Application of Tumbling Melt Granulation Method to Prepare Controlled-Release Beads by Coating with Mixture of Functional Non-meltable and Meltable Materials

Toru MAEJIMA,* Takashi OSAWA, Kingo NAKAJIMA, and Masao KOBAYASHI

Pharmaceutics Research Laboratory, Tanabe Seiyaku Co., Ltd., 16–89 Kashima-3-chome, Yodogawa-ku, Osaka, Japan. Received September 22, 1997; accepted November 4, 1997

A new coating method for use in preparing controlled-release beads was developed by modifying the tumbling melt granulation technique. The dissolution rate of the drug from the beads was controlled by coating the mixture of meltable and non-meltable materials by heating in a centrifugal fluidizing granulator without using any solvent. In experiments using talc as the non-meltable material, the resultant beads showed the sufficient ability to suppress the dissolution of the drug and no change in the dissolution characteristics by wetting agent and in a stability test at high temperature. Using functional polymer as the non-meltable material, the controlled-release beads with various dissolution characteristics could be prepared: entero-soluble-release beads using entero-soluble polymer, and zero-order-release beads using hydrophilic gel-forming agent and talc.

Key words beads; tumbling melt granulation; wax; controlled-release; centrifugal fluidizing granulator; functional powder

We previously showed that the coating of hydrogenated castor oil (HCO)[1] or a mixture of HCO and fatty acid[2] on core beads by the tumbling melt granulation (TMG) method was effective for the preparation of controlled-release (CR) beads. Part of the molten meltable material adhered the not-molten meltable material on the core beads when heated, forming the CR layer. Thus, the operating temperature should be controlled strictly to avoid the agglomeration generated at higher temperature or insufficient coating efficiency generated at lower temperature.

We also studied the granulatability of the TMG method and showed that the mixture of meltable and non-meltable materials could efficiently and tightly adhere to the seed when the bed temperature was maintained at least 5 °C higher than the melting point of the meltable material, and the optimum mixing ratio of the meltable material was chosen.[3,4]

A newly modified coating method was developed based on this method: the mixture of meltable and non-meltable materials as coating materials instead of meltable material alone; this was expected to make it possible to prepare the CR layer without strictly controlling the operating temperature. We prepared CR beads using this new technique with talc as a non-meltable material and compared such properties as ability to suppress the dissolution rate, and resistance against the wetting agent and the stability test, with those achieved by the previous method. We also prepared CR beads with various dissolution characteristics using functional polymers as non-meltable material.

Experimental

Materials Nicotinamide (NA; Yuki Gosei Kogyo, Tokyo, Japan) was JP grade and was used after being ground in a hammer mill. As seed material, nonpareil (350—500 μm; Freund Industrial Co., Ltd., Tokyo, Japan) was used. As meltable materials, HCO (mp 85 °C; Kawaken Fine Chemical, Tokyo, Japan) was JP grade and was passed through a 200-mesh sieve (74 μm) by a Turbo Screener (Turbo Kogyo, Yokosuka, Japan).

As functional non-meltable materials, talc (D_{50}, 11 μm; Nippon Talc, Japan) and magnesium stearate (D_{50}, 15 μm; Nippon Oil & Fats Co., Ltd., Japan), hydroxypropylmethylcellulose (TC-5; D_{50}, 60 μm; Shin-Etsu Chemical Co., Ltd., Japan) and hydroxypropylmethylcellulose acetate succinate (HPMC-AS; D_{50}, 5 μm; Shin-Etsu Chemical Co., Ltd., Japan) were used. The first three were JP grade and the last one was JPE grade. All the powders were used without further treatment.

Preparation of Spherical Core Beads and CR Beads The spherical core beads and CR beads were prepared in the same way using centrifugal fluidizing granulator (CF-360S: Rotor diameter 360 mm, Freund Industrial Co., Ltd., Tokyo, Japan) as described.[1,2]

Evaluation of Coating Producibility The recovery % of coating mass (Rec%) and the yield % of single core beads (Ysc%) were determined as previously.[1,2]

Dissolution Test and Calculation of Permeability Coefficient A dissolution test was performed in purified water, the 1st fluid (pH 1.2), and the 2nd fluid (pH 6.8), and the permeability coefficient (P) was calculated using the apparent zero order dissolution rate at the initial stage up to 20—50% release as previously.[1,2]

Stability Test The CR beads prepared were stored in a glass bottle at 40 °C. After 6 months of storage the dissolution rate of the stored beads was evaluated and compared with that of the initial beads.

Results and Discussion

Preparation of CR Beads by Modified Coating Method First, the modified coating method was used with talc as non-meltable material since it does not dissolve in any dissolution media and has a lubricating and anti-adherent effect. To evaluate the suppression ability of the dissolution rate, NA with high solubility was used as a model drug. The core beads containing NA were coated with the mixture of HCO and talc (weight ratio, 15 : 85), altering the coating levels up to 100%.

As shown in Fig. 1, the dissolution of NA in purified water was almost completely suppressed at the coating level of more than 80%, and suggesting the effectiveness of this method. The permeability coefficients were calculated and plotted against the thickness of coated layer as shown in Fig. 2, in comparison with those of the beads coated with HCO alone stated in the previous paper.[1]

The permeability coefficient of the new method was remarkably lower, showing that it suppressed the dissolution rate more effectively than the previous method.

---

* To whom correspondence should be addressed.

Cross sections of the coated layers were compared under scanning electron microscope (Fig. 3). It was found that the mixture of talc and HCO was compacted very tightly and few voids were observed with the new technique, while the HCO mass, presumed to be originated from imperfectly molten wax, and many voids were seen with the previous method. The difference in the suppression ability thus seemed to be due to the compactness of the coated layer.

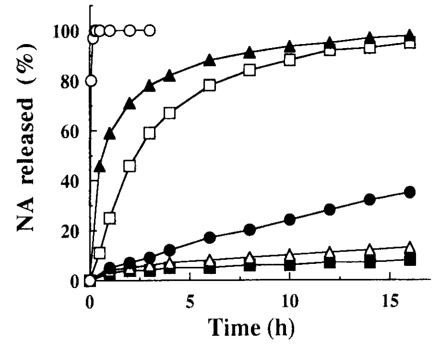

Fig. 1. Dissolution of NA from Beads Coated with HCO and Talc at Various Coating Levels

Coating level: ○, 0%; ▲, 20%; □, 40%; ●, 60%; △, 80%; ■, 100%. The dissolution test was performed in purified water using beads with particle sizes in the range of 500 to 1000 μm (paddle method, 37 °C, 100 rpm).

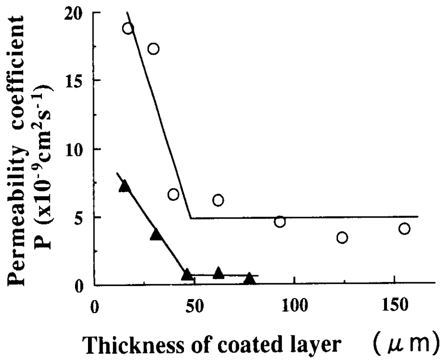

Fig. 2. Comparison of Permeability Coefficient between Beads Coated with HCO Alone and Those Coated with Mixture of HCO and Talc

○, HCO alone; ▲, mixture of HCO and talc.

Further, effect of wetting agent added to the dissolution medium on the dissolution rate[5] and the stability of dissolution characteristics[6-9] were evaluated for beads coated with the mixture of talc and HCO, and were compared with those using HCO alone. The dissolution rates of beads prepared by the previous method tended to be rapid with the addition of the surfactant and after 6-months storage at 40 °C, while those prepared by the new method were hardly altered (data not shown), suggesting the advantage of this new technique.

Preparation of CR Beads with Various Functions 1) Alteration of Talc to Magnesium Stearate: Magnesium stearate was used in place of talc in the above experiment. As shown in Fig. 4, the dissolution profile of NA from the resultant beads showed an entero-soluble property, while that of the beads using talc showed less pH dependency (data not shown). This seemed to be due to the hydrophilicity of magnesium stearate perhaps being changed with pH of the dissolution medium. This system appeared effective for a basic drug with low solubility in the neutral to alkaline region since the drug permeability through the CR layer increased in the gastrointestinal (GI) region where its solubility was less. Thus, the dissolution rate of the drug could be kept less variable in GI tract. In addition, the drug amount remaining in this coated beads without dissolving could be less than that remaining in the CR beads on which talc and HCO were used as coating material.

2) Preparation of Entero-Soluble Beads: The mixture of HCO, HPMC-AS, and talc (weight ratio, 20:20:60) was adhered on NA core beads up to a 50% coating level. The structure of the resultant beads is shown in Fig. 5A. The dissolution test was performed in the 1st fluid for 2 h and then the dissolution medium was changed to the 2nd fluid.

As shown in Fig. 5B, the dissolution of NA was completely suppressed in the 1st fluid for the first 2 h, while NA was released rapidly after changing the dissolution medium to the 2nd fluid. This showed that the entero-soluble beads could be prepared easily with this TMG method using an enteric polymer.

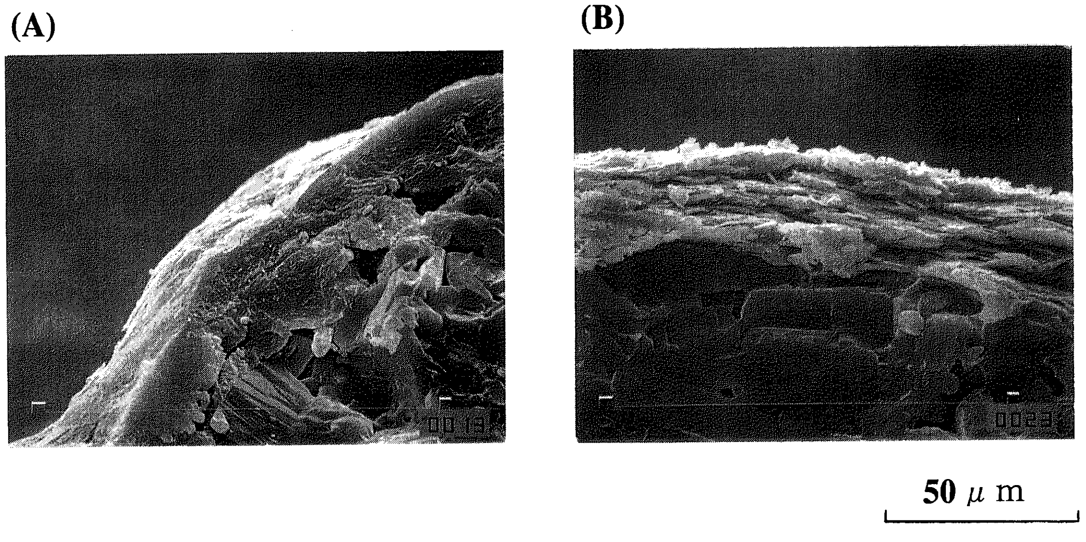

Fig. 3. Microphotographs of Coated Layer's Cross Section of Beads Coated with HCO Alone or with Mixture of HCO and Talc

(A), HCO alone; (B), mixture of HCO and talc.

3) Preparation of Zero-Order Sustained Release Beads: The mixture of HCO and TC-5 (weight ratio, 35:65) was first adhered on the NA core beads up to a 200% coating level, followed by a coating with the mixture of HCO and talc (weight ratio, 15:85) up to a 100% coating level. The structure of the resultant beads is shown in Fig. 6A. The dissolution test was performed by changing pH of the dissolution medium and the rotation speed of the paddle (100 to 200 rpm). The apparently zero-order dissolution profile was obtained (Fig. 6). The dissolution rate changed little when the pH of the dissolution medium was changed (data not shown), and the rotation speed of the paddle was increased from 100 to 200 rpm. This suggested that the dissolution of NA from the beads prepared by this method would be less affected by GI physiology at all coating levels.

As described above, various types of CR beads were prepared by the new technique. In all cases the producibilities were excellent (Rec% and Ysc% were over 95%). Thus, it was concluded that this latest method was very useful and had wide applicability.

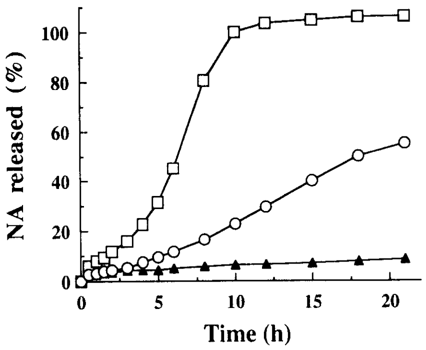

Fig. 4. Dissolution Profile of NA from Beads Coated with Magnesium Stearate and HCO

Dissolution medium: ○, purified water; ▲, 1st fluid; □, 2nd fluid. The dissolution test was performed by paddle method using beads with particle sizes in the range of 500 to 1000 μm (37 °C, 100 rpm).

References

1) Maejima T., Osawa T., Nakajima K., Kobayashi M., *Chem. Pharm. Bull.*, **45**, 904—910 (1997).
2) Maejima T., Osawa T., Nakajima K., Kobayashi M., *Chem. Pharm. Bull.*, **45**, 1332—1338 (1997).
3) Maejima T., Osawa T., Nakajima K., Kobayashi M., *Chem. Pharm. Bull.*, **45**, 518—524 (1997).
4) Maejima T., Osawa T., Nakajima K., Kobayashi M., *Chem. Pharm. Bull.*, **45**, 1833—1839 (1997).
5) Efentakis M., Al-Hmoud H., Buckton G., Rajan Z., *Int. J. Pharmaceut.*, **70**, 153—158 (1990).
6) Suzuki Y., Takeyama T., Fujii T., Noda K., Sakamoto T., Abstracts of Papers, The 108th Annual Meeting of Pharmaceutical Society of Japan, Hiroshima, April 1988.
7) Maki T., Ueki N., Ozawa Y., *J. Soc. Technol. Jpn*, **25**, 338—343 (1988).
8) Ghali E. S., Klinger G. H., Schwartz J. B., *Drug Dev. Ind. Pharm.*, **15**, 1311—1328 (1989).
9) Akiyama Y., Yoshioka M., Horibe H., Hirai S., Kitamori N., Toguchi H., *J. Controlled Release*, **26**, 1—10 (1993).

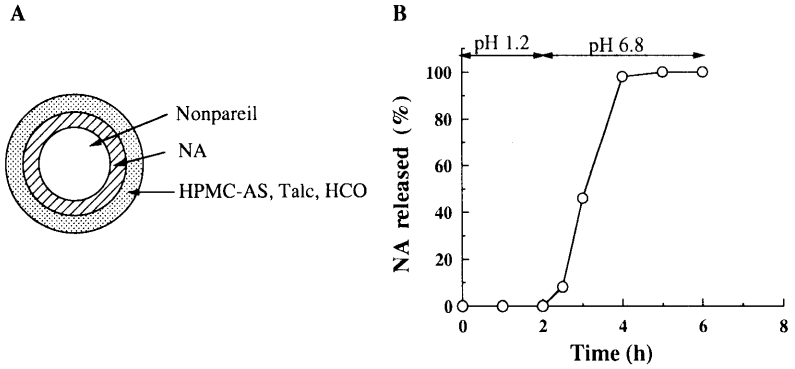

Fig. 5. Dissolution Profile of NA from Beads Coated with Mixture of HPMC-AS, Talc, and HCO

A, structure of the resultant beads; B, dissolution profile of NA from the resultant beads. The dissolution test was performed in the 1st fluid for 2 h and then the dissolution medium was changed to the 2nd fluid using beads with particle sizes in the range of 500 to 1000 μm (paddle method, 37 °C, 100 rpm).

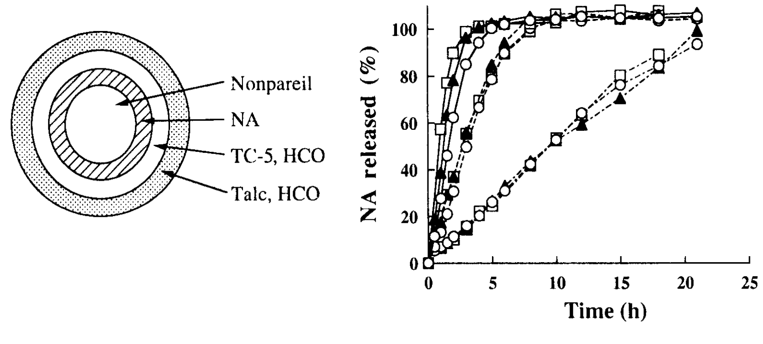

Fig. 6. Dissolution Profile of NA from Beads Coated with Mixture of TC-5 and HCO, and Mixture of Talc and HCO

A, structure of the resultant beads; B, dissolution profile of NA from the resultant beads; coating level of HCO and talc: ——, 60%; ------, 80%; -----, 100%; paddle rotation speed: ○, 100 rpm; ▲, 150 rpm; □, 200 rpm. The dissolution test was performed in purified water using beads with particle sizes in the range of 500 to 1000 μm (paddle method, 37 °C).