Preparation of Spherical Beads without Any Use of Solvents by a Novel Tumbling Melt Granulation (TMG) Method

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A new method, the tumbling melt granulation (TMG) method, for preparing spherical beads without any use of solvents, was developed. A powdered mixture of meltable materials and non-meltable materials was fed gradually and successively onto the seed materials, which were blown with hot slit air using a centrifugal fluidizing bed granulator. As a consequence, the mixture adhered to the seed materials to spontaneously form the spherical beads. First, the effects of several factors concerned with granulatability were investigated using nonpareil as the seed materials; lactose as the non-meltable material; and polyethylene glycol, hydrogenated rape oil, and fatty acids as meltable material. In order to prepare spherical beads with a narrow particle size distribution and a smooth surface, it was concluded from this series of experiments that the bed temperature during the processing should be maintained at least 5 °C higher than the melting point of the meltable material; particle sizes of both the meltable and the non-meltable materials should be lowered below one-sixth of the diameter of the seed materials; and the mixing ratio of the meltable material in the powdered mixture should be set at an optimum value. Then, the TMG method was applied to several kinds of drugs with various physicochemical properties. It was revealed that this method was very useful and widely applicable since even bisbentiamine, with which it was difficult to prepare spherical beads by the wet powder coating method, could be granulated easily by this new method. Further, it was shown that this method could be applied successfully to seed materials whose shape was non-spherical, such as cube-shaped sucrose crystals.

Key words bead; tumbling melt granulation; centrifugal fluidizing granulator; granulatability; drug property; seed material

A number of sustained-release, enteric-release, or controlled-release beads, as well as capsules filled with these beads, have been put to practical use. Such multiple-unit dosage forms have a physiological advantage in that the administered beads are spread widely throughout the gastrointestinal tract and tend to vary less in terms of gastrointestinal transit.

In formulating these beads, it is advantageous to use spherical beads which have a narrow particle size distribution and a smooth surface as the cores to be coated with the controlled-release layer[1] in order to accurately control the dissolution rate.

Many granulation methods for preparing spherical beads such as tumbling granulation, extrusion-spheronization, spray-chilling granulation, spray-drying granulation, *etc.*, have been developed so far. Among them, the tumbling granulation method is widely used to obtain core beads of which particle sizes are in the range of 500 to 3000 μm.[1-3] Tumbling granulations using a centrifugal fluidizing granulator[4-6] or a tumbling fluidized-bed granulation[7-11] have been reported, but most of the papers have reported using a wet granulation method.

On the other hand, dry granulation methods such as compression granulation, disintegration granulation, agitation and fluidized-bed granulation with meltable materials[12,13] have been developed for the following purposes: namely, granulating active ingredients which are unstable in water, or simplifying the preparation procedures by eliminating the massing and drying processes. However, the granules obtained by these methods often have an irregular shape and a rough surface.

Thus, we have developed a novel and simple granulation method for the preparation of spherical beads without using any solvents, namely the tumbling melt granulation method (abbreviated as the TMG method). In this method, non-meltable materials adhere onto the surface of a seed material with the molten meltable material acting as a binder at a temperature which is higher than the melting point of the meltable material. In this study, the effects of bed temperature, the particle sizes of the meltable and the non-meltable materials in comparison with the seed material, and the mixing ratio of the meltable material in the powdered mixture, on the granulatability were investigated to prepare spherical beads with a narrow particle size distribution and a smooth surface. Further, this method was applied to drugs having different physicochemical properties and to irregularly shaped seed material.

Materials and Methods

Materials As seed materials, nonpareil (710—840 μm; Freund Industrial Co., Ltd., Tokyo, Japan) and sucrose crystals (500—710 μm; Ensuikou Seito, Yokohama, Japan) were used.

As meltable materials, hydrogenated rape oil (abbreviated as HRO; Kawaken Fine Chemical, Tokyo, Japan) and polyethylene glycol (PEG6000; Sanyo Kasei, Kyoto, Japan) were used. These meltable materials were of JP grade. Stearic acid was of JP grade. Myristic acid and behenic acid were of JPCI-II grade. HRO and higher fatty acids (Katayama Chemical, Osaka, Japan) were passed through a 200-mesh sieve (74 μm) by a Turbo Screener (Turbo Kogyo, Yokosuka, Japan). PEG6000 was separated by the above screener into four fractions: less than 74, 105—149 μm, 149—250, and 250—350 μm.

As non-meltable materials, lactose (DMV, the Netherlands) was separated by the above screener into four fractions: less than 74, 105—149, 149—250, and 250—350 μm.

Nicotinamide (NA), diltiazem hydrochloride (DH) and theophiline (THEO) were of JP grade. These original sources were as follows: NA (Yuki Gosei Kogyo, Tokyo, Japan), DH (Tanabe Seiyaku, Osaka, Japan), and THEO (Tokyo Kasei, Tokyo, Japan). Bisbentiamine (BB) was produced by Tanabe Seiyaku Co., Ltd. These model drugs were used after being ground in a hammer mill.

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Evaluation of Drug Properties Solubility of the Drugs: The solubilities of the four drugs (NA, DH, THEO, and BB) were determined at 37 °C in purified water. The drugs were suspended in the solvent and these suspensions were occasionally stirred for 20 h at 37 °C, then the suspensions were filtered using a membrane filter and the filtrates were subjected to spectrophotometric assay.

Mean Particle Size of the Drugs: Cilas laser granulometry by a laser diffraction system (Granulometer model 715, Cilas Aikatel Co., Ltd., France) was used for the slightly water-soluble drugs, THEO and BB. The powdered drugs were dispersed in their saturated aqueous solutions and were applied to the granulometry. Optical micrographs were used for the water-soluble drugs, NA and DH.

TMG TMG was carried out by the use of CF (CF-360S: Rotor diameter 360 mm; Freund Industrial Co., Ltd., Tokyo, Japan), as shown in Fig. 1. A mass of seed material was heated previously in the CF by blowing hot slit air. The powdered mixture of meltable materials and non-meltable materials was gradually and successively fed to the driving bed of the seed material. As illustrated in Fig. 2, the meltable material was melted on the surface of the pre-heated seed material, and then the molten meltable material acting as a binder led the non-meltable material to adhere onto the seed material. By continuous tumbling and heating, the resultant melt granulation layer was gradually compacted and the surface of the outer layer became smooth. The bed temperature was kept constant during the granulation process. After feeding the designated amount of the powder mixture, the resultant beads were taken out of the CF and cooled at room temperature. Single-core beads were then obtained by sieving with 350 and 1000 μm sieves in open diameter to remove the agglomerates and the non-adhering fine powder.

Evaluation of Granulatability The granulatability was estimated by the following two values: the recovery % of granulation mass (Rec%) and the yield % of single core beads (Ysc%, fraction ranged from 350 μm to 1000 μm) against the charging amount of the seed material and the powdered mixture. Therefore, when both Rec% and Ysc% were over 93%, we considered that the granulatability was excellent.

Bead Characteristics The shape of the sucrose crystals and the resultant BB beads were observed by an optical microscope (Type SZH: Olympus, Tokyo, Japan). The particle size distribution of the beads was determined by a sieve method using 10 g of sample.

The circularity[14] of the sucrose crystal and the resultant BB beads was determined by use of the following equation:

$$\text{circularity} = HP/PM$$

where HP is the heywood perimeter and PM is the perimeter of the sucrose crystal and the resultant BB beads. HP and PM were determined by a computer-assisted color image analyzer (Olympus, Tokyo, Japan). The system consisted of an optical microscope (Type SZH: Olympus, Tokyo, Japan), a video camera, a computer connected to an image processor and a TV monitor (Type TVIP-5100: Olympus, Tokyo, Japan). Image enhancements and measurements were made using the system software (Image Command 5098: Olympus, Tokyo, Japan).

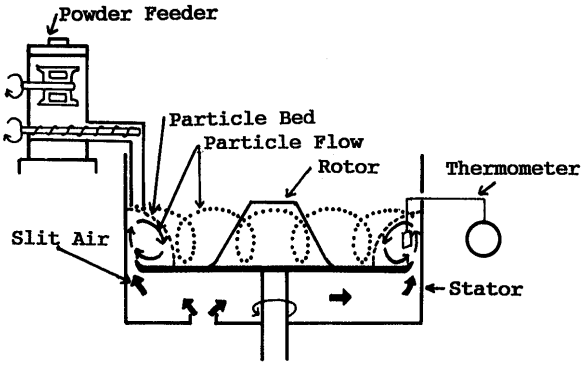

Fig. 1. Scheme of CF Granulator

Results and Discussion

Factors Affecting the Granulatability Effect of Bed Temperature: In general, melt agglomerating granulation begins when the meltable material is melted. In the TMG method, the non-meltable material adheres onto the surface of the seed material after the meltable material is melted, as shown schematically in Fig. 2. Therefore, the bed temperature of the seed material is an important factor for the granulatability. Thus, the granulation by changing the bed temperature was performed using such different melting point meltable materials as PEG6000, myristic acid, stearic acid, behenic acid and HRO, and by using lactose as a non-meltable material. The mixing ratio of the meltable material in the powdered mixture of a meltable material and lactose as a non-meltable material was therefore fixed as 20%.

As shown in Fig. 3, both Rec% and Ysc% were low at temperatures lower than the melting point of the relevant meltable material, and were improved by raising the bed temperature in every cases. A particular critical point of temperature seemed to exist in each case, over which the Rec% and Ysc% were over 93%, and excellent granulatability was achieved. In Table 1, the critical temperature for each meltable material is shown, together with its melting point.

As shown in Table 1, the critical temperatures were 5 °C higher than the melting points of each meltable material in each case, except for HRO. If the bed temperature was lower than such critical point, both the Rec% and Ysc% were reduced. It was presumed that parts of the lactose and meltable materials did not adhere to the seed sufficiently and were lost out of the CF granulator through the exhaust duct at the lower temperature.

In the case of HRO, the critical point was mostly in agreement with the melting point. This could be due to the fact that some components in HRO might have been melted, and acted as binders at its melting point, since it was made from a natural source and consisted of several

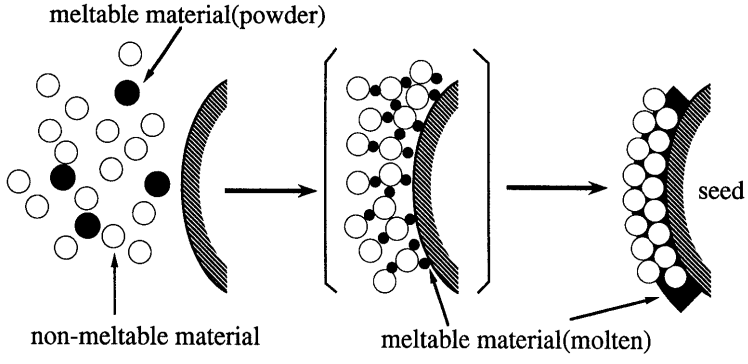

Fig. 2. Schematic Representation of Principle of TMG Method

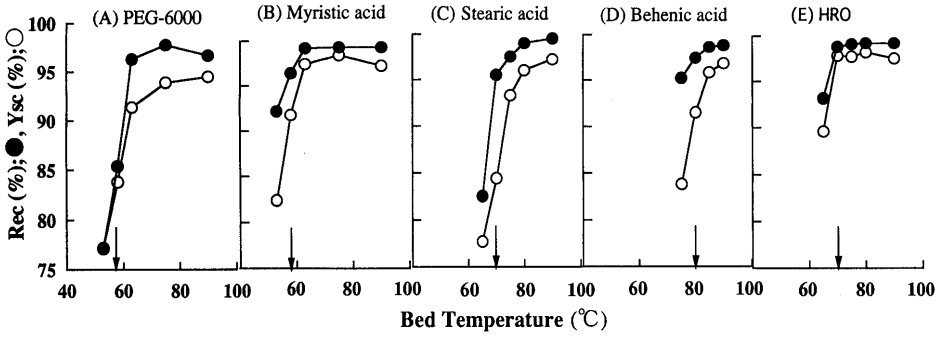

Fig. 3. Effect of Bed Temperature on Granulatability

●, Rec% (recovery percentage); ○, Ysc% (yield of single core beads); seed material, nonpareil (710—840 μm); Meltable material, PEG6000 (less than 74 μm, mp 58 °C), myristic acid (less than 74 μm, mp 58 °C), stearic acid (less than 74 μm, mp 70 °C), behenic acid (less than 74 μm, mp 80 °C), HRO (less than 74 μm, mp 70 °C); non-meltable material, lactose (less than 74 μm); mixing ratio of meltable material, 20%; adhering level of powdered mixture of PEG6000 and lactose against nonpareil, 30%. Arrows show the melting point of each meltable material.

Table 1. Melting Point and Critical Temperature of Meltable Materials

Meltable material	mp (°C)	Critical temperature (°C)
PEG6000	58	63
Myristic acid	58	63
Stearic acid	70	75
Behenic acid	80	85
HRO	70	70

triglycerides.

On the other hand, both Rec% and Ysc% were more than 93% and didn't vary when the bed temperature was at least 5 °C higher than the melting point of every meltable material. Thus, this TMG method seemed to have such an advantage that excellent granulatability could be achieved without strict control of the bed temperature when the temperature was maintained at a sufficiently high level.

Effect of Particle Sizes of Meltable Material and Non-Meltable Material: In wet fluidized-bed granulation, the particle size of the powder and the droplet size in the spray mist of the binder solution commonly affect the characteristics of the obtained granules, such as particle size distribution, crushing strength, shape, and so on.[15-17] It is also well known that the particle sizes of the powder and wax greatly affected granulatability in melt agglomerating granulation.[18] As this TMG method is classified as one kind of powder-coating granulation technology, the particle sizes of the raw materials as the non-meltable material acting as a coated powder, and the meltable material acting as a binder, were considered to be important factors in determining the granulatability. So, to clarify the effect of particle sizes of such materials, granulation was performed by changing the particle sizes of PEG6000 and lactose.

A) Effect of Particle Size of Meltable Material: In Fig. 4, Rec% and Ysc% were shown when granulations were performed using lactose (less than 74 μm) and 4 fractions of PEG6000 having different particle size ranges (less than 74, 105—149, 149—250, and 250—350 μm) at 75 °C of bed temperature when the mixing ratio of PEG6000 was 20% in the powdered mixture.

When PEG6000 of less than 74 and 105—149 μm was used, excellent granulatability was attained. Lactose and PEG6000 were mixed well and they adhered on the nonpareil (710—840 μm) instantly after being fed. In contrast, when 149—250 μm fraction of PEG6000 was used, the Ysc% decreased to less than 93%, and when 250—350 μm fraction was used, the Ysc% was very low, around 30%, and the agglomerations of the nonpareils, of which the particle size was larger than that of the lactose, were observed in the granulation process.

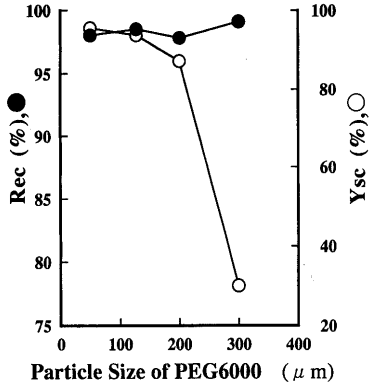

Fig. 4. Effect of Particle Size of Meltable Material, PEG6000, on Granulatability

Symbols are the same as in Fig. 3. Seed material, nonpareil (710—840 μm); meltable material, PEG6000 (mp 58 °C); non-meltable material, lactose (less than 74 μm); mixing ratio of meltable material, 20%; bed temperature, 75 °C; adhering level of powdered mixture of PEG6000 and lactose against nonpareil, 30%.

The presumed agglomeration process generated in the granulation is shown schematically in Fig. 5. In the case of the 250—350 μm fraction of PEG6000 (Fig. 5A), the bridge of the nonpareils through the molten PEG6000 could occur with high probability, and consequently, a part of lactose could not adhere on the nonpareil due to the lack of a binder, the molten PEG6000. Then, a part of lactose and PEG6000 were removed from the driving bed *via* an exhaust duct, rendering the Ysc% especially low. This phenomena of producing agglomerates is very similar to those formed in the spray coating process due to local overwetting on the core granules when the droplet size in the spray mist was too large. In the case of the 149—250 μm fraction of PEG6000 (Fig. 5B), small granules were formed by the adhesion of lactose around the molten PEG6000 of a large size, and then they seemed to

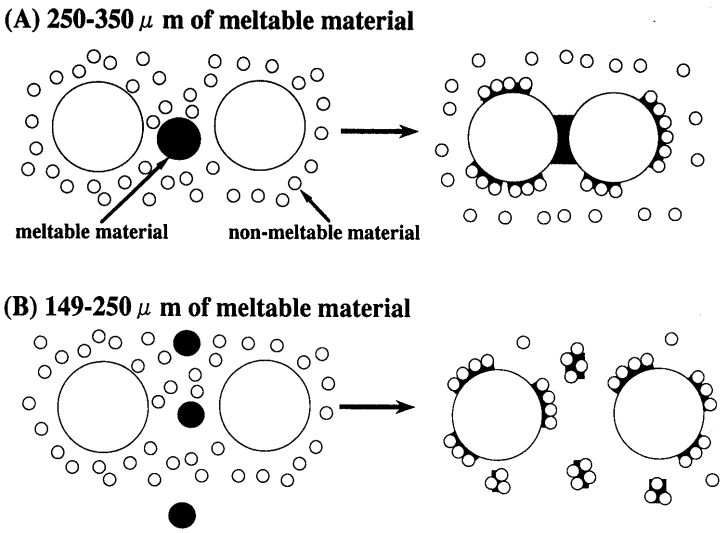

Fig. 5. Schematic Representation of Granulating Process Using Large Size Meltable Material

increase, and consequently, the Ysc% might be low. Thus, it was concluded that the particle size of the meltable material should be reduced to less than about one-sixth of the diameter of the seed material to attain excellent granulatability.

Schaefer *et al.*[18] reported that the particle size of PEG6000 hardly affected the granulatability in the melt agglomerating granulation performed using a high shear mixer. This difference could be due to the fact that the melting rate of PEG6000 and its spread on the lactose surface could easily occur due to the high rotating speed and high shear stress generated in the high shear mixer. In contrast, the rotating speed and the shear stress are much milder in the CF granulator than in the high shear mixer, and thus the melting rate and the spreading rate of PEG6000 decreased with the increase in particle size of PEG6000; consequently, the granulatability showed dependency on the particle size of PEG6000.

B) Effect of Particle Size of Non-meltable Material: The effect of the particle size of the non-meltable material was also investigated by changing the particle size fractions of lactose (less than 74, 105—149, 149—250, and 250—350 μm).

As shown in Fig. 6, the Rec% and Ysc% were excellent using lactose with particle size ranges of less than 74 and 105—149 μm. However, using lactose with particle size ranges of 149—250 and 250—350 μm, the Rec% and Ysc% were quite low.

By using lactose of less than 74 and 105—149 μm, PEG6000 and lactose were mixed well, and the adhesive force necessary to adhere to the surface of nonpareil should be small. In addition, the deformability of the coated layer in the TMG process seemed to be easy as the coated layer was constituted with smaller lactose. These factors should have contributed to the good granulatability. However, in the case of 149—250 and 250—350 μm, a bigger adhesive force is required for lactose to adhere to the nonpareil. As a result, the lactose didn't efficiently adhere and consequently both the Rec% and Ysc% were low. From the above results, it was confirmed that the particle sizes of the non-meltable materials should be reduced to below

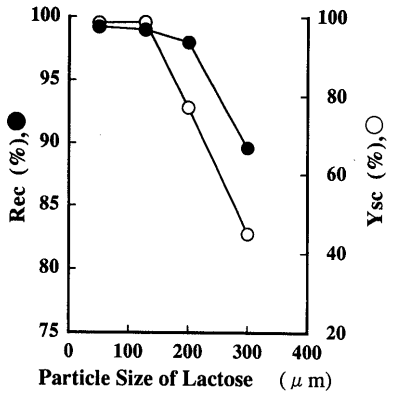

Fig. 6. Effect of Particle Size of Non-meltable Material on Granulatability

Symbols are the same as in Fig. 3. Seed material, nonpareil (710—840 μm); meltable material, PEG6000 (less than 74 μm, mp 58 °C); non-meltable material, lactose; mixing ratio of meltable material, 20%; bed temperature, 75 °C; adhering level of powdered mixture of PEG6000 and lactose against nonpareil, 30%.

one-sixth of the diameter of the seed materials to attain excellent granulatability. This was similar to the results with the meltable materials.

Myo[6] reported that the surface roughness of the beads was affected by the particle sizes of the coated powder and the seed material in wet powder coating granulation. Assuming the droplet size produced by the spraying instrument was negligible, he concluded from a theoretical calculation that the particle size of the coated powder should be reduced to below one-tenth of the diameter of the seed material to obtain spherical beads.

Comparing the above results with his calculation, the particle size ratio of a coated powder against seed material in the TMG was a little larger than that in the wet powder coating granulation reported by Myo. In the wet granulation, the droplet of the sprayed binder solution seemed to spread and permeate into the coated powder during a short time since the process accompanied the following drying. By contrast in the TMG, the droplets of the molten meltable material which acted as a binder could spread and permeate gradually through all the TMG process. Thus the adhesion and deformability of the

coated layer can be attained more easily in TMG, and consequently, excellent granulatability could be attained, even when lactose with a rather larger particle size was used.

Effect of Mixing Ratio of Meltable Material: The effect of the mixing ratio of meltable material in the powdered mixture was determined by changing the mixing ratio of PEG6000 (less than 74 μm) and lactose (less than 74 μm) at 75 °C, which was at least 5 °C higher than the melting point of PEG6000.

As shown in Fig. 7, both the Rec% and Ysc% reached a maximum when the mixing ratio of PEG6000 was 20%. When the mixing ratio was more than 20%, the Rec% decreased a little and Ysc% decreased significantly with the increase of mixing ratio. This could be caused partly by the agglomeration of beads due to the existence of an excess amount of binder around the seed materials, as illustrated in Fig. 8A, and partly by the adhesion of the excess meltable material to the inside wall of the apparatus, such as the rotor and stator in the CF granulator. On the other hand, the Rec% decreased significantly and Ysc% decreased a little with the decrease in the mixing ratio when PEG6000 was less than 20%. This could be due to the fact that part of the lactose did not sufficiently adhere to the seed due to the lack of molten PEG6000, as schematically shown in Fig. 8B.

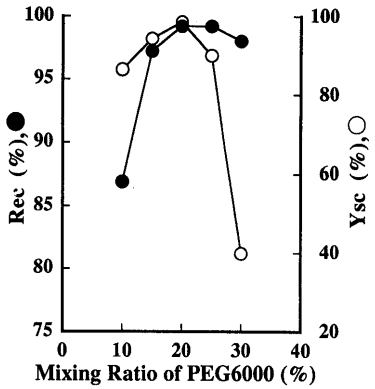

Fig. 7. Effect of Mixing Ratio of Meltable Material on Granulatability

Symbols are the same as in Fig. 3. Seed material, nonpareil (710—840 μm); Meltable material, PEG6000 (less than 74 μm, mp 58 °C); non-meltable material, lactose (less than 74 μm); bed temperature, 75 °C; adhering level of powdered mixture of PEG6000 and lactose against nonpareil, 30%.

Applicability of the TMG Method As described above, spherical beads with a smooth surface could be prepared when the bed temperature, the particle sizes of each raw material, and the mixing ratio of the meltable material in the powdered mixture were relevantly optimized. The TMG method was applied to the granulation of several drugs and to granulation using a sucrose crystal as a seed material.

Application to Four Kinds of Drugs: In the previous paper,[5] we reported that the wettability of a drug against the binder solution was the main factor affecting the granulatability in wet powder coating granulation. Thus, the wettability of the drug against the molten meltable material was also expected to affect the granulatability in TMG method. In order to determine the applicability of this TMG method, it was tested with the four drugs: NA, DH, THEO, and BB, having widely different solubilities which were closely related with the wettability. In this series of experiments, HRO was used as a meltable material, instead of PEG6000. The granulating results and drug properties are summarized in Table 2.

As shown in Table 2, the granulatabilities of all four drugs were very excellent. Thus, it was found that the TMG method could be applied to many drugs for preparing spherical beads, irrespective of such drug properties as particle size, true density, and solubility.

Among the four drugs, the good result in BB should be

Table 2. Properties of Drugs and Their Granulatabilities

Drug	Particle size (μm)	True density (g/cm^3)	Solubility in water (w/v%)	Rec (%)	Ysc (%)
NA	40	1.44	997	97.4	95.4
DH	23	1.30	473	98.4	96.7
THEO	30	1.50	11.2	98.6	96.4
BB	6	1.38	0.006	97.6	96.0

Seed material, nonpareil (500—710 μm); meltable material, HRO (less than 74 μm); mixing ratio of meltable material, 20%; bed temperature, 80 °C; adhering level of powdered mixture of HRO and drug against nonpareil, 100%; true density, determined by autopycnometer.

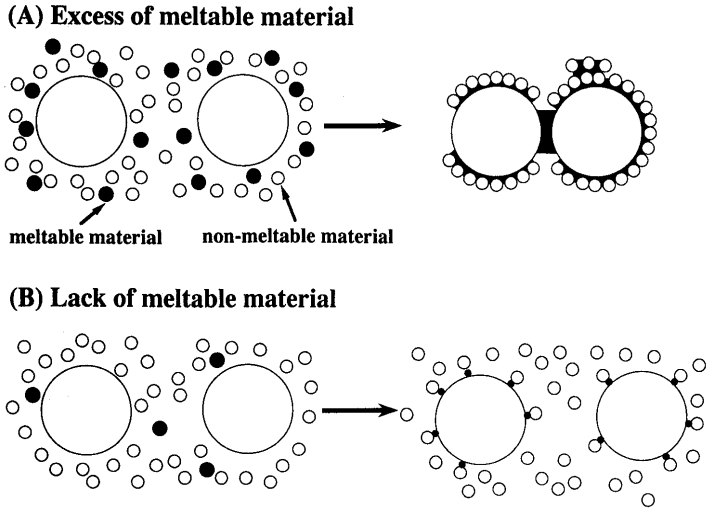

Fig. 8. Schematic Representation of Granulating Process except Optimal Mixing Ratio

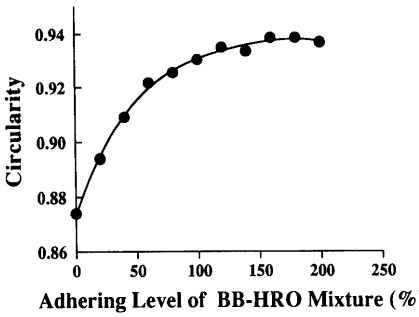

Fig. 9. Relationship between Circularity and Adhering Level of BB–HRO Mixture

Seed material, sucrose crystal (500—710 μm); meltable material, HRO (less than 74 μm, mp 70 °C); non-meltable material, BB (mean particle size, 6 μm); bed temperature, 80 °C; adhering level of powdered mixture of HRO and lactose against sucrose crystal, up to 200%.

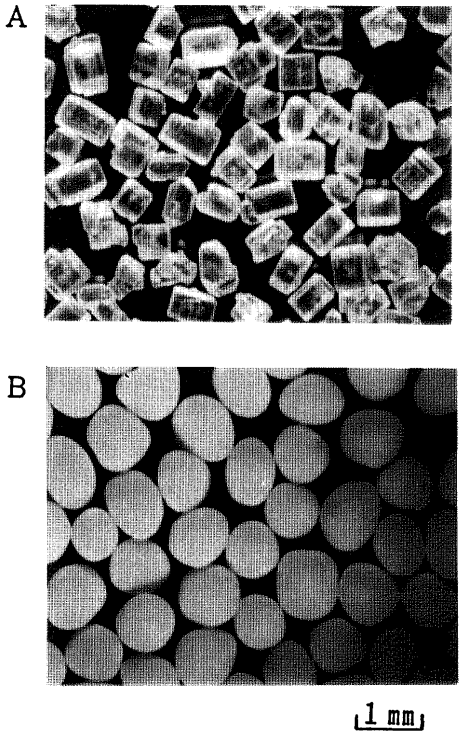

Fig. 10. Microscopic Observation of Seed Material and Resultant Beads

A, sucrose crystal as a seed material; B, resultant beads adhered with 200% of BB–HRO mixture to the weight of the seed material.

noted, because it was very difficult to prepare spherical beads with a smooth surface by the wet powder coating granulation using a CF granulator as long as the poor wettability was not improved by the addition of ethanol into the binder solution, as shown in the previous paper.[5] Granulatability in the TMG method might be less affected by the wettability than that in wet powder coating granulation. The effect of wettability on TMG granulatability will be described in detail in a subsequent paper.

Application to Non-spherical Seed Material: Hitherto, we showed only the results in which nonpareil was used as a seed material. Nonpareil has a spherical shape and hence it should serve as the most advantageous core for applying this method. However, the applicability of this method can be expanded widely to non-spherical seed

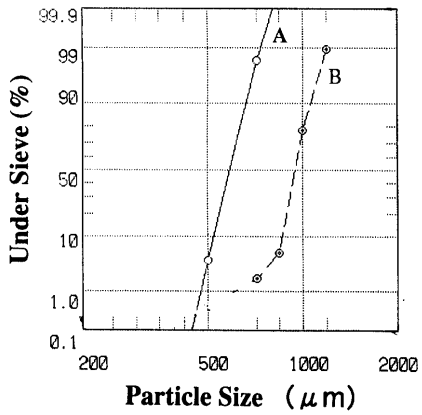

Fig. 11. Particle Size Distribution of Seed Material and Resultant Beads

A and B correspond to Fig. 10, respectively.

material. As an example, we tried to use cube-shaped sucrose crystals as a seed material.

In order to investigate the granulatability, a powdered mixture of BB and HRO was fed and adhered to the cube-shaped sucrose crystals (500—710 μm). Both the Rec% and Ysc% were over 95% at 20% of the mixing ratio of HRO in the powdered mixture of HRO and BB. The circularity of the resultant BB beads increased with the increase in adhering level of the BB–HRO mixture until about 140% of the adhering level, as shown in Fig. 9. At the adhering level over 140%, the circularity led to equilibrium (almost 0.94), which revealed that the shape of the beads was nearly spherical. Optical micrographs of the sucrose crystal and the resultant beads (200% of the adhering level) are shown in Fig. 10, and their particle size distributions are also shown in Fig. 11. Although the original shape of the sucrose crystal as the seed material was almost cubical, spherical beads with a smooth surface and a narrow particle size distribution could be obtained by this TMG method.

It was found that spherical beads with a smooth surface and narrow particle size distribution could be obtained by this TMG method when the bed temperature, the particle sizes of each raw material, and the mixing ratio of the meltable material in the powdered mixture were relevantly optimized. Consequently, this method could be applied to prepare spherical beads even when drugs with different physicochemical properties, such as particle size, true density and solubility, and also non-spherical shaped seed materials were used. These results indicate that this TMG method is an excellent granulation methods with very wide applicability.

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