# Effect of Starch Paste Preparation Temperature in Fluidized-Bed Granulation on Resultant Tablet Properties

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**An Onlator®, a heat exchanger, was utilized as a continuous starch paste supplier for a fluidized-bed granulator. Ascorbic acid was used as a model drug substance and cornstarch as the binder. To control the temperature of cooking starch paste, modes of proportional control (P control) and proportional integral deviation (PID control) were used to distinguish their respective effects on the tablet properties. It was shown that the PID control caused less variation in the temperature of cooking starch paste and, in accordance with this, that variation in disintegration time for the resultant tablets was less. There was, however, little difference in tablet hardness between these two modes of control.**

**Key words** starch paste; fluidized-bed granulation; PID control; tablet disintegration time; hardness

The wet granulation technique must still be used to prepare numerous formulations, especially those containing drugs with a high bulk density, poor compressibility, or poor flowability. For example, high-content ascorbic acid tablets were manufactured by wet granulation procedure mainly because of their poor compressibility.[1)]

Fluidized-bed granulation for pharmaceutical coating was developed by Wurster[2,3)] and has been applied to the production of granules for tableting intended for various pharmaceutical products. One advantage of fluidized-bed granulation is its improvement in the compressibility due to the added binder which coats individual powder particles, and also the good flowability attained with the uniform-sized granules formed. From this viewpoint, increasing attention is presently being focused on fluidized-bed granulation for producing granules intended for use in the manufacture of tablets.

Several devices for fluidized-bed granulation have recently been reported to produce better granules: for example, a fluidized-bed granulator equipped with an agitation blade on the bottom of a cylindrical vessel,[4)] and moisture control methods during granulation.[5)]

In many cases, fluidized-bed granulation is carried out in a batchwise manner similarly to other conventional granulation techniques. The fluidization process in tablet granulation on a continuous basis has been reported in several articles.[6,7)] In these systems, however, the binder solution had to be prepared on a batchwise basis, and this batchwise preparation of binder solution required a large-capacity tank.

Starch paste is widely used as a binder for making granules for tablet manufacture owing to its superior characteristics. Actually, in the granulation of ascorbic acid powders, the use of starch paste binder is recommended because of compatibility in formulation.[1)] In starch pastes, cooking temperature or the degree of gelatinization can affect the properties of the resulting tablets.[8)]

The present report is the results obtained from a study wherein a fluidized-bed granulator was connected, at the production site, with a continuous starch paste preparation unit (Onlator®) to produce ascorbic acid granules for tableting.The conditions of starch paste preparation were investigated through a comparative experiment with special reference to the temperature control by proportional (P) and proportional integral deviation (PID) control.

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## Experimental

**Materials** Table I shows the composition of the present vitamin C tablet formulation.

Ascorbic acid and sodium ascorbate used were the regular powders manufactured by Takeda Chemical Industries, Ltd. Cornstarch used as the binder was supplied by Nippon Cornstarch, and magnesium stearate as the lubricant by Sakai Kagaku.

**Granulation System** A schematic diagram of the fluidized-bed granulation system is shown in Fig. 1. The system consists of a fluidized-

TABLE I. Formulation of Vitamin C Tablet

| Ingredient | Amount charged-in (kg) | |
|---|---|---|
| Ascorbic acid | 87.5 | |
| Sodium ascorbate | 87.5 | |
| Corn starch | 31.01 | |
| Corn starch | 3.15 | Paste |
| Water | 64.4 | Paste |
| Magnesium stearate | 0.84 | |

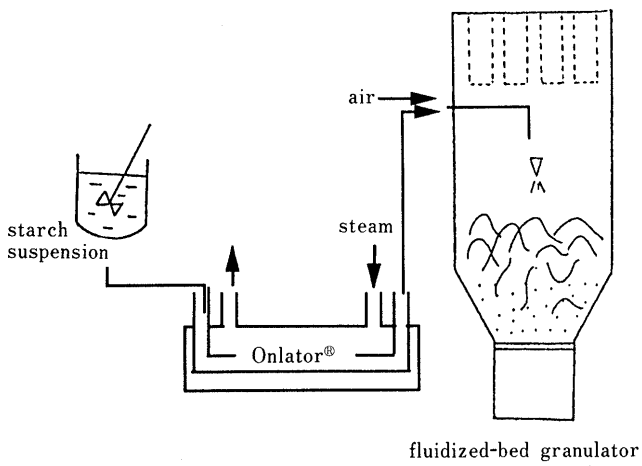


Fig. 1. Flowchart for Production

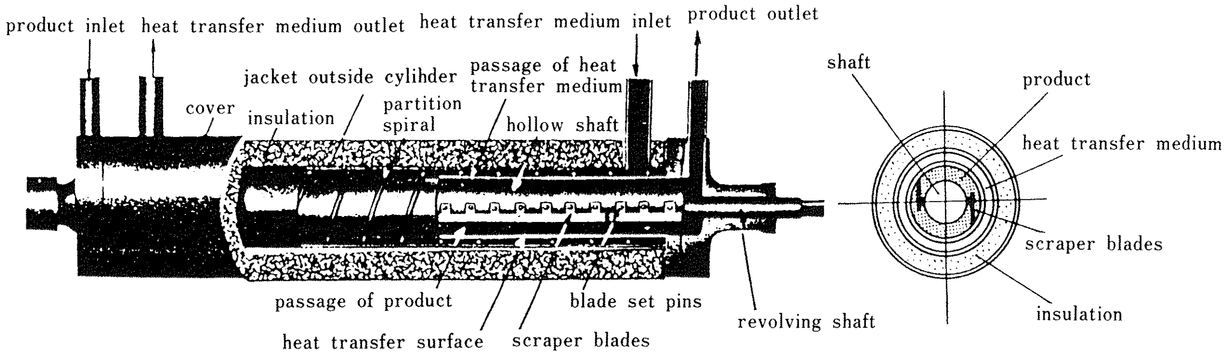


Fig. 2. Structure of Onlator®

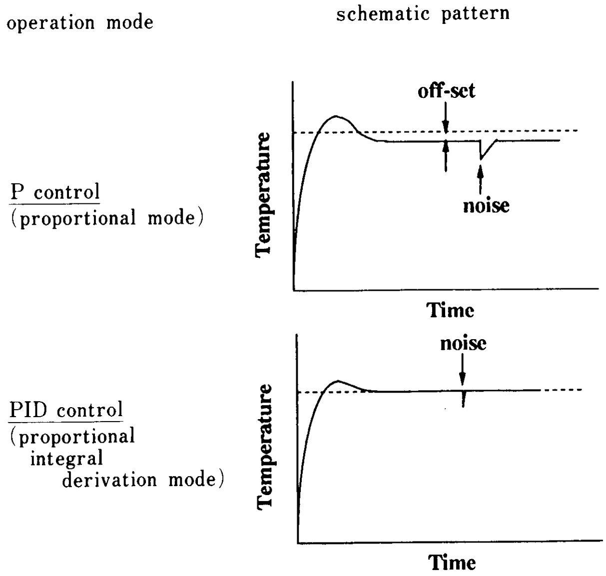


Fig. 3. Operation Mode and Characteristics of Temperature Control Unit

bed granulator, a heat exchanger for cooking starch paste, a mixing tank for preparing a starch suspension, and a pump to feed the starch suspension from the mixing tank to the heat exchanger.

**Preparation of Starch Paste** Purified water was poured into the mixing tank. Cornstarch was subsequently added under stirring to make a 6% (w/w) suspension. The suspension was pumped into the heat exchanger to convert it into starch paste, which was sprayed into a fluidized-bed granulator.

**Temperature Control for Preparing Starch Paste** The structure of the heat exchanger, Onlator® (HAX-1008, Sakura Seisakusho), is illustrated in Fig. 2. This system is composed of a cylinder with a revolving shaft and a jacket. The heat transfer medium used was steam. The temperature of starch paste was determined by a thermister set at the outlet of the cylinder, and the steam volume was controlled by the thermister setting to maintain the temperature of the starch paste at 75 °C.

Figure 3 shows the operation mode and characteristics of the temperature control unit.

The conventional mode of control is proportional control (P control), wherein the corrective action taken is proportional to the deviation from the preset temperature. However, this system has drawbacks in that small deviations are apt to occur in temperature control and that corrective action cannot catch up with an abrupt rise or fall in temperature as noise. On the other hand, the recent trend is to adopt a more precise control termed proportional integral deviation (PID control) comprising integral correction action (I Action (No. offset)) and derivation action (D Action (No. noise)) in combination with proportional control. The present study compared P control and PID control (Yamatake Honeywell).

**Granulation** A fluidized-bed granulator (Model STRE-M6, Powrex) was used. Table II shows its operating conditions. The dried granules were passed at 2000 rpm through a cutter mill(Powermill, Model P-7; Showa Kagaku) equipped with a 1.2 mm sieve. Three batches of granules obtained were mixed with magnesium stearate in a tumbler mixer (Model TM3; Showa Kagaku) for 5 min.

Table II. Operating Conditions for Fluidized-Bed Granulation

| | |
|---|---|
| Temperature of inlet air | 90 °C |
| Flow rate | 70—100 $m^3$/min |
| Spray rate | 1800 ml/min × 2 guns |
| Air pressure for spraying | 5 kg/$cm^2$ |
| Temperature of final outlet air | 65 °C |
| Temperature of final product | 70 °C |

**Compression** Tablets 300 mg in total weight, 8.5 mm in diameter and 3.70 mm in thickness were compressed on a rotary tablet machine (Clean Press D67, Kikusui Seisakusho) at 45 rpm.

**Evaluation** Disintegration Time: Disintegration time was measured with a disintegration tester (Model T-2H; Toyama) following the procedure specified under Disintegration in Japanese Pharmacopoeia (JP XII). The medium was water, without the use of a disc.

Hardness: Hardness of 10 tablets was measured on a hardness tester (TH-204K; Toyama).

## Results and Discussion

**Modes of Control Systems** The control chart for inlet and outlet air temperatures and temperatures of starch paste under P and PID control modes during three consecutive batches is shown in Fig 4. In the conventional system of P control, the cooking temperature of starch paste, preset at 75 °C, showed a variation of $\pm 5$ to 7 °C, all 3 batches exhibiting a similar pattern. In PID control, variation in the temperature, preset at 75 °C, fell within the range of $\pm 2$ °C, indicating much greater control of the cooking temperature.

**Mode of Control and Tablet Disintegration Time** Variation in cooking temperature of starch paste caused by two different modes of temperature control is predicted to affect the resultant tablets. Variation in tablet disintegration time is shown in Fig. 5. The first 30 lots were processed under P control, while the remaining lot Nos. 31 to 60 were processed under PID control. Although the disintegration time for all these lots met the requirement specified in JP XII (within 30 min), the mean of disintegration time and variation in PID control were greatly reduced when compared with P control. Inter- and intralot variations also were found to be smaller in PID control. This means that the control of paste temperature exerts a great influence on the disintegration time of the resulting tablets. It should be noted that in this study variation in the conditions for starch paste preparation directly in-

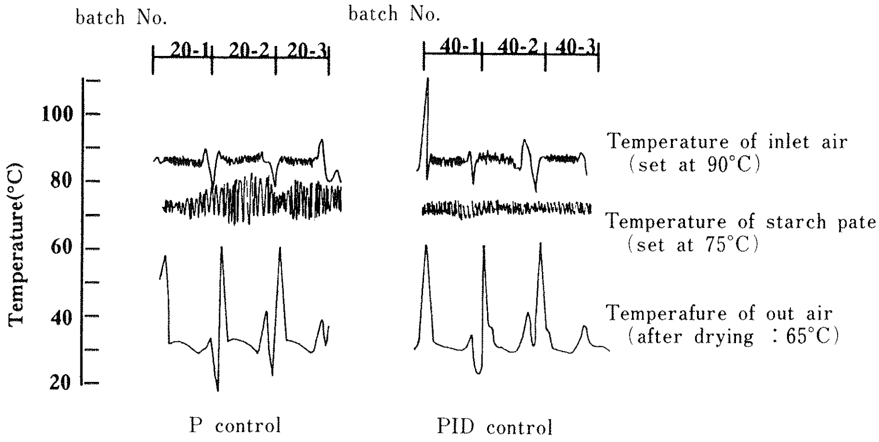


Fig. 4. Variation in Starch Paste Temperature by Control Mode

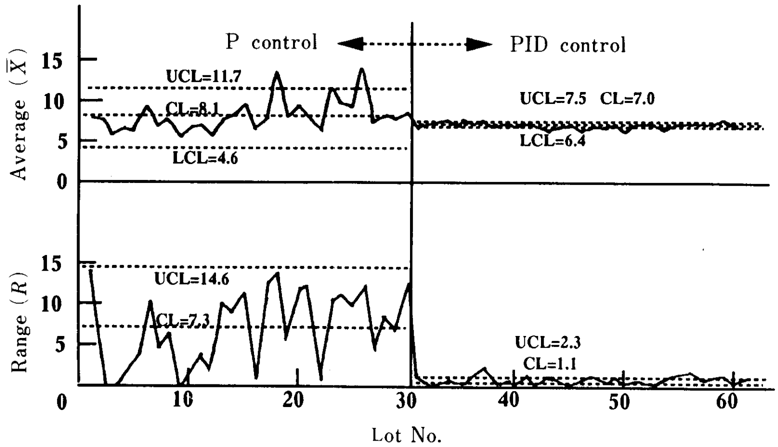


Fig. 5. Variation in Tablet Disintegration Time

USL, upper control limit; CL, central line; LCL, lower control limit.

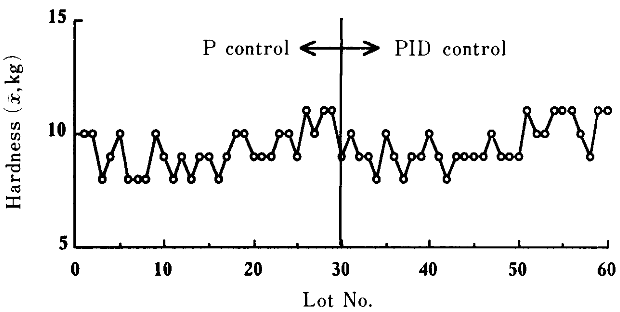


Fig. 6. Variation in Tablet Hardness

fluenced the properties of tablets produced from the resultant granules. This was considered especially remarkable in the fluidized-bed granulation because, by this technique, all particles are uniformly coated with the binder. As has been reported previously,[8] this again means that the disintegration time depends on the starch paste preparation temperature, or gelatinization degree, and it is inferred that variation in disintegration time is a function of how the adhesive layer is formed over starch particles.

**Mode of Control and Tablet Hardness** Figure 6 shows the hardness of the tablets prepared. No difference in hardness between the modes of control is detected. This is probably because, as has been reported previously,[8] the relationship between the cooking temperature of starch paste and the tablet hardness includes a plateau above 75 °C. The advent of this plateau may reflect the saturation of amylopectin, the binding power[9] of gelatinized starch, when the temperature rises (to 75 °C).

**Summary** It was found that a control system utilized on the actual production site to regulate the cooking temperature of starch paste caused significant variation in the disintegration time of the resultant tablets. By PID control, variation in the cooking temperature of starch paste became less, and variation in disintegration time and inter- and intralots was also reduced significantly.

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