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RESEARCH PAPER

Application of Fluidized Hot-Melt Granulation (FHMG) for the Preparation of Granules for Tableting; Properties of Granules and Tablets Prepared by FHMG

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ABSTRACT

The objective of this study was to investigate the properties of granules and tablets prepared by a novel Fluidized Hot-Melt Granulation (FHMG) technique. Macrogol 6000 (polyethylene glycol 6000, PEG 6000), macrogol 20000 (polyethylene glycol 20000, PEG 20000), and glyceryl monostearate (GMS) were used as binders with different levels of viscosity and water solubility. The properties of both granules and tablets were compared with those obtained using the Standard Tablet Formulation (STF, lactose/corn starch/hydroxypropylcellulose/magnesium stearate: 66/30/3.5/0.5) for fluidized-bed granulation, which is widely used for wet granulation. To obtain suitable flowability as granules for tabletting, the content of the melting material should be approximately 10 w/w%. The rate of increase in the mean diameter of the granules during FHMG was affected by both the melting temperature and the viscosity of the melting material used in the granules. The compression properties of granules prepared by FHMG were also investigated, demonstrating that these granules had a high pressure transmit-

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tance. The hardness and the disintegration time of tablets obtained from granules prepared by FHMG were influenced by the properties of the melting material, such as its compaction behavior, solubility, and wettability. No significant differences of hardness were observed when compared to STF tablets. Tablets prepared from FHMG granules disintegrated within 15 min, whereas the STF tablets showed faster disintegration. It was also demonstrated that the hardness and disintegration time of tablets prepared from FHMG granules were not affected by the tablet porosity. Therefore, tablets with a constant quality may be obtainable under a wide range of compression forces. The results of this study suggested that FHMG is a useful method of preparing granules for tableting without using any solvents or water.

Key Words: *Fluidized hot-melt granulation; Granules; Tablets; Compaction; Heckel plots; Porosity; Disintegration*

INTRODUCTION

Granulation is an important process in the production of solid dosage forms of drugs. Granulation also improves the flowability and compressibility of powders. Granules for tableting are prepared by two major production methods, which are the wet and dry methods. Wet granulation is widely used in pharmaceutical production. Fluidized-bed granulation, high shear mixer granulation, and extrusion are the most common methods used for wet granulation. However, these processes require multiple steps and strict control of the operating conditions. In addition, wet granulation cannot be applied to drugs that are unstable when moist.

On the other hand, direct compression, roller compaction, and the slug method are common techniques for dry preparation of granules. Hot-melt granulation (HMG), using meltable materials as thermal binders, is also classified as a dry method. HMG is a well-known granulation technique that utilizes adhesion caused by the melting or softening of materials heated to near or above their melting point (1).

Currently, HMG or hot-melt coating are of great interest in the pharmaceutical field, since granules may be prepared simply without using any solvents or water. Schæfer et al. studied the effect of process (2,3) and formulation variables (4–6) on melt granulation with low molecular weight Polyethylene glycols (PEGs) using a high-shear mixer. Ukita and Murakami demonstrated that melt granulation prevented the vaporization of essential oils during the granulation process because the melted materials covered the surface of the granules (7). The melt granulation process can be applied to prepare sustained-release dosage forms of drugs. Maejima et al. developed the Tumbling Melt Granulation (TMG) technique, which is a type of powder coating method using hydrophobic melting materials, such as fatty acids and hydrogenated castor oils, for the production of sustained-release beads (8–10). HMG is also a very useful method for granulating and stabilizing drugs that are susceptible to hydrolysis (11). Furthermore, this technique has advantages for scaling-up and process validation because there are only a few controlling parameters (12).

In general, conventional HMG is performed in a high shear mixer or a tumbling mixer with a low melting point material and other powder excipients, and approximately 20–30 w/w% content of the melting material is required for HMG formulation (1). After granulation, a process for breaking up and reducing the size of the granules is needed to prepare suitable granules for tableting. As a result, granules prepared by the HMG method are dense and very hard, so their tableting properties are extremely poor (1). Thus, few reports have described the application of HMG to obtain the granules for tableting.

We have developed a novel Fluidized Hot-Melt Granulation (FHMG) technique (13–16). This technique is very simple and easily controlled, so we have investigated its usefulness in the field of pharmaceutical formulation and production technology (15). Our studies have shown that the granules prepared by the FHMG method were softer than those obtained by the conventional HMG method. In general, fluidized-bed granulation is a suitable method to prepare granules for tableting, because the lack of any shear force during granulation results in porous granules with a low strength (17,18).

In previous studies, FHMG has been shown to have the capability to make fine, taste-masked granules containing a bitter drug substance (13), as well as being useful for making a controlled release formulation and enteric dosage formulations (14).

The objective of the present study was to investigate the properties of granules prepared by FHMG, including their compression behaviors. The characteristics of tablets produced from FHMG granules were also evaluated. Our final goal is to establish new production techniques to make granules for tableting using the FHMG method. To assess the advantages of this technique, the results were compared with those obtained using the standard tablet formulation (STF, lactose/corn starch/hydroxypropylcellulose/magnesium stearate: 66/30/3.5/0.5), which was studied by Sunada et al. (17–20).

MATERIALS AND METHODS

Materials

The three melting materials used as binders for FHMG were macrogol 6000 (polyethylene glycol 6000; PEG 6000, NOF Corp., Tokyo, Japan), macrogol 20000 (polyethylene glycol 20000; PEG 20000, NOF Corp.), and glyceryl monostearate (GMS, Riken Vitamin Co. Ltd., Tokyo, Japan). PEG 6000 and GMS were sieved and the fractions under 150 μm were used for granulation. PEG 20000 was micronized with a sample mill (SAM-0, Nara Machinery Co. Ltd., Tokyo, Japan, rotor speed: 10,000 rpm) and was also sieved with a 150 μm sieve. α-Lactose monohydrate 450 mesh (Pharmatose 450 M) and anhydrous lactose (Pharmatose DCL 21) were purchased from DMV (Veghel, The Netherlands). The other materials used were corn starch (Nihon Shokuhin Kako Co. Ltd., Tokyo, Japan), low substituted hydroxypropylcellulose (L-HPC, LH-11, Shin-Etsu Chemical Co. Ltd., Tokyo, Japan), hydroxypropylcellulose (HPC Type L, Nippon Soda Co. Ltd., Tokyo, Japan), and magnesium stearate (Nitto Kasei Kogyo Co. Ltd., Kanagawa, Japan).

Methods

Characterization of the Melting Materials and Excipients

A laser scatter particle size analyzer (MICROTRAC MK-II, LEEDS & NORTHRUP Co., North Wales, PA) was used to measure the mean particle size (volume median diameter) of melting materials suspended in ethanol. The viscosity of molten liquids was measured with a B-type viscometer (BL, Tokyo Keiki Co. Ltd., Tokyo, Japan) at various temperatures. Thermograms of the melting materials were obtained using a differential scanning calorimeter (DSC-6200, Seiko Instruments Inc., Tokyo, Japan). The instrument was calibrated with an indium standard before measurement. Powder samples of approximately 10 mg were weighed into an open aluminum pan, and then covered with a lid. An empty pan with a lid was used as the reference. Scanning was done under a nitrogen purge at a heating rate of 5°C/min and a cooling rate of 10°C/min to simulate the granulation process. The true density of each powder used in this study was determined using an air comparison pycnometer (model 930, Beckman Instrument Inc., Irine, CA), with three replicates determinations for each condition.

Fluidized Hot-Melt Granulation

Granules for tableting were prepared by the FHMG technique using a fluidized-bed system (SPIR-A-FLOW LABO, FL container, Freund Industrial Co. Ltd., Tokyo, Japan). Table 1 shows the formulations used for FHMG. The content of the melting material varied from 4 to 10 w/w%, and the total amount was adjusted using corn starch. The melting material and the other powders were added to the fluidized bed, and then the inlet temperature and shaking/interval were set at 80°C and 2 s/15 s, respectively. The air flow rate was adjusted to 0.3 m^3/min. The powders were heated and held for

Table 1

The Formulations Used for Fluidized Hot-Melt Granulation (FHMG)

Component	Composition (%)				Remarks
Melting material	4.0	6.0	8.0	10.0	
Lactose	40.8	40.8	40.8	40.8	DMV, 450 M
Corn starch	12.1	10.1	8.1	6.1	
Anhydrous lactose	33.3	33.3	33.3	33.3	DMV, DCL 21
L-HPC	9.8	9.8	9.8	9.8	LH-11
Total	100	100	100	100	

10 min after the powder bed temperature reached 65°C, after which the powders were cooled to 40°C.

Measurement of the Flowability Index of Granules and Physical Mixtures

The powder properties of the granules and physical mixtures were determined using a powder tester (PT-E, Hosokawa Micron Corp., Osaka, Japan). Flowability indexes were calculated by Carr's method (21–23).

Measurement of Mean Granule Diameter

Sieve analysis was carried out using a ro-tap shaker (Iida Seisakusyo Co. Ltd., Osaka, Japan), and the mean diameter of the granules was calculated from the log-normal distribution equation.

Scanning Electron Microscopy (SEM)

Granules were mounted on SEM samples-stubs using double-faced adhesive tape and were coated with a 20-nm layer of gold–palladium. Observation was carried out at a voltage of 20 kV on an SEM instrument (JSM-5600LV, JEOL Ltd., Tokyo, Japan).

Compaction Study of the Granules

Granulated powders were sieved and the fraction under 1000 μm was selected for tablet production. Before tableting, the selected granules were blended with 1 w/w% magnesium stearate in a V-blender. Approximately 200 mg of granules prepared by the FHMG method were compressed into a tablet using a compaction machine (Autograph AG-2000A, Shimadzu Co., Kyoto, Japan) with a 8-mm flat face punch. The compression rate was fixed at 5 mm/min (24,25). Tablets prepared by physical mixture were also investigated.

Determination of Tablet Porosity

Tablet porosity (ε) was calculated using the following equation:

$$\varepsilon(\%) = 100(1 - W/\pi \cdot r^2 \cdot h \cdot \rho_t)$$

where W is the weight of the tablet, r is the radius of the tablet, h is the thickness of the tablet, and ρ_t is the true density of material. The thickness and diameter of the tablets were measured using a micrometer ($n = 3$).

Heckel Plots Analysis

Compaction-force data taken from the upper and lower load cells were analyzed using the Heckel equation (26),

$$\ln 1/(1 - D) = K \cdot P + A$$

where D is the ratio of the apparent density of the compact at pressure P to the true density of the materials, K is the slope of the linear portion of the plot, and its reciprocal is taken to be the yield pressure (P_y); and A is a constant. The apparent axial recovery of each ejected tablet was corrected by its thickness.

Tablet Hardness and Disintegration

The hardness of the tablets was determined using a Tablet hardness tester (TBH28DR, Erweka GmbH, Heusenstamm, Germany). Disintegration tests were performed in water with a disintegration tester (NT-20H, Toyama Sangyo Co. Ltd., Osaka, Japan). These procedures were carried out by the JP method using tablets that had been left for 1 day at room temperature after compression.

RESULTS AND DISCUSSION

Characteristics of the Melting Materials

Various characteristics of the melting materials, such as the melting point, the solidifying point, and the mean diameter, are summarized in Table 2. The viscosity of the materials after melting is shown in Fig. 1. PEG 6000 and PEG 20000 had approximately the same melting and solidifying temperatures, but the viscosity of PEG 20000 after melting was about 10-fold greater than that of PEG 6000. On the other hand, GMS had higher melting and solidifying temperatures, whereas its viscosity after melting was quite low. From these results, the melting materials used as binders in this study were classified as water

Table 2

Characteristics of the Melting Materials

Melting Material	Melting Temp. (°C)	Solidifying Temp. (°C)	Mean Diameter (μm)
PEG 6000	59	49	67
PEG 20000	61	50	91
GMS	67	65	102

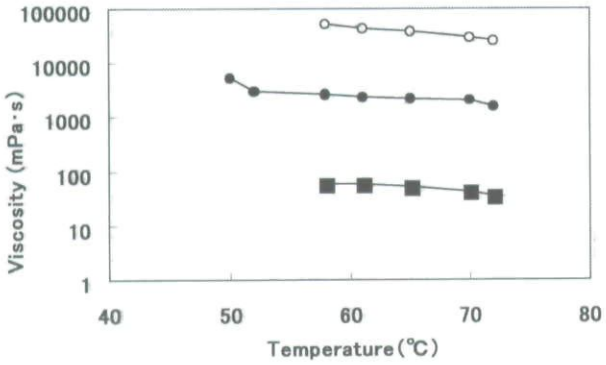

Figure 1. Effect of temperature on the viscosity of the melting materials: ●, PEG 6000; ○, PEG 20000; ■, GMS.

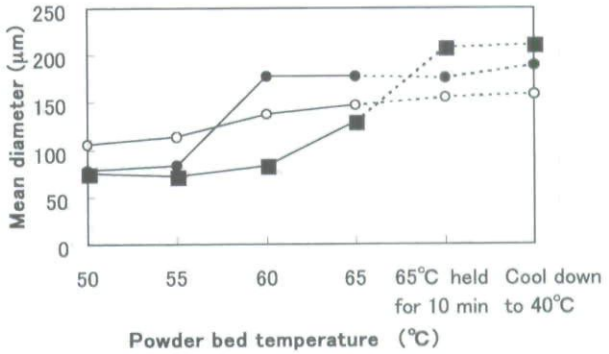

Figure 2. Effect of powder bed temperature on the mean diameter of FHMG granules containing 10 w/w% melting material: ●, PEG 6000; ○, PEG 20000; ■, GMS.

soluble with moderate viscosity (PEG 6000), water soluble with high viscosity (PEG 20000), and insoluble in water with low viscosity (GMS).

Fluidized Hot-Melt Granulation (FHMG)

During the FHMG process, a small portion of powder samples were taken and the mean diameter of the granules was estimated. Figure 2 shows the changes during FHMG in the mean diameter of granules containing 10 w/w% melting material. The mean diameter of granules containing PEG 6000 or PEG 20000 increased after the powder bed temperature reached 55°C, but no significant further increase in diameter was observed after holding for 10 min at 65°C. On the other hand, the mean diameter of granules containing GMS increased after the temperature reached 60°C, and then a significant further increase in diameter was observed after holding for 10 min at 65°C. The growth rate of granules containing PEG 6000 or GMS was rapid and the final mean diameter was twice the initial diameter, whereas granules containing PEG 20000 grew slowly and the mean final diameter was about 1.5 times the initial diameter. Since growth in the mean diameter of the granules depends on adhesion caused by softening or melting of the melting material (15), these results indicate that the growth rate of granules during FHMG was strongly influenced by the viscosity of the melting material and that granulation occurred as molten liquid flowed into the spaces between powder particles adhering to the granules (15).

The morphological features of granules obtained by the FHMG method were investigated using SEM. Figure 3 shows scanning electron micrographs of granules containing 10 w/w% PEG 6000 that were created at a powder bed temperature of 55°C and 65°C. Below the melting temperature of PEG 6000 (Fig. 3A), granulation was insufficient, and many ungranulated particles were observed. After reaching the melting point of PEG 6000 (Fig. 3B), however, most of the particles underwent granulation and developed a round shape, indicating good flowability. The granules prepared by FHMG had a porous and smooth surface and their diameter was similar to that of ungranulated anhydrous lactose.

The flowability of granules is an important factor in the tableting process, since it affects the uniformity of tablets during the stable or continuous production. To investigate suitable melting materials for the FHMG process, Carr's flowability index and the degree of flowability of granules with various concentrations of melting materials were estimated (Table 3). After FHMG, the flowability of the granules was markedly improved compared with the physical mixture of all formulations. Granules containing approximately 10 w/w% of the melting material showed good flowability, which was similar to that of STF granules. Therefore, the optimum content of the melting material for FHMG should be approximately 10 w/w%.

Compaction Study of Granules Prepared by FHMG

Figure 4 shows the pressure transmittance at 147 MPa of granules prepared by the FHMG method with various amounts of melting material. In addition, the pressure transmittance of STF granules and the physical mixture without the melting materials were also examined for reference (Fig. 4). The pressure transmittance of FHMG

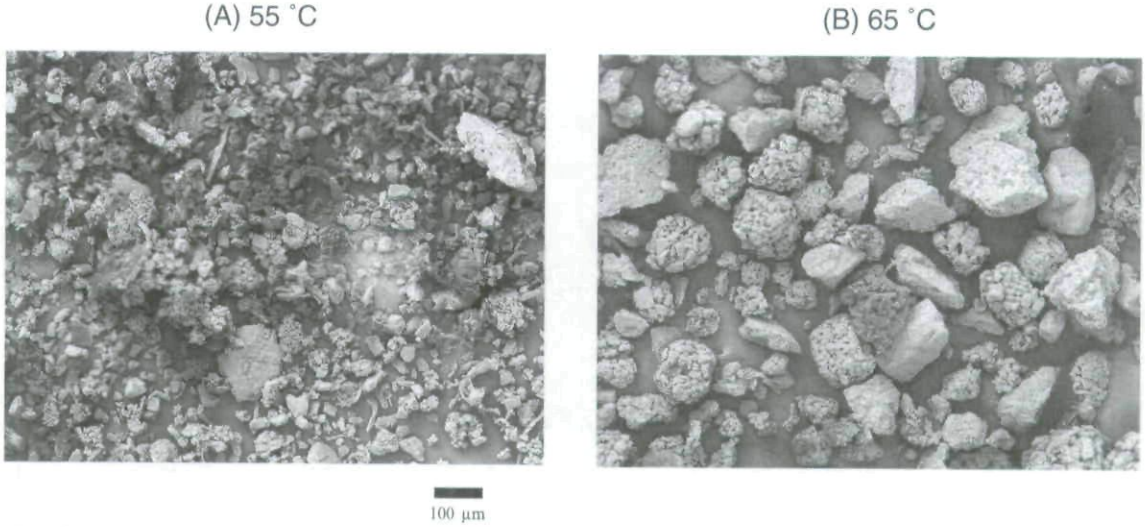

Figure 3. Scanning electron micrographs of granules containing 10 w/w% PEG 6000 prepared by FHMG (magnification: ×100). Powder bed temperature: (A) 55°C, (B) 65°C.

Table 3

Flowability Index of Hot-Melt Granules and Physical Mixtures

	PEG 6000				PEG 20000				GMS			
Amount of melting materials (%)	4	6	8	10	4	6	8	10	4	6	8	10
Flowability index												
Granules	69	73	80	79	68	62	71	72	61	68	73	78
Physical mixture	—	—	—	28	—	—	—	31	—	—	—	41
Degree of flowability[a]												
Granules	N	G	FG	G	N	N	G	G	N	N	G	G
Physical Mixture	—	—	—	B	—	—	—	B	—	—	—	NG

[a]*B, Bad; NG, Not Good; N, Normal; G, Good; FG, Fairly Good.
Standard formulation for fluidized bed (STF): flowability index, 76; degree of flowability, good.

granules was much higher than that of the physical mixture. In the case of PEG 6000 and PEG 20000, the pressure transmittance increased with an increase of the melting material content. Hence, the pressure transmittance of granules containing PEG 6000 or PEG 20000 prepared by FHMG was strongly influenced by the content of melting material. In the case of GMS, which had the highest pressure transmittance, the influence of the amount of melting material on pressure transmittance was less marked. Many types of granules containing 10 w/w% melting materials prepared by FHMG showed better pressure transmittance than the STF granules. Therefore, granules prepared by FHMG would show high compaction property. The high pressure transmittance of these granules was probably related to modification of the granulated powders by the melting material and a decrease of friction between powders during compression as a result of the spread of the melting material around the granules.

Changes in the porosity of tablets prepared from fluidized hot-melt granules containing 10 w/w% melting material under various pressures are demonstrated in Fig. 5. Whereas no significant differences of porosity were observed between granules containing PEG 6000 or PEG 20000, the lowest porosity was observed with granules containing GMS, even at a low pressure. This was probably related to the better compressibility of GMS compared with PEG 6000 and PEG 20000. Moreover, granules

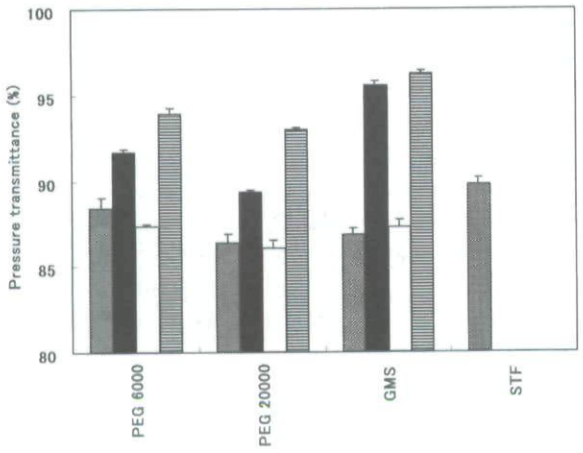

Figure 4. Effect of the amount of melting materials on the pressure transmittance of granules prepared by FHMG or physical mixture: ▩, 4 w/w% melting material, physical mixture; ■, 4 w/w% melting material, FHMG, □, 10 w/w% melting material, physical mixture, ▤, 10 w/w% melting material, FHMG, ■, STF. Bars represent the mean ± SD ($n = 3$).

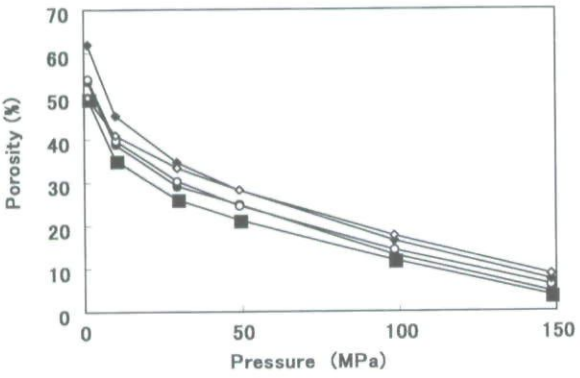

Figure 5. Effect of pressure on the porosity of tablets containing 10 w/w% melting material. ●, PEG 6000, FHMG; ○, PEG 20000, FHMG; ■, GMS, FHMG; ◆, STF; ◇, granules without a melting material.

containing 10 w/w% melting material had a lower porosity at each pressure than STF granules. In addition, the changes of porosity in granules without melting materials were less marked due to the higher friction between the powders and the low deformability of powders.

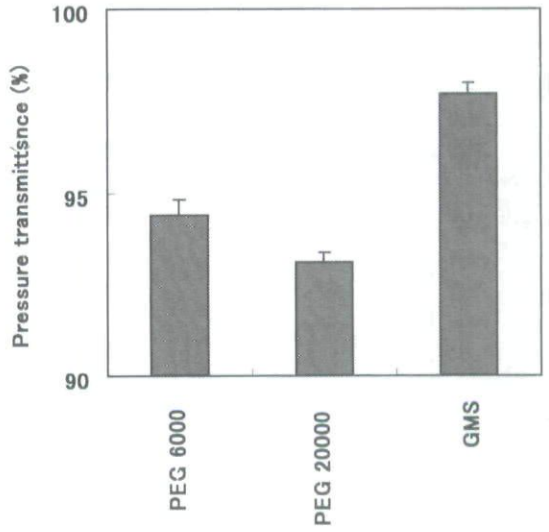

Figure 6. Pressure transmittance of melting materials at 147 MPa. Bars represent the mean ± SD ($n = 3$).

To clarify the influence of the melting material on the compressibility of granules prepared by FHMG, the compaction properties of each melting material were evaluated. Figure 6 shows the pressure transmittance of the melting materials at a pressure of 147 MPa. Each material showed relatively high pressure transmittance, but GMS has much higher transmittance than PEG 6000 or PEG 20000. Similar results were observed at pressures of 49 and 98 MPa. A Heckel plot of the compaction behavior of the melting materials is shown in Fig. 7. During the early stage of compression, rearrangement of each melting material occurred with an increase of pressure, but GMS was the most compressible based on the rate of decrease in porosity as the pressure was increased. The calculated mean yield pressures of PEG 6000, PEG 20000, and GMS were 88.5, 89.3, and 62.1 MPa, respectively. Yield pressure values were determined by linear regression from the linear portion of the Heckel plots shown in Fig. 7. A low yield pressure indicates that a material shows good compressibility (24). GMS had the lowest yield pressure, indicating better compressiblity than either PEG 6000 or PEG 20000. These results indicated that the compressibility of granules containing a melting material was strongly influenced by the presence of that material.

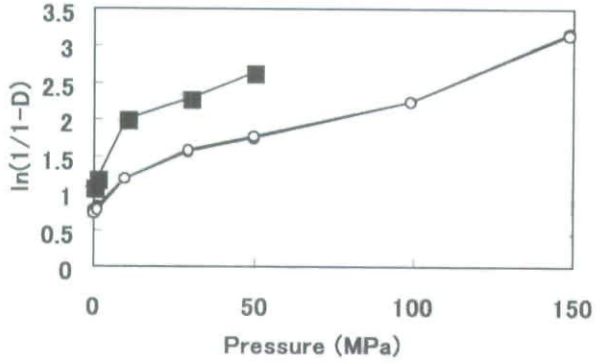

Figure 7. Heckel plots of the melting materials: ●, PEG 6000; ○, PEG 20000; ■, GMS.

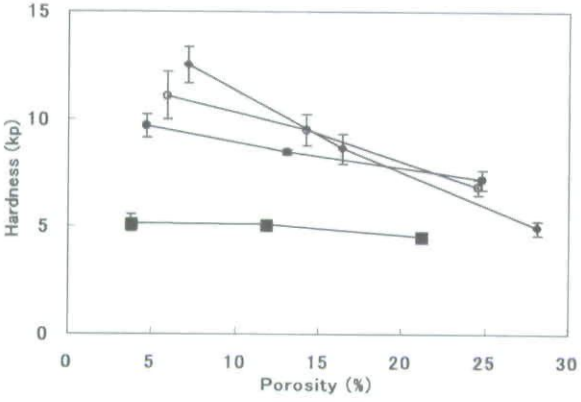

Figure 8. Effect of porosity on the hardness of tablets containing 10 w/w% melting material prepared from FHMG granules and STF granules. ●, PEG 6000, FHMG; ○, PEG 20000, FHMG; ■, GMS, FHMG; ◆, STF. Bars represent the mean ± SD ($n=5$).

Characteristics of Tablets

The characteristics of tablets made from granules prepared by FHMG were investigated. Figure 8 shows the influence of porosity (i.e., pressure) on tablet hardness. When tablets were prepared from granules containing 10 w/w% melting material, the tablets containing PEG 6000 or PEG 20000 were harder than those prepared from STF granules at a porosity of more than 20%. At a low porosity (i.e., a high pressure) of below 15%, tablets containing PEG 20000 were the hardest. Tablets containing GMS showed the lowest hardness at all porosities tested. Dependence of tablet hardness on porosity was observed for STF granules, whereas the hardness of tablets prepared from FHMG granules showed less dependence on porosity.

The effect of porosity on the disintegration time of tablets containing 10 w/w% melting material was also investigated (Fig. 9). Although the disintegration time of uncoated tablets is specified at 30 min in the JP XIII, the desirable disintegration time is not more than 20 min. Tablets containing PEG 6000 or PEG 20000 had a disintegration time of approximately 10 min. However, tablets containing 10 w/w% GMS showed the slowest disintegration despite having a low hardness. These results indicated that the disintegration time of tablets prepared from granules containing PEG 6000 or PEG 20000 was not significantly dependent on their porosity. Tablets prepared from STF granules showed the most rapid disintegration and the disintegration time was not dependent on porosity. On the other hand, the disintegration time of tablets containing GMS was significantly affected by the porosity when it reached more than 12%. As shown in Fig. 8, the hardness of tablets containing GMS was not affected by porosity, so the disintegration time might have been influenced more by the rate at which water penetrated the tablets than by the binding strength between the tablet particles. These results suggested that tablets of consistent quality could be prepared from FHMG granules under a wide range of compression pressures.

The hardness and disintegration time of tablets prepared from FHMG granules containing 10 w/w% melting material under various pressures are sum-

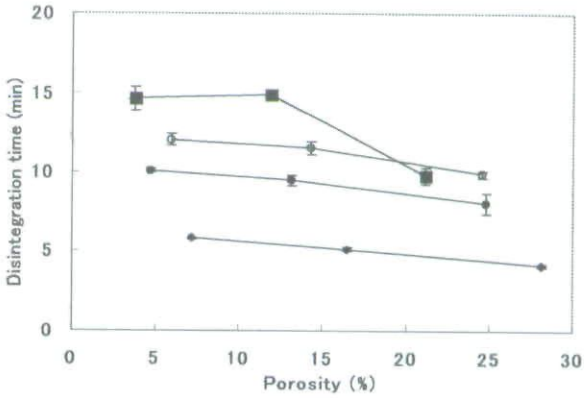

Figure 9. Effect of porosity on the disintegration time of tablets containing 10 w/w% melting material prepared from FHMG granules and STF granules: ●, PEG 6000, FHMG; ○, PEG 20000, FHMG; ■, GMS, FHMG; ◆, STF. Bars represent the mean ±SD ($n=6$).

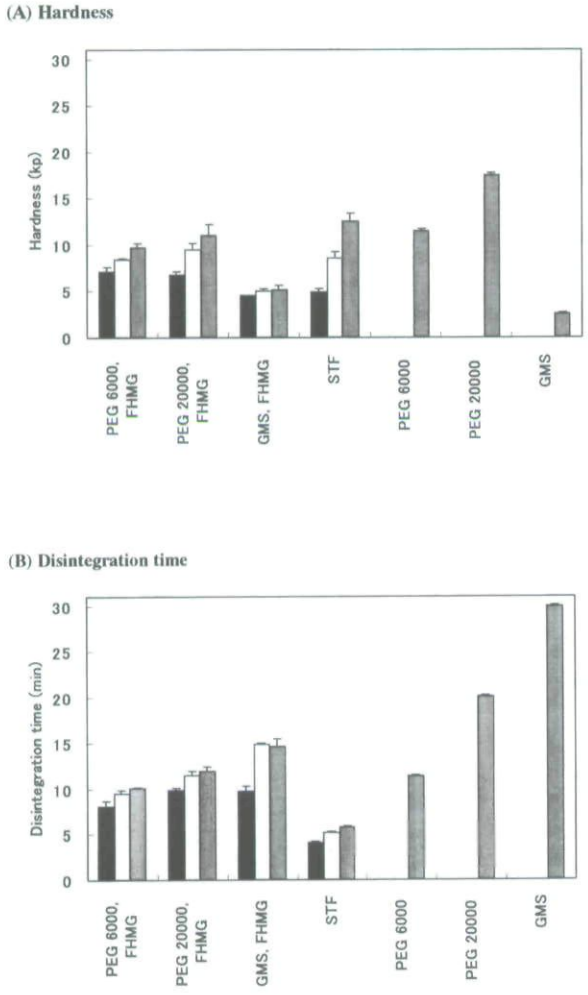

Figure 10. Hardness and disintegration time of tablets prepared from FHMG granules containing 10 w/w% melting material or melting materials alone under various pressures. (A) Hardness: ■, 49 MPa, □, 98 Mpa; ▩, 147 MPa. Bars represent the mean ± SD ($n=5$). (B) Disintegration time: ■, 49 Mpa; □, 98 Mpa; ▩, 147 MPa. Bars represent the mean ±SD ($n=6$).

marized in Fig. 10. The properties of tablets prepared from each melting material alone at a compression force of 147 MPa are also shown. Tablets prepared from PEG 6000 showed less hardness and faster disintegration than those made from PEG 20000. On the other hand, tablets prepared from GMS showed the slowest disintegration, despite having the lowest hardness. GMS has both a lower solubility and a higher contact angle for water than PEG 6000 or PEG 20000. These results demonstrated that the hardness and disintegration time of tablets prepared from FHMG granules closely reflected the properties of the melting material, such as compaction behavior, water solubility, and wettability. The melting material probably coats the powder particles and the surface of the granules produced by FHMG, so that tablets exhibit similar properties to those of the melting material itself because contact points between the melting material in the individual granules is markedly increased by tableting.

CONCLUSIONS

A novel FHMG method was applied to prepare granules for tableting using three different melting materials (PEG 6000, PEG 20000, and GMS). The growth rate of granules during FHMG was strongly influenced by the viscosity of the melting material used. When the flowability of granules obtained by FHMG was evaluated, good flowability was found with 10 w/w% melting material. The pressure transmittance increased with an increase of the melting material content. Granules prepared by FHMG had a higher pressure transmittance than both physical mixture and STF granules, presumably because the melting material spread between the powder particles and covered the surface of the granules after melting, thus increasing elastic deformation of the granules and reducing friction between granules during compression.

The hardness and disintegration time of tablets prepared from FHMG granules were strongly influenced by the properties of the melting material used, such as its compaction behavior, water solubility, and wettability. However, those properties were very little affected by the porosity of the tablets prepared from FHMG granules containing PEG 6000 or PEG 20000. Thus, tablets of a constant quality may be obtained over a wide pressure range. The results of this study indicate that FHMG is a simple and useful method of preparing granules for tableting without the need for solvents or water.

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