Application of Tumbling Melt Granulation (TMG) Method to Prepare Controlled-Release Fine Granules

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The tumbling melt granulation (TMG) method was applied to prepare controlled-release fine granules of diltiazem hydrochloride (DH). The entire process, from the preparation of the cores by the adherence of DH to the sucrose crystal to the subsequent coating of the controlled-release layer, was performed without using any solvent. A mixture of meltable material, talc, and ethylcellulose was used for the controlled-release layer and controlled-release fine granules approximately 400 μm in diameter were obtained with excellent producibility. The dissolution rate of DH from these fine granules was similar to that of a once-a-day dosage form obtained in the market; further, the dependency of the dissolution profile on pH of the media was less. Thus, it was concluded that this TMG method was very useful for preparing not only controlled-release beads of granule size (usually 500 to 1400 μm) but also fine granules.

Key words fine granule; tumbling melt granulation; wax; controlled-release; centrifugal fluidizing granulator

Fine granules (usually less than 500 μm) are very popular dosage forms in Japan since their moderately small size and good fluidity make them easy to administer to the patients. Thus, controlled-release (CR) fine granules could be useful especially for the elderly patient due to ease of administration, reduction in dosing frequency, and increased patient compliance.[1] Most CR preparations on the market, however, have been developed as tablets or granules, and there are very few fine granules because the preparation of CR fine granules is technically difficult due to the smaller particle size and the larger specific surface area.[2,3]

Some researchers have prepared them by spray congealing,[1] but their structure was of the matrix system which seemed hard to apply to highly water soluble drugs. To sufficiently suppress the drug release, the coating of hydrophobic materials on the core beads seemed to have many advantages over the matrix system. But the fine granules of this reservoir type required more coating than larger granules to achieve a given film thickness and thus the coating process took much time. In addition, fine granules easily agglomerate in a coating process when the conventional spraying method with polymer solution or molten wax is used. Such technical difficulties should be overcome to formulate CR fine granules.

In previous papers,[4] we showed that the tumbling melt granulation (TMG) method, a simple powder coating method which used no solvent, was advantageous in the preparation of CR beads of granule size (usually 500 to 1400 μm). This method did not require much time for the coating process and the CR beads obtained had sufficient suppression ability of the dissolution rate. Powders with various properties could adhere to the core material. The method, therefore, seemed to offer an effective way to overcome the difficulties accompanying the preparation of CR fine granules. We then attempted to apply this technique to the preparation of CR fine granules.

Experimental

Materials Diltiazem hydrochloride (DH: Tanabe Seiyaku, Osaka, Japan) was of JP grade. DH was used after being ground in a hammer mill. Sucrose crystals (105—177 μm; Ensuikou Seito, Yokohama, Japan) were used as seed materials. As a meltable material, hydrogenated rape oil (HRO) of JP grade (mp 70 °C, Kawaken Fine Chemical, Tokyo, Japan) was used. HRO was passed through a 200-mesh sieve (74 μm) by a Turbo Screener (Turbo Kogyo, Yokosuka, Japan). Talc (D_{50}, 11 μm; Nippon Talc, Japan) and ethylcellulose (#10; D_{50}, 4.5 μm; Shin-Etsu Chemical Co., Ltd., Japan) were the non-meltable materials used . The former was JP grade and the latter was JPE grade. Both powders were used without further treatment.

Preparation of CR Fine Granules Five hundred grams of sucrose crystal were placed on a centrifugal fluidizing (CF) granulator and heated to a bed temperature at 80 °C (at least 5 °C higher than the melting point of HRO). The mixture of HRO and DH was gradually and continuously fed onto the seed (sucrose crystal), keeping the bed temperature at 80 °C. After the feeding of the mixture had been completed, the coated beads were driven for another 5—10 min. The hot beads were then taken out of the CF granulator and cooled at room temperature. These core fine granules were again put back in the CF granulator and coated with a mixture of ethylcellulose, talc, and HRO as done in the preparation of the core granules.

Evaluation of Producibility Producibilities of the core granules and the coated fine granules were estimated by the recovery % of the coating mass (Rec%) and the yield % of single core granules (Ysc%, fraction ranged from 105 to 500 μm) against the charging amount.

Dissolution Test A dissolution test was carried out according to the paddle method of JP XIII in purified water, the 1st fluid (pH 1.2), the 2nd fluid (pH 6.8), and pH 7.5 buffer described in the disintegration test of JP IX.

Electron Probe Microanalysis A scanning electron microphotograph of cross-section of the CR fine granules and the corresponding relative distribution map of the drug (DH) and CR layers were examined using an electron probe microanalyzer equipped with a wavelength dispersive X-ray spectrometer (EPMA-8705, Shimadzu Co., Ltd., Kyoto, Japan). The CR fine granules were embedded in wax and sliced to give a cross-sectional view. The drug and CR layers contained hydrochloride and talc, respectively, so that the X-ray characteristics of chlorine and magnesium were emitted and selectively detected. The emitted X-rays were depicted on the microphotograph as dots.

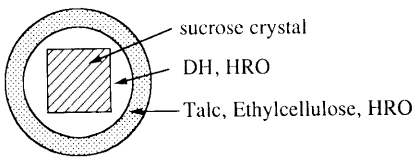

Fig. 1. Structure of CR Fine Granules of DH

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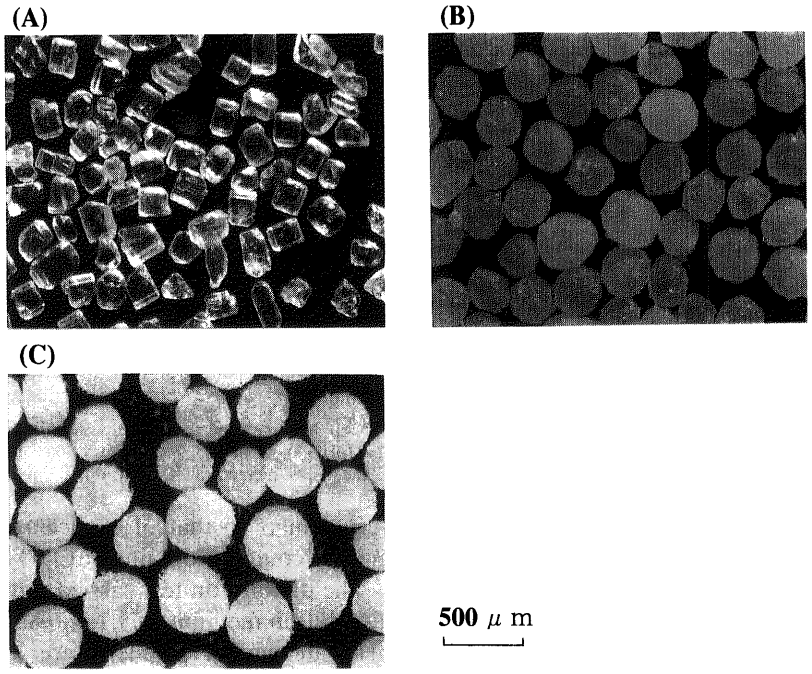

Fig. 2. Microphotographs of Seed Material, Core Fine Granules, and CR Fine Granules

(A), seed materials; (B), core fine granules; (C), CR fine granules at 100% coating level. Microphotographs were taken by an optical microscope (Type SZH: Olympus, Tokyo, Japan).

Table 1. Producibility of DH Core and Controlled-Release Fine Granules

	Rec (%)	Ysc (%)
DH core fine granules	98.9	97.5
DH controlled-release fine granules	99.1	98.2

Results and Discussion

Preparation of CR Fine Granules DH was used as a model drug since it is a highly water soluble drug, and suppression of the dissolution rate is not easy. Further, many CR preparations of DH have been supplied to markets worldwide, and comparison of the dissolution rate with other products in the market seemed easy.

The structure of the CR fine granules of DH is schematically shown in Fig. 1. To reduce the core granule size, sucrose crystal (105—177 μm) was employed as a seed material instead of nonpareil as used in previous studies. The mixture of DH and HRO was first layered on the sucrose crystal to prepare the core fine granules. Then, a coating mixture of ethylcellulose, talc, and HRO (weight ratio, 40:40:20) was applied by the TMG method. Here, ethylcellulose and talc had hydrophobic properties and were expected to efficiently suppress the release rate.

The yields of the spherical core and CR fine granules were over 95% (Table 1) showing that the producibilities were excellent.

Optical microphotographs of the seed material, the core fine granules, and the resultant CR fine granules are shown in Fig. 2 and distribution of their particle size in Fig. 3. Although the original shape of the sucrose crystal was almost cubical, the core and CR fine granules were spherical. Both had a very narrow particle size distribution, the mean being approximately 300 and 400 μm, respectively.

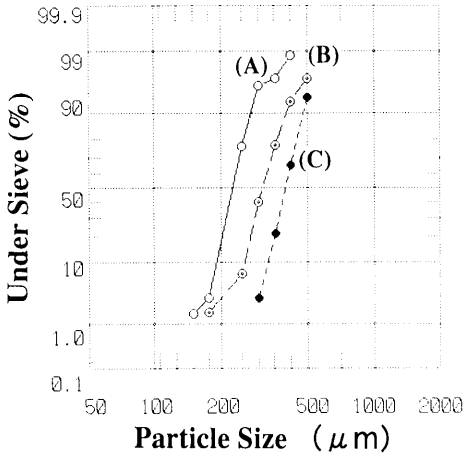

Fig. 3. Particle Size Distribution of Seed Materials, Core Fine Granules, and CR Fine Granules

(A), (B), and (C) correspond to Fig. 2, respectively.

An electron probe microanalysis of the cross-section of the resultant CR fine granules is shown in Fig. 4. While the boundary between the drug and CR layers was unclear in the SEM microphotograph, it is much clearer on the dot map. The structure of the resultant CR fine granules was almost the same as that shown in Fig. 1 schematically, suggesting that the producibility was excellent.

Dissolution Behavior of CR Fine Granules The dissolution profiles of DH from the CR fine granules coated with various coating levels were determined in purified water (Fig. 5).

The dissolution rate decreased as the coating level increased, and the suppression ability of the release rate was shown to be adequate, although the particle size was much smaller than that of the beads (usually 500 to 1400 μm). It was also shown that a dissolution pattern

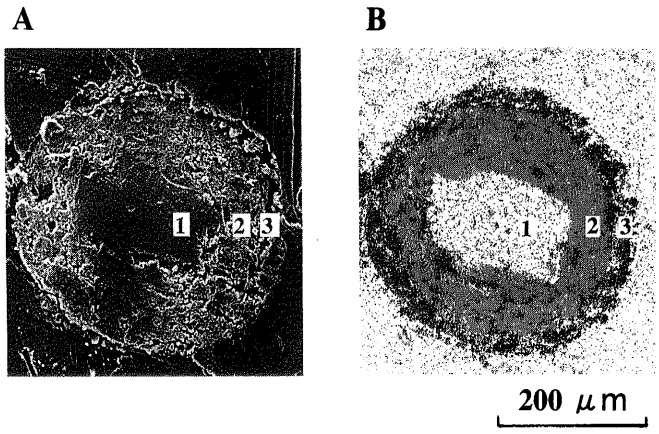

Fig. 4. SEM Microphotograph of Cross-Section of CR Fine Granules and Corresponding Dot Map

A, SEM microphotograph; B, corresponding dot map. 1, seed materials; 2, DH layer; 3, CR layer. The CR fine granules at 100% coating level were used for this electron probe microanalysis.

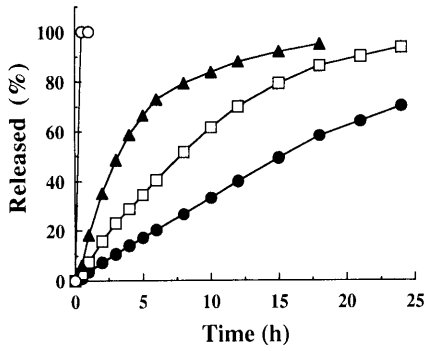

Fig. 5. Dissolution of DH from CR Fine Granules

Coating level: ○, 0% coated fine granule; ▲, 60%; □, 80%; ●, 100%. The dissolution test was performed by the paddle method (37 °C, purified water, 100 rpm).

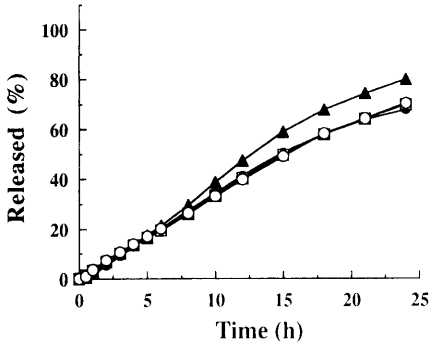

Fig. 6. pH Dependency of Dissolution Rate of DH from CR Fine Granules

Dissolution medium: ○, purified water (pH 6.0); ▲, 1st fluid (pH 1.2); □, 2nd fluid (pH 6.8); ●, pH 7.5. Coating level, 100%. The dissolution test was performed by the paddle method (37 °C, 100rpm).

very similar to that of a once-a-day dosage form in the market could be obtained at 80% coating level.

The dissolution test carried out by changing pH of the dissolution medium (pH 1.2, 6.8, 7.5) showed that almost pH independent profiles were displayed (Fig. 6). This was also an advantageous point of this method since the dissolution rate seemed not to be affected by the pH change of gastrointestinal juice.

Thus, CR fine granules with high producibility were prepared without use of any solvent. This method is very simple and cost-effective, so that its wide applicability for the preparation of CR dosage forms can be expected.

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