutical materials require granulation e.g. improvement of the flow properties and compaction characteristics of the mix [1]. In fluidized bed granulation, the particles are fluidized in a stream of air and granulation fluid is sprayed from a nozzle onto the powder bed. It can prove difficult with fluidized bed granulation to obtain the desired granule properties since this requires balancing a great many process variables, including spray rate, binder solution concentration, atomization, inlet air temperature, airflow rate and humidity. In order to reduce batch-to-batch variation and to obtain a quality end product, there must be control of the process variables and conditions. The development of Process Analytical Technologies (PAT) described by U.S. Food and Drug Administration [2] improves the understanding and the efficacy of the fluidized bed granulation process.

Moisture is one of the most important parameters in fluidized bed granulation: liquid binders are needed to produce granules but excess moisture may cause bed collapse during the process. To optimize the granule properties by adjusting process parameters, the moisture content of the granules should be measured with sufficient accuracy in-line.

Typically, a single analytical method has been utilized in the in- or on-line monitoring of the fluidized bed granulation process. For example, near infrared (NIR) spectroscopy [3–6], Raman spectroscopy [7–9], triboelectric probes [10,11] imaging methods

* Corresponding author at: School of Pharmacy, University of Eastern Finland, Kuopio Campus, Yliopistonranta 1 B P.O. Box 1627, FI-70211 Kuopio, Finland.
Tel.: +358 40 355 2580; fax: +358 17 162252.
E-mail address: jari.leskinen@uef.fi (J.T.T. Leskinen).

1385-8947/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.cej.2010.08.064

[12–14], and acoustic emissions (AE) [15–18] have been successfully used as a single monitoring method for the measurements during fluidized bed granulation. However, relying on a single method for analyzing the properties of a fluidized bed typically has several disadvantages. Two commonly used techniques NIR and Raman spectroscopy are problematic if the probe or optical window becomes clogged by the wet, agitated powder. Two technical solutions have been published for the similar problem, although, for particle imaging applications [13,14]. The acoustic emission technique is sensitive to background fluidizing air flows, such as turbulent streams or acoustic noise emitted by the pressurized nozzle spraying, and external interferences nor can it penetrate to visualize what is happening inside the granulation process. Recently, Tok et al. [19] reported the responses of three inline techniques, namely focused beam reflectance measurement, a single-point NIR spectroscopy and AE, applied simultaneously to monitor a pilot-scale fluidized bed granulation process. When compared to a single process analytical technique, simultaneous measurements provided better process understanding and reduced the need for precautionary system set-ups.

In the present study, novel PAT tools, flash topography particle size analyzer and multi-point NIR probes were developed. These techniques and acoustic emission method were applied simultaneously to monitor a labscale fluidized bed processes and measure, directly or indirectly, particle size and moisture content changes.

2. Materials and methods

2.1. Materials

Ready-to-use commercial microcrystalline cellulose granules, Cellets^R, and protease A and B granules, were used to test particle size measurement by acoustic emission (AE) and a flash topography particle size analyzer (TOPO). The Cellets^R samples were kindly donated by Harke Pharma, Germany. Cellets^R are prepared from microcrystalline cellulose, and show perfect sphericity with a sphericity degree > 0.9 reported by the manufacturer. The studied Cellets^R samples included six size fractions: Cellets^{R}100, (size 100–200 μm), Cellets^{R}200 (200–355 μm), Cellets^{R}350 (350–500 μm), Cellets^{R}500 (500–710 μm), Cellets^{R}700 (700–1000 μm) and Cellets^{R}1000 (1000–1400 μm). Three Cellets^R mixtures were made: Cellets^{R}100 and Cellets^{R}1000; Cellets^{R}350 and Cellets^{R}500; and Cellets^{R}200, Cellets^{R}350 and Cellets^{R}500 were mixed with equal proportions. Protease A and B granules with the mean size of 481 and 534 μm, respectively, were kindly donated by Genencor Inc., Finland. An offline particle size analyzer (PartAn, Sci-Tec Inc., Sandy Hook, CT, USA) was used to measure the reference particle size of the protease granules. The mass of granules was 300 g in each fluidization experiment.

The formulation used in the granulation experiment comprised of 80 w/w% of lactose monohydrate (Pharmatose 200M, DMV) and 20 w/w% of caffeine anhydrous (Scharlau, Spain) to yield the total dry mass of 200 g. The powder mass was manually mixed for 2 min prior to feeding it into the granulator. The binder liquid contained 16.7% of polyvinylpyrrolidone (PVP, Kollidon K30, BASF, Germany) and 83.3% of purified water, and 55 g of it was sprayed during the process.

2.2. Methods

The studies were carried out using a modified Aeromatic STREA-1 fluidized bed granulator (Aeromatic-Fielder AG, Switzerland) equipped with a top spray unit and a custom made granulation chamber (Fig. 1) of 485 mm in height. During fluidization, air spraying was applied through Ø0.8 mm nozzle and 0.6 bar atomizing pressure was used. For the caffeine granulation, the PVP binder solution was added during the wet granulation phase. The process included three phases where the volumetric fluidizing air flow was 18 m^3/h at the beginning of the mixing period and increased up to 36 m^3/h to maintain adequate fluidization during the wet granulation phase. In the drying phase, fluidizing air flow was 25 m^3/h.

A set of PAT sensors were instrumented into the fluidized bed granulator for real-time non-invasive process monitoring purposes. The measurement setup consisted of a five-module granulator chamber instrumented with AE module, TOPO camera and eight NIR probes. Both the NIR probes and TOPO looked through glass windows whose surfaces were smoothly aligned with the inner metal surface of the granulation chamber. It is thus expected that the NIR measurement is fully non-invasive and the presence of probes do not disturb the flow properties of the system. This is also the case with the AE detection because the probes are outside the chamber wall and do not affect at all the conditions inside the chamber. It was also equipped with inlet and outlet air temperature and humidity sensors (EE21, E+E Elektronik, Austria) and bed mass temperature (T-type thermocouple, Amestec Oy, Finland) and an outlet air velocity sensor (MiniAir 6 anemometer, Schiltknecht Messtechnik AG, Switzerland). A Grant Squirrel SQ800 data logger (Grant Instruments Ltd., U.K.) monitored the temperature, RH and air flow measurements.

The acoustic recording module consisted of a 16-bit A/D card (USB-6251M, National Instruments, Austin, TX, USA), amplifier (AEP4, Vallen-Systeme GmbH, Germany), preamplifier (AEP3, Vallen-Systeme GmbH, Germany) and wideband (100–450 kHz) AE transducer with the peak resonance of 150 kHz (VS-150 M, Vallen-Systeme GmbH, Germany). AE was recorded with custom made program and Matlab 7.3 with Data acquisition toolbox (Mathworks Inc, USA). The sampling frequency of 1.25 MHz was used for 0.1 s at each measuring point with 1.6-s intervals.

Frequency information was calculated from the AE signal using the fast Fourier transform (FFT). The frequency band of 50–300 kHz was segmented into 32 frequency segments. A linear combination (Eq. (1)) of three frequency bands (low: 50–100 kHz, middle: 110–150 kHz and high: 200–300 kHz); was used for a measurement point i to estimate the particle size (the mean diameter) z_i:

$$z_i = (\theta_1 I_{\mathrm{low},i} + \theta_2 I_{\mathrm{mid},i} + \theta_3 I_{\mathrm{high},i} + \theta_4) \quad (1)$$

where θ_1, θ_2 and θ_3 are linear coefficients and θ_4 is constant. The coefficients were obtained from the fluidization measurements by least squares fitting (Eq. (2))

$$\boldsymbol{\theta}_{LS} = (\mathbf{H}^{\mathrm{T}}\mathbf{H})^{-1}\mathbf{H}^{\mathrm{T}}\mathbf{z} \quad (2)$$

where $\mathbf{H} = [\mathbf{I}_{\mathrm{low}}\ \mathbf{I}_{\mathrm{mid}}\ \mathbf{I}_{\mathrm{high}}\ \mathbf{1}]$ and $\mathbf{z}$ is the vector containing the measured particle size information. Vectors $\mathbf{I}_{\mathrm{low}}$, $\mathbf{I}_{\mathrm{mid}}$ and $\mathbf{I}_{\mathrm{high}}$ contain the measured and normalized AE mean intensity values related to each particle size. The normalization was performed by dividing the intensity of each AE band recorded as function of reference size by the intensities of AE bands' recorded from Cellets^{R}100 test.

For the granulation experiment, the granule size was estimated with an simplified algorithm based on a comparison of two AE frequency bands F_1: {96.9–120.3}kHz and F_2: {175.0–198.4}kHz. Ratio R of mean AE magnitudes $M_i = 20\log_{10}(I_i)$, where i: {1, 2}, was used as

$$R = \frac{M_2}{M_1} \quad (3)$$

The particle size distribution of formulation was measured by sieve analysis before and after the granulation process and the mean particle size values of the samples were used as the reference values for calculations.

TOPO was developed by VTT, Technical Research Centre of Finland (Oulu). The module for particle size and topography consisted

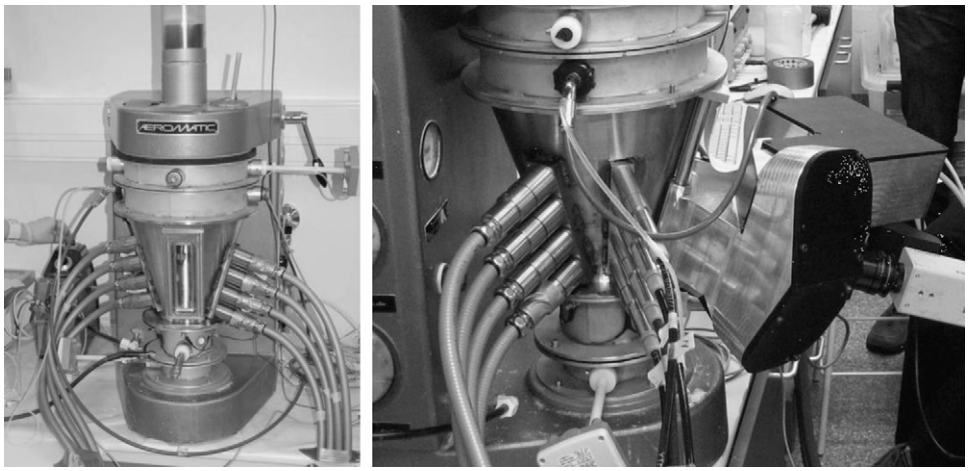

Fig. 1. Aeromatic STREA-1 fluidized bed granulator with custom made modular chamber system. Left: Multi-point NIR probes: R1. . .R4 stand for right-hand-side from top (R1) to bottom (R4) and L1. . .L4 stand for left-hand-side from top (L1) to bottom (L4). Right: Flash topography particle size analyzer.

of a prototype device including LED light source, projection optics, control and synchronizing electronics and a Hitachi HV-F22 3CCD camera. The projection optics projected the pattern just behind the granulator process window with an exposure time of 50 μs. It is essential to use such short pulses in order to eliminate the motion blur in the images. The image resolution was 1280 × 960 pixels, with a pixel dimension of 8 μm × 8 μm. The images were captured and transferred to a PC with an IEE1394 interface with a frame rate of 0.5 fps. Particle size estimation was made by capturing the images of the fluidizing powder through a glass window of 25 mm in width and 175 mm in height in the conical section of the granulator. The particle size in this approach was estimated using an imaging based method, where the 3-D structure of the particles was evaluated. The principle of this technique is to project a collimated light pattern into the objects to be measured and the pattern is captured with a different camera from a different angle. Thus, the surface of the objects modulates the pattern and the height map can be computed [20] by extracting the modulation component. An illustration of this is shown in Fig. 2. The algorithm is based on ellipse fitting. First, the particles are detecting using scale invariant features [21]. Detection gives estimates the spatial coordinates of each detected particle, along with a rough estimate of its size. Using this as an initial approximation, an iterative ellipse fitting method is used to refine the size distribution. In the approach used here, a sinusoidal pattern was used, similar to that described by Quan et al. [22].

The used multi-point NIR module was developed by VTT, Technical Research Centre of Finland (Oulu). It is based on an SWIR spectral camera (Specim Oy, Oulu, Finland) which provides accurate and simultaneous spectral measurement from each probe (up to one hundred parallel probes) at high a rate (up to 100 Hz) and in the full NIR range of 1000–2500 nm. The probes are equipped with an internal reference. The probes R1. . .R4 stand for right-hand-side from top (R1) to bottom (R4) and L1. . .L4 stand for left-hand-side from top (L1) to bottom (L4) (Fig. 1).

With the current instrumentation, the measured data are transformed into absorbance units by taking 10-base logarithm of the inverse of the reflectance spectra. In addition to the strong increase in absorbance at the water peak locations, the presence of water is observed as increased baseline in the absorbance spectra which is caused by the decrease in the intensity of the backscattered light.

In the granulation experiment, no reference moisture values were measured, and the moisture of the granules was only studied qualitatively. The purpose was to show that the moisture content can be successfully extracted from the measured data. The NIR spectra were collected at the rate of 3 Hz with the exposure time of 8 ms. Three consecutive spectra were averaged to obtain one spectrum per second. To permit the estimation of temporal moisture profiles, the augmented linear model [23,24]

$$\mathbf{x}_i = a_i\mathbf{1} + \sum_{j=1}^{3} c_{ij}\mathbf{s}_j + d_i\boldsymbol{\lambda} + e_i\boldsymbol{\lambda}^2 + \boldsymbol{\varepsilon}_i \tag{4}$$

was assumed for the measured spectral signals. Here, a column vector $\mathbf{x}_i$ is the measured $\log_{10}(1/R)$ spectrum at any of the channels at the time instant i. The second term on the right-hand-side contains the pure analyte spectra of lactose, caffeine and granulation liquid, which were measured offline in laboratory conditions, as the vectors $\mathbf{s}_j$, $j = \{1, 2, 3\}$. The elements of the vectors $\mathbf{1}$, $\boldsymbol{\lambda}$ and $\boldsymbol{\lambda}^2$ follow constant, linear and quadratic functions of the wavelength, respectively, and they attempt to explain changes in the offset, tilt and curvature of the spectral baseline. The unmodelled residuals are represented here by the vector $\boldsymbol{\varepsilon}_i$. The scalar coefficients a_i, c_{ij}, d_i and e_i were estimated for each measured spectrum in the least squares (LS) sense as

$$[\,\hat{a}_i \quad \hat{c}_{i1} \quad \hat{c}_{i2} \quad \hat{c}_{i3} \quad \hat{d}_i \quad \hat{e}_i\,] = \mathbf{x}_i^{\mathrm{T}}\mathbf{P}\left(\mathbf{P}^{\mathrm{T}}\mathbf{P}\right)^{-1} \tag{5}$$

where $\mathbf{P} = [\mathbf{1}\,\mathbf{s}_1\,\mathbf{s}_2\,\mathbf{s}_3\,\boldsymbol{\lambda}\,\boldsymbol{\lambda}^2]$. The estimated coefficient $\hat{c}_{i3}$ the weight of granulation liquid spectrum, was assumed to be proportional to the moisture level of the measured powder.

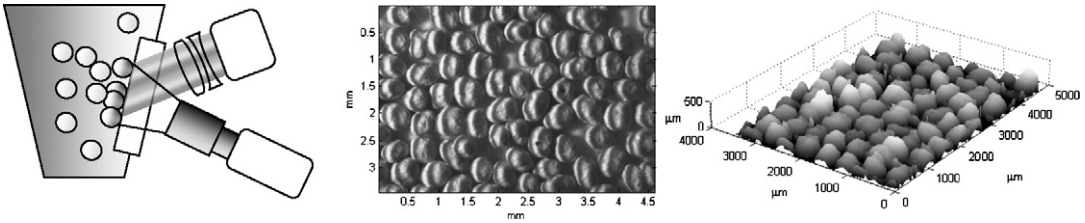

Fig. 2. An illustration of camera based structured light technique used for extracting 3-D information.

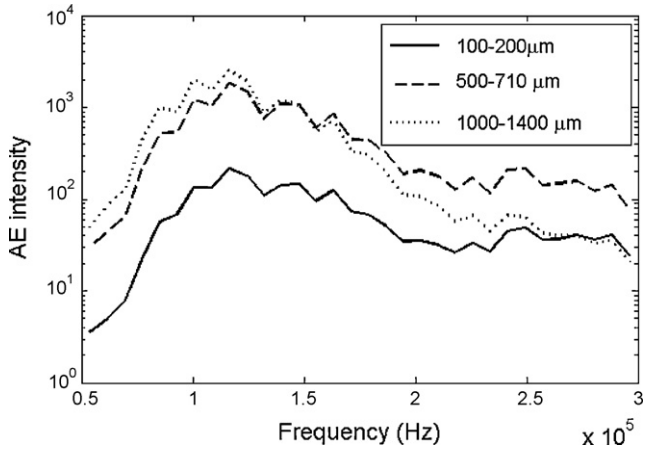

Fig. 3. AE spectra of three different particle sizes of Cellets^R measured during the fluidization.

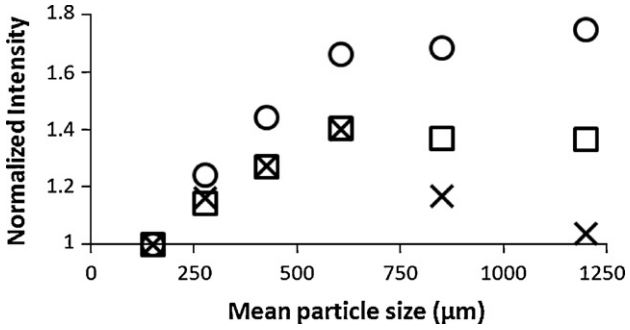

Fig. 4. Normalized acoustic intensities of three frequency bands, I_{Low}: 50–100 kHz (circles); I_{mid}: 110–150 kHz (squares) and I_{high}: 200–300 kHz (crosses) as function of reference diameter.

3. Results and discussion

3.1. Particle size

AE spectrometry and TOPO images were used for the particle size analysis of the Cellets^R and protease A and B granule samples. The AE spectrometry was used also to determine the mean particle size of mixtures of Cellets^{R}100&1000, Cellets^{R}350&500 and Cellets^{R}200&350&500.

The AE spectra of fluidizing Cellets^{R}100, Cellets^{R}500 and Cellets^{R}1000 samples are presented in Fig. 3. The mean particle sizes of the samples were estimated by using Eq. (1) and LS (Eq. (2)) optimized coefficients: $\theta_1 = 2689.6$, $\theta_2 = 726.9$, $\theta_3 = 2587.1$ and $\theta_2 = 760.7$ and the normalized mean AE intensities shown in Fig. 4. Each particle size measurement resulted in three calibration values, namely I_{low}, I_{mid} and I_{high} (Fig. 4).

In the present study, a flash topography particle size analyzer was developed for in-line measurements. Captured TOPO images

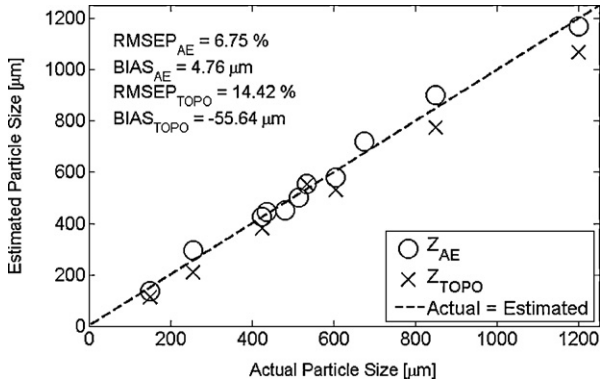

Fig. 6. The mean particle diameter, z, determined by acoustic emission (AE) and flash topography particle size analyzer (TOPO) as a function of measured reference size. Root mean square error of prediction (RMSEP) and the mean bias (BIAS) for AE and TOPO are calculated. Slope 1 (dashed) line stands for virtual, unbiased situation.

of Cellets^{R}100, Cellets^{R}500 and Cellets^{R}1000 samples during the fluidization are presented in Fig. 5(i), (ii) and (iii), respectively.

Both AE spectrometry and TOPO were successful methods for determining particle size of the studied samples as the predicted particle size of the sample was comparable to the particle size measured by the offline reference method. The root mean square error of prediction, RMSEP [25], for AE and TOPO was 6.7% and 14.4%, respectively. Therefore AE may be considered more accurate in this setup. The both size estimation methods, AE and TOPO, had good precision (Fig. 6), although TOPO underestimated the results approximately 55 μm according to the systematic error of prediction, the mean BIAS [25], while AE overestimated the particle size approximately 5 μm.

Belchamber et al. [26] showed an association between AE and the particle size of the sample. However, studies considering the relationship between the size of a pharmaceutical granule and acoustic emission in fluidized bed are rare [15,18]. Particle behavior in a fluidized bed granulator can be monitored and characterized by assessing the sounds, once the correlation between particular sounds and particle motion is established [15]. In the present study, the mean particle diameter of Cellets^R and protease granule samples was successfully determined by Eq. (1) based on the normalized acoustic intensity values of three frequencies of different size of Cellets^R granules.

In addition to AE, the particle size was estimated using a novel imaging based method, where the 3-D structure of the particles was evaluated. Compared with the traditional 2-D imaging based methods, this technique enables robuster detection and more sophisticated analysis of the particles.

3.2. Granulation monitoring

In the caffeine granulation process experiment, the mean particle size obtained with sieving was 129 and 530 μm at the beginning

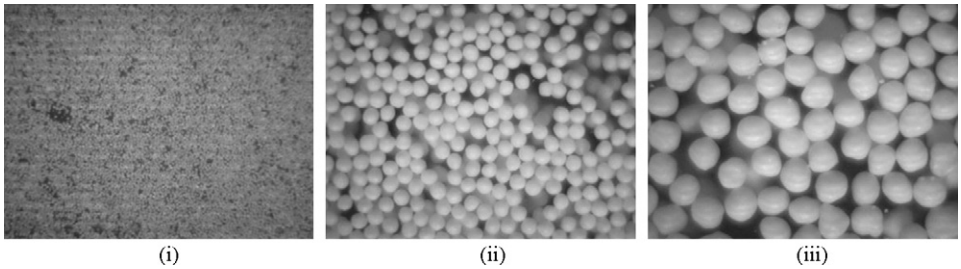

Fig. 5. Photos captured during fluidization of Cellets^{R}100 (i), Cellets^{R}500 (ii) and Cellets^{R}1000 (iii).

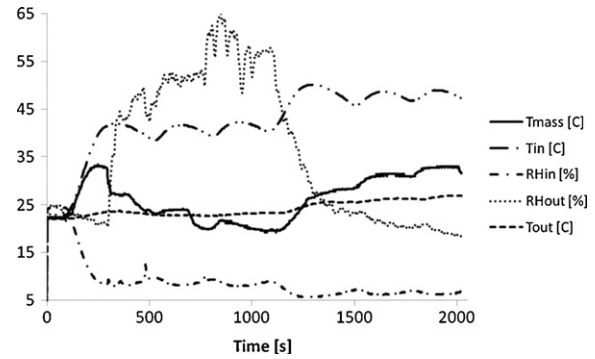

Fig. 7. Traditional process parameters measured during caffeine granulation. Tmass: temperature of the powder bed, Tin: inlet air temperature, RHin: relative humidity of inlet air, RHout: relative humidity of outlet air, Tout: outlet air temperature.

of agglomeration (300 s) and at the end of drying (2000 s), respectively. Traditional process parameters i.e. fluidizing mass and air temperature values and relative humidity values were measured (Fig. 7). Temporal excessive wetting is shown especially in granule temperature (Tmass) and outlet humidity (RHout) after 700 s.

Different stages of the granulation process, namely mixing (60–300 s), wet agglomeration (300–1100 s) and drying (1100–2000 s), were clearly distinguished with the AE measurement (Fig. 8).

In an earlier study [19], correlation between measured AE intensity without spectral analyses and the granule properties was not evident. However, the granule size and water content of granules could be determined during the process by the multivariate methods able to preserve and extract physical information from the acoustic emission spectra of fluidization and granulation [18]. In this study, the spectral data was utilized, and the granule size (Fig. 9) during wetting and drying phases was estimated with Eq. (3).

Drastic changes in granule size were observed at 600, 700, 800 and 1200 s (Fig. 9). Most likely, this was due to wetting induced mass sticking to and drying induced peeling from the chamber walls because the formulation was challenging due to its proneness to stick on the granulator walls throughout the process.

In the present study, the multi-point NIR was developed for monitoring of fluidized bed granulation as granule properties, such as particle size and water content, may be totally heterogeneous throughout the granulation process [27]. As an example, eight simultaneously measured absorbance spectra (Eq. (4)) are shown

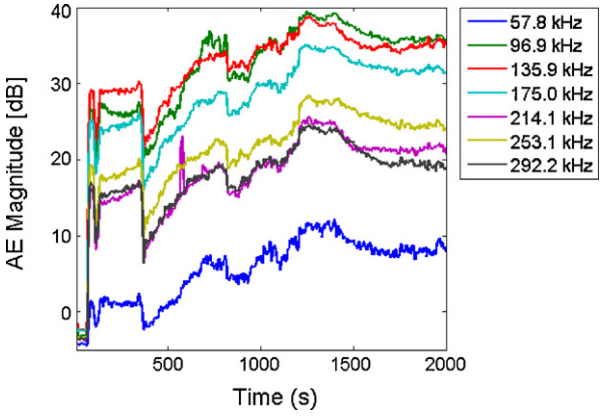

Fig. 8. Acoustic emission magnitude of seven different frequencies recorded from the granulation chamber wall. Mixing (60–300 s), wet agglomeration (300–1100 s) and drying (1100–2000 s) phases are clearly distinguished.

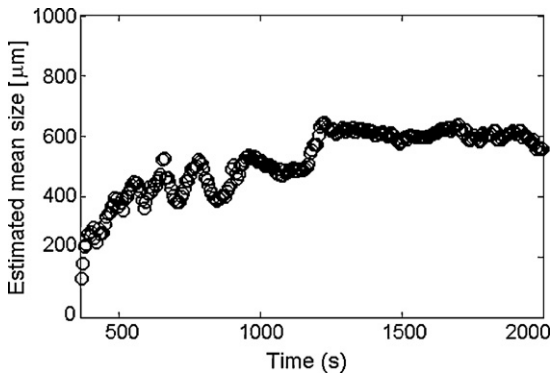

Fig. 9. Estimated mean granule size during granulation. Drastic changes are seen at 600, 700, 800, 900 and 1200 s.

in Fig. 10. The plots represent a single time point during the drying phase. As seen in Fig. 10, the different channels exhibit very different baseline offsets which may be attributed to the varying light intensity measured by the different probes. Variations in both powder packing density in front of the probe window and the moisture content of the powder influence the intensity of backscattered light. The best signal quality was generally observed with the probes located near to the bottom screen (R4 and L4) and the changes in moisture content were also the most apparent in them.

Water has a high absorptivity in the NIR band. Generally, the most applicable regions for water content measurement cover the regions 1400––1450 and 1900––1950 nm. The locations of the absorption peak maxima change slightly due to sample matrix effects and changes in temperature. Thus, as opposed to measuring the absorbance at just a few discrete wavelengths, the collection of the whole NIR spectrum provides the possibility to make the NIR method robuster with respect to these effects.

The estimated relative temporal moisture profiles (Eq. (5)) are illustrated for the four lowest channels (i.e. R3, R4, L3 and L4) in Fig. 11. As the data were not calibrated, the moisture values are given in arbitrary units (A.U.). Changes in the water content were the most apparent in these four channels which are located 10–15 cm above the bottom screen of the granulator. The moisture level is seen to remain relatively constant in all channels during the mixing phase. After 300 s, the binder spraying started to moisten the fluidized powder. After 700 s, the powder bed experienced inhomogeneous or excessive wetting (Fig. 11). Due to the fact that

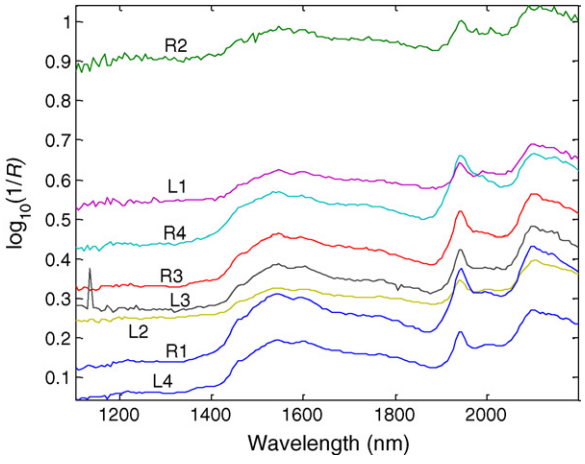

Fig. 10. Multi-point NIR: eight absorbance spectra of the eight channels plotted at a single time point during drying phase. R1. . .R4 stands for right-hand-side from top (R1) to bottom (R4) and L1. . .L4 stands for left-hand-side from top (L1) to bottom (L4) (probes shown in Fig. 1).

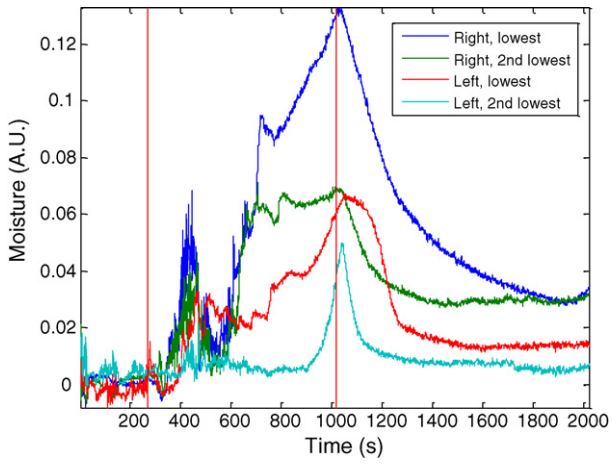

Fig. 11. Relative plot of moisture content in the granulation chamber measured with probes R3, R4, L3 and L4. Mixing (60–300 s), wet agglomeration (300–1100 s) and drying (1100–2000 s) phases are clearly distinguished.

the spectral baseline effects (offset, tilt and curvature) were taken into account when the moisture profiles were estimated in least squares sense, it is expected that the differences between the different probes were standardized for and that the relative moisture values given by the different probes may also be compared with each other.

The present instrumentation involves simultaneous moisture measurement at eight different locations at which different moisture content is expected and calibration should be performed offline and calibration transfer should be used in order to evaluate actual water content in-line. However, the power of multi-point NIR spectroscopy lies in the fact that estimates for the moisture level may be gathered simultaneously at multiple locations in the granulation chamber. The fluidized powder mass may be very heterogeneous with respect to the moisture level due to the process parameters and granule properties. Multi-point NIR enables a quick detection of such heterogeneity.

4. Conclusions

Advanced process-control technologies are required for process monitoring in the pharmaceutical industry. In the present study, a novel flash topography particle size analyzer and multi-point NIR were introduced to monitoring of a fluid bed granulation process. Furthermore, acoustic emission methods were utilized. Both the topographic camera prototype and the acoustic emission spectroscopy demonstrated their potential as real-time measurement systems providing precise particle size analysis over a wide particle size range. Further, multi-point NIR (eight probes) and acoustic emission methods were able to detect the three granulation phases, mixing, agglomeration and drying. Single location monitoring does not reflect the heterogeneous sample during granulation, and thus, more information can be obtained by multi-point NIR. All of the examined PAT techniques proved to be suitable for in-line monitoring of fluid bed granulation. It is important that one chooses the most suitable PAT tool(s) which have scale up possibilities for process development. The most informative data are obtained when multiple PAT techniques are applied simultaneously for in-line process monitoring.

Acknowledgements

This research was funded by the Finnish Funding Agency for Technology and Innovation (PATKIVA project). The authors want also thank M.Sc. (Tech.) Jyrki Savela from VTT Optical Centre, Oulu, Finland for technical design support and M.Sc. (Pharm.) Maiju Järvinen from the School of Pharmacy, University of Eastern Finland, Kuopio, Finland for practical laboratory granulations. M.Sc. Lauri Kurki, M.Sc. Anne Heikkilä and Ph.D. Janne Paaso from VTT Optical Centre, Oulu, Finland are acknowledged for their help with the multi-point-NIR setup and process measurement issues and M.Sc. (Tech.) Eero Hietala and M.Sc. Jussi Tenhunen from VTT Optical Centre, Oulu, Finland for setup and Measurements. Finally, we thank also Ph.D. Ossi Korhonen, from School of Pharmacy, University of Eastern Finland, Kuopio, Finland for CFD simulations, Mr. Pekka Vähä-Vahe from Genencor, Inc., Hanko, Finland (part of the Danisco Group) and Ph.D. Markku Tiitta, from the Department of Physics and Mathematics, University of Eastern Finland, Kuopio, Finland for their scientific discussion concerning of this work.

References

[1] M.E. Aulton, M. Summers, Granulation, in: M.E. Aulton (Ed.), Pharmaceutics: The Science of Dosage Form Design, 2nd ed., Elsevier Limited, Churchill Livingstone, 2002, pp. 364–378.
[2] U.S. Food and Drug Administration, PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance, Guidance For Industry, 2004.
[3] P. Frake, D. Greenhalgh, S.M. Grierson, J.M. Hempenstall, D.R. Rudd, Process control and end-point determination of a fluid bed granulation by application of near infrared spectroscopy, International Journal of Pharmaceutics 151 (1) (1997) 75–80.
[4] J. Rantanen, S. Lehtola, P. Ramet, J.P. Mannermaa, J. Yliruusi, Online monitoring of moisture content in an instrumented fluidized bed granulator with a multichannel NIR moisture sensor, Powder Technology 99 (2) (1998) 163–170.
[5] J. Rantanen, E. Räsänen, J. Tenhunen, M. Känsäkoski, J.P. Mannermaa, J. Yliruusi, In-line moisture measurement during granulation with a four-wavelength near infrared sensor: an evaluation of particle size and binder effects, European Journal of Pharmaceutics and Biopharmaceutics 50 (2) (2000) 271–276.
[6] J. Rantanen, E. Räsänen, O. Antikainen, J.P. Mannermaa, J. Yliruusi, In-line moisture measurement during granulation with a four-wavelength near-infrared sensor: an evaluation of process-related variables and a development of nonlinear calibration model, Chemometrics and Intelligent Laboratory Systems 56 (1) (2001) 51–58.
[7] D.S. Hausman, R.T. Cambron, A. Sakr, Application of on-line Raman spectroscopy for characterizing relationships between drug hydration state and tablet physical stability, International Journal of Pharmaceutics 299 (1–2) (2005) 19–33.
[8] J. Aaltonen, K. Kogerman, C.J. Strachan, J. Rantanen, In-line monitoring of solid-state transitions during fluidisation, Chemical Engineering Science 62 (1–2) (2007) 408–415.
[9] K. Kogerman, J. Aaltonen, C.J. Strachan, K. Pöllänen, J. Heinämäki, J. Yliruusi, J. Rantanen, Establishing quantitative in-line analysis of multiple solid-state transformations during dehydration, Journal of Pharmaceutical Sciences 97 (11) (2008) 4983–4999.
[10] F. Portoghese, F. Berruti, C. Briens, Use of triboelectric probes for online monitoring of liquid concentration in wet gas-solid fluidized beds, Chemical Engineering Science 60 (22) (2005) 6043–6048.
[11] F. Portoghese, F. Berruti, C. Briens, Continuous on-line measurement of solid moisture content during fluidized bed drying using triboelectric probes, Powder Technology 181 (2) (2008) 169–177.
[12] S. Watano, K. Miyanami, Image processing for online monitoring of granule size distribution and shape in fluidized bed granulation, Powder Technology 83 (1) (1995) 55–60.
[13] S. Watano, Direct control of wet granulation processes by image processing system, Powder Technology 117 (1–2) (2001) 163–172.
[14] T. Närvänen, K. Seppälä, O. Antikainen, J. Yliruusi, A new rapid on-line method to determine particle size distribution of granules, AAPS PharmSciTech 9 (1) (2008) 282–287.
[15] H. Tsujimoto, T. Yokoyama, C.C. Huang, I. Sekiguchi, Monitoring particle fluidization in a fluidized bed granulator with an acoustic emission sensor, Powder Technology 113 (1–2) (2000) 88–96.
[16] M. Halstensen, P. de Bakker, K.H. Esbensen, Acoustic chemometric monitoring of an industrial granulation production process—a PAT feasibility study, Chemometrics and Intelligent Laboratory Systems 84 (1–2) (2006) 88–97.
[17] J. Villa Briongos, J.M. Aragon, M.C. Palancar, Fluidised bed dynamics diagnosis from measurements of low-frequency out-bed passive acoustic emissions, Powder Technology 162 (2) (2006) 145–156.
[18] S. Matero, S. Poutiainen, J. Leskinen, K. Järvinen, J. Ketolainen, S.-P. Reinikainen, M. Hakulinen, R. Lappalainen, A. Poso, The feasibility of using acoustic emissions for monitoring of fluidized bed granulation, Chemometrics and Intelligent Laboratory Systems 97 (1) (2009) 75–81.
[19] A.T. Tok, X. Goh, W.K. Ng, R.B.H. Tan, Monitoring granulation rate processes using three PAT tools in a pilot-scale fluidized bed, AAPS PharmSciTech 9 (4) (2008) 1083–1091.

[20] J. Batlle, E. Mouaddib, J. Salvi, Recent progress in coded structured light as a technique to solve the correspondence problem: a survey, Pattern Recognition 31 (7) (1998) 963–982.
[21] T. Lindeberg, Shape measurement of small objects using LCD fringe projection with phase shifting, International Journal of Computer Vision 30 (2) (1998) 77–116.
[22] C. Quan, X.Y. He, C.F. Wang, C.J. Tay, H.M. Shang, Feature detection with automatic scale selection, Optics Communications 198 (1) (2001) 21–29.
[23] H. Martens, J.P. Nielsen, S.B. Engelsen, Light scattering and light absorbance separated by extended multiplicative signal correction. Application to near-infrared transmission analysis of powder mixtures, Analytical Chemistry 75 (3) (2003) 394–404.
[24] Z.P. Chen, J. Morris, E. Martin, Extracting chemical information from spectral data with multiplicative light scattering effects by optical path-length estimation and correction, Analytical Chemistry 78 (22) (2006) 7674–7681.
[25] T. Naes, T. Isaksson, SEP or RMSEP, which is best? NIR News 2 (1991) 16.
[26] R.M Belchamber, D. Betteridge, M.P. Collins, T. Lilley, C.Z. Marczewski, A.P. Wade, Quantitative study of acoustic emission from a model chemical process, Analytical Chemistry 58 (1986) 1873–1877.
[27] F. Nieuwmeyer, K. van der Voort Maarschalk, H. Vromans, The consequences of granulate heterogeneity towards breakage and attrition upon fluid-bed drying, European Journal of Pharmaceutics and Biopharmaceutics 170 (1) (2008) 402–408.