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Research paper

Feedback control in high shear granulation of pharmaceutical powders

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Abstract

A novel system has been developed to control granule growth in high shear granulation. The system basically consisted of an image-processing device and a fuzzy control system. A computer-controlled image processor, an air purge unit, a high-energy xenon lighting system and an image probe with a CCD camera comprised the image processing device. A fuzzy control system using a linguistic algorithm employing if–then rules with a process lag element taken into consideration has been developed to accurately control granule growth without any excessive growth. This newly developed system was applied to actual high shear granulation of pharmaceutical powders and validity of the system was investigated. It was found that the system could control granule growth with high accuracy, regardless of changes in physical properties of starting materials and the operating conditions. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Granulation; High shear mixer; Control; Granule growth; Image processing; Fuzzy control

1. Introduction

The recent trend in granulation technology is toward an improvement of process efficiency, stability of product quality, safety manufacturing and labor saving. With such improvements and the demand for granulation, the use of high shear mixers has become of major interest lately especially in the pharmaceutical, food, agriculture and chemical industries. One of the principal reasons is that high shear granulation produces spherical and well-compacted granules in a relatively short time and the equipment itself is very simple in construction.

However, in addition to the numerous advantages, granulation in a high shear mixer is very sensitive to even minor changes in moisture content, amount of binder, physical properties of starting materials and the operating conditions [1]. Therefore, there is a great need for reliable system for process monitoring and control of granule growth.

To date, a number of investigations have been done regarding different devices to monitor the process conditions and to terminate granulation operation at the optimal operating time (end point). Torque measurement of a main driving shaft using a strain gauge technique was described by Lindberg et al. [2,3]. Leuenberger [4,5] measured motor drive power consumption and tried to monitor process conditions. Bier et al. [6] reported that records of power consumption and torque were in good agreement. Holm et al. [1] investigated the relationship between granule growth and power consumption curves and also demonstrated the possibility of end-point determination by power consumption meters [7]. Although many different studies regarding the measurement of high shear granulation have been conducted, all of them were based on indirect methods, thus they were easily affected by the changes in powder properties and operating conditions. It is clear that no reliable tools have been developed so far to monitor the granule growth directly, much less to self-control the granulation process with a high accuracy.

The aim of the present investigation has been to develop a system for controlling granule growth during high shear granulation. A novel system has been developed for on-line monitoring of granule growth by means of an image-processing system. A control algorithm based on a fuzzy logic considering complex dynamic characteristics and process lag element was also established to feed back control of the granule size during the granulation. Performance of the system and accuracy of control were also investigated experimentally using different kinds of pharmaceutical powders and various operating conditions.

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2. Experimental

2.1. Apparatus

Fig. 1 shows an apparatus of a high shear granulator [8,9] and Fig. 2 displays a schematic diagram. A high shear mixer (SPG25, Fuji Paudal Co. Ltd.) was used for wet granulation. The vessel had an inner diameter of 400 mm and a capacity of 25 liters. 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 side wall so as to break up wetted masses into small granules. The direction of both agitator and chopper agitation was counter-clockwise. Binder liquid was sprayed through an air-less fluid nozzle from the upper lid.

Granule growth during granulation was measured by a developed image processing device [8–10] shown in Fig. 3. This system consisted of an image probe and an image processing system. The main body of a particle image probe was a cylinder made of stainless steel with a diameter of 56.5 mm and a length of 227 mm, comprising a CCD camera, lighting unit, telephoto lens and air purge unit. A 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 probe extremity. By using the narrow slit, the Xe light lit up a standing plane at 90° to the CCD camera axis. Since the CCD camera focused on the light plane, only the lit-up granules on the light plane were detected, facilitating the correct measurement of granule size. In addition, granules behind the light plane or granules out of focus due to their being too close received a considerably smaller quantity of light, thus being easily removed in a binarization procedure afterwards. Depth of the CCD focus and of the light plane can be adjusted depending on the mixer's geometry.

The probe can be installed from the side wall of the high shear mixer (Fig. 4a) as well as from the top lid (Fig. 4b). Due to the function of a flexible flange, angle and depth of the probe can be adjusted. As long as the granule space density is high enough, the probe can take clear images of granules. Also, a single probe is sufficient to take granule images that represent the size distribution of whole granules, the reason being that (i) there was almost no segregation in the high shear granulation with high-speed agitation [8] and (ii) the number of granules used for image processing was large enough (this is mentioned later). This probe has already been used with larger equipment and the results confirmed the validity of using the single probe.

In this study, the probe was installed on the side wall of the vessel at 195 mm above the vessel bottom, making an angle of 80° between a straight line passing from agitator central cone to chopper and a straight line connecting the agitator central cone and the CCD camera (Fig. 4a). At this position, the probe was able to take the clearest and most

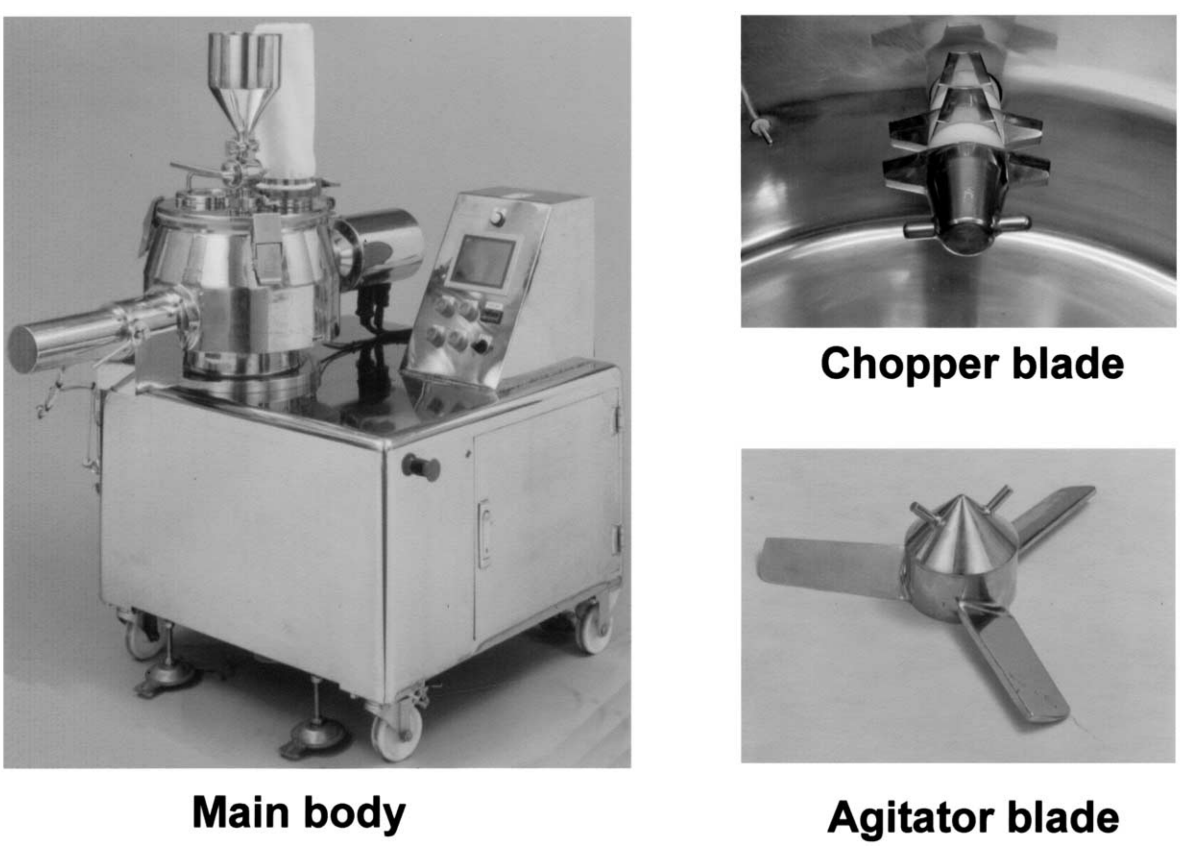

Fig. 1. Appearance of high shear granulator.

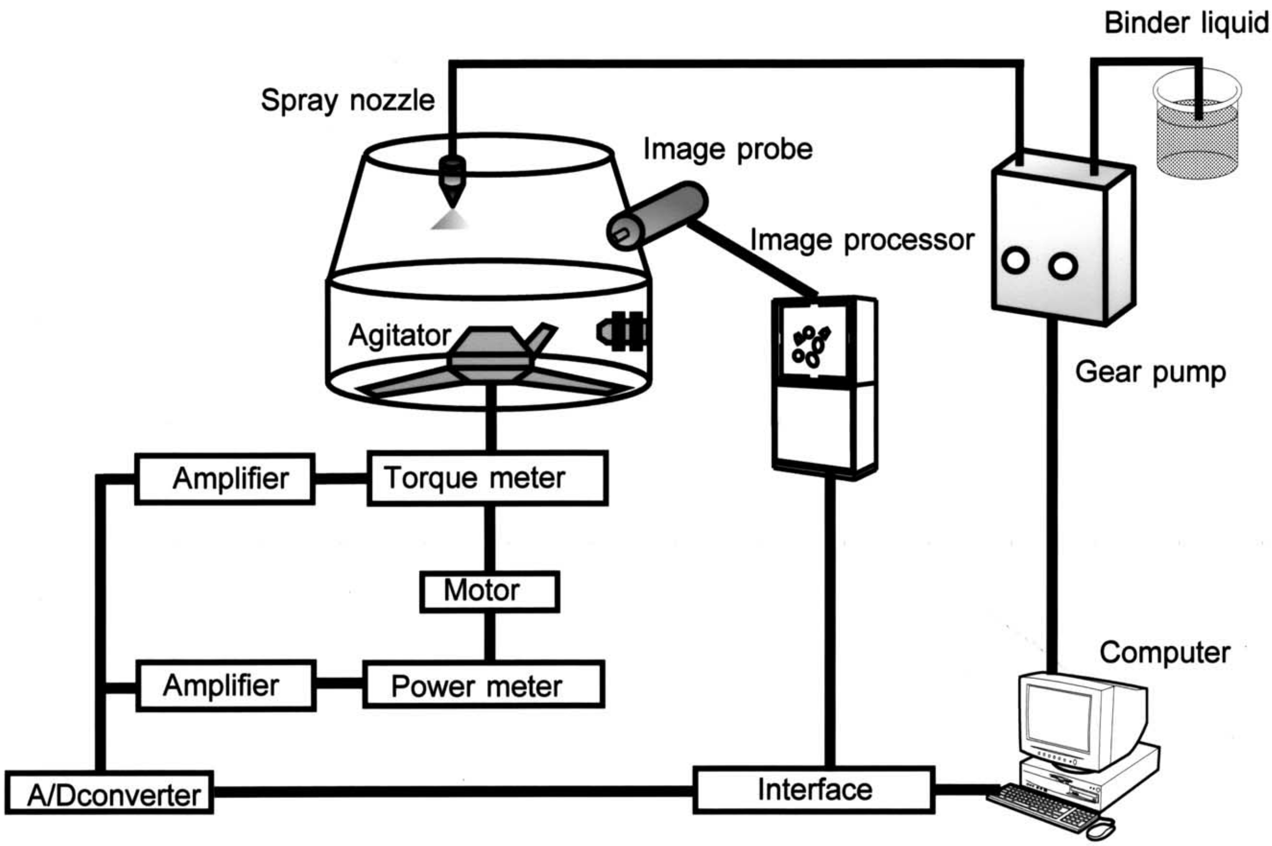

Fig. 2. Schematic diagram of experimental apparatus used.

distributed image of granules, which were thrown up by the high-speed chopper agitation.

Granule images, received by the CCD camera, were continuously digitized by an A/D converter to yield an image of 512 × 480 dots in size with gray scale of 256 levels. This was memorized into a large-capacity frame memory (maximum 256 pictures). Preprocessing such as filtering, binarization and noise reduction were accelerated via pipeline processing [11]. Image processing, such as labeling, pattern recognition, segregation of overlapped particles, and metric feature measurement, which formerly required much time, were conducted via parallel processing. These processes were conducted using an image processor.

Segregation of overlapped particles was conducted by

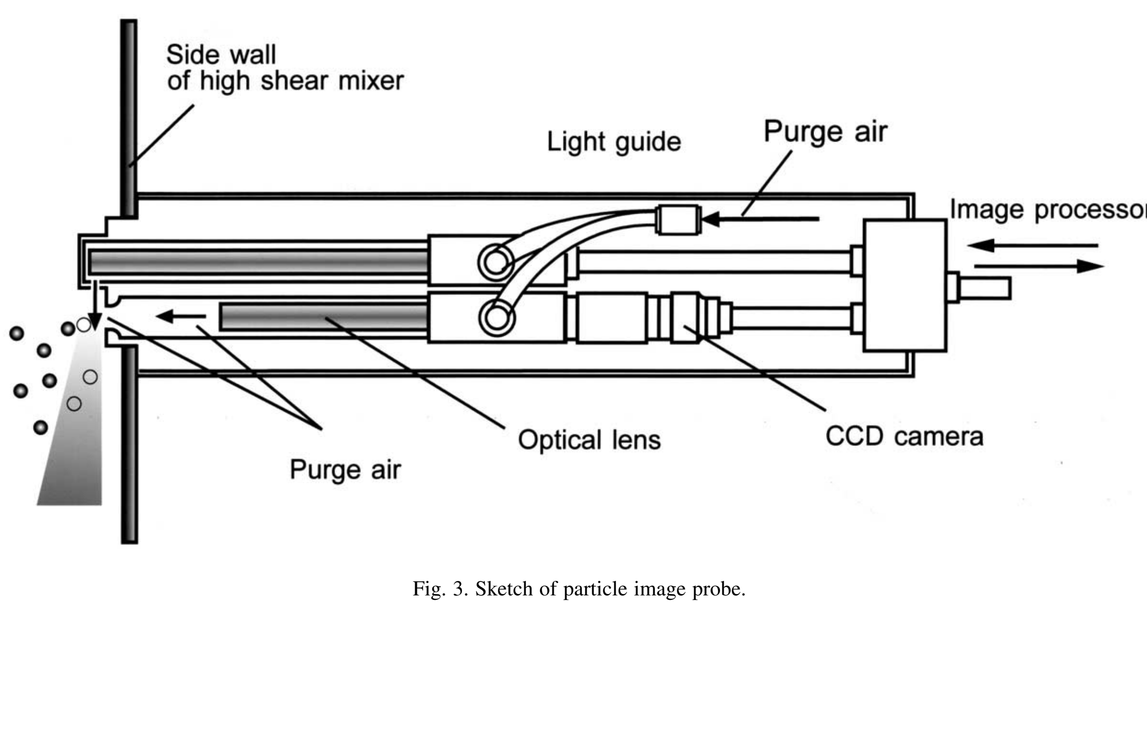

Fig. 3. Sketch of particle image probe.

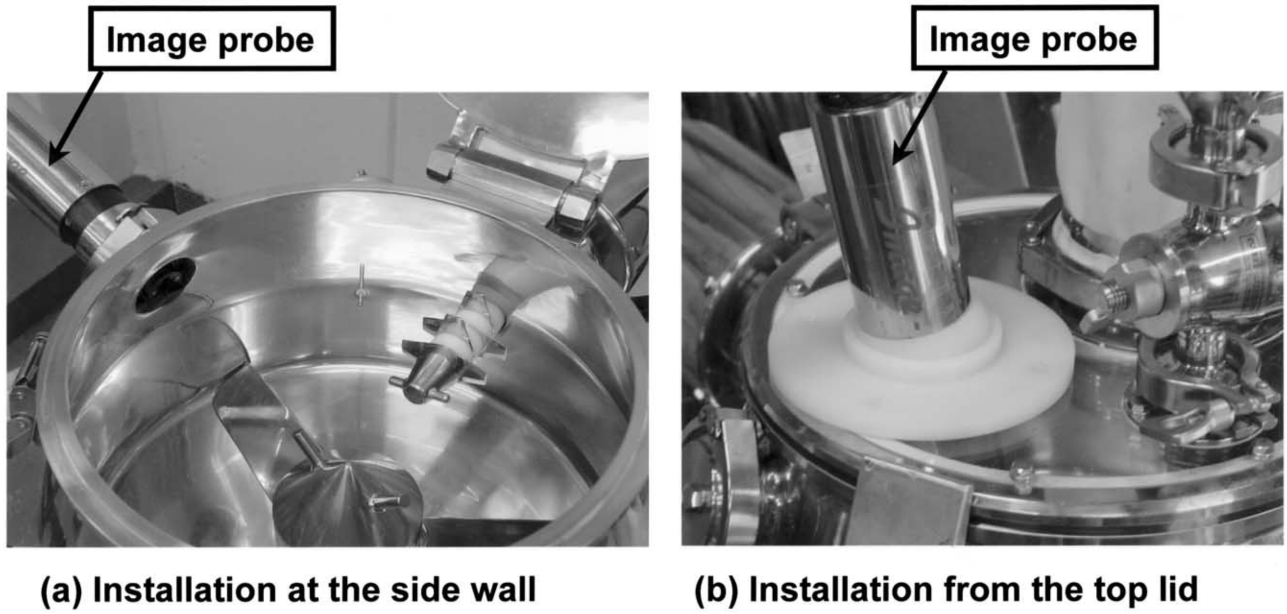

Fig. 4. Installation of an image probe.

using a circle pattern matching or an eight-neighbor erosion method as previously reported [10].

Parameter setting, data input/output and individual calculations were controlled by a personal computer (Pentium III processor, 600 MHz). The image data were statistically treated in a computer to give granule size distribution, median diameter, product yield of various size ranges, and shape factor (aspect ratio and sphericity). This image processing system can process 10,000 granules within 1 s. In this study, the photographing speed was 0.5 s and output interval (control output) of the image analysis was set at 10 s. Normally, every picture contained 50–200 granule images, so that at least 1,000 granules were counted and analyzed during each output interval.

2.2. Powder samples

Powder samples used are listed in Table 1. Starting materials consisted of the following excipients: lactose, cornstarch and crystalline cellulose and the active ingredient, namely, sparingly water-soluble acetaminophen and slightly water-soluble ethenzamide. Both are widely used antipyretics. Dry hydroxypropylcellulose (HPC-L) (0.222 kg) was adopted as a binder, which was mixed 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

Table 1
Powder samples

	Number median diameter (μm)	Charge ratio (charge weight)				
		Sample I	Sample II	Sample III	Sample IV	Sample V
Lactose[a]	60	67.2% (4.973 kg)	47.2% (3.493 kg)	47.2% (3.493 kg)	60.5% (4.477 kg)	33.6% (2.486 kg)
Cornstarch[b]	15	28.8% (2.131 kg)	20.2% (1.495 kg)	20.2% (1.495 kg)	25.9% (1.917 kg)	14.4% (1.066 kg)
Crystalline cellulose[c]	40	4.0% (0.296 kg)	4.0% (0.296 kg)	4.0% (0.296 kg)	4.0% (0.296 kg)	4.0% (0.296 kg)
Acetaminophen[d]	44	–	28.8% (2.131 kg)	–	–	–
Ethenzamide[e]	40	–	–	28.8% (2.131 kg)	9.6% (0.7104 kg)	48.0% (3.552 kg)
Total		100.0% (7.400 kg)	100.0% (7.400 kg)	100.0% (7.400 kg)	100.0% (7.400 kg)	100.0% (7.400 kg)
Hydroxypropyl cellulose[f]	21			3.0% (0.222 kg)		
Purified water				22.0% (1.628 kg)		

[a] DMV (Pharmatose 200M).
[b] Nihon Shokuhin Kako Co. Ltd. (Cornstarch W).
[c] Asahi Chemical Industry Co. Ltd. (Avicel PH-101).
[d] Yamamoto Chemical Co. Ltd.
[e] Shizuoka Caffeine & Co. Ltd.

run at the prescribed rotational speed (agitator rotational speed was at 300 rpm, and chopper at 3600 rpm), while the binder solution (purified water) was added from the top of the vessel using a single fluid nozzle (top spray).

2.2.1. Evaluation of granulated products

Mass median diameter of granules was calculated by a 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.

Bulk density of granules was measured by a powder tester (Hosokawa Micron, Powder Tester PT-E). Basically, granules were slowly discharged into a cylinder and its density was calculated based on its mass and apparent volume.

Strength of granules was analyzed by a strength measurement system (Grano, Okada Seiko). In the system, a punching lid moved down from the top at a speed of 1 cm/min and pressed a granulated particle on a flat stage. The applied force and pressed displacement were then measured continuously. The strength of the granulated particle was measured by the force when the granulated particle was crushed.

3. Results and discussion

3.1. On-line monitoring of granule growth

Fig. 5 indicates mass median diameter of granules calculated by both on-line and off-line measurements. In this figure, open marks indicate on-line results by the developed image processing system and closed ones show off-line measurements (volume of each granule was calculated based on the measured size, and then translated into the volume-base distribution, which was basically equivalent to the mass-base distribution under the assumption that the granule density was almost the same regardless of its size).

In the off-line measurements, wet granules were sampled out during granulation, followed by the mild drying at 323 K for 24 h in a shelf drier in order to prevent granule size changes. The dried granules were sieved to analyze the granule size distribution. Here, the sampling was conducted using a sampling cup of about 100 g of granules from the place where the image probe was installed. The sampled granule size distribution has already been confirmed to have the same distribution as the whole granulated products [8].

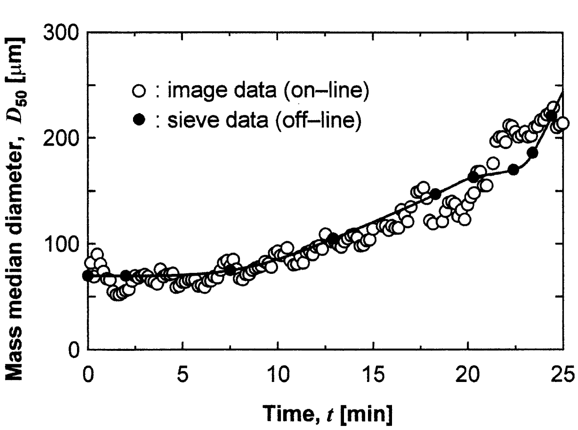

Fig. 5. Comparison of on-line image data with off-line sieving data.

As seen in Fig. 5, the on-line data showed close agreement with the off-line data; granule size increased slowly at the initial low moisture content range, followed by the rapid increase at the high moisture content range. Typically, in the pharmaceutical industries, a fluidized bed drying is often used after the high shear granulation. In such a case, granule physical properties such as size, shape and density may change due to the abrasion, crushing and compaction during fluidizing. However, if these changes can previously be calculated, the image processing system can be used to monitor and control by setting the larger desired value into the system. In other words, the granules having larger size by its decrease during drying should be produced in the high shear granulation if the precise control is required.

Fig. 6 illustrates digital pictures of granules taken by the image probe during a 0.5-s flushing interval. Due to the slit lighting system, the pictures had almost no overlapped granules in the depth direction and showed very clear images of well-dispersed granules from the initial to the final stage of granulation. The high-speed chopper agitation and purge air blowing were thought to have contributed to the image quality. Also, at $t = 5$ min, the probe could even take clear pictures of very fine granules which were almost at the initial powder stage. In the order A, B and C, it was obvious that the granule size increased significantly and shape became more spherical.

Regarding the on-line shape monitoring, we have already confirmed that the shape factor (aspect ratio and circularity) can be well monitored by the system developed [8,9].

3.2. Control of granule growth by fuzzy logic

As previously reported [9], granulation processes have complicated dynamic characteristics including lag and delay elements, so that the accurate control of granule growth is very difficult even if the granule growth can be directly measured by our developed image processing system. Therefore, we tried to use a fuzzy logic system [12], which can utilize human knowledge based on expert operators' experiences, in order to control granule growth accurately. In this experiment, we aimed to remove excessive granule growth and improve control stability and response using linguistic algorithms employing if–then rules, in which granule size, its changing rate and process lag element were taken into consideration.

Fig. 7 shows a block diagram of granule size control system based on a fuzzy logic. Deviation $D(t)$, the difference between desired (D_d) and measured values ($D_m(t)$) of granule size, and its changing rate $\Delta D(t)$ were adopted as input

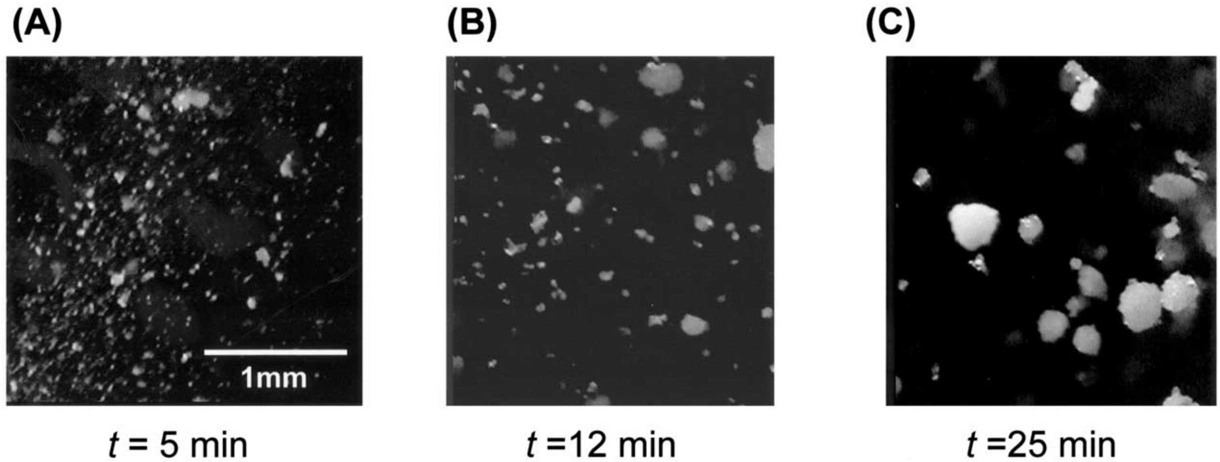

Fig. 6. Digital pictures of granules taken by the image probe.

variables (no smoothing method was applied to the input variables); they were defined as follows.

$$D(t) = D_d - D_m(t) \tag{1}$$

$$\Delta D(t) = D_m(t) - D_m(t-1) \tag{2}$$

The result of fuzzy reasoning $V(t)$ was used to control the output power of liquid feed pump. Here, K_1 and K_2 represent gains of the input variables.

Fig. 8 indicates the normalized membership functions for granule size control. Triangular representation was used for the input variables of $D(t)$ and $\Delta D(t)$. The range of $D(t)$ was between 0 and $+D_d$, which was translated into 0 to +1 by a normalized parameter of D_d. The normalized parameter for $\Delta D(t)$ was determined by a possible maximum granule growth rate of 50 μm/min. To simplify the fuzzy logic, we used a real number [13] for $V(t)$, despite the use of fuzzy set. The $V(t)$ was also normalized by a maximum feed speed of the pump (140 g/min). In this experiment, the following five fuzzy variables were used: ZR (Zero), PS (Positive Small), PM (Positive Medium) and PL (Positive Large).

The production rules for granule size control are listed in Table 2. In total, ten rules were made based on the expert operators' experiences and were used for the fuzzy reasoning. For example, Rule 1 was designed to feed maximum pump output, regardless of granule size changing rate, when the deviation was large. However, Rule 8 decreased the pump output in advance when the deviation was small (granule size was approaching to the desired value), despite small size changing rate. Also, output of the pump was terminated beforehand when the size-changing rate was very fast (Rule 6). Rules 6–8 were used to prevent excessive granule growth (overshoot) by having the controller recognize that granule size would exceed the desired value if the pump fed large amounts of binder liquid as it was, if the measured granule size closely approached the desired value or if size-changing rate was very fast.

To determine the optimum membership functions and production rules, the following procedures were used: (i) first, typical triangular membership functions which equally divide the full range of $D(t)$ and $\Delta D(t)$ were set; (ii) production rules were constructed based on the expert operator's knowledge and intuition; (iii) granulation experiments under various desired values were conducted to modify the membership functions and the production rules with reference to a debug tool.

In the fuzzy controller, fuzzy reasoning [12] was conducted by means of a min-max composition method [14] using triangular-shaped membership functions and if–then rules. The resultant fuzzy reasoning was defuzzified by using a center-of-gravity method [13].

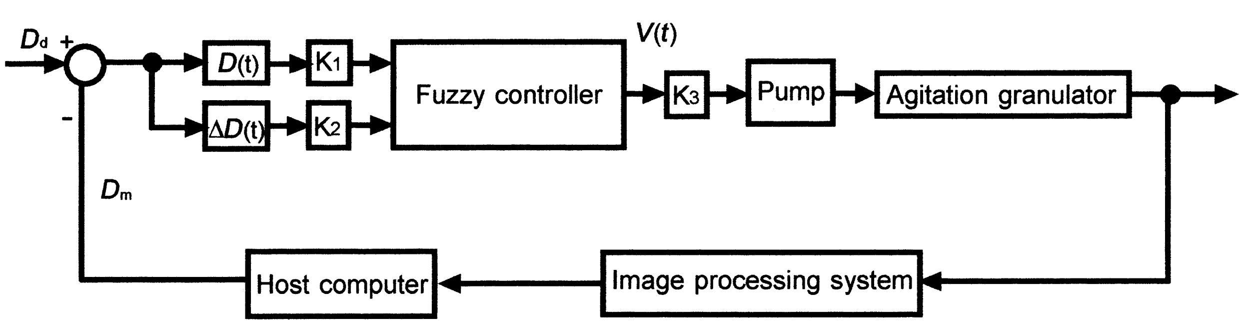

Fig. 7. Block diagram of granule size control system.

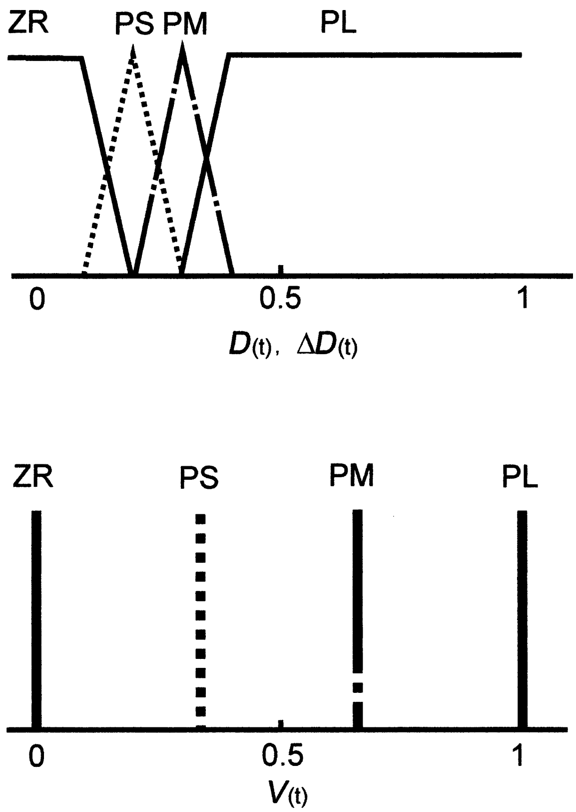

Fig. 8. Membership functions for fuzzy logic.

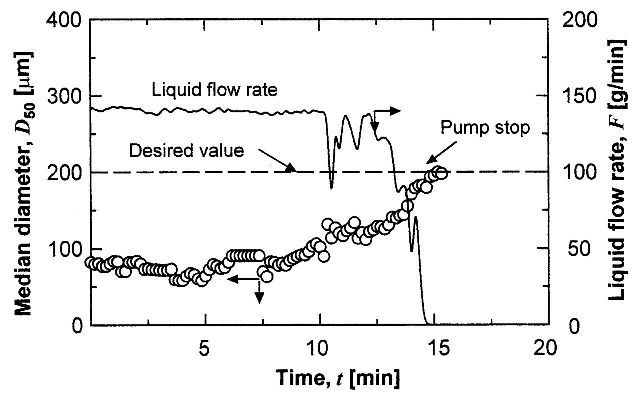

Fig. 9. Results of fuzzy control.

Fig. 9 illustrates temporal change in granule median diameter, D_{50}, and liquid flow rate, F, respectively as a result of fuzzy reasoning. As seen in Fig. 9, excessive granule growth was not observed and excellent control stability was achieved throughout the granulation; at the initial stage of granulation, granule size was small enough that the pump fed maximum output power. At $t = 10$ min, decrease in the pump output was observed to reduce granule growth rate. When granule size was closely approaching the desired value ($t = 12$ min), output power of the pump decreased markedly and finally stopped at $t = 14$ min. Due to the previous suppression of pump output, granule growth was very gentle when the measured diameter was near the desired value. Consequently, no excess granule growth was observed.

Fig. 10 illustrates results of fuzzy control under various kinds of powder samples. Despite the change in powder physical properties, the developed system was able to control the granule growth at the desired value without changing either the rules or the membership functions.

Fig. 11 also describes control results under various liquid flow rates. Even if the liquid flow rate was varied, the

Table 2
Production rules for fuzzy control[a]

Rule no.	$D(f)$	$\Delta D(t)$	$V(t)$
1	PL		PL
2	PM	PL	ZR
3	PM	PM	PS
4	PM	PS	PM
5	PM	ZR	PM
6	PS	PL	ZR
7	PS	PM	ZR
8	PS	PS	PS
9	PS	ZR	PS
10	ZR		ZR

[a] (Description) If $D(t)$ = PL then $V(t)$ = PL (Rule 1). If $D(t)$ = PS and $\Delta D(t)$ = PL then $V(t)$ = ZR (Rule 6). If $D(t)$ = PS and $\Delta D(t)$ = PS then $V(t)$ = PS (Rule 8).

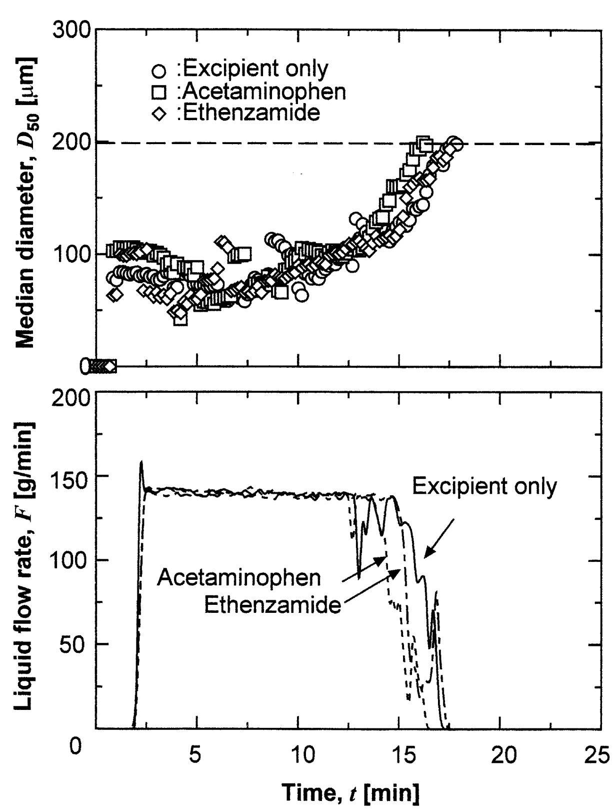

Fig. 10. Results of fuzzy control under various kinds of powder samples.

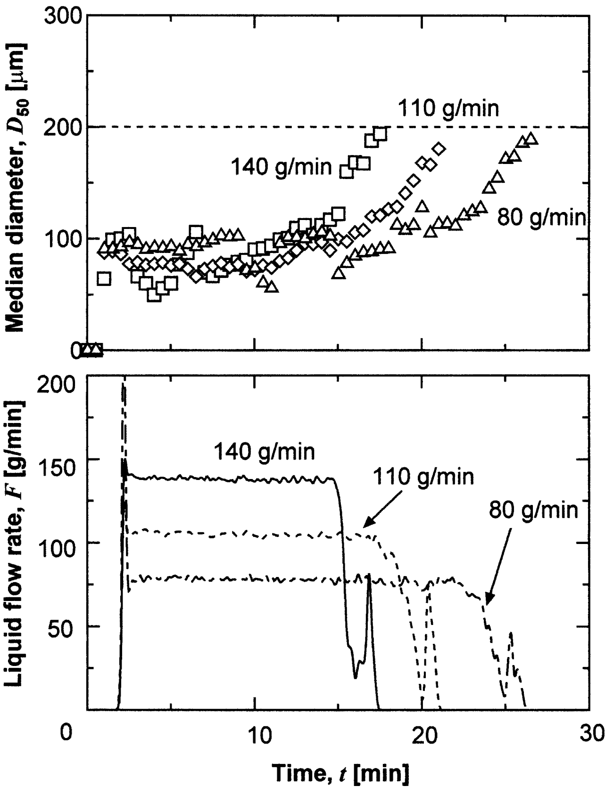

Fig. 11. Results of fuzzy control under various liquid flow rates.

system could terminate the granulation operation at the desired value (end-point).

Fig. 12 shows the effect of liquid flow rate on the granule density and strength. As is clear from Fig. 13 (scanning electron microscope photographs of granules), the granule shape made spherical and the surface smooth when the liquid flow rate was lower. This clearly proved the possibility of controlling granule density/hardness by using granule shape factor; our image system can continuously monitor the granule shape factor [8,14], so that the granule density

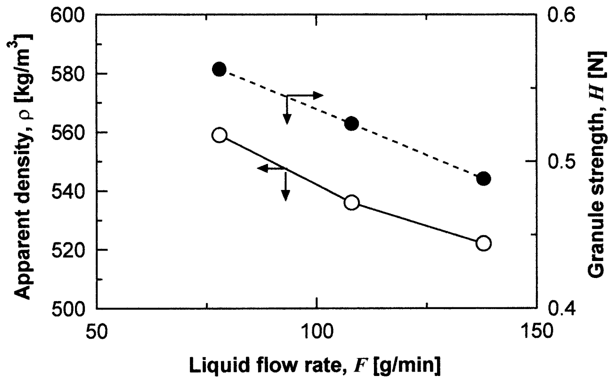

Fig. 12. Granule density and strength as a function of liquid flow rate.

can roughly be understood by monitoring granule shape factor during granulation.

It was found that high shear granulation aimed to produce subtilized granules could be well controlled without any excessive granule growth by means of a developed fuzzy control system. Applying different kinds of powder samples and operating conditions (liquid flow rate) also proved the robustness and generality of the system. The scale-up of high shear granulation by the image processing system will be described in the next paper.

4. Conclusions

Based on image processing and fuzzy logic, a system was established for on-line measurement and control of growth in high shear granulation. Linguistic algorithms employing if–then rules, in which the process lag element was taken into consideration, were constructed using the experience of expert operators. Good controllability, response and stability without any excessive granule growth were achieved by using the developed control system. Excellent performance of control was also obtained under various powder samples and operating conditions.

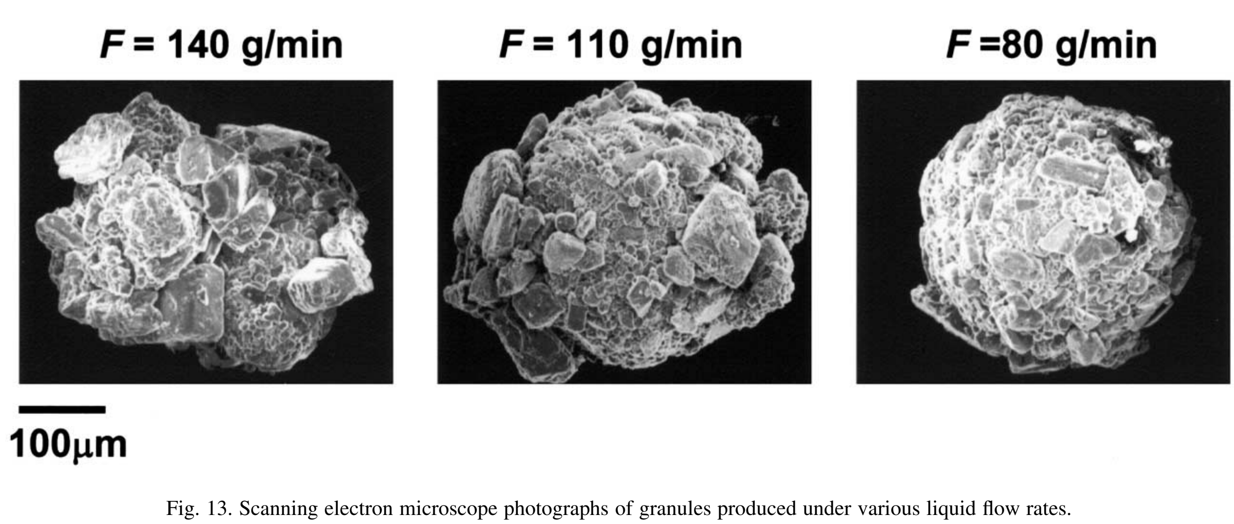

Fig. 13. Scanning electron microscope photographs of granules produced under various liquid flow rates.

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