Behavior of Pregelatinized Starch during Granulation and Its Influence on Tablet Properties

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Using pregelatinized starch as a binder, fluidized-bed granulation and agitation granulation were attempted to investigate the behavior of starch and to examine its relationship with the resultant tablet properties (hardness and disintegration). The amounts of soluble starch before and after granulation were measured. Also, hardness and the disintegration time of the resultant tablets were measured. In fluidized-bed granulation, the soluble starch content did not change noticeably during granulation, thus exerting no influence on tablet properties. On the other hand, in agitation granulation, the soluble starch content increased, so that the disintegration time of the resultant tablets was prolonged. This may be because the soluble starch increased during agitation granulation due to a large shearing force and inhibited water penetration into the tablet and/or because some changes occurred in the swelling properties of the pregelatinized starch.

Therefore, when pregelatinized starch is used as a binder, the fluidized-bed method is recommended to consistently obtain satisfactory tablet properties.

Key words pregelatinized starch; fluidized-bed granulation; agitation granulation; soluble starch; tablet hardness; disintegration time

Partially pregelatinized starch as an excipient for solid dosage forms is still widely used. To exemplify commercially available products, PCS (Asahi Chemicals)[1] is a physically denatured cornstarch, an excipient of natural origin, and is used in tablet production as an additive such as a binder, disintegrant, or absorbant. Starch 1500 (Nippon Colorcon)[2] is also an excipient meeting the requirements specified under Partially Pregelatinized Starch in Japanese Pharmaceutical Excipients.[3] Since pregelatinized starch acts not only as a binder but also as a disintegrant, it is incidentally called an all-purpose excipient. However, it is known that this substance frequently causes variations in tablet properties, depending on the method and conditions of granulation.[4] Especially, when a high-speed mixer is used for granulation, a large shearing force is thought to be applied to the wet mass, leading to large power consumption and the elevation of temperature during granulation.[5] This shearing force and/or the elevation of temperature may cause changes in the degree of gelatinization of pregelatinized starch.

The present paper reports the results obtained from a study wherein pregelatinized starch was used as an excipient to investigate the relationship between the degree of gelatinization of the starch in the granules during fluidized-bed granulation or agitation granulation and the properties (hardness and distintegration time) of the resultant tablets.

Experimental

Samples Six parts of lactose (DMV 200#), three parts of phenacetin (Yamamoto Chemical), and one part of PCS (Asahi Chemical) or Starch 1500 (Nippon Colorcon) or Amicol C (Nichiden Chemical) were used.

Granulation/Mixing/Tableting In fluidized-bed granulation, 500 g of powder was granulated in a small fluidized-bed granulator (FS-35, Powrex). The conditions applied were: spraying rate of 15 g/min (water added: 300 ml), spraying pressure of 1 kg/cm^2, and temperature of inlet air at 80 °C. After drying, the granules were milled with a hammer mill (Power Mill P3-S, Showa Chemical Works) equipped with a 1.5-mm i.d. screen. In agitation granulation, 1 kg of powder was granulated using a Henschel type mixer (Vertical granulator VG-10, Powrex) for 5 min. The conditions applied were: rotation of 500 rpm and amounts of solution varying from 100 to 180 ml. After granulation, the wet mass was vacuum-dried (40 °C, 5 to 10 mmHg, 16 h), followed by milling as in the case of fluidized-bed granulation. The mean particle diameter was 200 to 300 μm in fluidized-bed granulation and 300 to 400 μm in agitation granulation.

The dried granules were mixed with magnesium stearate for 3 min in a tumbler mixer (TM-15, Showa Chemical Works).

Tableting Tablets each weighing 200 mg, 8 mm i.d. in diameter and 12R, were produced using a rotary tableting machine (Correct Pure Press 19K, Kikusui). The tableting pressures varied from 800 to 2000 kg/cm^2.

Evaluation 1) Amount of Soluble Starch[6]: a) Calibration Line for Soluble Starch Content of Each Pregelatinized Starch: One gram of each pregelatinized starch was added to 50 g of distilled water, which was stirred with a magnetic stirrer for 10 min. Subsequently, this mixture was filtered with filter paper (Toyo Advantec No. 5C) to obtain a filtrate containing soluble starch. Using the residue on drying from about 40 g of the filtrate (dried out at 105 °C, followed by another 1 h of drying), the soluble starch content of each pregelatinized starch was obtained. The filtrate was serially diluted with distilled water by which the soluble starch content was changed stepwise. Thirty microliters of iodine testing solution was added to each solution, and absorbance at 660 nm was measured by spectrophotometry (0.2 iodine and 2.0% potassium iodide as an aqueous solution).

b) Soluble Starch Content of the Granules: Ten grams of granules (corresponding to 1 g of each pregelatinized starch) was dispersed in 50 ml of distilled water using a magnetic stirrer for 10 min. The filtrate was diluted with distilled water. The concentration of soluble starch was calculated by the iodine coloration method, which was followed by the calculation of soluble starch per unit weight of each pregelatinized starch.

2) Table Properties: a) Hardness: The tensile strength of tablets was measured using a hardness tester (TH-203CP, Toyama Sangyo). The mean value of ten measurements was used.

b) Disintegration Time: Following the procedures specified in the Japanese Pharmacopoeia, the disintegration time of tablets in water was measured on a disintegration tester (NT-2HS, Toyama Sangyo). The mean value of the six measurements was calculated.

Results and Discussion

Determination of Soluble Starch Soluble starch, as reported by Nikuni,[6] is a water-soluble component of

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starch having been freed from mutual molecular association (hydrogen bonds), which consists mainly of amylose and low molecular-weight amylopectin resulting from the gelatinization of starch. Gelatinization is a process of enzymatic attack undergone by starch by the glucoamylase method, and this implies an increase in the degree of swelling and amorphousness due to the loosened molecular network.

Thus, soluble starch can be an indicator of gelatinization. A calibration line for soluble starch content against absorbance was calculated for each pregelatinized starch.

PCS	$Y=1.04X+0.03$ $(r=0.989)$
Starch 1500	$Y=1.81X-0.02$ $(r=0.995)$
Amicol C	$Y=2.09X-0.01$ $(r=0.997)$

Y (absorbance), X (soluble starch %)

Although a linear relationship between absorbance and soluble starch content was obtained, the slopes differed depending on the type of pregelatinized starch used. It was found that, under the assumption that no change occurs in the molecular weight distribution and branching molecular structure of starch during granulation, the amount of soluble starch can be calculated.

Contents of Soluble Starch before and after Granulation Figures 1 and 2 illustrate the difference in the content of soluble starch before and after the two modes of granulation.

In the fluidized-bed granulation, the soluble starch content in each pregelatinized starch did not noticeably change during granulation. Since no shearing force was applied in the wet state to the granules, further gelatinization of the pregelatinized starch did not occur.

In agitation granulation, on the other hand, the soluble starch content in each pregelatinized starch was remarkably increased during granulation. This may be due to the shearing force applied during granulation to pregelatinized starch, which caused some damage, leading to enhanced gelatinization. Thus, in the case of highly gelatinized Amicol C, additional molecular cleavage will occur to increase the soluble starch content.

Relationship to Tablet Hardness Figures 3 and 4 exhibit the relationship between tableting pressure and the hardness of tablets made from granules by different granulation methods.

The relationship between the degree of gelatinization and the hardness of the resultant tablets has already been reported[7]; the hardness of tablets was found to lead to a plateau above a certain level of gelatinization degree. In this study also, little difference was detected among each of the partially gelatinized starches. A difference in hardness was noted exclusively within the low-pressure region in the agitation granulation. The particle size of pregelatinized starch may be one of the contributing factors.

Relationship between Tablet Hardness and Distintegration Time Figures 5 and 6 show the relationship between tablet hardness and disintegration time.

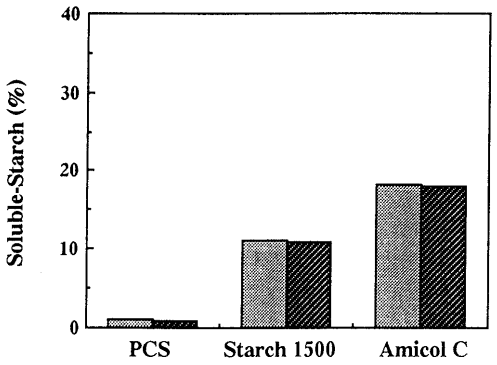

Fig. 1. Content of Soluble Starch in the Granules Produced by Fluidized-Bed Granulation

▩, before granulation; ▨, after granulation.

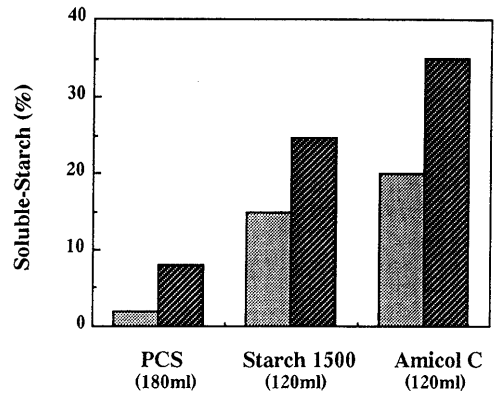

Fig. 2. Content of Soluble Starch in the Granules Produced by Agitation Granulation

▩, before granulation; ▨, after granulation. ( ): Amount of paste.

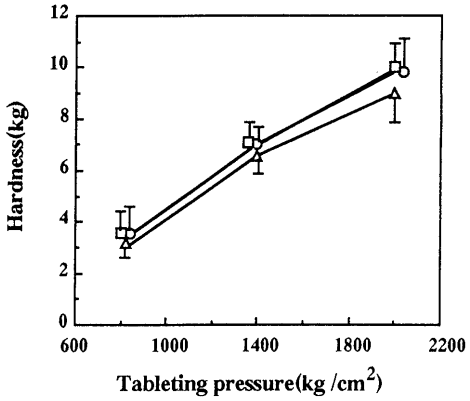

Fig. 3. Hardness of Tablets Made from Granules by Fluidized-Bed Granulation

○, PCS; □, Starch 1500; △, Amicol C. Mean±S.D.

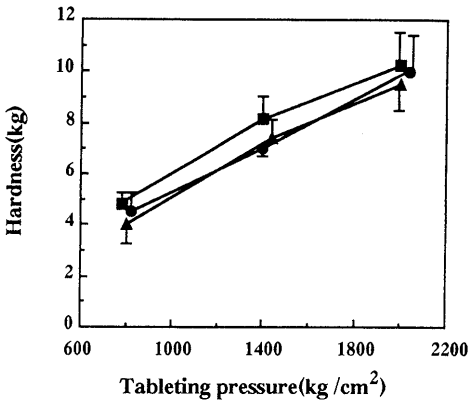

Fig. 4. Hardness of Tablets Made from Granules by Agitation Granulation

●, PCS; ■, Starch 1500; ▲, Amicol C. Mean±S.D.

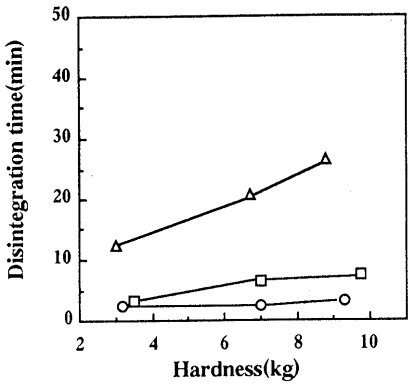

Fig. 5. Hardness of Disintegration Time for Tablets Made from Granules by Fluidized-Bed Granulation

○, PCS; □, Starch 1500; △, Amicol C.

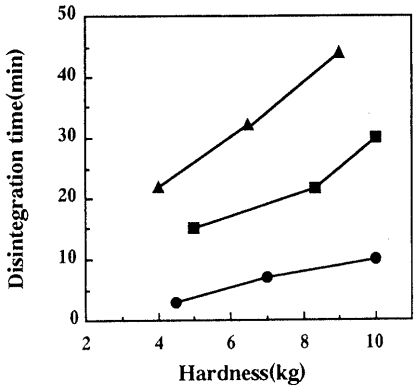

Fig. 6. Hardness and Disintegration Time for Tablets Made from Granules by Agitation Granulation

●, PCS; ■, Starch 1500; ▲, Amicol C.

Regarding the influence of granulation method on tablet properties, the effect of hardness on disintegration time was less in fluidized-bed granulation. This is considered to be associated with the amount of soluble starch generated by the damage to the gelatinized starch during granulation.

Additionally, with respect to the type of pregelatinized starch, the use of PCS slightly prolonged tablet disintegration time due to an increase in tablet hardness. With formulations including Starch 1500 or Amicol C, an increase in tablet hardness resulted in prolonged disintegration time. This was probably because soluble starch increased during the granulation process and inhibited water penetration into the tablet,[8] and because some changes occurred in the swelling/disintegrating properties of the pregelatinized starches.

Relationship between the Content of Soluble Starch and Tablet Disintegration Time The relationship between the content of soluble starch and tablet disintegration time is shown in Fig. 7.

As seen in Fig. 7, a positive correlation exists irrespective of the granulation method or the type of pregelatinized starch used. As the soluble starch content increased, the disintegration time of the resultant tablets was prolonged.

It is suggested that the decrease in the rate of water penetration into the tablet due to the dissolution of soluble starch, as well as changes in the swelling property

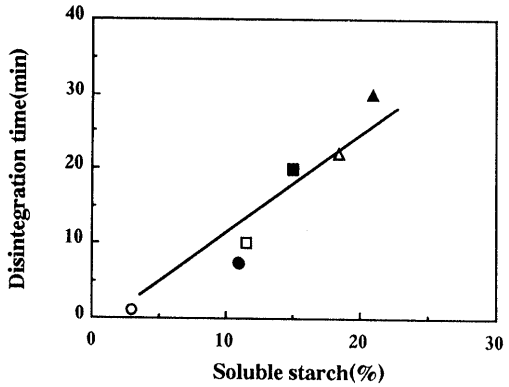

Fig. 7. Relationship between the Content of Soluble Starch and Disintegration Time of Tablets Made from Granules by Fluidized-Bed Granulation and Agitation Granulation

Tableting pressure: 1400 kg/cm^2. Fluidized-bed granulation: ○, PCS; □, Starch 1500; △, Amicol C. Agitation granulation: ●, PCS; ■, Starch 1500; ▲, Amicol C.

of the pregelatinized starch itself, was the rate determining factor in the disintegration behavior of the tablet.

PCS exhibits larger swelling/disintegrating properties and a smaller increased content of soluble starch due to the resistant particle shell structure against the shearing force applied externally.

The several facts mentioned above have hitherto been known as precautions to take when using a pregelatinized starch as an excipient. However, when pregelatinized starch is to be used as an effective excipient, granulation should be carried out under a condition which avoids gelatinization completely rather than simply controlling the degree of gelatinization.

Conclusions

The behavior of starch in the formulation containing pregelatinized starch during fluidized-bed and agitation granulation has been investigated. It was found that in fluidized-bed granulation, practically no change in the soluble starch content occurred during granulation, and the tablet properties did not change; however, in agitation granulation, the content of soluble starch increased during granulation, which caused a prolongation of the disintegration time of the tablets produced. In this case, it may be considered that the large shearing force applied damaged the pregelatinized starch during granulation and facilitated gelatinization, resulting in an increase in adhesiveness. Therefore, the proper use of pregelatinized starch in tablet formulation should be taken into considerartion in selecting the method and conditions of granulation.

References

1) Kamata E., Miyamoto H., *Avicel Review*, **44**, 2 (1986).
2) Schwartz J. B., Martin E. T., *J. Pharm. Sci.*, **64**, 328 (1975); Chilankurti R. W., Rhodes C. T., *Drug Develop. & Indust. Pharm.*, **8**, 63 (1982).
3) "Japanese Pharmaceutical Excipients," Yakuji-Nippo, Tokyo, 1993, p. 270.
4) Kamata E., Miyamoto H., *Avicel Review*, **51**, 2 (1993).
5) Holm P., Schaefer T., Kristensen H. G., *Powder Technol.*, **43**, 213 (1985).
6) Nikuni J., Editorial supervision, "Handbook of Starch Science," Asakura Publishing, Tokyo, 1980, p. 174.
7) Makino T., Kitamori N., *Chem. Pharm. Bull.*, **43**, 514 (1995).
8) Lowental W., *J. Pharm, Sci.*, **61**, 1695 (1972).