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Determination of End-Point by Frequency Analysis of Power Consumption in Agitation Granulation

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A granulation experiment was conducted with a high speed type granulator. Power consumption was measured during the experiment and, in accordance with data, frequency analysis was performed to quantitatively determine the granulation process. The method for frequency analysis was the computation of fluctuation (standard deviation) of power consumption and FFT (fast Fourier transform) analysis.

As a result, the granulation end point was determined and the mechanism was made clear by the use of fluctuation (standard deviation) of power consumption and intensity of spectrum obtained by FFT analysis. With these efforts, establishment of a self-control system of granulation has been made possible.

Keywords Granulation end point; fast Fourier transform analysis; fluctuation of power consumption; self-control system; high speed agitation granulator

Introduction

In the pharmaceutical industry, "Good Manufacturing Practice" has become a serious subject of discussion. To clear up this difficulty as well as to produce easily reproducible uniform quality, the introduction of factory automation has been indispensable. Production of a solid dosage form is nowadays the norm in the majority of medical supplies, but to establish whole factory automation of this production process, measurement and control of individual unit operation is necessary.

Granulation, which is a necessary manufacturing process, is carried out to stabilize the principal ingredient or arrange the particle size suitably for making tablets and so on. In the field of granulation, however, operations are still dependent upon human experience and intuition. Therefore, development of a self-measurement system has been an earnest requirement.

We forcused our attention on the agitation–granulation process which produced well-compacted, spherical particles.

Some authors have carried out a great deal of investigation to understand the granulation mechanism and the process applying different devices such as agitation torque, power consumption and product temperature. Lindberg *et al.*[1,2] measured the torque of the main shaft by a strain gauge technique. Measurement of power consumption was described by Luenberger,[3] who showed records of power consumption and torque were in good agreement. Holm *et al.*[4] measured power consumption and temperature changes during granulation.

As a fundamental study of this paper, we have already reported on a method using power consumption to determine the granulation end point at which high yield of spherical, well compacted granules are produced.[5-8]

In reference to self-control of the granulator, however, this research was insufficient in finding a relationship between granule properties and quantitative analysis.

In this paper, we reported about frequency analysis in accordance with the measurement of power consumption to quantitatively determine the granulation process. In the first step, we focused our attention on the fluctuation of power consumption related to the granulation process. In the second step, to investigate the above mentioned results more accurately, we applied frequency analysis using FFT (fast Fourier transform) to power consumption changes. To match this data with granule properties, particle size distribution, apparent density, and shape index were measured from the granules sampled out during the granulation experiment. From these results, determination method of the granulation end point was discussed. Eventually, establishment of a self-control system of granulation was made possible.

Experimental

Materials and Composition Materials and composition used in the granulation experiment are described in Table I. Starting materials were 0.3 kg of a mixture of lactose, corn starch and crystalline cellulose (mixing weight ratio is 6:3:1, respectively). 0.009 kg of hydroxypropylcellulose 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.

Apparatus and Method A high speed type granulator was used for the granulation experiment. The granulator apparatus and the self-measurement system of power consumption are illustrated in Fig. 1.

The vessel was laboratory size, with a capacity of 2 l. The bottom of the vessel was equipped with an agitation blade rotating horizontally which promoted agglomeration and compaction. In addition it was provided with a chopper blade on a side wall, operated so as to arrange particle size distribution.

Power consumption of the agitator and the chopper blade of the granulator was read as an electrical signal, which was amplified in an operational amplifier. This signal was digitalized by a 12-bit A/D converter, then calculated by a personal computer. Control of the A/D converter was programmed in assembly language, and the sampling interval selected in this system was 50 ms, in consideration of the correctness and resolving power of the A/D converter. As a countermeasure to prevent disturbance of the power supply, we used a stabilizing power supply and noise filter.

Experiment was carried out as follows. First, powder samples (shown in Table I) and a binder (which was in dry powder form) were fed into the mixer and agitated for 180 s. Next, the agitator blade was set to run at 13.3 rps and the chopper at 8.33 rps, while the binder solution was added instantaneously from the top of the vessel. These experimental conditions were determined on the basis of preparatory experimental results, and were selected because of the minimal adherence of particles.

TABLE I. Materials and Composition

Materials	Mean particle size (μm)	Mixing weight (kg)
Lactose[a]	104	0.21
Corn starch[b]	42	0.09
Hydroxypropylcellulose[c]	65	0.015
Total		0.315

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

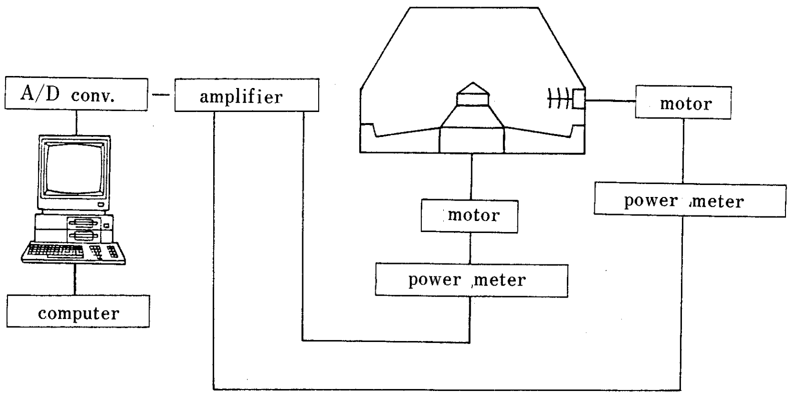

Fig. 1. Auto Measuring System of Power Consumption

Evaluation of Granule Properties Granule size distribution was determined by sieve analysis with a rotating sieve shaker. The screen opening of the sieves were 75, 106, 150, 177, 250, 297, 500, 840, 1410, and 2380 μm, respectively. About 10 g of the granules were shaken for 180 s. After measuring the weight of the granules on each sieve, particle size distribution was calculated by log-normal distribution with a computer.

Results and Discussion

Method to Determine Granulation End-Point Based on Fluctuation (Standard Deviation) of Power Consumption The power consumption curve obtained during the granulation experiment with a high speed type granulator is shown in Fig. 2.

In Fig. 2, the middle curve indicates the power consumption P of the agitator, and the curve changing near the horizontal axis (time axis) is the P of the chopper. The value before $t=0$ is power consumption needed while mixing the materials, and at $t=0$ the binder solution (purified water) was added instantaneously. Here, P in the figure is the substance power consumption deducted from the value required when vessel was empty. In Fig. 2, P of the agitator was high in the first step of the granulation process, then gradually decreased with some fluctuation. According to previous study,[5-8] the granulation end point based on a power consumption curve was near a constant power consumption P_s. From this figure, however, we were not able to discern a constant power consumption P_s. Therefore, the granulation process was obscure and the granulation end point was indeterminable. Consequently, as a new attempt to determine the granulation end point, we calculated the value of fluctuation (standard deviation) of power consumption during granulation. The equation used was as follows.

From a recorded data variable $x(t)$ of power consumption, the standard deviation representing the value of fluctuation could be expressed as

$$\sigma=\left\{\frac{1}{T}\times\Sigma(x(t)-\bar{x})^2\right\}^{0.5} \qquad (1)$$

where $\bar{x}$ was a mean value of power consumption at $0\leqq t\leqq T$. (Here, T indicated the caluculation end time, and the calculation interval of this method was selected to be 15 s.)

To examine the effect of fluctuation (standard deviation) of power consumption on the granulation process, we calculated the σ from Eq. 1.

Figure 3 provides the relationship between the value of fluctuation (standard deviation) of power consumption and granulation time. In the figure, solid line indicates the value of fluctuation (standard deviation) of the agitator, and the broken line is the chopper. Standard deviation of the agitator was initially a large value; however, as the granulation time progressed, this value tended to decrease with fluctuations little by little, until near $t=420$—480 s, a minimum value was achieved. After that, the value gradually increased again with the passage of granulation time. On the other hand, standard deviation of the chopper hardly changed during the granulation operation. Therefore, we decided to discuss the granulation process with the value of fluctuation calculated from the power consumption of the agitator blade.

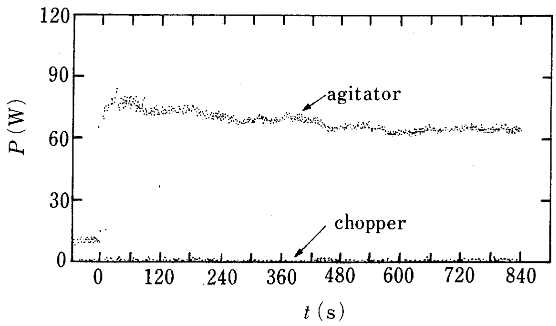

Fig. 2. Relationship between Power Consumption, P and Granulation Time, t

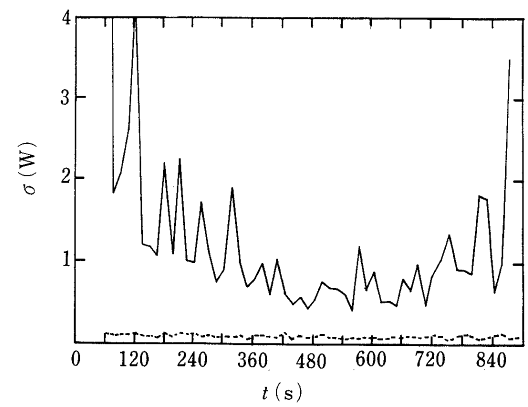

Fig. 3. Relationship between Fluctuation of Power Consumption, σ and Granulation Time, t

—, agitator; ---, chopper.

Particle size distribution of the ganules sampled out at an interval of 60—120 s was calculated to investigate the relationship between fluctuation (standard deviation) and the granulation process. The resulting relationship between 50% mean particle diameter D_{50}, geometry standard deviation σ_g, and granulation time t was indicated in Fig. 4.

To examine the compactness and the appearance shape of the granules over elapsed time, the relationship between apparent density ρ_a, shape index ψ_e and granulation time t was illustrated in Fig. 5. Here, apparent density ρ_a, and the shape index ψ_e were measured in the same manner as previously reported[8] (the shape index indicates the mean ratio of short/long diameters of 50 granules).

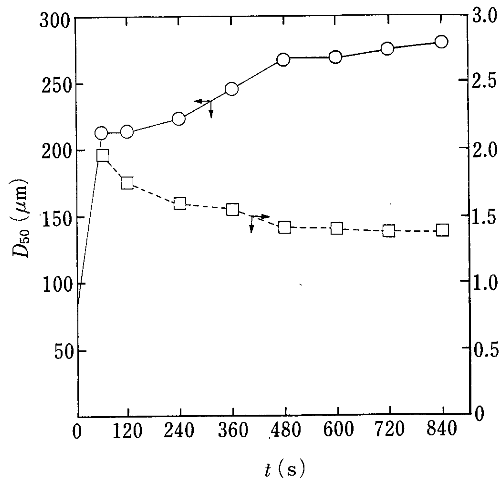

Fig. 4. Relationship between 50% Mean Particle Diameter, D_{50}, Geometric Standard Deviation, σ_g and Granulation Time, t

○, 50% mean particle diameter, D_{50}; □, geometric standard deviation σ_g.

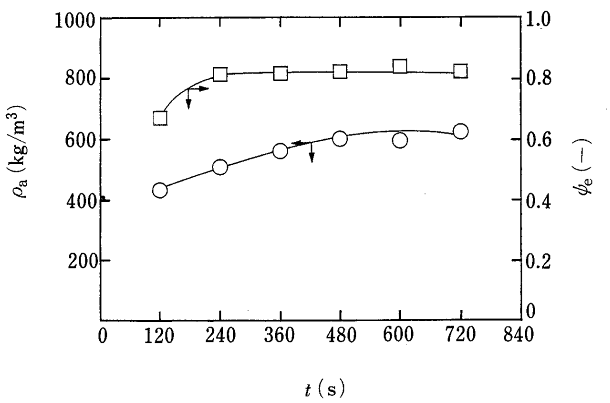

Fig. 5. Relationship between Apparent Density, ρ_a, Shape Index, ψ_e and Granulation Time, t

○, apparent density, ρ_a; □, shape index, ψ_e.

According to granule growth (Figs. 4, 5), fluctuation was influenced by granule properties. Eventually, in the region where granule growth was abrupt, fluctuation was found to be large. This is attributed to the fact that the stress and impulsive force from particles were dispersed because of wide particle distribution and an unevenness of particle shape, and also because the blade received a partial strong stress caused by irregular distribution of the binder solution. A small value of fluctuation was thought to indicate that the granule growth was gentle and particle size distribution was narrow. In Fig. 3, a large value of fluctuation after the minimum value ($t \geqq 480$ s) was attributed to secondary agglomeration of the granules by the liquid which soaked through due to the shearing stress of the blade. In this region, slight growth of the granules was found. (Fig. 4)

As a result, we determined that the granulation end point was near the region where there was a minimum value of fluctuation.

Determination of Granulation End-Point Based on the Frequency Analysis of Power Consumption We understood that by using the fluctuation of power consumption, we could look at the granulation mechanism and granulation end-point in materials which had been difficult to determine by using ordinary analysis based on a power consumption curve. In the respect of control, however, quantitative analysis was needed. Therefore, power consumption was frequency analyzed. Power consumption of agitator, which was closely connected to the granulation process, was frequency analyzed using FFT. The relationship between the intensity of spectrum calculated by FFT analysis and granulation time t was illustrated in Fig. 6.

Here, the equation used to calculate the intensity S was as follows. Power consumption at time t was $x(t)$, $X_T(\omega)$ was defined as a transformed form with Fourier transform,

$$X_T(\omega) = \Sigma(x(t) \times \exp(-j\omega t)) \quad (2)$$

mean-square value of $X_T(\omega)$ was intensity of spectrum $S_x(\omega)$,

$$S_x(\omega) = \frac{1}{T} \times \Sigma X_T(\omega)^2 \quad (3)$$

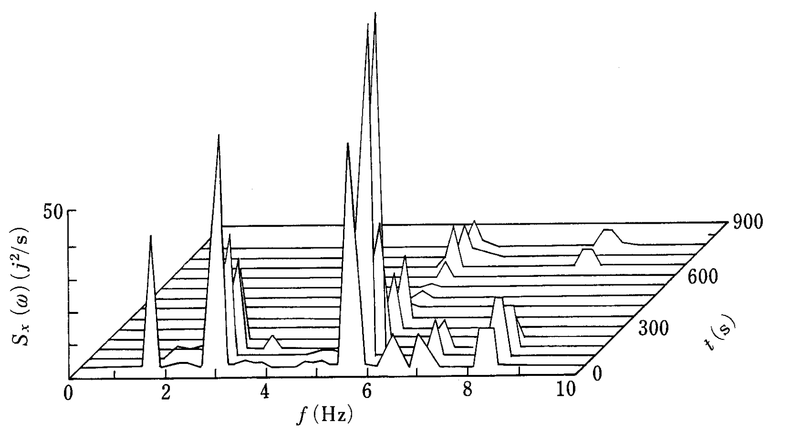

Fig. 6. Relationship between Intensity of Spectrum, $S_x(\omega)$, Frequency, f and Granulation Time, t

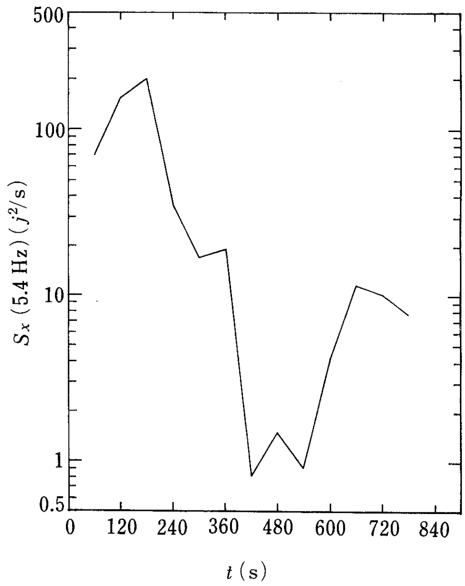

Fig. 7. Relationship between Intensity of Spectrum at 5.4 Hz, S_x(5.4 Hz) and Granulation Time, t

$S_x(\omega)$ was a large value at the initial phase of granulation, and many peaks merged over the wide range of frequency. As the granulation time passed, $S_x(\omega)$ gradually decreased, and the range where peaks of $S_x(\omega)$ merged tended to be narrow. Finally, after an indicated maximum value at $t=420$—540 s, $S_x(\omega)$ tended to increase again. In addition, maximum spectrum was continuously merged at about 5.4 Hz. This frequency was thought to be originated from the number of proper vibrations of this high speed type granulator regardless of rotation speed, which we confirmed using another FFT analyzer.

Here we focused our attention on the maximum spectrum near 5.4 Hz. To examine the change of intensity, we illustrated the maximum intensity at 5.4 Hz in Fig. 7. Intensity of the spectrum at 5.4 Hz, S_x(5.4 Hz) showed the same tendency as the fluctuation (Fig. 3).

As a consequence of this data, we could point out that from the intensity of S_x(5.4 Hz), as well as from the fluctuation of power consumption, we could understand the granulation process and, moreover, determine the granulation end point.

Conclusion

The quantitative analysis needed for self-control, which was indispensable to factory automation, was performed using a value of fluctuation (standard deviation) of power consumption and also the intensity of spectrum obtained by FFT analysis. From these analyses we learned the following:

1. Fluctuation σ of power consumption was closely related to the agitation granulation process and was influenced by the state of the granule particle. σ was large when the stress distribution was wide as a result of wide particle size distribution, irregular granule shape index, *etc.* In this phase, the 50% mean particle diameter, D_{50}, changed greatly, showing the rapid growth of the granules. A small value of σ indicated that the stress distribution was sharp, meaning granule growth was gentle. The phase where σ reached a minimum value was thought to be the granulation end point.

2. Frequency analysis of power consumption with FFT analysis was carried out. The result was that the intensity of the spectrum showed the same tendency as the fluctuation change. Eventually, the phase near the minimum spectrum proved to be the granulation end point.

3. We understood that by using a fluctuation of power consumption and intensity of spectrum obtained by FFT analysis, we could determine the granulation mechanism and granulation end point of the materials which had been difficult to determine by using ordinary analysis based on a power consumption curve.

4. We confirmed that the establishment of self-control system of granulation was possible using frequency analysis.

5. Without a precision apparatus such as the FFT analyzer, a personal computer was sufficient to determine the granulation mechanism accurately.

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