Effects of the centrifugal coating and centrifugal fluidized bed coating methods on the physicochemical properties of sustained-release microparticles using a multi-functional rotor processor

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Abstract

The purpose of the present study was to examine the effect of coating processes on the physicochemical properties of sustained-release microparticles prepared by centrifugal coating (CC) and centrifugal fluidized bed coating (CFC) using a multi-functional rotor processor.

Acetaminophen (APAP)-loaded microparticles (DP) were coated with 30% w/w aqueous polymer dispersion of Eudragit® RS (RS) by CC or CFC methods with the apparatus until a dry polymer weight gain of 30%, 60%, 150% and 200% w/w was achieved, and these coated microparticles were abbreviated as CC-DP-RS and CFC-DP-RS, respectively. Both coated microparticles had similar physicochemical properties, but some differences in the drug dissolution behaviors of CC-DP-RS and CFC-DP-RS at lower coating levels were observed. That is, the coated microparticles prepared by CC showed faster release than that by CFC. As a result of dissolution study using Talc seal-coated microparticles and thermal study using differential scanning calorimeter, the rapid dissolution behaviors from CC-DP-RS at the lower coating levels of RS might be due to APAP migration to the coating film during coating due to the weak drying efficacy of the CC method.

These findings suggest for the first time that CFC is a suitable method for the coating of functional polymers at lower polymer coating levels, whereas, for the CC method, adjustment of operational conditions (e.g., product temperature, inlet air volume and liquid flow rate) would be required.

**Keywords:** Multi-functional rotor processor; microparticle coating; sustained-release; centrifugal coating; centrifugal fluidized bed coating

**Abbreviations:** APAP, acetaminophen; CC, centrifugal coating; CFC, centrifugal fluidized bed coating; CT, computed tomography; DP, drug layered particles; DSC, differential scanning calorimeter; HPC, hydroxypropylcellulose; RS, Eudragit® RS; SEM, scanning electron microscopy; $T_g$, glass transition temperature
1. Introduction

Microparticle coating using functional polymers is a method in which functionalities such as sustained or delayed release can be added to particles containing drugs with a particle size less than 200 μm. The use of particles of this size, in general, ensures that a feeling of “roughness” in the mouth is avoided. The coating of microparticles is often carried out using the top-spray [1], bottom-spray (Wurster-type) [2] or side-spray [3] fluidized bed coating method. These coating mechanisms and processes are quite different [4-6]. Hence, the physicochemical properties, such as particle size distribution, flowability, and dissolution behavior of the coated particles prepared by these methods are also expected to be different.

Yang et al. [7] reported that, when comparing the top- and bottom-spray fluidized bed coating methods with tangential-spray centrifugal coating by attaching a spray nozzle to the side wall of the fluidized bed apparatus, the spray position and the chamber geometry are the most important factors affecting the drug dissolution behavior of coated particles. In addition, Takei et al. [8] reported that, when comparing diagonal-top-spray and tangential-spray centrifugal coating methods with the top-spray fluidized bed coating method, the spray position also affected the coating efficiency and surface structures as well as the drug dissolution behavior of coated particles. However, these comparisons were carried out under different operational conditions, such as inlet air flow volume, liquid flow rate, and product temperature and/or different types of fluidized bed apparatus. That is, although the particle circulation pattern and the drying capacity of the apparatus might (in a practical sense) be involved in the particle properties and the drug dissolution behavior, reports focusing on these concerns are lacking. Therefore, if it is possible to directly compare coating processes using an apparatus under identical operational conditions, new insights into the effect of the coating process on particle properties and its drug dissolution behavior could be obtained.
Against this background, we focused on a multi-functional rotor processor (Granurex®; GX-20; Freund Industrial Co., Ltd., Tokyo, Japan; abbreviated as GX-20; Fig. 1). This apparatus enables to carry out centrifugal coating (CC; Fig. 1A) and centrifugal fluidized bed coating (CFC; Fig. 1B) without changing the spray position (the tangential-spray mode) because an up-and-down drying device (MOV-A-BLO) was equipped in the middle of the apparatus. Fundamentally, CC allows the particles to tumble onto a rotor, whereas CFC allows the particles to tumble on the rotor and become fluidized by the air flow from the MOV-A-BLO which can be positioned near the rotor. The purpose of the present study was to examine the effect of the coating processes, CC and CFC, on the physicochemical properties and drug dissolution behaviors of sustained-release microparticles.
2. Experimental

Nonpareil®-108 (100) (Freund Industrial Co., Ltd.) was layered with 70% w/w ethanol aqueous solution containing 20% w/w acetaminophen (APAP; Iwaki Pharmaceutical Co., Ltd., Tokyo, Japan) and 2% w/w hydroxypropylcellulose (HPC-L; Nippon Soda Co., Ltd., Tokyo, Japan) by CFC method with GX-20, and 30% w/w APAP-loaded microparticles (drug layered particles; DP) were finally obtained. In addition, DP were coated with an aqueous dispersion containing 10% w/w talc (Matsumura industrial Co. Ltd., Tokyo, Japan) and 1% w/w HPC-L by CFC method with GX-20, until a weight gain of 10% w/w was achieved, and talc seal-coated microparticles (DP-Talc) were obtained. The prepared DP or DP-Talc were then coated with 30% w/w aqueous polymer dispersion of Eudragit® RS ((poly (ethylacrylate-methylmethacrylate-trimethylammonioethyl methacrylate chloride) copolymer with a ratio of 1:2:0.1), abbreviated as RS, Röhm Degussa, Germany) containing 5% w/w dibutyl sebacate as a plasticizer (based on the dry polymer mass; Sigma-Aldrich Japan Co. Ltd., Tokyo, Japan) and 25% w/w talc as an anti-adherent (based on the dry polymer mass) by CC or CFC methods with GX-20 until a dry polymer weight gain of 30%, 60%, 150% and 200% w/w was achieved. These polymer-coated microparticles were abbreviated as CC-DP-RS, CFC-DP-RS, CC-DP-Talc-RS and CFC-DP-Talc-RS, respectively. The polymer-coated microparticles were then blended with 0.5% w/w hydrophilic fumed silica (AEROSIL® 200, Nippon Aerosil Co. Ltd., Tokyo, Japan) as an external anti-tacking agent and subsequently cured in an oven for 2–12 h at 70°C. The process parameters for the drug-layering, seal coating and polymer-coating processes are listed in Table 1. Especially, during the polymer-coating processes, to make the product quality same as far as possible in each coating method, inlet air temperature was adjusted to 45–55°C for CC method and 40-50°C for CFC method, respectively, resulting the product temperature was maintained to be 30°C.

The yield of the final product (% w/w) was calculated by dividing the mass of the polymer-coated product by that of the DP or DP-Talc and dry polymer substance. The particle size
distribution was obtained by sieve analysis of approximately 10 g of polymer-coated microparticles using testing sieves (Tokyo Screen Co., Ltd., Tokyo, Japan) with aperture sizes from 45 μm to 212 μm. A 100 mL cylinder container was filled with an accurately weighed granule sample and the top of the sample was leveled off. Bulk density was calculated as the ratio of the mass to the volume of the sample. Dissolution behaviors of APAP from polymer-coated microparticles were examined in accordance with the paddle method described in the Japanese Pharmacopoeia 16th edition. The test medium was 900 mL of distilled water, and the medium was heated to 37±0.5°C. The paddle rotation speed was 100 rpm. The amount of APAP released from coated microparticles was quantified by determining the absorbance at 243 nm of the filtered solution under test. The coating efficiency was calculated by dividing the actual amount of APAP in coated microparticles by the theoretical one. Surface and inner structures of the coated microparticles were assessed using a scanning electron microscope (JSM-5310LV, JEOL, Tokyo, Japan) and computed tomography (CT) with synchrotron X-ray radiation (BL37XU, SPring-8) [9, 10]. The films were prepared by casting RS dispersion containing APAP onto Teflon® plates. APAP loading was varied from 5% to 20% (w/w, based on the dry polymer substance). Films were dried in an oven for 72 h at 40°C. The thermal analysis of the films and coated microparticles were performed using a differential scanning calorimeter (DSC 7020, Seiko Instruments Inc., Tokyo, Japan; abbreviated as DSC). Samples were analyzed under a nitrogen atmosphere at a heating rate of 20°C/min at a temperature range of 0°C to 100°C. Statistical analyses were performed using the Student t-test. A probability value of $P < 0.05$ was considered to indicate statistical significance.
3. Results and discussion

The yield, median diameter, bulk density, and coating efficiency of CC-DP-RS and CFC-DP-RS are presented in Table 2. No significant differences between any of these physicochemical properties were observed amongst these particles. These findings indicate that the coating process and coating levels of both methods did not affect these parameters. However, when comparing the drug dissolution behaviors from CC-DP-RS and CFC-DP-RS, some differences at the coating levels of 30% and 60% were observed (Fig. 2). That is, at the 30% coating level, the ratios of APAP dissolved 20 min after the start of the dissolution test from the CC-DP-RS and CFC-DP-RS were 71.7% and 55.3%, respectively, whereas, at the 60% coating level, those at 45 min were 92.7% and 65.0%, respectively. No significant differences were observed at coating levels of 150% and 200%. These results suggest that polymer-coated microparticles prepared by CC at lower coating levels gave a faster release than those prepared by CFC.

To clarify the differences in dissolution behaviors from CC- and CFC-particles, their surface and inner structures were determined by scanning electron microscopy (SEM) and synchrotron X-ray radiation methods because differences in these structural characteristics could affect the dissolution behaviors of the particles [8]. Globular particles with a smooth surface were observed in both types of coated microparticles (Figs 3A and B). CT measurements using synchrotron X-ray radiation revealed that APAP and RS layers were formed on the surface of Nonpareil®-108 in both particles (Figs 3C and D). The white part in the RS layer appeared to be talc, and very dense RS films without pores were observed in both types of coated particles. These results demonstrated that CC-DP-RS and CFC-DP-RS had similar surface and inner structures, and these features were found not to affect the differences in drug dissolution behaviors.

Therefore, although the inner structures were similar upon CT analysis, we hypothesized that APAP in the DP surface was dissolved in the coating liquid during the CC coating operation because the drying efficacy of the CC method might be inferior compared with that of the CFC.
method as shown in Fig. 4. Subsequently, the diffusion distance of the drug from the layer was shortened. Consequently, rapid dissolution would have been observed in CC-DP-RS. Actually, as a preliminary study, when the liquid flow rate was increased from 3 g/min to 4 g/min, polymer coating was successfully finished for CFC method, whereas, as for the CC method, some agglomerates were loaded on the rotors and enough polymer coating was not successfully completed, indicating that this phenomenon could be directly explained by the inferiority of drying performance in CC method. We then examined whether APAP migration to the coating film during the coating operation was involved in the differences in drug dissolution behavior observed between CC-DP-RS and CFC-DP-RS. DP-Talc in which the APAP layer was seal-coated by the talc layer to prevent APAP migration was prepared. CC-DP-Talc-RS and CFC-DP-Talc-RS, which had similar particle properties (data not shown) were then obtained by CC and CFC methods. Interestingly, no significant differences between the dissolution behaviors of CC-DP-Talc-RS and CFC-DP-Talc-RS were observed at each RS coating level (Figs 5A–D). These results suggest that differences in drug dissolution behaviors observed between CC-DP-RS and CFC-DP-RS might be derived from APAP migration to the coating films.

Siepmann et al. [11] reported that, when some drugs such as ibuprofen and chlorpheniramine maleate, were added to the RS polymer dispersion, the drug acted as a plasticizer for the polymer membrane, causing a decrease in the glass transition temperature ($T_g$) of the polymer. Therefore, the values of $T_g$ for the RS film containing APAP and coated microparticles were measured using DSC. In the case of RS films, the $T_g$ decreased gradually from 57.2°C to 47.9°C, in an APAP content-dependent manner (Fig. 6A). This result suggests that APAP acts as a plasticizer for the RS polymer as well as other drugs. In addition, the $T_g$ of RS polymer in CC-DP-RS decreased at coating levels of 30% and 60% in comparison to that in CFC-DP-RS, whereas there were no significant differences in the $T_g$ of coated particles at coating levels of 150% and 200% (Fig. 6B). Furthermore, no changes in the $T_g$ of CC-DP-Talc-RS and CFC-DP-Talc-RS
were observed due to the seal-coating of talc between the drug and polymer layers (Fig. 6C).

Therefore, it was shown that the rapid dissolution behaviors from CC-DP-RS at lower coating levels of RS might be caused by APAP migration to the coating film during coating, whereas at the higher coating levels of RS, because the RS layer was thicker, this APAP migration would not have a significant effect on dissolution.

4. Conclusion

In the present study, we determined the effect of the coating processes of CC and CFC methods on the physicochemical properties of microparticles using a multi-functional rotor processor with a tangential spray mode. Both coated microparticles had similar physicochemical properties, but some differences in the drug dissolution behaviors of CC-DP-RS and CFC-DP-RS at lower coating levels were observed. In addition, this phenomenon might be explained by the migration of APAP to the coating film during the CC coating process due to the weak drying efficacy of the CC method. These findings suggest that CFC is a suitable method for the coating of functional polymers at lower polymer coating levels, whereas, for the CC method, further study for adjusting operational conditions (e.g., product temperature, inlet air volume and liquid flow rate) would be required to make functional microparticles at lower polymer coating levels.

Acknowledgments

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References


### Table 1. Operational conditions.

<table>
<thead>
<tr>
<th>Core material</th>
<th>Drug layering</th>
<th>Seal coating</th>
<th>Polymer coating</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nonpareil®</td>
<td>DP</td>
<td>DP</td>
</tr>
<tr>
<td>MOV-A-BLO state</td>
<td>Lower</td>
<td>Lower</td>
<td>Upper, Lower</td>
</tr>
<tr>
<td></td>
<td>CFC</td>
<td>CFC</td>
<td>CC, CFC</td>
</tr>
<tr>
<td>Rotor speed (rpm)</td>
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<td>300</td>
<td>300</td>
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<tr>
<td>Air flow rate (L/min)</td>
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<td>400</td>
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<tr>
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<td>40–50</td>
<td>45–55, 40–50</td>
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<tr>
<td>Product temperature (˚C)</td>
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<td>30</td>
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<tr>
<td>Spray air pressure (MPa)</td>
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<td>0.3</td>
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<tr>
<td>Liquid flow rate (g/min)</td>
<td>8.0</td>
<td>4.0</td>
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</table>

### Table 2. Particle properties of DP-RS prepared by CC and CFC methods.

<table>
<thead>
<tr>
<th>Coating level</th>
<th>30%</th>
<th>60%</th>
<th>150%</th>
<th>200%</th>
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<tr>
<td></td>
<td>CC</td>
<td>CFC</td>
<td>CC</td>
<td>CFC</td>
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<tr>
<td>Yield (%)</td>
<td>90.0</td>
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<td>93.2</td>
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<td>Median diameter (μm)</td>
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<td>115</td>
<td>118</td>
<td>118</td>
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<tr>
<td>Bulk density (g/cm³)</td>
<td>0.689±0.001</td>
<td>0.691±0.003</td>
<td>0.698±0.001</td>
<td>0.697±0.001</td>
</tr>
<tr>
<td>Coating efficiency (%)</td>
<td>102.7±4.2</td>
<td>97.86±2.5</td>
<td>96.9±1.7</td>
<td>99.1±1.7</td>
</tr>
</tbody>
</table>
Figure 1. Schematic diagram of (A) centrifugal coating and (B) centrifugal fluidized bed coating using a multi-functional rotor processor.

Figure 2. Dissolution profiles of APAP from CC-DP-RS and CFC-DP-RS at the polymer coating levels of (A) 30%, (B) 60%, (C) 150% and (D) 200%.

Figure 3. Surface and cross sectional images by SEM and CT. Images by SEM were (A) CC-DP-RS and (B) CFC-DP-RS, and those by CT were (C) CC-DP-RS and (D) CFC-DP-RS, respectively. In the cross sectional images, X-ray linear attenuation coefficients values between 0 and 70 are shown in 8 bit grayscale with the value 70 and higher as white.

Figure 4. Schematic representation of film formation mechanism achieved by CC and CFC method.

Figure 5. Dissolution profiles of APAP from CC-DP-Talc-RS and CFC-DP-Talc-RS at the polymer coating levels of (A) 30%, (B) 60%, (C) 150% and (D) 200%.

Figure 6. Changes in the glass-transition temperatures of (A) RS films, and (B) DP-RS and (C) DP-Talc-RS prepared by CC and CFC methods.
Figure 3

(A) (B)

(C) (D)

Nonpareil®
APAP layer
RS layer
Talc

50 μm
50 μm
50 μm
50 μm
Figure 4

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CC method

Low drying efficacy
APAP migration

Eudragit® RS 30 D

Curing step
Polymer particle deformation

APAP layer
Nonpareil®

CFC method

High drying efficacy

Eudragit® RS 30 D

Curing step
Polymer particle deformation

APAP layer
Nonpareil®

Eudragit® RS layer
APAP layer
Nonpareil®
Figure 5

(A) 30% coating level
(B) 60% coating level
(C) 150% coating level
(D) 200% coating level

CC method
CFC method

APAP released (%) vs. Time (h)
Figure 6

(A) RS film

(B) DP-RS

(C) DP-Talc-RS

Glass transition temperature (˚C)

Coating level (%)

APAP content (%)

P < 0.01

P < 0.05

CC method

CFC method