# Effect of Starch Paste Concentration on Particle Size Distribution of Fine Granules Produced by Agitation Granulation

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**Particle size distribution of fine granules produced by agitation granulation was investigated as a function of the concentration of starch paste. The time course of granulation was investigated in a high speed type mixer using 5% starch paste having a good fluidity and 15% starch paste having no fluidity at all, like a gel. In agitation granulation, aggregation and deaggregation of particles and/or granules occurred simultaneously.**

**At a low concentration of starch paste, massing of the granules, namely the growth of granules, occurred mainly during the agitation granulation, since the relatively large amount of free water was available from the paste. Therefore, in this case, only the mean size shifted toward a larger measurement without any change in the width of the granules during the granulation.**

**At a high concentration of starch paste, rapid deaggregation of granules by shear force applied occurred following the formation of large granules immediately after the addition of paste. Since a small amount of water exudes from the paste during the agitation, massing proceeds slowly. This means that in the case of granulation using a high concentration of starch paste, deaggregation proceeds predominantly, so that the size distribution of the granules becomes more narrow. Fine granules may be produced by agitation granulation when a high concentration of starch paste is used and when granulation is executed under sufficient shear or rotation speed that guarantees satisfactory dispersion of the gel.**

**Key words** Starch paste, fine granules, agitation granulation, size distribution

Fine granules for use as powdered pharmaceutical are defined as those in which of more than 85% of the particles are able to pass through a 30-mesh (500 μm) sieve and remain on the a 200-mesh (75 μm) sieve, according to Japanese Pharmacopoeia.[1] On the other hand, the dispensability of fine granules has been studied by many researchers. Reportedly,[2,3] a particle size of approximately 300 μm gives an excellent result. Therefore, in the production of fine granules, the most important factor lies in how far the size distribution can be sharpened while keeping the mean size in the proximity of 300 μm.

One of the methods of producing such granules is by fluidized-bed granulation.[4-6] However, agitation granulation is still one of the most useful methods for producing fine granules, because this method is convenient, yet there have been few reports which have studied agitation granulation.[7] It is known by experience that binders play an important role in granulation. For example, in the case of starch paste, the concentration is important.[8-12] Chowhan[10] investigated the relationship between starch paste concentration and the properties of the resultant granules and tablets.

The present paper reports the results of the effect of starch paste concentration on the size distribution of the resultant granules in agitation granulation.

## Experimental

**Powder Mixture** Eighty percent lactose (powder lactose, HMS [B. V Hollandsche Melksuikerfabriek] in which more than 70% of the fraction passes through a 325-mesh sieve) and 20% cornstarch (yellow starch. Nippon Cornstarch) were mixed. This was used as the test powder mixture.

**Starch Paste** Two different concentrations of starch paste, 5 and 15% (w/w), were used. The starch suspension in water was gelatinized at 85 °C, (the degree of gelatinization, judging from the results of the previous study,[8] is inferred to be not lower than 90%.) and cooled to room temperature (*ca.* 25 °C). The 5% starch paste had good fluidity, while the 15% paste was semisolid, like a gel, and exhibited no fluidity,.

**Granulation** Using a 6-l high speed type mixer (Super Mixer™, Kawata Works), agitation was carried out at 500 rpm. Nine hundred grams of powder mixture were charged-in and mixed for 2 min prior to the addition of starch paste. Four different levels were used in the 5% starch paste series, 0.15. (water: 0.14), 0.17 (water: 0.16), 0.19 (water: 0.18), and 0.21 (water: 0.20) grams starch paste per gram of powder mixture, while three levels were used in the 15% series, 0.21 (water: 0.18), 0.24 (water: 0.20), and 0.26 (water: 0.22) grams starch paste per gram of powder mixture. About 20 g of granules were sampled at appropriate intervals and were dried for 16 h at 40 °C *in vacuo*. The size distribution of dried granules was determined by sieving through JIS standard screens after the loose aggregates were crushed to pieces by hand.

## Results

**Particle Size Distribution** The change in the particle size distribution of granules during the granulation of the powder mixture with 5% starch paste is shown in Fig. 1, and that with 15% paste is shown in Fig. 2. Although the size distribution in the case of 15% paste follows Rosin–Rammler distribution satisfactorily, no mathematical equation successfully expressed the distribution in all cases. The amount of water used for granulation was kept identical, 0.18 (g water/g powder) in both cases; therefore, the amount of paste in wet or dried base was different between the two cases.

In the case of the low concentration of paste, as shown in Fig. 1, the particle size distribution was already broad immediately after the addition of paste, and then it shifted toward larger sizes during the granulation without any change in its width. On the other hand, in the case of the high concentration paste, as shown in Fig. 2, the smaller and larger particles were rich in the initial stage, followed by a rapid deaggregation of the granules to produce finer ones, resulting gradually in sharper size distributions; finally the distribution shifted toward larger sizes without

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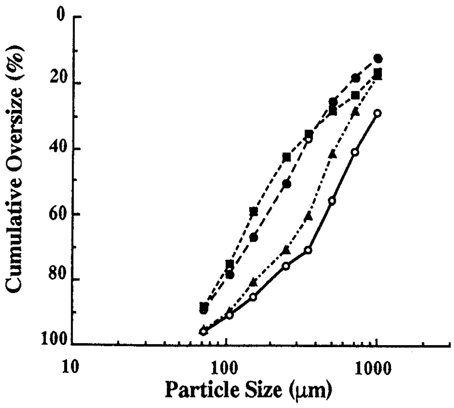


Fig. 1. Change in Granule Size Distribution during the Granulation with the 5% Starch Paste (0.19 g/g Powder)

Granulation time: ●, 1.0 min; ■, 2.5 min; ▲, 5.0 min; ○, 7.5 min.

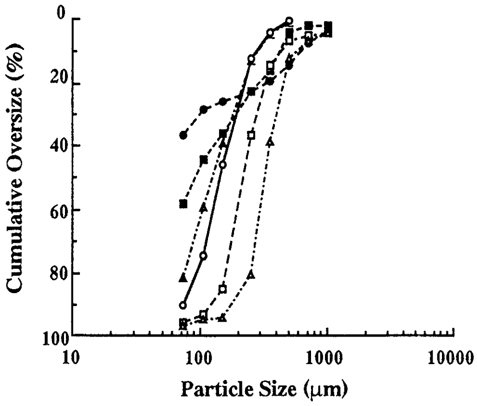


Fig. 2. Change in Granule Size Distribution during the Granulation with the 15% Starch Paste (0.21 g/g Powder)

Granulation time: ●, 1.0 min; ■, 2.5 min; ▲, 5.0 min; ○, 10 min; □, 20 min; △, 30 min.

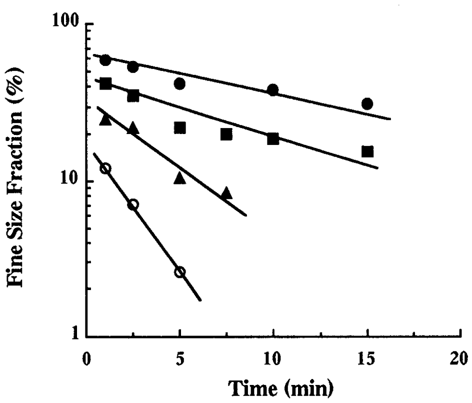


Fig. 3. Changes in the Fine Size Fraction during the Granulation with Different Amounts of the 5% Paste

Starch paste: ●, 0.15 g/g powder; ■, 0.17 g/g powder; ▲, 0.19 g/g powder; ○, 0.21 g/g powder.

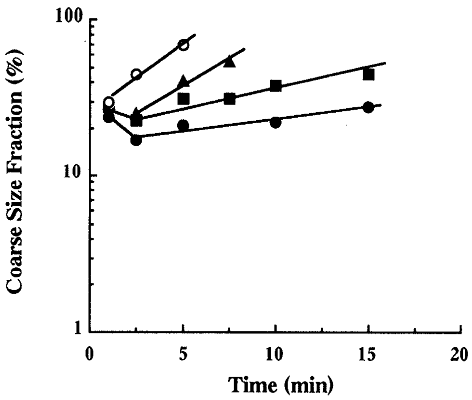


Fig. 4. Changes in the Coarse Size Fraction during the Granulation with Different Amounts of the 5% Paste

Starch paste: ●, 0.15 g/g powder; ■, 0.17 g/g powder; ▲, 0.19 g/g powder; ○, 0.21 g/g powder.

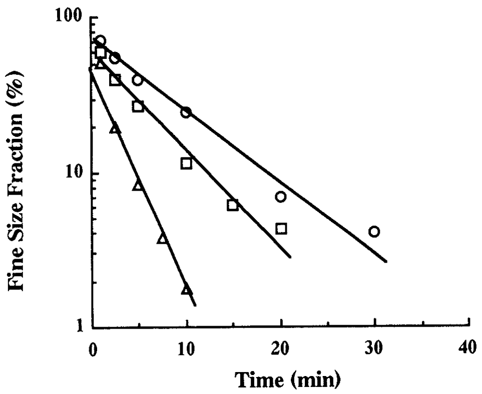


Fig. 5. Changes in the Fine Size Fraction during the Granulation with Different Amounts of the 15% Paste

Starch paste: ○, 0.21 g/g powder; □, 0.24 g/g powder; △, 0.26 g/g powder.

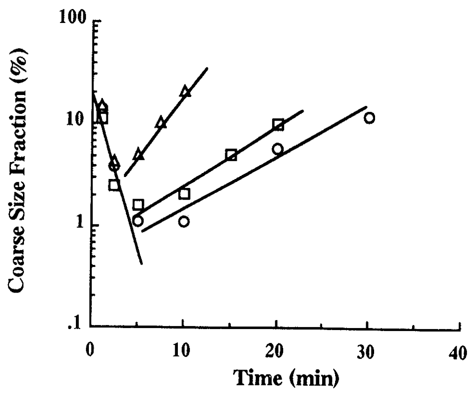


Fig. 6. Changes in the Coarse Size Fraction during the Granulation with Different Amounts of the 15% Paste

Starch paste: ○, 0.21 g/g powder; □, 0.24 g/g powder; △, 0.26 g/g powder.

changing the shape of the distribution.

**Fine and Coarse Size Fractions** Both the fine and coarse size fractions have to be minimized in order to obtain a good yield in producing fine granules by agitation granulation. Granulation using different amounts of 5 and 15% paste was carried out. The amounts of fine size fraction (smaller than 75 $\mu$m) and coarse size fraction (larger than 500 $\mu$m) were measured during the granulation.

Figure 3 shows changes in the amount of fine size fraction, and Fig. 4 shows those in the coarse size fraction when the 5% paste was used, while Figs. 5 and 6 show the corresponding changes in the 15% paste. Logarithms of fine or coarse size fractions were favorably plotted against time.

The amount of the fine size fraction decreased rapidly immediately after the addition of paste from 100% to a certain percent, and then the amount decreased linearly.

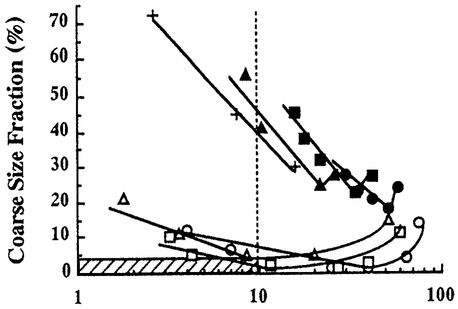


Fig. 7. Relationship between the Coarse Size Fraction and Fine Size Fraction

Starch paste: 5% paste: ●, 0.15 g/g powder; ■, 0.17 g/g powder; ▲, 0.19 g/g powder; +, 0.21 g/g powder. 15% paste: ○, 0.21 g/g powder; □, 0.24 g/g powder; △, 0.26 g/g powder.

The initial decrease and the rate of decrease thereafter became larger and faster when the amount of paste added was larger, namely, when the amount of water added was larger. The decreasing rate was at a higher concentration of starch paste than at a lower concentration of paste, even though the amounts of water added were equal.

The amount of the coarse size fraction decreased in the early stage of granulation, and then a gradual increase was observed after a certain time. Therefore, the minimum amount of the coarse size fraction was achieved at a certain time. The minimum value and the time to achieve the minimum value depended upon the amount of paste or the concentration of paste to be used. The smaller minimum value was obtained when a larger amount of paste was used or a higher concentration of paste was used for granulation. In the case of the large amount (0.21 g of paste/powder) of the 5% paste, the coarse size fraction continuously incresed even when the amount of the fine size fraction was reduced.

Figure 7 shows plots of the amount of the coarse size fraction against that of the fine size fraction.

In the case of the 15% paste, a decrease in the fine size fraction is related to a decrease in the coarse size fraction, until a minimum is exhibited when the amount of the fine size fraction is in the proximity of 10%; thereafter the amount starts to increase. If a comparison is made at identical amounts of the fine size fraction, the coarse size fraction is much smaller in the 15% paste than in the 5% paste. Thus, the requirements for fine granule preparations can only be met by the use of 15% paste under the above restricted conditions.

## Discussion

The relationship between the concentration of the paste and the particle size distribution of the resultant granules was investigated. The experimental results revealed that when compared with the 5% paste having good fluidity, the 15% paste with no fluidity gave more sharp granule size distribution.

When the paste is added to the powder mixture, the paste itself catches hold of the powder to make some large aggregates. Breakage of these large aggregates would occur by the shear force of the agitaing impeller to decrease the amount of coarse size fraction. The new surfaces caused by the breakage catch the fine powder particles so that the amount of the fine size fraction decreases at the same time. The massing of the aggregates or granules by the shear force of the agitating impeller, however, would accelerate the growth of these granules by aggregation of each other. These events take place simultaneously in the powder mass during the agitation granulation. The degree of these events would be different depending upon the concentration of the starch paste and the amount of the paste added, as well as upon the scale and agitation speed and so on.

Generally, starch is composed of amylose and amylopectin (cornstarch contains about 27% of amylose[13]). When the water suspension is heated above a critical temperature, the amorphous portions swell and assume gigantic networks, which contribute to an increase in viscosity.

In the 5% paste, the amount of water is enough for starch to assume its utmost swollen network structure. The excess water can be easily squeezed from the paste. On the other hand, in the case of the 15% paste, starch cannot reach its maximum swollen state due to insufficient water content, and most of the water would be kept in the partially swollen network structure of starch. Only a small amount of water is available from the paste.

During agitation granulation, the crushing of particles by shearing and the growth of particles by compaction are considered to proceed simultaneously.

In the 5% starch paste, the rich free water content allow the simultaneous occurrence of particle destruction by shearing and particle growth by compaction, leading to a broadened particle size distribution.

In the 15% starch paste, on the other hand, granulation is difficult because most water is entrapped in the starch particles, and therefore particle destruction can occur due to shearing. Thus, at the initial stage of granulation, dispersion of the binder is considered to occur principally, leading to a sharp particle size distribution. Afterwards, compaction gradually forces out intraparticular water, thus granulation progresses slowly. Namely, particle destruction by shearing that precedes particular growth by compaction is inferred to be the cause of sharpened size distribution.

### References

1) The Japanese Pharmacopoeia, Twelfth Edition, A96 (1991).
2) Aoki M., Fukuda T., *Yakuzaigaku*, **27**, 189 (1967).
3) Kozatani J., Kitaura T., *Yakuzaigaku*, **29**, 53 (1969).
4) Shinoda Y., Nasu T., *J. Pharm. Sci. Technol. Jpn.*, **36**, 83 (1976).
5) Nishimura K. Kakizawa H., *J. Pharm. Sci. Technol. Jpn.*, **38**, 196 (1978).
6) Watano S., Miyanami K., *Chem. Pharm. Bull.*, **42**, 133 (1994).
7) Terashita K., "Handbook of Granulation," ed. by Japan Society of Powder Technology, Ohm Publishing, Co., 1991, p. 379.
8) Makino T., Kitamori N., *Chem. Pharm. Bull.*, **43**, 473 (1995).
9) Philip M., *J. Pharm. Sci.*, **65**, 313 (1976).
10) Chowhan Z. T., *J. Pharm. Sci.*, **65**, 1561 (1976).
11) Schubair M. S., Dingwell D., *Manuf. Chemist. Aerosol News*, **47**, Oct., 52 (1976).
12) Schubair M. S., Dingwell D., *Manuf. Chemist. Aerosol News*, **47**, Nov., 43 (1976).
13) Nikuni J., "Handbook of Starch," Asakura Publishing, Tokyo, 1980, p. 300.