Granulation Process in A Fluidized Bed

Granulation Process in A Fluidized Bed

Keijiro TERASHITA,* Hiroki TOMOZAWA** Kei MIYANAMI*
and Yoshifumi OSAKO***

(Received November 15. 1989)

A granulating experiment was conducted in which the speed that the binding solution was added as well as its concentration were varied. The purpose of the experiment was to investigate the granulating process in a fluidized bed and to study the effects of diffrent conditions to obtain high yields of fine granules. A comparison with the agitation granulating processing was made.

The fluidized bed granulation process is divided into two periods. The first period is to aggregate nuclear particles into small granules. The second period is to aggregate the fine granules produced in the first period into large granules using a second aggregation. By stopping the granulating action near the 50% mean granule diameter refraction point a high yield of fine granules can be obtained. A higher granule yield is possible by adding a binder, rather than a powder. The distribution of the pariticle size of granules produced by the fluidized bed as well as the distribution of those produced by the granulating process, using the agitation method, both are log normal.

1. Introduction

The oral pharmaceuticals, which are commonly adopted, aer prepared in solid forms, such as, powders, granules, capsules, and tablets and are granulated by mixing the medicine with bulking agents. Using granulation, the liquidity, formability, and solubility are improved. Impalpable powders can also be prevented from scattering. Recently, the fluidized bed granulator has been rapidly replacing the agitation granulator. This is because the fluidized bed granulator has the following advantages.

(1) It fits the GMP plan by integrating in a single apparatus the processes of mixing, granulation, and drying.
(2) It allows easy manipulation and automation.
(3) Soft granules are produced

The fludized bed granulator has been well studied. The mechanical structure of the granules as well as their manipulation to produce well-compacted forms have been

* Department of Chemical Engineering, College of Engineering
** Graduate Student, Department of Chemical Engineering, College of Engineering
*** Technical Department, Fuji Paudal Co.,Ltd

widely reported[1~4]. Not much, however, is known about the granulation process itself. In this research project the relationship between the granule particle size distribution and the granulation time was studied. The experiments studied the effects of changes in the concentration of the binding solution as well as changes in the rate at which the solution was added. The inspiration temperature and spray pressure were also studied to help clarify the granulation process. The relationship between the geometric standard deviation, the fine granules (powder) yield and the graule yield were also studied. From the data, the 50% mean granule diameter refraction point (D_{50}) was determined. This allowed the granulation terminal, for obtaining high-yield fine granules, to be found. The binding solution concentration was manipulated to obtain a high yield of fine granules and granules. In addition, A comparison with the particle size distribution from the agitating granulator process was conducted.

2. Apparatus and manipulation

2-1. Powder sample and formulation

The powder sample and the particle size used for this experiment are shown in Table 1. The formulation for the sample is also included. Using the additive solution system, the binder and HPC are dissolved in purified water. This becomes the binding solution for granulation. Using the additive solution system, experiments were conducted at different solution densities. The research compared the particle size distributions of solutions from an additive solution and an additive powder system.

Table 1 Powder samples and formuation

Powder	D_{50}〔μm〕	σ_g〔−〕	additive solution〔kg〕	additive powder〔kg〕
Lactose	104	1.50	0.686	0.664
Corn starch	42	1.20	0.294	0.286
Binder(HPC)	76	1.60	0.000	0.050

2-2. Fluidized bed and experiments

An outline of the top spray-type fluidized bed used in the granulating experiment (GPCG-1, Glatt Co.-Fuji Paudal Co., Ltd.) is shown in Figure 1. Using this system the powder particles in the apparatus are blown by the hot wind from the rectifier and form a free fluidized bed in the air. This causes the binding solution to spray downward. The mist blows in the direction of the wind and promotes granulation, by adhering to the particles, thus forming the fluidized bed. During the granulation experiment the apparatus is heated to a specific temperature to prevent the adhesion of the powder samples to the walls of the fluidized bed. Then, a specific quantity of the powdered samples are passed through a 50 mesh sieve, that is supplied with the apparatus, so that the samples will become fluidized. The samples are then mixed for 10 minutes. Next, a specific quantity of the binding solution is added via a twin-fluid nozzle, set in a predetermined mode. Then the samples are moved to begin

the drying process, The drying process is completed when the temperature rises to 7K greater than that of the exhaust air from the granulating process. Samples were taken for study at diffeent intervals during the granulating process.

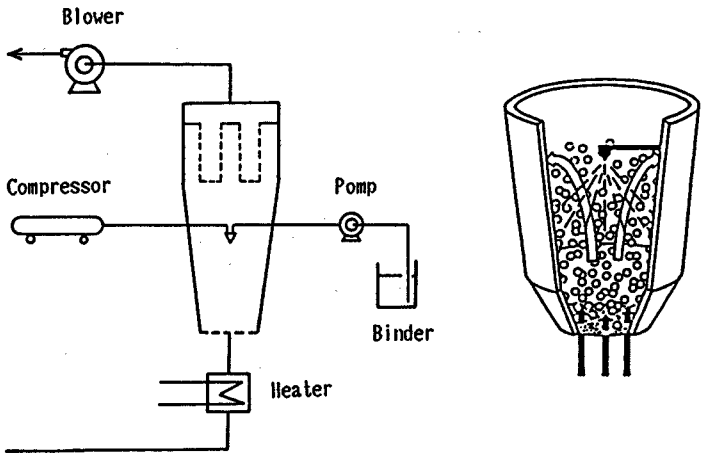

Fig 1 Apparatus of fluidized bed

The conditions of the experiment, unless otherwise stated, were:fluidized bed granulation using the powder additive system, a binding solution addition speed of 3.90×10^{-4} kg/sec, an inspiration temperature of 318.2K, and a spray pressure of 1.5×10^{5} pa.

3. Experimental results and discussion

3. 1 Binder adding speed and solution concentration

The fluidized bed granules aggregated because of the liquid bridge in the binding solution. Because the vaporizing time is shorter for this process, than for the agitation granulation process, the speed at which the binding solution is added is very important. The relationship between the 50% mean granule diameter (D_{50}) and the granulation time t resulting from the application of different binder addition speeds is shown is Figure 2. The changes in D_{50} are divided into two period. The first tow periods (called the first phase) shows a moderate rise during the initial stage of granulation. The second period (called the second phase) shows a rapid rise. Both rises occurred regardless of the speed the binder was added. In the second phase the fine granules from the first phase are aggergated into larger granules. The point where the rapid secondary aggregation develops in the second phase is called the refraction point. Figure 2 shows that the higher the addition speed q, the steeper the rise in D_{50}, after the refraction point. This implies that the higher additon speed triggers a more rapid secondarg aggregation. The relationship between the binding solution addition speed q and the granule yield Y_g is shown in Figure 3.

The relationship between the binding solution addition speed q and the fine granule

(powder) yield Y_S is shown in Figure 4.

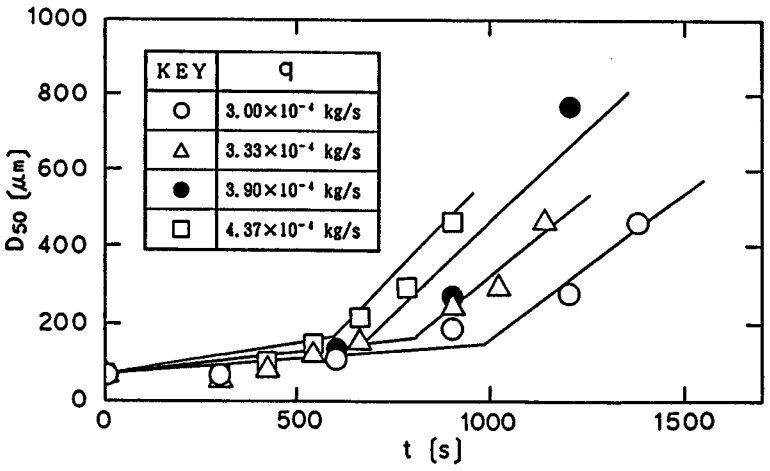

Fig. 2 Relationship between D_{50} and granulation time t

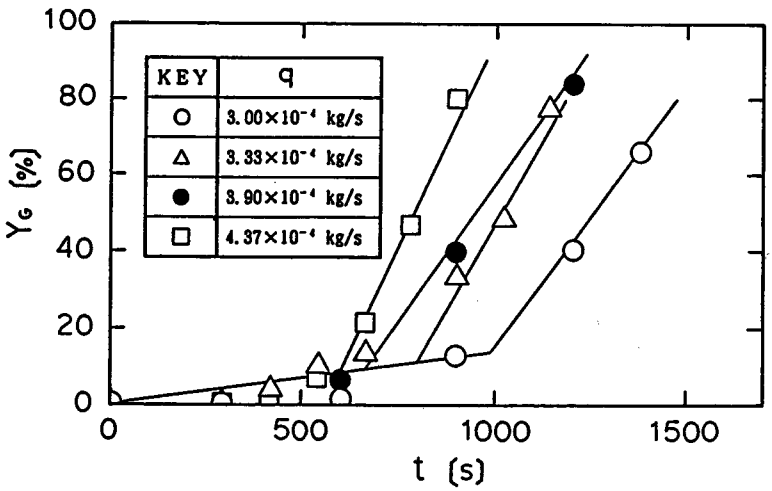

Fig. 3 Relationship between granule yield Y_g and t

Granule yield Y_g was calculated as

(−12 mesh to +48 mesh granule production) ／ (total granule production).

fine granule (powder) yield Y_s was calculated as

(−32 mesh to +200 mesh granule prodution) ／ (total granule production).

The granule yield Y_g illustratecl in Figure 3 shows a phase with a slow rise in granulation time t and another phase with a rapid rise. Near the refuraction point D_{50} (Figure 2) a distinct Y_g refraction point is observed. The refraction point was determined from the relationship between the granule yield Y_g and the granulation

time t. From the refraction point the refraction generating granulation times (t_{ref}) were obtained. The results are shown in Table 2. The Table indicates that the higher the additon speed the shorter the granulation time. This implies that the higher addition speed causes the humidity quickly to increase in the fluidized bed thereby shortening the secondary aggregation generating time. Consequently, the determination of the refraction point is an essential point in the control of the granulation process.

Table 2 Reration between binder adding speed, q and refraction generating graulation time, t_{ref}

q[kg/s]	3.00×10^{-4}	3.33×10^{-4}	3.90×10^{-4}	4.37×10^{-4}
t_{ref}[sec]	993	807	667	599

Figure 4 shows that the fine granule yield Y_s rises along with the granulation time t but drops past the refraction point. This is attributed to the shift from small particle (powder) to large particle (granules) granulation mode. This implies that the granulation terminal for high-yield small grains is located near the refraction point. The fine granules yield is approximately 90%, regardless of the additive time q. A very high yield of 93% was obtained with $q=3.90\times10^{-4}$ kg/s and t=900 sec. This implies that this q value is the optimum binding solution additive speed.

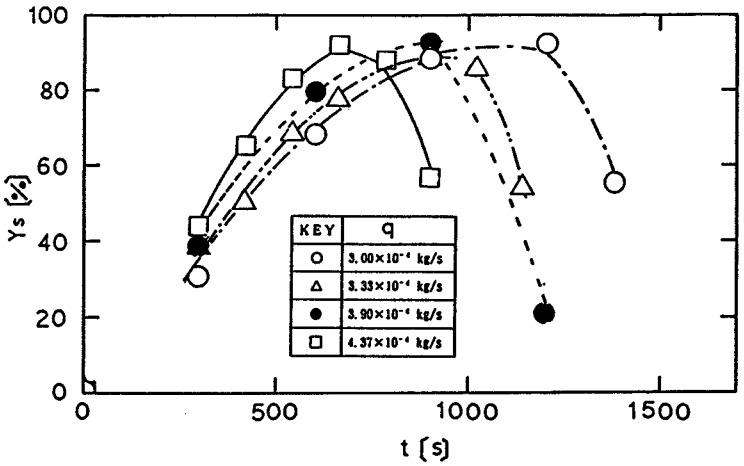

Fig. 4 Relationship between small grain yield(powders) Y_s and t

The effect on the binder additive concentration and 50% mean granule diameter D_{50} from varying the concentration C of the binder solution is shown in Figure 5. Figure 5 also shows the D_{50} (o mark) for the powder additive system. Figure 5 shown that the D_{50} of the binder solution additive system (C= 3 %, 4 %, 5 %) rises along with the rise in solution concentration C. This is attributed to the increase in

the binding ability of the liquid bridge caused by the rising viscosity of the binding solution resulting from the rising solution concentration. The D_{50} in the additive powder system showed larger values than the additive solution system. This is attributed to the comparatively larger wettability of powder compounds by the binding solution. The geometric standard deviation σ_g using the additive solution system is smaller than that using the additive powder system. This implies the former method has a more uniform granular diameter σ_g.

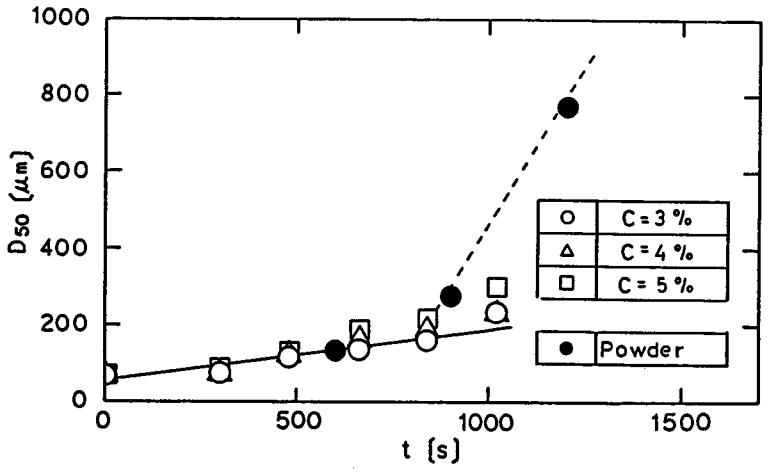

Fig. 5 Relationship between D_{50} and granulation time t

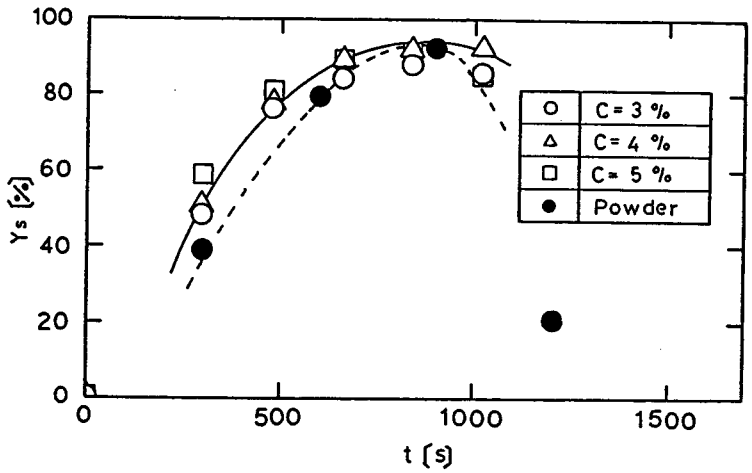

Fig. 6 Relationship between small grain yield(powder) Y_S and t

Figure 6 shows the relationship between the fine granules yield Y_S and the granulation time t. The Y_S from the additive solution system was greater than from the additive powder system, during the initial granulation stage. Y_S equaled 80% for as long as 600 seconds. A particularly high samll grain yield was obtained by

applying a solution concentration of C=4.0%. This shows that, by adding a HPC binder solution with a concentration of C=4.0%, a high fine granules yield with a sharp particle size distribution is obtainable.

3. 2 Inspiration temperature

In addition to the binding solution additive speed, the inspiration temperature of the fluidized air contributed to the humidity of the fluidized bed. Figures 7 and 8, respectively, show the relationship between the 50% mean granule diameter and the granulation time t, and the relationship between Y_g and t. For both Figures the inspiration temperature was T_{in}. Figure 7 shows that a higher inspiration temperature T_{in} causes a lower D_{50}. This implies that the higher inspiration temperarure causes a somewhat lower humidity in the fluidized bed inhibiting the granulation to some extent. Using Figure 8 the refraction points were calculated. The t_{ref}=667 seconds at a T_{in}=318.2K. The t_{ref}=748 seconds at a T_{in}=333.2K. This implies that the lower humidity in the fluidized bed caused the delay in the appearance of the point. The differnces were less significant, however, compared to the effect of the binder additive speed. The granule yield Y_g was unchanged by variatio in T_{in}. The inspiration temperature range adopted in this experiment did not seriously affect the granulation process or granule yield.

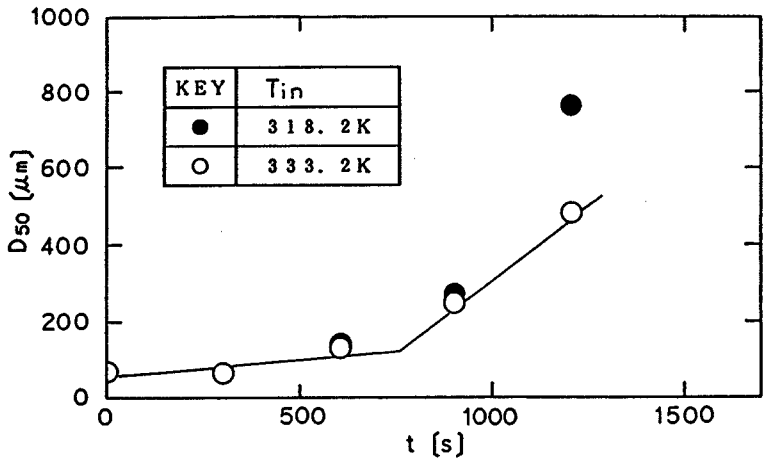

Fig. 7 Relationship between D_{50} and granulation time t

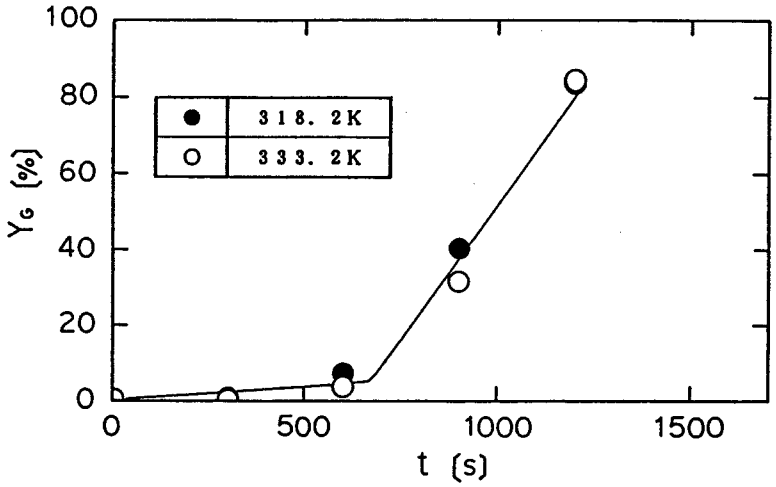

Fig. 8 Relationship between granule yield Y_g and t

3. 3 Spray pressure

The size of the liquid drops in the spray mist was controlled by varying the spray pressure. The drop diameter is generally smaller with higher spray pressure and the distribution narrows. The results of the granulation experiments under different spray pressures P_{atm} are shown in Figures 9 and 10. Figure 9 indicates a somewhat samller D_{50} for the higher spray pressure, implying a smaller drop size. The higher spray pressure causes the binding solution to be more susceptible to evaporation and subsequent non-aggregation. Thus, higher spray pressures narrows the granule particle size distribution. This is because the smaller drops caused by the higher spray pressure makes the formation of the liquid bridge, which promotes the secondary aggregation in the granulation process, difficult. This results in the selective capture of fine granules.

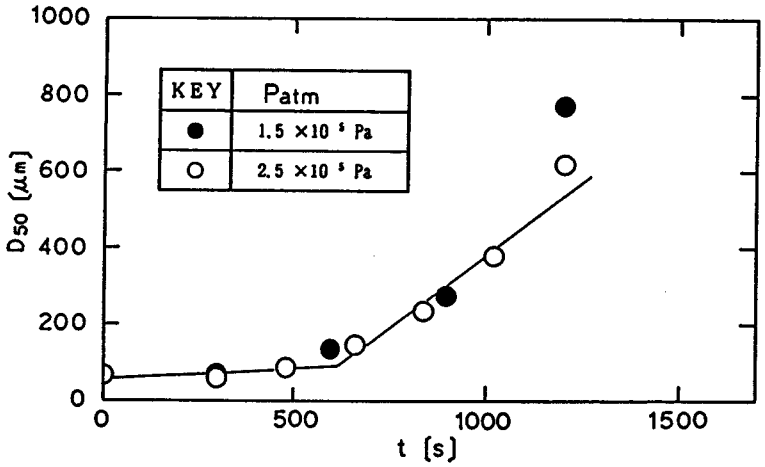

Fig. 9 Relationship between D_{50} and granulation time t

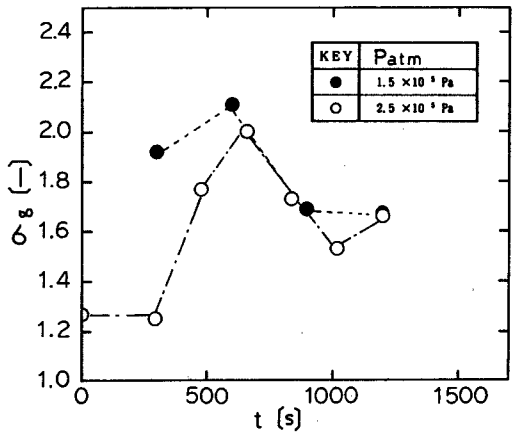

Fig. 10 Relationship between σ_g and granulation time t

A granule yield of 85% to 90% was miantained regardless of the spray pressure level. Higher spray pressures generated a refraction point while increasing the granulation time.

3. 4 Comparison Between Fluidized Bed Granulation and Agitation Granulation

The granulating mechanism of the fluidized bed method is the adhesion at the contact point of the powder particles with the liquid bridge. The mechanism of the agitation method involves shearing, rotation, and consolidation by the rotation of the agitating wing of the powder particles. The affects from the differences between these methods on the particle size distribution is described below. The paricle size distribution of the agitation granulation method and the fluidized bed granulation method are shown, respectively, in Figure 11 and Figure 12. Figure 11, form the agitation granulation method, shows that the particle size distribution is not log-normal for granule sizes above a diameter D≧500μm. This change in the distribution is caused by the aggregation generated by adding the binding solution during the initial granulation process. Later in time, however, after the granulation particle diameter becomes uniform because of the crushing action of the agitating wing, the particle size distribution starts to approach a geometric standard distribution.

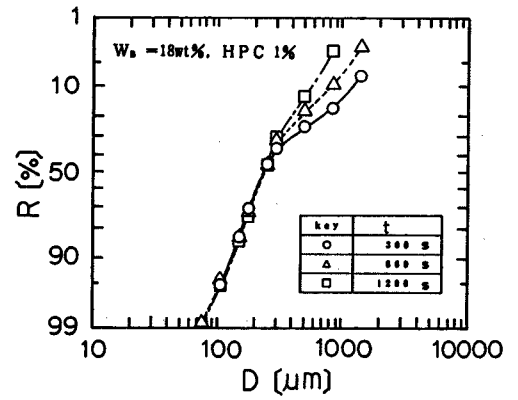

Fig. 11 Particle size distribution (agitation granulation)

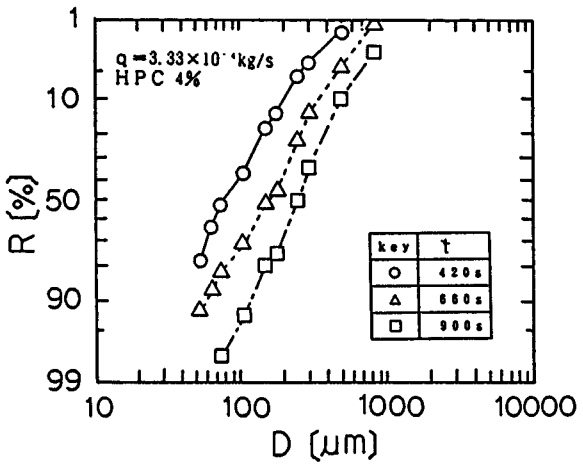

Fig. 12 Particle size distribution (fuidized bed granulation)

Figure 12, from the fluidized bed method, shows that the particle size distribution is log-normal because there was no aggregation during the initial stage. With the passage of granulation time t the particle size grew larger and sharp granules were produced, while the geometric standard deviation was maintained.

Therefore, the fluidized bed granulation process promoted by the powder particle adhesion process yields sharp granules in a log-normal distribution.

4. Conclusions

1) The fluidized bed granulation method consists of a phase to generate granules from the aggregation of small nuclear particles. These particles are produced by a liquid bridge between the powder grains, from the addition of the binding solution, and another phase. Then, larger granules are produced by secondary aggregation.

2) A high yield of fine granules with a sharp particle size distribution was obtained by completing the granulation process near a refraction point of 50% mean granule diameter D_{50}, implying that the refuraction point should be identical with the terminal point of the granulation to obtain an optimum fine granules yield.

3) The refraction point appears earlier when the binding solution is added quicker, the inspiration temperature is lower, or the spray pressure is lower. When the spray pressure is lower the humidity is higher in the fluidized bed.

4) The additive solution binder system incerases the fine granule yield of granules with a sharp particle size distribution, over a longer time span than the additive powder system. To obtain the optimum fine granule yield the concentration of the binder (HPC) should be approximately 4%.

5) The particle size distribution of granules obtained by the fluidized bed granulation method show a log-normal distribution from the initial granulation

stage, which remains unchanged and sharpens as the granulating time processes. The paricle size distribution of granules produced by the agitaion method, however, is not log-normal during the initial stage of granulation. As the granulating time progresses, a log-normal distribution appears because of the progressive crushing of aggregates.

Nomenclature

C :solution concentration, wt%
D_{50} :50% mean granule diameter,μm
t :granulatin time,sec
t_{ref} :refraction generating granulation time, sec
q :binding solution addition speed, kg/sec
Y_g :granule yield,−
Y_s :fine granule yield,−
T_{in} :inspiration temprature, K
P_{atm} :spray pressure, P_a
R :ratio of minuselectrification, %
W_B :binder content, wt%
σ_g :geometric standerd devalution,−

Refernces

1) Sagawa, Y. et al.: J. of the Society of Powder Technology, Japan, **21**(7), 3(1984).
2) Sagawa, Y. et al.: J. of the Society of Powder Technology, Japan, **21**(4),10(1984).
3) Nihon Funtai Kogyo Kyokai: "Zoryu Binran", Ohm Co., (1975).
4) Koishi: "Biryusi Sekkei", Kogyo Chyosa Kai,(1975).