On-line Monitoring of Granule Growth in High Shear Granulation by an Image Processing System

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A novel system has been developed to continuously monitor granule growth in a high shear granulation. The system consists of an image processing system and a particle image probe comprising a CCD camera, lighting unit and air purge system. Segregation during powder mixing was investigated experimentally and the optimal positioning of the probe was determined.

High shear granulation was conducted using pharmaceutical powders, and granule size and product's yield of various size ranges were continuously measured by the developed system. Sieve analysis of the granulated products sampled out during the granulation was simultaneously conducted, and the obtained data was compared with that by the on-line image processing system. An extremely close relationship could be found between both data, proving that the developed system could monitor the granule growth accurately and continuously throughout the granulation. An on-off control system was developed to control the granulation process, and the performance of the system was confirmed.

Key words: high shear granulation; monitoring; image processing; image probe; granule growth; operational end-point

Granulation, defined as a process of size enlargement, is widely used in pharmaceutical, food, chemical, agriculture, animal feed, and other industries in order to produce particulate materials having desired size, density, shape and other physical properties. Among many different techniques applied, the use of high shear granulation has increased considerably in recent years because this type of wet granulation has significant advantages in producing spherical and well-compacted granules with a relatively short operational time. It has been found, however, that the granulation in a high shear mixer is very sensitive, even if the amount of binder liquid or operating conditions is controlled. Therefore, there is a great need for reliable instrumental methods for process monitoring and determination of the operational end-point.

In order to monitor the process condition and to detect the granulation end-point, a number of investigations have been carried out regarding different devices for monitoring and controlling particle growth in a high shear granulator. Lindberg et al.1,2 measured the torque of a main shaft by a strain gauge technique. Measurement of power consumption was described by Leuenberger.3,4 Bier et al.5 reported that records of power consumption and torque were in good agreement. Other researchers5 also measured the power consumption for process monitoring. Holm et al.7 investigated the correlation between granule growth and power consumption curves. Holm et al.8 also demonstrated the possibility of granulation end point control by power consumption meters.

Although many different studies on the measurement and control of high shear granulation have already been conducted, no reliable tool has been developed to directly monitor the granule growth.

In this paper, a novel system was developed for the on-line monitoring of granule growth in a high shear granulation using an image processing system. Performance of the system was confirmed by the granulation of pharmaceutical powders. A granulation control system was also developed and its validity was investigated experimentally.

Measurement Principle Up to this time, an image processing system has been applied to monitor granule growth in fluidized bed granulation.9-11 A mechanical sampling device using a sticking tape,9,10 as well as a direct measuring technique by an image probe, have been developed to take granule images during granulation, together with an automated image processing system to continuously analyze granule size and shape. In the fluidized bed, fluidized air suspends each particle and this is favorable for taking a clear image of well-dispersed granules. In addition, the granule growth speed is relatively slow so that the image processing speed should not be necessary first. In the high shear granulation, however, probe location should carefully be considered; otherwise, a clear image of well-dispersed particles is hard to achieve. Also, the sampling speed should be fast enough to analyze rapid granule growth in high shear granulation.

In this study, an image probe and an image processing system, which was developed in our laboratory for fluidized bed granulation, has been improved to adjust for high shear granulation. We have also tried to apply high shear granulation to directly and continuously monitor granule growth. We believe that this is the first attempt to directly and continuously monitor granule growth in high shear granulation.

Experimental Apparatus Figure 1 shows a schematic diagram of an experimental apparatus used. A newly developed high shear mixer (SPG25, Fuji Paudal Co., Ltd.) was used for high shear granulation. The vessel was laboratory size, with an inner diameter of 400 mm and a capacity of 25 L. The bottom of the vessel was equipped with an agitator blade (main impeller) rotating horizontally, which promoted agglomeration and compaction. A chopper blade was also provided on the sidewall to break up wetted masses into small granules.

Power consumption of both the agitator and chopper blades was measured by a digital power meter. Torque of the agitator shaft was measured by a digital torque meter. Granule moisture content and temperature were measured by an IR (Infrared) moisture sensor12 and a thermometer (PT 100Ω), respectively, which were both installed on the sidewall of the vessel.

Granule growth during granulation was measured by a developed image processing system. As shown in Fig. 2, the main body of a particle image probe was a cylinder made of stainless steel with a diameter of 455 mm and a length of 340 mm, comprising a CCD camera, lighting unit, telephoto lens and air purge unit. Although basic functions were almost the same as previously reported,13 each unit was modified for better performance. A

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stroboscope with a high energy Xe lamp, which gave flushing light at 1 μs intervals, was used as a light source. Optical fibers transmitted the light to a slit at the extremity of the probe. By using the narrow slit, the Xe light could light up a standing plane at 90 degrees to the CCD camera axis. Since the CCD camera was focused on the light plane, it could detect only the lift-up granules on the light plane, leading to correctly measure the granule size. In addition, granules behind the light plane or granules out of focus due to their too close locations obtained a considerably smaller quantity of light, and thus could be easily removed in a binarization procedure afterwards. The depth of CCD focus and of light plane was newly adjusted for the high shear granulation. Magnification of the telephoto lens was fixed to ×5, which can measure granule sizes from 7 to 3500 μm. For practical use, this system can be used for granulation having a final product median size between 100 to 500 μm (geometric standard deviation of particle size ranges from 1.2 to 2.5).

Granule images, received by the CCD camera, were continuously digitized by an A/D converter to yield an image of 512×480 dots with a gray scale of 256 levels. This was memorized in a large capacity frame memory (maximum 256 pictures). Preprocessing, such as filtering, binarization and noise reduction, was accelerated via a pipeline processing.13 Image processing, such as labeling, pattern recognition, segregation of overlapped particles, and metric feature measurement, which formerly required much time, were conducted using parallel processing. These processes were conducted in an image processor. Parameter setting, data input/output and individual calculations were controlled by a microprocessor. The image data was statistically treated in a host computer to give granule size distribution, median diameter, product's yield of various size ranges, and shape factor (aspect ratio and sphericity). This image processing system could process 4006 granules within a few seconds. Output interval (control output) of the image analysis was set at 10 s. Output signals from the sensors and the image processing system were simultaneously digitized by a 12 bit A/D converter, then monitored via personal computer.

Figure 3 illustrates the locations of the probe. The probe was installed at an attachment flange on the side wall of the vessel at 60 mm and 195 mm above the vessel bottom (both locations were at the center of the lower straight and the upper tapered vessels), both making an angle of 80 degrees between a straight line passing from the agitator central to the chopper and a straight line connecting the agitator central and the attachment flange. At the upper location, the probe could take image of granules thrown up by the chopper blade, while images of granules moving awfully fast in a spiral direction along with the vessel wall could be taken at the lower positioning. As shown in Fig. 3, both the agitator and chopper blades rotated in an anticlockwise direction.
Table 1. Powder Samples

<table>
<thead>
<tr>
<th>Samples</th>
<th>Number median diameter ($\mu$m)</th>
<th>Charge mass ratio (%)</th>
<th>Charge mass (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactose</td>
<td>60</td>
<td>67.2</td>
<td>4.975</td>
</tr>
<tr>
<td>Cornstarch</td>
<td>15</td>
<td>28.8</td>
<td>2.125</td>
</tr>
<tr>
<td>Crystalline cellulose</td>
<td>40</td>
<td>4.0</td>
<td>0.300</td>
</tr>
<tr>
<td>Hydroxypropyl cellulose</td>
<td>21</td>
<td>3.0</td>
<td>0.225</td>
</tr>
<tr>
<td>Purified water</td>
<td>22.0*</td>
<td>1.678</td>
<td>9.303</td>
</tr>
<tr>
<td>(Total)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(a)\) DMV (Pharmatene 200 M); \(b)\) Nippon Shokuhin Kako Co., Ltd.; \(c)\) Asahi Chemical Industry Co., Ltd. (Avicel PH-101); \(d)\) Nippon Soda Co., Ltd. (HPC-L). *Charge mass ratio of purified water is based on the powder total mass (7.625 kg).

**Powder Samples** Materials used are listed in Table 1. Starting materials (apparent density: 0.42 g/cm³) were 7.625 kg of a mixture of lactose, cornstarch and crystalline cellulose. 0.225 kg of hydroxypropyl cellulose (HPC-L) was adopted as a binder, which was mixed in the form of a dry powder into the starting materials before granulation. Purified water was used as a binder solution. Experiments were conducted as follows. The weighed powder samples were fed into the granulator and mixed for 120 s. The agitator and the chopper blade were set to run at the prescribed rotational speed (agitator rotational speed was 300 rpm, and chopper at 3600 rpm), while the binder solution (purified water) was added instantaneously from the top of the vessel (one minute to discharge all water). After the granulation, granulated products were dried in a shelf drier at 50°C for 24 h. The initial stationary bed height was 15 cm, while it decreased to less than 10 cm after granulation.

In the case of measuring particle segregation during particle mixing, spherical particles (Celphere, Asahi Chemical Industry Co., Ltd.) made of crystalline cellulose, having two different sizes (median sizes are 600 and 250 μm), each of which was mixed 1:1 by weight, were used. 4.0 kg of big particles were placed flat at the bottom of the vessel to form a layer of several centimeters deep, followed by a layer of 4.0 kg of small particles placed flat. After being mixed for a predetermined time, the suction of particles through a pneumatic sampling tube (i.d. 8 mm) was conducted at eight points on the same plane having three different depths (0, 4 and 8 cm from the powder surface), and segregation of bigger particles was investigated. Here, segregation \(\zeta\) is defined as the ratio of big particle mass to the ideal mass of a big particle (50%, initial mixing mass ratio) among the sampled particles. The value of 1.0 indicated that mixing was complete (ideal mixing). Positive deviation from 1.0 showed that the ratio of the big particle was greater than the small ones, while negative deviation showed the small particle ratio was greater than big.

**Evaluation of Granulated Products** Size distribution of the granulated products was determined by sieve analysis with a rotating sieve shaker. About 100 g of the products were shaken for 180 s. After measuring the weight of the products on each sieve, size distribution was calculated by a log-normal distribution with a personal computer. The sieves used were 200 M (Mesh) (opening size 75 μm), 145 M (105 μm), 100 M (150 μm), 83 M (180 μm), 60 M (250 μm), 50 M (300 μm), 42 M (355 μm), 30 M (500 μm), 18.5 M (850 μm) and 12 M (1400 μm), respectively.

**Results and Discussion**

**Segregation Inside the Granulator** Figure 4 illustrates the temporal change in particle segregation \(\zeta\) at the three different layers. The segregation was within 5%. The first layer (upper surface) showed positive deviation and the others negative (small particle ratio was larger) throughout the mixing operation. As compared to the other mixing devices, \(^{12}\) it could be regarded that there was almost no segregation during the mixing. Taking into account the particle high shear mixing with chopping function, ideal mixing was occurring during the mixing operation. However, when the operation was stopped every 10 s for sampling, the small particles tended to fall downward easily because of their good flowability, leading to a slight segregation. It could thus be safe to mention that there was no obvious segregation if the probe was installed anywhere at the wall.

Figure 5 shows the effect of probe positioning on the measured particle size. Two different heights were investigated for the probe positioning: one was 60 mm and the other 195 mm in height from the vessel bottom, as shown in Fig. 3. For investigating the effect of the positioning on size measurement, spherical particles (Celphere, Asahi Chemical Industry Co., Ltd.) made of crystalline cellulose, having a wide particle size range from 200 to 700 μm with their number median size 315 μm, were used.

From Fig. 5, the number median size measured at the upper position showed the same value as the representative value (number median diameter of the powder sample), while the data at the lower position indicated much larger particles, although both positioning should indicate the same values.
according to the results obtained in Fig. 4.

Seen from the digital images obtained by the probe (Fig. 6), the number of particles were enormous when measured at the lower position. In this case, segmentation of overlapped particles took a long time to determine and sometimes could not be carried out correctly due to the large number of overlapped particles. Although optimum tuning of the segmentation parameters could successfully conduct the segmentation, it always required tuning by trial and error. Contrary to the lower position, the image at the upper position showed that particles were well dispersed and they hardly overlapped. Due to the easy segmentation process, the image processing system could accurately measure the number median size of particles.

As a result of these findings, the optimal height of the image probe was determined to be 195 mm above the bottom, at which particles thrown up by the chopper agitation collided and the clearest images could be taken.

**Monitoring of Granule Growth by a Developed Image Processing System** Figure 7 shows the results of typical monitoring methods, by power consumption, agitation torque, moisture content and granule temperature during high shear granulation. Granule temperature increased with time, and moisture content slightly decreased due to the slight drying by the granule temperature increase and by the sealing air of the agitator blade shaft. From the moisture and temperature profiles, monitoring of granule growth was obviously impossible.

As previously reported, the agitator torque and the agitator power consumption measurements showed almost the same behaviors, showing a large value at the initial stage of granulation, followed by a gradual decrease; almost constant values were finally reached after $t=1500$ s. From these data, although the granule growth and operational end-point could roughly be understood, quantitative analysis of granule growth was obviously impossible.

Figure 8 indicate the monitoring results by both on-line measurements via the developed image processing system and off-line measurement by sieve analysis. In this figure, closed circles indicate Feret diameter by the particle image processing system and open circles show granule mass median diameter obtained by sieve analysis. Since granule size distribution obtained by the image processing method was a number base distribution, it was impossible to compare the image data with the conventional sieve analysis data since the latter involved mass base distribution. Fortunately, granule size distribution was not so broad, and it obeyed log-normal distribution: its geometric standard deviation was within 1.7 to 2.0. Thus the obtained number base size distribution could be transformed into mass base distribution using Hatch’s well-known equation:

$$\ln(MMD) = \ln(NMD) + 3 \ln^2 \sigma_g$$

where MMD, NMD and $\sigma_g$ show mass median diameter, number median diameter and geometric standard deviation, respectively.

From Fig. 8, close agreement was obtained between the results of image processing and sieve analysis. Also, the granulation process could be understood as follows: granule me-
Median diameter increased with time because of the dispersion of the binding liquid. The maximum size was taken at \( t=1500 \text{ s} \), followed by a decrease in size. The decrease was supposed to be caused by the grinding of granules due to excess agitation and surface drying, as indicated in Fig. 7. It was found that the developed system could continuously detect granule size with high accuracy and also analyze the granulation process in detail.

Figure 9 shows digital pictures of granules taken by the image probe during granulation. Pictures A—D agree with the same symbol marked in Fig. 8. Due to the slit lighting system, each picture had almost no overlapped granules in the depth direction and showed a very clear image of well-dispersed granules from the initial to final stages of granulation. Also, the picture at \( t=1980 \text{ s} \) showed the existence of small fragments produced by the grinding described in Fig. 8.

Figure 10 represents product's yield plots as a function of operational time. In this figure, closed marks indicate on-line data by the image processing system and open marks show off-line data by sieve analysis. Depending on the particle size range, three product's yields were defined here: fine granule size range \((D_p<106 \mu m)\), subitized granule size range \((106 \leq D_p < 500 \mu m)\) and coarse granule size range \((500 \mu m \leq D_p)\).

Seen from the figure, each product's yield by the image processing system was in good agreement with the one by the sieve method throughout the granulation process. At the beginning of the granulation, fine and coarse granule yields were large while subitized granule yield was small, showing that the dry un-granulated granules and over-wetted agglomerated masses both existed due to the instantaneous dumping of the binding liquid. With an increase in operational time, the binding liquid gradually dispersed to indicate an increase in the subitized yield, as well as a decrease in the fine and coarse yields. After \( t=1500 \text{ s} \), fine and subitized yields obviously increased again, proving that the granules were actually ground.

Control of Granule Growth by a Developed Image Processing System

Figure 11 illustrates a schematic diagram of the granulation control system. Based on the image processing data, the addition of binding liquid was regulated by a controller. After the initial granulation by a instantaneous dumping of the predetermined amount of binding liquid \((W=18\%)\), comparison of measured granule size with a desired value was conducted every 400 s, and if the granule size was smaller than the desired value, 0.2 kg of the binding liquid was fed into the granulator instantaneously and granule growth was observed. When the measured granule size exceeded the desired value, the granulation was terminated by shutting down the agitator and chopper motor drives.

Figure 12 indicates the control result of granulation by a developed system. In the initial granulation, granule growth was insufficient and measured size was much smaller than the desired value \((300 \mu m)\), leading to the addition of binding liquid \((water)\) at \( t=600 \text{ s} \). Since the binding liquid was insufficient enough to increase granule size, binding liquid was added again at \( t=1000 \text{ s} \). This time, binding liquid was sufficient to exceed the desired value and the granulation was stopped at \( t=1120 \text{ s} \). If we compared the mass median size of final product by the developed image processing with the one measured by sieve analysis after drying (● in the figure), both data showed close agreement. This confirmed the accuracy of measurement by the image processing system when applied to the control experiment. It is noteworthy that if the amount of water or interval for water addition decreased,
even more accurate control should be possible. In the next paper, we will demonstrate far advanced control system by applying a fuzzy logic.

Conclusion
An on-line monitoring system was developed based on a particle image probe and an image processing system. The performance of this system was evaluated in the high shear granulation of pharmaceutical powders and showed good agreement with conventional sieve analysis. It was also shown that the system could continuously and accurately analyze the granulation process. Control of granulation was also conducted by means of on-off control of the binding liquid based on the image processing data. It was found that high shear granulation could actually be controlled at the desired granule size. The developed system provided a practical means of on-line monitoring as well as a method of controlling granule growth in high shear granulation.

References