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Research Article

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A New Rapid On-Line Imaging Method to Determine Particle Size Distribution of Granules

Tero Närvänen,[1,3] Kari Seppälä,[1] Osmo Antikainen,[2] and Jouko Yliruusi[2]

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Abstract. The purpose of this research was to study the feasibility of the new image analysis method in the particle size determination of the granules. The method is capable of forming a three-dimensional topographic image of a sample surface from a digital picture. In the method, a flat granule bed surface was illuminated from three different directions, using the 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. The particle size distribution was then calculated from the image data. The particle size analysis method was tested both off-line and on-line. Off-line particle size measurement results determined by the image analysis method corresponded quite well to those of sieve analysis in the size fraction range 250–1,000 μm. In on-line application, images were successfully retrieved and median granule size trend could be calculated and followed during fluid bed granulations.

KEY WORDS: fluid bed granulation; image analysis; on-line particle size; topography.

INTRODUCTION

Particle size analysis is widely used in the various fields of pharmaceutical powder technology, especially those multivariate processes where particle size should be enlarged in a controlled way. Wet granulation processes, such as fluid bed granulation, are widely used in the pharmaceutical industry (1). Fluid bed granulation is a good example of a multivariate process in which effective and reliable process-control tools are necessary to ensure end-product quality. However, at present there is no fast and reliable granule size measurement method that performs successfully in fluid bed granulation. Previously, granule size analyses were performed by taking wet granule samples during granulation, drying the granules and finally delicately breaking the largest agglomerates prior to actual size determination (2). It is evident that such procedures are highly operator-dependent and have poor repeatability. One major issue in off-line methods is how to retrieve a representative sample during the process.

During recent years there has been increasing interest in the development of particle size determination techniques using near infrared (NIR) spectroscopy (3–6). Accurate NIR in-line particle size analysis of moving granules is challenging, because the scattering and absorptive properties of the granules vary. In addition, since particle size data are not directly obtained using NIR techniques, pretreatment of spectra and chemometric modeling are needed. The Focused beam reflectance method (FBRM) and spatial filtering technique (SFT) can be used for in-line particle size determination in fluid bed processes. Both methods determine the chord length of particles using a special probe (7,8). The FBRM has been largely applied in crystallization processes, but its usability in fluid bed processes has not been well documented. In-line particle size analysis from a fluid bed granulation process is very demanding because the probes and windows are prone to coating. If coating of the measuring window occurs, no reliable particle size information can be obtained from the process.

To overcome the challenges in in-line measurement, both on-line and at-line applications have been developed. Laitinen *et al.* (9) described a novel at-line particle size analysis method that could be used for rapid granule size determinations during granulation. The method was based on surface imaging and could also be used for wet granules. The laser light diffraction technique has also been applied to milling processes utilizing special sampling systems (10,11). However, implementation of these systems into a fluid bed granulator is more challenging. Halstensen et al. (12,13) studied an acoustic technique in fluid bed processes. When the chemometric models were established, acoustic monitoring of the process was possible. Acoustics does not give direct information on particle size and therefore interpretation of the results can be quite demanding.

Images, however, do give direct information on particles. The image analysis process is composed of five steps: image acquisition, preprocessing, segmentation, extraction, and representation of the characteristic parameters (14). Since particles are not well dispersed and overlap, various segmen-

[1] Orion Corporation, Orion Pharma, Orionintie 1, P.O. Box 65, 02101 Espoo, Finland.
[2] Division of Pharmaceutical Technology, Faculty of Pharmacy, University of Helsinki, P.O. Box 56, 00014 Helsinki, Finland.
[3] To whom correspondence should be addressed. (e-mail: tero.narvanen@orionpharma.com)

Table I. Description of the Granulation Batches

	Batch I	Batch II	Batch III	Batch IV
Granulation liquid feed rate (g/min)	70	50	90	70[a]
Purpose of the batch	Produce granules	Slow granule growth process	Fast granule growth process	Modified granule growth process
SAY-3D testing level	Off-line	On-line	On-line	On-line

[a] After half of the liquid was sprayed, the liquid feed was shut down for 1 min every third minute

tation algorithms are used. Watano *et al*. used image analyses in a real-time particle size determination of agitation fluid bed granulation and also applied it later to a high-shear granulator (15,16). The method consisted of an image probe with a charge-coupled device (CCD) camera, stroboscope, and telephoto lens.

In other disciplines further interest has recently focused on the utilization of three-dimensional (3D) and colored images. Yu and Kim demonstrated an optical tomography method providing full-color 3D views of tissue structures (17). Gómez-Pedrero *et al*. (18) measured surface topography, utilizing an RGB (red, green, blue) CCD camera, and could analyze different surface defects of fuselage tiles. Surface imaging by 3D has even been exploited in stereotactic radiotherapy (19). In the pharmaceutical powder technology area, most image analysis studies have focused on the use of traditional 2D black-and-white pictures. It is very likely that the utilization of 3D color pictures will also open new possibilities there. The purpose of this article was to introduce a new 3D imaging method and to study its feasibility in the particle size determination of the granules. The method was tested first off-line and thereafter on-line in a fluid bed granulation process.

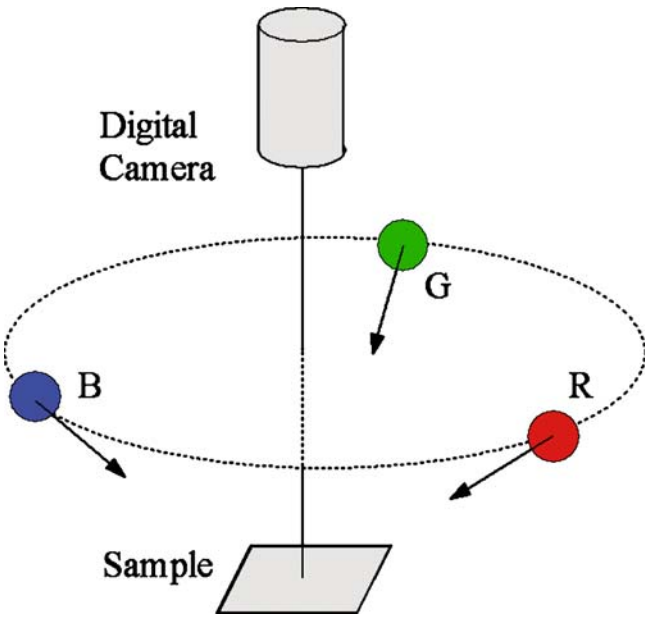

Fig. 1. Measuring principle of SAY-3D

MATERIALS AND METHODS

Manufacturing of Granules

Four different batches were manufactured in a bench-scale fluid bed granulator (Glatt WSG 5; Glatt GmbH, Binzen, Germany) as described in Table I. The batches consisted of 2.0 kg of theophyllin anhydrate (200 M, BASF Aktiengesellschaft, Ludwigshafen, Germany) and 2.0 kg of α-lactose monohydrate (200 M, DMV International GmbH, Veghel, The Netherlands) that were granulated with 2 kg of a 7.5% aqueous solution of polyvinylpyrrolidone (Kollidon K-30; BASF Aktiengesellschaft, Ludwigshafen, Germany). The inlet air temperature was 40°C and 60°C in the spraying and drying phases, respectively. The atomization pressure of the granulating liquid was 0.1 MPa and nozzle height was 45 cm from the distributor plate. The inlet air volume rate was adjusted to 0.08 m^3/s.

Image Analysis Method

In the image analysis method (SAY-3D) a granule bed surface was illuminated through the window from three sides, using the ultra bright RGB leds. Illumination angle to the bed surface was 27°. The maximum luminuous intensities of the red, green and blue leds were 7,400, 9,500 and 3,500 mcd, respectively. Illumination intensities were adjusted so that each color contributed to the illumination equally. One color picture was taken by a 6-megapixel CCD camera (Canon PowerShot S3 IS, Canon Inc.) with 4× close-up lens using

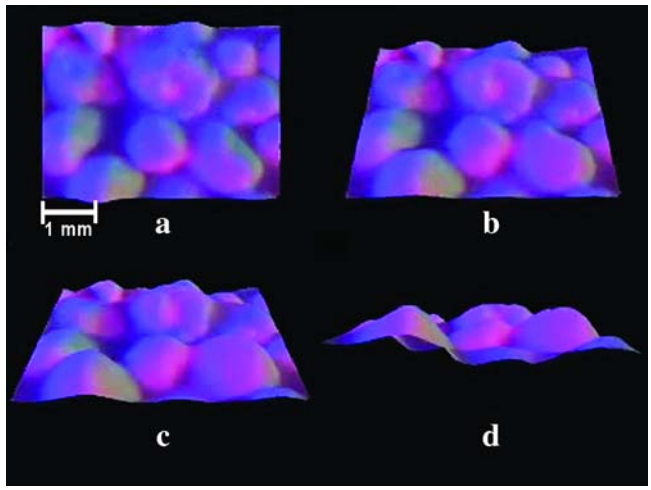

Fig. 2. Topographic view of granule bed **a** surface from above **b–d** projections of the surface from various angles

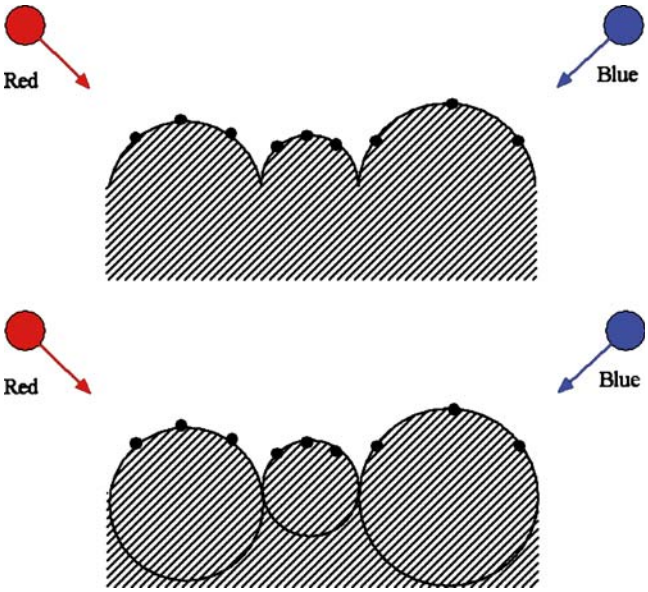

Fig. 3. Granule size determination from topographic data

1-ms illumination. The measuring arrangement is schematically described in Fig. 1. Camera was controlled to take images and send them to computer (IBM Think Pad, levono T60) by Canon's own software (Remote shooting, Camera Window, Canon Inc.). A topographic picture of the object was constructed based on the color intensities using Visual Basic 6 (Visual Studio, Microsoft corp.) programming language. Resolution of 14×14 μm was used.

In Fig. 2 part of one topographic image taken from a granule bed is shown. Figure 2a shows the surface directly from above. After the topography was calculated, the surface could be studied in real-time from various directions. The other three virtual pictures (Fig. 2b–d) illustrate the projections of the same surface from various angles.

The sizes of the individual granules were determined from the topographic data. Figure 3 describes the granule surface as it is projected directly from the side. The granules were approximated to ideal spheres. Using the topographic data, three points were selected to represent each granule. Since the height data of the surface were known and since it is possible to draw a circle through three points, the granule size of each particle was obtained. With a computer used here the software was able to determine the sizes of 2,000 particles from one image in a few seconds. Consequently, the number particle size distribution from each image was gathered.

Fig. 5. On-line sampler in the granulation chamber

Off-Line Particle Size Determination

The sieve fractions (250–355, 355–500, 500–710, and 710–1,000 μm) of batch I were used to evaluate the preliminary accuracy and precision of the SAY-3D method in an off-line installation. A standard glass cuvette (40×28×15 mm) was filled with the sample and pictures were taken. From each fraction 40 images were taken for analyses. The sample was mixed before each measurement.

Sieve Analysis

The final granules of batches II-IV were analyzed by means of traditional sieve analyses. A 50-g sample was vibrated with an automatic sieve shaker (Fritsch analysette, Idar-Oberstein, Germany) for 5 min. The sieve analyses (range 71–2,000 μm with √2 increment) were performed in

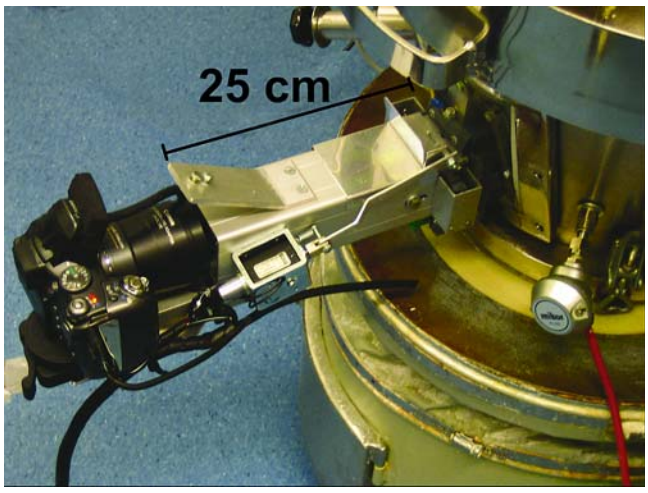

Fig. 4. Imaging installation attached to a fluid bed chamber

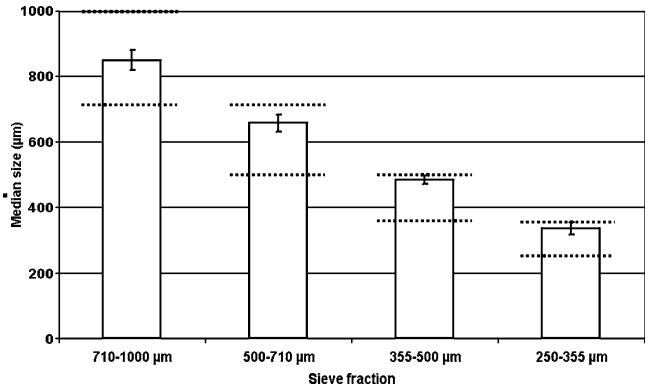

Fig. 6. Comparison of off-line SAY-3D particle size results with sieve analysis (batch I). The *dotted lines* show the upper and lower limits for various sieve fractions

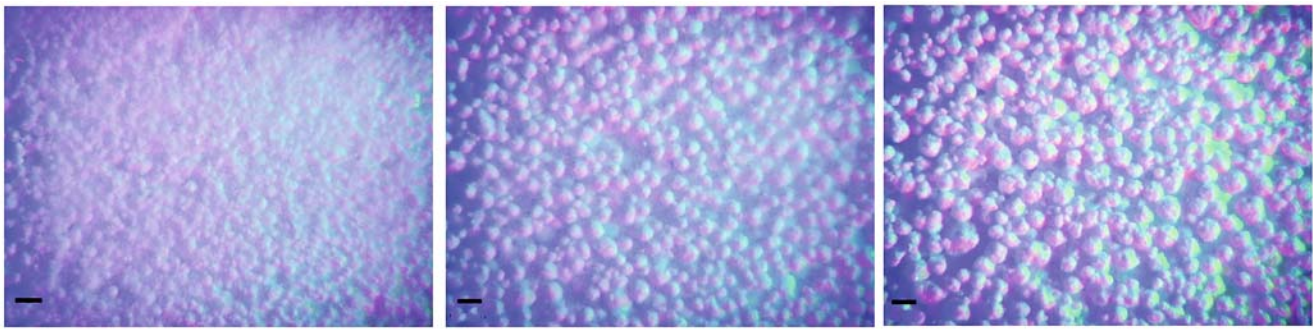

Fig. 7. Raw images of granules taken on-line from the fluid bed process. The image sizes are 20×15 mm (*bar* 1 mm)

triplicate for each batch and the mean values for mass median particle size were determined.

Installation of SAY-3D into the Granulator

The SAY-3D apparatus was attached to the Glatt WSG5 granulator, as illustrated in Fig. 4. Apparatus consisted of a digital camera with close-up lens (11×8×13 cm) and the body (6×6×21 cm) where the cuvette and leds were located. The sampler orifice (20×35 mm) was installed at a height of approximately 13 cm from the distributor plate. This position is usually used for manual sampling in a fluid bed granulator of this size. The orifice of the sampler in the granulation chamber is shown in Fig. 5. Samples were collected into the same cuvette as in off-line measurement. Pulsed air pressure was used to return the sample to the process between images. Five images per minute were taken during the process and the pictures were sent to a computer for near real-time image analyses. The image size was 15×20 mm; about 350 pictures were taken during each granulation process.

Treatment of the Particle Size Data

The number particle size data determined with SAY-3D were transformed to volume particle size distribution. The median size from the volume particle size distribution was used to compare SAY-3D results with sieve fraction measurement results. Additionally, the moving average median size of ten consecutive images was monitored during the process.

RESULTS AND DISCUSSION

Off-Line Particle Size Analysis

The off-line particle size measurement results determined by the SAY-3D corresponded quite well to those of sieve analysis in the size fraction range 250–1,000 μm; in every case the value determined was within the measured sieve fraction size range. The standard deviations of these determinations were also similar; in every case the relative standard deviation was less than 5%, which was regarded as favorable. The largest granule sizes were determined very accurately, whereas some of the smallest granules were not identified at all. This is seen in Fig. 6, where the determined average median values of the smallest size fractions approached to the upper limits.

On-Line Particle Size Analysis

Three raw images taken during the granulation process of batch III are presented in Fig. 7. The increase in granule size can be clearly seen from the pictures. All three batches (in which the SAY-3D apparatus was installed on-line) could be manufactured, with no problems in image acquisition or image analysis, and the median granule size trend could be followed during the process.

The slow and continuous median granule size increase is seen in Fig. 8 as a moving average trend line. There were large differences between the individual results (depicted as

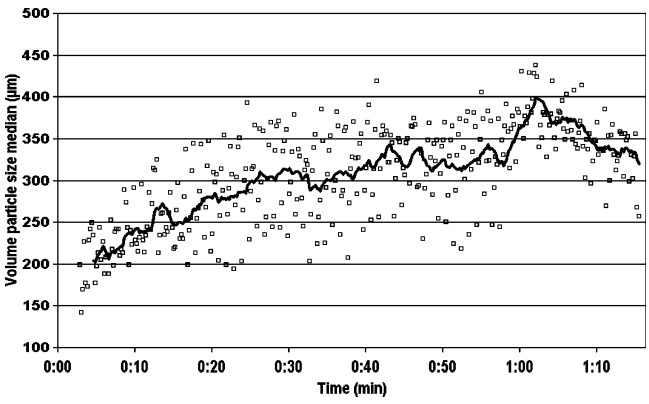

Fig. 8. Example of slow and continuous granule growth (batch II). The *squares* represent individual on-line determinations and the *continuous curve* is a moving average of ten consecutive determinations

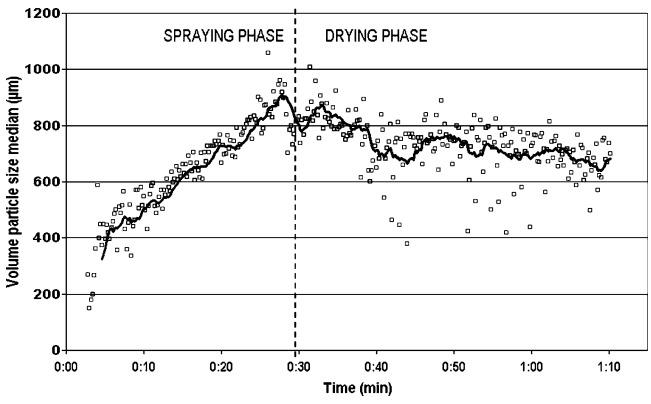

Fig. 9. Development of granule size during granulation and drying (batch III). The *squares* represent individual on-line determinations and the *continuous curve* is a moving average of ten consecutive determinations

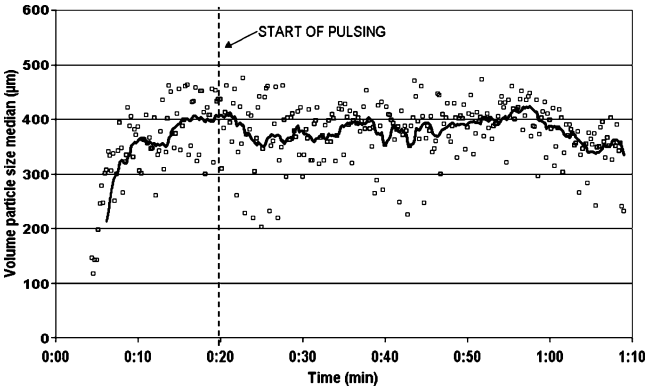

Fig. 10. Preventing granule growth by granulation liquid feed pulsing (batch IV). The *squares* represent individual determinations and the *continuous curve* is a moving average of ten consecutive determinations

squares); however, this is a real effect due to the granulator's working principle. Every minute the filter bags are shaken for 7 s while the fluidizing airflow is stopped. Hence, when the SAY-3D cuvette is filled during the filter-shaking period, the fine particles released from the filter significantly influence the size results.

An example of a rapid granule growth process is seen in Fig. 9. During the 30-min spraying time, the median granule size measured by the SAY-3D increased to approximately 900 µm. It can also be seen that in the drying phase the median granule size decreased and the variability between individual measurements widened. This phenomenon was probably due to breakage of the weakest granules and the appearance of fine particles by surface attrition during the drying phase.

Granulation liquid feed pulsing (i.e. interrupting the liquid feed for predetermined periods) was used to test the sensitivity of the SAY-3D to small granule size growth changes during the process (Fig. 10). As soon as pulsing was initiated no further increase in median granule size was obtained. The granulation liquid feed was shut off every third minute, but no repetitive time sequence in the granule size change could be seen. However, based on experience gained from previous batches, the shaking of the filter bag masks any minor granule size changes. This is particularly apparent while monitoring a moving average trend during the process.

The average median granule size of the last ten images from the process was compared with the sieve analysis results determined for the final granules in Table II. Both techniques gave similar results for batches II and IV, whereas significant differences were observed in the median size values for batch III. When the last ten images were examined visually afterwards, it was revealed that the SAY-3D determined the granule size correctly from the pictures, suggesting that the largest granules no longer fluidize to the SAY-3D cuvette orifice and consequently no representative sampling is retrieved anymore. Insufficient fluidization was also observed visually during the process with this batch. Size segregation phenomenon in fluid bed granulation has been studied previously and the phenomenon can be significant, especially when very large granules (>800 µm) are present (20,21). Although the batch III was manufactured in extreme conditions in order to generate very big granules, the fluidization of the granules and hence the representative distribution of the granules should be considered more in future studies.

Limitations of the Method and Future Development

Since the SAY-3D assumes particles to be spherical, particle morphology and high surface roughness influence the particle size determination. However, the same assumption is also made in many other currently used methods. Because surface topography is constructed by color intensity data, particles with very high reflective properties, e.g. glass spheres, cannot be determined with SAY-3D. Although high moisture content can affect the reflective properties of the particles, especially free surface water, no difficulties were obtained in this study with moist granules. In order to widen the size measurement range of the SAY-3D the quality of the images should be improved. Consequently, optimization of the image quality for the on-line granule size determination will be one goal in future development.

CONCLUSION

The described method seems promising; off-line particle size measurement results determined by the image analysis method corresponded quite well to those of sieve analysis in the size fraction range 250–1,000 µm. In on-line application, images were successfully retrieved and median granule size trend could be calculated and followed during fluid bed granulations. Optimization of the optics was identified as an important goal for future method development.

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Table II. Median Granule Size (µm) of the Three Granulation Batches

	SAY-3D (ten last on-line determinations)		Sieve Analysis (n=3)	
Batch	Mean	SD	Mean	SD
II	320	37	314	17
III	683	63	1,033	27
IV	335	56	377	28

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