Control of Granule Growth in Fluidized Bed Granulation by an Image Processing System

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In this paper, the control of granule growth in fluidized bed granulation was carried out using a newly developed image processing system. Granule images measured by a particle image probe were digitized by an image processing system during granulation to continuously calculate granule size distribution. To avoid excessive granule growth, fuzzy logic using a linguistic algorithm employing if-then rules with a process lag element taken into consideration was adopted for the control algorithm. This newly developed system was applied to actual fluidized bed granulation under various powder samples and operating conditions, and the validity of the system was investigated. It was found that the system could control granule growth with high accuracy, regardless of changes in powder samples and operating conditions.

Key words image processing system; granulation; fluidized bed; control; fuzzy logic

Process validation, defined by the FDA (Food and Drug Administration) as establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes, has become a serious subject in the pharmaceutical industry. In order to clarify the inspection of the validation or to make these standards easily adaptable to the GMP (Good Manufacturing Practice), monitoring and control of the manufacturing process is strongly required.

Granulation, defined as a process of size enlargement, is an important operation in the pharmaceutical industry, but is difficult to control. Although several methods, such as the monitoring of moisture content,[1,2] power consumption[3-5] and temperature,[6] have been developed up to this point, they are susceptible to changes in powder properties and operating conditions, thus they cannot always produce constant products if the powder sample lot and the operating conditions vary.

To overcome the above mentioned difficulties, we have developed a particle image probe and an image processing system,[7,8] which have been applied to fluidized bed granulation, and confirmed that the system could monitor granule size, size distribution and shape of granules with high accuracy. However, an automated control system of granule growth has not yet been established, although it is of great importance to achieve validity and reproducibility of the product quality.

In this paper, an automated control system of granule growth in fluidized bed granulation was established using an image processing system and a control algorithm based on fuzzy logic. A linguistic algorithm, employing if-then rules with a process lag element taken into consideration, was adopted to control granule growth accurately under any operating conditions or powder sample types. The validity of the system was also investigated.

Experimental

Equipment Figure 1 shows a schematic diagram of the experimental apparatus employed. An agitation fluidized bed[9,10] (NQ-160, Fuji Paudal Co., Ltd.) was used. An agitator blade, turned on a center axis, was provided at the bottom of the cylindrical vessel to create a tumbling and compacting motion on the granules. Heated air needed for the fluidization was blown through slit plates located under the blade, creating a circulating flow. Fine powders lifted up by the fluidizing air were entrapped by bag filters and brushed down by a pulsating jet of air.

Granule size distribution was continuously measured using an image processing system[7] developed previously. The image processing system consisted of two parts: a particle image probe and an image processing unit. The main body of a particle image probe (Fig. 2) was a cylinder comprising a charge-coupled devices (CCD) camera, optical fibers for lighting, a telephoto lens and an air purge unit. A stroboscope with for lighting, a telephoto lens and an air purge unit. A stroboscope with a Xe lamp which gives flashing light at 1 μs intervals was used as a light source; the optical fibers transmitted light to the extremity of the image probe. The flashing interval was controlled by the image processor. The heated purged air was blown to prevent powder adhesion. As shown in Fig. 1, the probe was attached to the side wall of the upper tapered vessel, located 190 mm above the agitator blade.

Figure 3 shows a schematic flow of the algorithm for the image processing. Granule image, received by a CCD camera ($\times 10$), was continuously digitized by an A/D converter to yield an image 512×480 dots in size with a gray scale of 256 levels. This image was stored in a large capacity frame memory (maximum 256 pictures). Image processing, such as labeling, pattern recognition and metric feature measurement, which formerly required considerable time, were conducted by parallel processing in an image processor. The image data was statistically treated in a host computer to yield particle size distribution, median diameter and shape factor of granules. This image processing system can process 4096 granules within a few seconds.

Powder samples Table 1 lists the properties of powder samples used. For wet granulation, powder samples comprised of lactose and

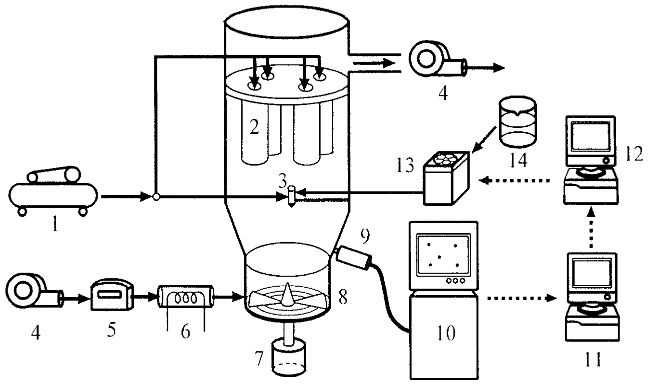

Fig. 1. Schematic Diagram of the Experimental Set up Used

1, air compressor; 2, bag filters; 3, spray nozzle; 4, blower; 5, hot-wire anemometer; 6, heater; 7, motor; 8, agitator blade; 9, particle image probe; 10, image processing system; 11, host computer; 12, personal computer; 13, pump; 14, binder liquid.

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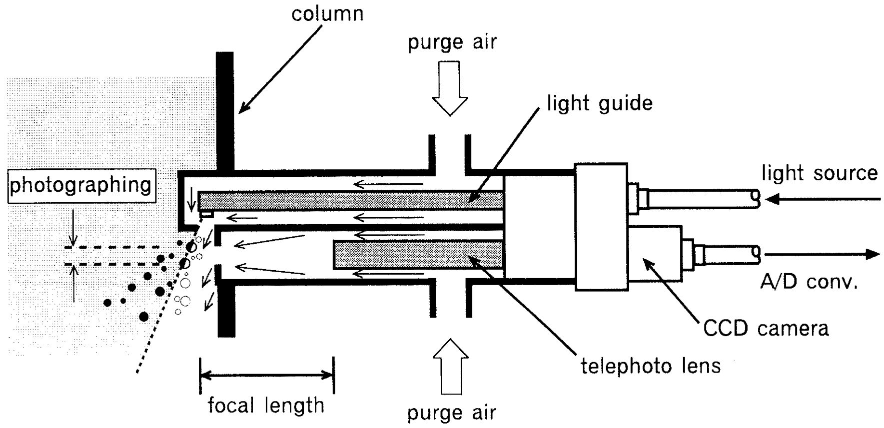

Fig. 2. Sketch of Particle Image Probe

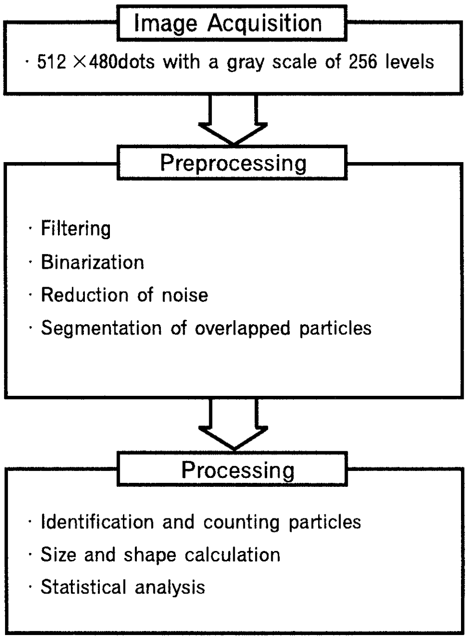

Fig. 3. Flow of Image Processing

Table 1. Properties of Powder Samples Used

Sample	Number median diameter [μm]	Geometric standard deviation [—]
Lactose[a)]	60	1.502
Cornstarch[b)]	15	1.540
Hydroxypropylcellulose[c)]	21	1.507

a) Pharmatose 200M, DMV. *b)* Cornstarch W, Nippon Shokuhin Kakou Co., Ltd. *c)* HPC-EFP, Shin-Etsu Chemical Co., Ltd.

cornstarch, of which the charge mass ratio varied, were used. Purified water was used as a binder liquid, which was sprayed through a binary nozzle located above the powder bed (top spray method).

Results and Discussion

Control of Granule Growth by On-Off Control Figure 4 shows the results of the control experiment using an on-off controller, in which granulation was stopped when the measured granule diameter exceeded a predetermined desired value. Granule growth was gradually advanced during the initial $0 \leq t \leq 1000$ s, at which time the layering granulation mainly occurred. After that, rapid granule growth due to secondary granulation was observed. When

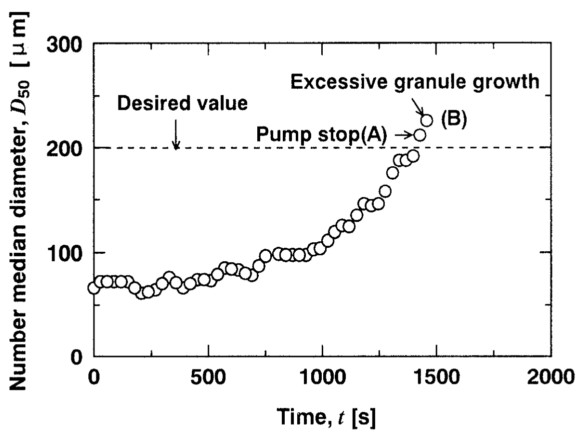

Fig. 4. Control of Granule Growth by On-Off Controller

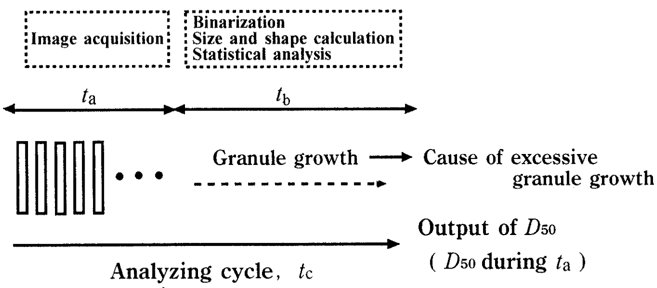

Fig. 5. Flow of Image Processing during Analyzing Cycle

the measured diameter exceeded the predetermined desired value (point A), the pump used for binder adding was actually stopped; however, granule diameter still increased to reach an excessive size (point B).

This phenomena was presumed to be caused by a process lag element; as shown in Fig. 5, the image processing system stored granule images during the processing time, t_a, then binarization, metric feature measurement and statistical treatment were conducted during the processing time, t_b, and after that, the result of the measurement was generated as a representative value during the analyzing cycle, t_c (t_c was changeable and its minimum value was 2 s). Therefore, if the system stopped the operation correctly, just when the measured D_{50} matched the desired value, granule growth would actually reach an excessive level during the system lag time t_b, because the D_{50} was the value analyzed during t_a. Also, if the system output the D_{50}, which was just a little smaller value than the

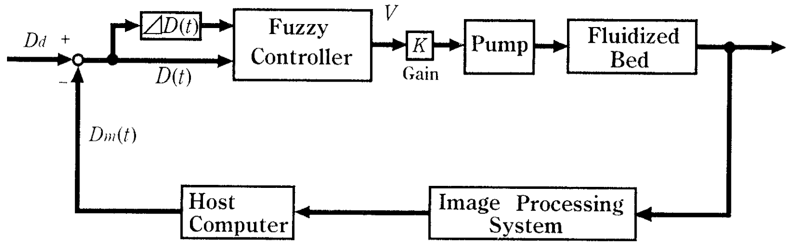

Fig. 6. Block Diagram of Granule Control System

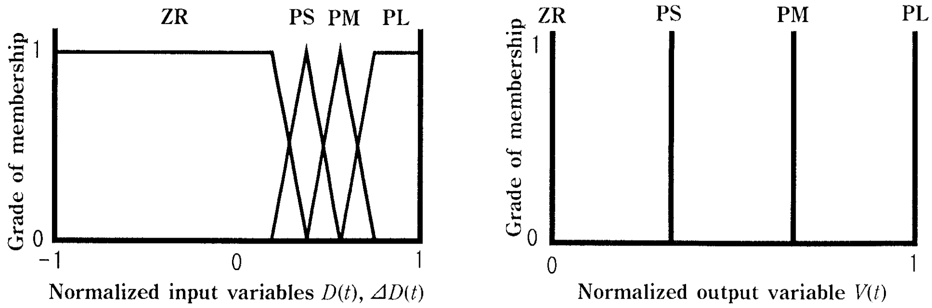

Fig. 7. Membership Functions

predetermined value, granulation would naturally continue and the excess would automatically occur during the analyzing cycle, because the granulation would continue until the system output a D_{50} larger than the desired value the next time.

Also, we have tried to simultaneously use a moving average method or another smoothing method to analyze granule images, but excessive granule growth could not be eliminated due to the system's delayed element; all of the methods summed up many images, then calculated the average value, thus the response decreased due to the process lag or element of delay.

As a result, the control of granule growth was intended to be achieved by an off-controller, however, the system could not prevent excessive granule size (overshoot) because of the system lag or element of delay.

Establishment of a Granule Growth Control System Based on Fuzzy Logic It was found that an excessive granule growth occurred when the granulation was controlled by an on-off controller, and the origin of the excessive development occurs with granule growth during the system lag time. In addition, granule growth during the lag time would change remarkably due to variations in operating conditions and in properties of the powder samples. Therefore, in this study, granule growth during the lag time was intended to be predicted by fuzzy logic[11] employing if-then rules considering a system lag element, and to control granule growth accurately.

Figure 6 illustrates a block diagram of the granule growth fuzzy control system employed. Deviation $D(t)$, the difference between desired (D_d) and measured values ($D_m(t)$) of granule number median diameter, and its changing rate $\Delta D(t)$ were adopted as input variables.

$$D(t)=D_d-D_m(t) \quad (1)$$

$$\Delta D(t)=D(t)-D(t-1) \quad (2)$$

The result of fuzzy reasoning $V(t)$ was used to control the output power of the liquid feed pump.

Table 2. Production Rules for Fuzzy Reasoning

Rule 1: If $D(t)=$PL	then $V(t)=$PL
Rule 2: If $D(t)=$PS and $\Delta D(t)=$PM	then $V(t)=$ZR
Rule 3: If $D(t)=$PS and $\Delta D(t)=$PS	then $V(t)=$PS
Rule 4: If $D(t)=$ZR	then $V(t)=$ZR

Figure 7 indicates the normalized membership functions for granule growth control. A triangular representation was used for the input variables of $D(t)$ and $\Delta D(t)$. Here, the range of $D(t)$ was between $-D_d$ and $+D_d$, which was translated to -1 to $+1$ by a normalized parameter, and the normalized parameter for $\Delta D(t)$ was determined by the granule growth rate during maximum damping speed and drying rate. To simplify the fuzzy logic, we used a real number[12] for $V(t)$, despite the use of a fuzzy set. In this experiment, the following four fuzzy variables were used: ZR (zero), PS (positive small), PM (positive medium) and PL (positive large).

The production rules for granule growth control are listed in Table 2. The rules were designed to increase the pump output, regardless of granule growth rate, when the deviation was large (rule 1), but to decrease the output power in advance when the granule growth rate was large, despite a small deviation (rule 2). Rule 2 was used to prevent excessive granule growth by enabling the controller to recognize that the granule diameter would exceed the desired value if the pump fed large amounts of binder liquid as it was, although the measured granule diameter closely approached the desired value. Rule 3 was devised to account for slow granule growth rate; if the granule growth rate was small, the binder feed rate was maintained as it was to keep the small granule growth rate.

Fuzzy reasoning was conducted by means of a min-max composition method[13] using triangular-shaped membership functions. The resultant fuzzy reasoning was defuzzified by using a center-of-gravity method.[13]

Figure 8 shows the result of granule growth control by

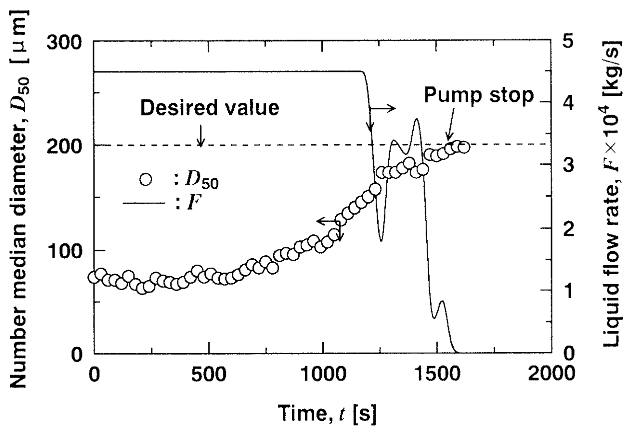

Fig. 8. Result of Granule Growth Control by Fuzzy Logic

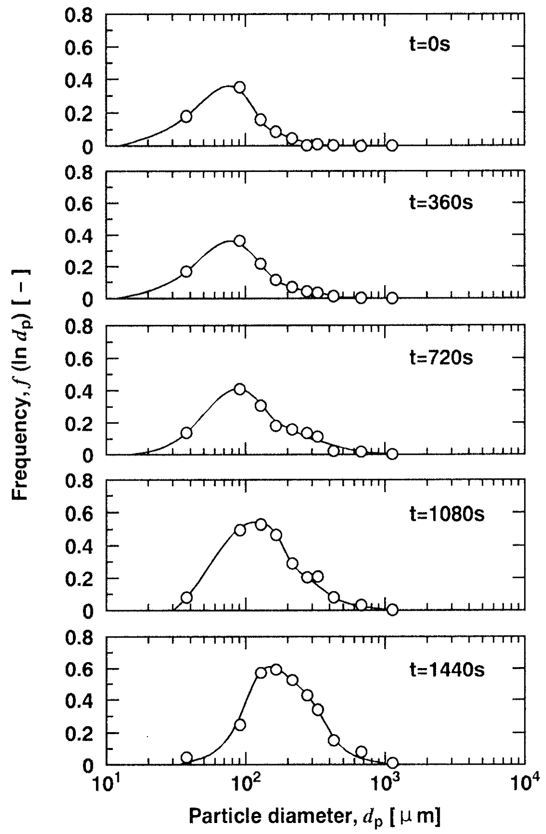

Fig. 9. Temporal Change in Granule Size Distribution

means of the system developed, and Fig. 9 indicates a temporal change in granule size distribution. Here, the analyzing cycle was selected to be 30 s, and more than 500 particles were analyzed based on the preliminary experiments.[8] Also in Fig. 8, plots show the D_{50} measured by the image processing system and the real line indicates the liquid flow rate of the binder liquid, F.

As seen in Fig. 8, granule growth was gradually advanced at the initial stage of granulation. Rapid granule growth was found at the stage over $t=1000$ s, in which narrow (sharp) granule size distribution was also confirmed from Fig. 9. When the measured D_{50} closely approached the desired value ($t=1200$ s), the pump reduced its output in order to prevent excessive granule growth and to control granule growth accurately. By means of this method, the measured granule number median diameter matched the desired value with high

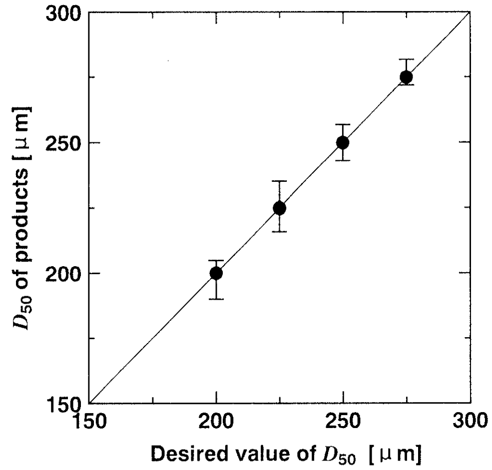

Fig. 10. Accuracy of Control

accuracy.

Figure 10 illustrates the reproducibility of the control system. In this figure, the horizontal axis is a desired value of D_{50} predetermined before granulation, and the vertical axis is the result of the control. Also, plots show the mean value, and bars indicate deviation of the D_{50} of the products. There was a good agreement between the obtained D_{50} and the desired value, and the accuracy of control was within $\pm 15\,\mu$m. As a result, it was concluded that the newly developed system could determine an operational end point accurately at various desired values.

Control of Granule Growth with Various Powder Samples and Operating Conditions In agitation fluidized bed granulation, it has been reported that the main factors which determine granule growth are the operational moisture content and the agitator rotational speed.[14,15] For example, if the agitator rotational speed increased with the same moisture content, granules were densified and their diameter decreased due to granule compaction and a decrease in adhesion probability. In such cases, the system could not maintain granule diameter because the diameter changed due to the variation in agitator rotational speed. Also, if powder sample properties such as water absorbing potential and coherent strength varied, the granule diameter changed markedly even if the moisture content was kept constant. Therefore, the widely used moisture control method, for example, can only control granule growth of a powder sample in which the relationship between granule moisture content and granule growth has been previously investigated. No other conventional methods has been shown to control granule growth under various operating conditions and powder samples.

By contrast, the image processing system is apparently free from the influences of varying operating conditions and powder properties, because it can measure granule diameter directly by the granule images. Also, if the developed control system can overcome the process lag element by using fuzzy logic, high accuracy of the control results are expected.

In the following, granule growth was intended to be controlled under various powder samples and agitator

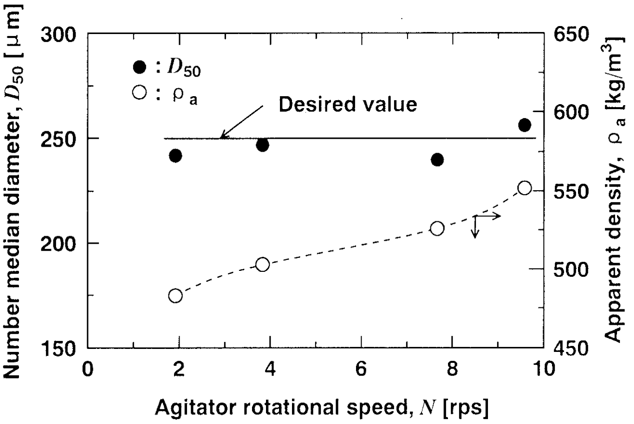

Fig. 11. Control of Granule Diameter at Various Agitator Rotational Speeds

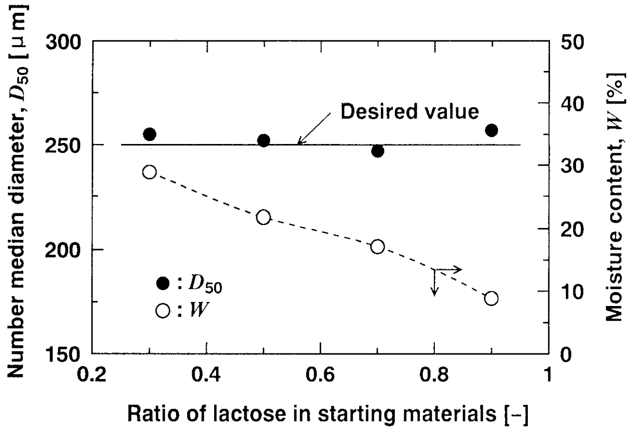

Fig. 12. Control of Granule Diameter at Various Powder Samples

rotational speeds, and the validity of the control system was investigated in detail.

Figure 11 illustrates the number median diameter and apparent density of granules controlled using the developed control system at various agitator rotational speeds. Here, closed circles show the number median diameter and open ones indicate the apparent density of granules. The real line expresses the desired value of the control experiments.

As seen in Fig. 11, the granule median diameter was maintained at a desired value, although the granules were densified with an increase in agitator rotational speed. Accurate control was considered to be obtained by the efficacy of direct measurement of the granule images.

Figure 12 shows the results of granule size control with various powder sample properties. Here, mass ratio of lactose in the starting materials was varied to prepare various powder properties. As can be seen in Fig. 12, granules with the desired diameter were produced, regardless of the lactose ratio. These results implied that the newly developed system could control granule growth accurately, even if the properties of powder sample varied. By contrast, judging from the result that the operational moisture content decreased markedly due to an increase in the lactose ratio, the conventional moisture control method could control granule size if only the appropriate moisture content was investigated beforehand.

Conclusions

A system to control granule growth, comprised of an image processing system and a control unit employing fuzzy logic, was developed to control granule size in agitation fluidized bed granulation. Fuzzy logic using a linguistic algorithm employing if-then rules with a process lag element taken into consideration was adopted as a control algorithm to avoid excessive granule growth. This newly developed system was applied to actual fluidized bed granulation, and the validity of the system was investigated using various operating conditions and powder samples. It was found that the system could control granule size with high accuracy, regardless of changes in powder samples and operating conditions.

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