Dry Powder Coating using Planetary Centrifugal Mixer

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ABSTRACT - Purpose: Extemporaneous compounding is an important part of pharmacy practice, and should be standardized and sophisticated to ensure the quality of the compounded preparations. Recently, we applied a planetary centrifugal mixer (PCM) to powder blending, which has attracted interest for its small scale and lack of contamination. In this study, we aimed to reveal the feasibility of dry powder coating through ordered mixing of fine particles using PCM. **Methods**: Cohesive lactose powders (Pharmatose450M) were dry coated with magnesium stearate (MgSt) using from 0.1 to 5%(w/w) content. The operational variables tested were operation time (1-30 min), operation speed (400-1000 rpm), vessel size (24-100 mL), and charging rate in the vessel (20-40%). The processed powders were evaluated for their surface morphology, flowability, and wettability. Furthermore, fine ibuprofen particles were coated with various lubricants, and then the dissolution profiles were examined. The crystallinity of ibuprofen was assessed using FT-IR and PXRD. **Results**: Lactose powders were successfully coated with MgSt using PCM. When the level of MgSt was over 1%, the surface of the lactose powders was thoroughly covered. Angles of repose were 51° and 41° for unprocessed and processed powders with 1% MgSt, respectively. The contact angle of the water drop on the 1% MgSt sample leached to be 132°, changing to a hydrophobic surface. Investigations under various operational conditions revealed that higher improvement was observed upon higher speed and longer time, and a smaller charging rate in the vessel. Vessel size had no impact. Moreover, improved dissolution of ibuprofen coated with both hydrophilic and hydrophobic lubricants was observed owing to good dispersing behavior. Besides, no alteration of crystallinity was detected. **Conclusions**: PCM is an effective tool for dry powder coating with low impact stress. The presented method will contribute a great deal to making crushed tablets a functional powder.

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INTRODUCTION

There are a limited number of suitable dosage forms commercially available for children due to the lack of financial viability for the pharmaceutical industry of such dosage forms (1). In practice, pharmacists are frequently challenged with providing a suitable formulation for patients who are unable to swallow solid dosage forms (2). The preparation of oral powders from crushed tablets or opening capsules is one solution to this problem for patients (3). However, certain crushed tablets or capsule contents have a problem regarding the physicochemical stability of the active pharmaceutical ingredient (API) (4, 5). To protect the API from the external environment, advanced methods are needed for extemporaneous compounding for pediatric preparations. When the preparation is dispensed to patients in the form of a powder, highly sophisticated techniques, which are practical processes in pharmacies and take a short amount of time, are required for protecting against light and moisture, and achieving taste masking of crushed tablets or opening capsules.

Dry powder coating techniques are widely used to modify the properties of powders, such as their flowability, wettability, flavor, and color, because they are simpler, cheaper, safer, and more environmentally friendly than solvent-based alternatives (6). Therefore, such techniques are worth introducing to the extemporaneous compounding of pediatric medicines. For example, powders made of crushed tablets are coated with a lubricant to improve the flow ability.

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Contents of capsules are prompted to adhere to core particles, such as lactose, cellulose, and sugar particles, and then coated with appropriate excipients in order to prevent the access of light or moisture. In addition, dry powder coating apparatus is now needed by pharmacists or compounders. A lot of technologies of dry particle coating, such as mechanofusion, hybridization, magnetic-assisted impaction coating, theta-composer, rotating fluidized bed coating, pressure swing granulation, and high shear mixing, have been developed (7). However, these machines are intended for use in industry, and are not appropriate for extemporaneous compounding in pharmacies because of their cost and space requirements.

We recently demonstrated that a planetary centrifugal mixer (PCM), which is conventional dispensing equipment for pharmacies, was effectively applied to dry mixing of powdered medicines without cross-contamination (8). The PCM is a mixer that exploits convective mixing force derived from revolution and rotation movements for the rapid dispersion and mixing of as much as 500 g of a variety of materials. Thus, the PCM needs no blade for mixing, avoids concern over cross-contamination, and it easy to clean. The application of the PCM to dry powder mixing has had a great impact because it can be operated in a dispensing process in pharmacies and is commonly available at pharmaceutical product manufacturing sites (9). In the course of our study, we identified the possibility of dry powder coating through ordered mixing. Therefore, the aim of this study is to introduce the equipment into dry powder coating in a short time and on a small scale. This is the first attempt not only in pharmaceutical compounding but also in the industrial field.

In this study, we investigated the feasibility of dry powder coating via PCM using two kinds of host-guest system. The first system was cohesive lactose powder and magnesium stearate (MgSt) as core and coating materials, respectively. Since the cohesive lactose powder-MgSt system has been previously used as a host and guest combination for

investigation of the performance of dry coating methods (10), we can characterize our method compared with the different types of mixer. The effects of these coatings on the surface morphology, change in particle size, powder flow properties, and wettability were used as indicators of the equipment's performance. Moreover, the effects of operational variables on those indicators were also investigated, such as operation time, operation speed, charging in the vessel, and vessel size. As a second system, we employed a fine ibuprofen (IBU) particle and lubricant system as a model drug-excipient system. IBU is a non-steroidal anti-inflammatory drug belonging to class II of the Biopharmaceutical Classification System (11); therefore it is micronized to improve solubility. However, the micronized particles, which are a white crystalline powder, tend to aggregate and are difficult to handle. For this reason, we used the fine IBU powder as a model drug. In this study, the drug powder was processed with commonly used lubricants using PCM, and then the resultant composite particles were examined for flowability, drug dissolution behavior, and alteration of the drug crystallinity.

METHODS

To reveal the feasibility of dry powder coating using a PCM, two kinds of typical combination of host and guest particle were employed, and resultant composite particles were examined for their properties.

Materials
An α-lactose monohydrate powder, Pharmatose450M (particle size approximately 20 μm), was donated by DFE Pharma (Tokyo) and chosen as a host particle with hydrophilicity. IBU (Ibuprofen25 US Quality) was donated by BASF (Tokyo), having a mean particle size of approximately 25 μm. The lubricants used in this study are listed in Table 1.

Table 1   Lubricants used in this study

Lubricant	Mean particle size *	Property
Aerosil 200	12 nm	hydrophilic
Aerosil 300	7 nm	hydrophilic
Aerosil R973	16 nm	hydrophobic
Magnesium stearate	5 μm	hydrophobic

* From the manufacturer's information sheet

Aerosil 200, Aerosil 300, and Aerosil R973 were generously supplied by Nippon Aerosil Co., Ltd. (Tokyo) and MgSt was obtained from Nacalai Tesque Inc. (Kyoto, Japan). All samples were used as received.

Dry powder coating process
A PCM (NR-500, Thinky Co., Ltd., Tokyo) was used to prepare the coated particles. The host and guest powders were placed into a vessel and the vessel was closed with a lid. Subsequently, the vessel was set in the mixer with a fitting adaptor. The mixer was operated at pre-determined speed and time. The ratio of the rotation and revolution speeds was fixed at 1:1 in this study.

The operational variables were operation speed, operation time, vessel size (UG container series, Umano Chemical Container Co., Osaka, Japan), and charging rate in the vessel. All of the vessels were made of polypropylene. The operational variables used in this study and their ranges are summarized in Table 2.

Assessment of flowability
The flowability of the samples was characterized through measuring the angle of repose (AOR) by the standard method according to the Japanese Pharmacopeia 16th ed. (12). AOR was determined from a circular cone formed on a cylinder of 30 mm in diameter, and measured directly from a digital photo. In general, powders with AOR values between 30 and 45° were considered easy-flowing, and lower AOR values indicate superior flow behavior (12). The experiments were repeated three times at room temperature and humidity ($24 \pm 2°C$, $50 \pm 5\%$ relative humidity).

The aerated bulk density was measured using the Japanese Pharmacopeia method (12). Samples (3.5 g) were slowly poured into a 25-mL measuring cylinder via a funnel at a fixed height. The volume was measured by inspection. The aerated bulk density was calculated by dividing the sample weight by the volume. The experiments were repeated three times.

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Scanning electron microscopy
The surface morphology of the samples was examined using a scanning electron microscope (SEM, JSM-6390LA, JEOL, Tokyo). Each sample was poured onto double-sided carbon black tape, which was mounted on a sample holder. The samples were then sputter-coated with platinum using an auto-coater (JFC-1600, JEOL, Tokyo).

Measurement of particle size distribution
The particle size distributions of both original and processed powder samples were measured using a laser diffraction particle size analyzer (LDSA-1500A, Nikkiso Co., Ltd., Tokyo) with dry dispersion capability. The dispersing air pressure was set at 3 kgf/cm^2 to avoid detachment of guest particles from host particles (13). Data are expressed as the average of three measurements.

Wettability test
The wettability was studied by the sessile drop method (14). A small water drop of 10 μL was deposited on the surface of a powder bed prepared for each sample. The shape of the drop profile was observed and used to determine the contact angle (15). Data are expressed as the average of five measurements

Drug dissolution test
Dissolution tests were performed according to the Japanese Pharmacopeia dissolution test 2nd method (paddle method) (12) using a dissolution tester (NTR-6100A, Toyama Sangyo Co., Ltd., Osaka, Japan). The dissolution medium (900 mL) was phosphate-citrate buffer (pH5.5) , and the temperature was maintained at $37 \pm 0.5°C$. The paddle rotating speed was 50 rpm . Powders equivalent to 200 mg of IBU were added to the dissolution medium. Sample medium was collected at 5 , 10 , 15 , 30 , 60 , and 120 min, and filtered through a 0.45-μm filter for quantitation. A quantitative test on the dissolved amount of drugs was carried out using a UV-VIS spectrophotometer (U-2010, Hitachi Co., Ltd., Tokyo) at 261 nm. All of the experiments were performed in triplicate.

Table 2 Operational variables of the planetary centrifugal mixer used in this study

Variable	Examined value	Potential range
Time (min)	1, 5, 10, 30	0-30
Speed (rpm)	400, 600, 800, 1000	400-1000
Charging rate (%)	20, 30, 40	0-80
Vessel size (mL)	24, 35, 58, 100	10-750

Turbidity test

To assess the dispersability of the powders, the optical turbidity of the suspension was measured using a UV-VIS spectrophotometer (U-2010, Hitachi Co., Ltd., Tokyo). A total of 100 mg of the powder sample was placed into 4 mL of water, and then dispersed using a vortex mixer. The resultant suspension was immediately analyzed at a wavelength of 660 nm. The turbidity is expressed as the mean ± S.D. of three measurements.

Attenuated total reflectance Fourier-transform infrared (ATR FT-IR) measurement

Samples were subjected to FT-IR spectroscopy using an IR Prestigate-21 spectrophotometer (Shimadzu Co., Kyoto, Japan) with a diamond ATR attachment. Scanning was conducted from 4000 to 500 cm^{-1} with 64 repeated scans averaged for each spectrum. The resolution was 4 cm^{-1} and the interval of scanning was 2 cm^{-1}.

Powder X-ray diffraction (PXRD) measurement

PXRD was conducted with MiniFlexII (Rigaku Co. Ltd., Tokyo) using Cu as a target at a voltage of 30 kV and a current of 15 mA. Samples were scanned for a 2θ range of 5-35° at 4°/min by a Cu-Kα radiation source.

STATISTICAL ANALYSIS

To compare the data obtained from different batches of samples, data were subjected to analysis of variance followed by Tukey's multiple range test. Statistical significance was considered at the level of $p < 0.05$ (SPSS, Version 22.0, SPSS Inc., Chicago, USA).

RESULTS

I. In the lactose-magnesium stearate systems
Effects of operational variables on flowability

We initially investigated the effects of operation speed, operation time, charging rate in the vessel, and vessel size on dry powder coating using the PCM in order to understand the process operational design space. The flowability of the processed powders was employed as an indicator of the coating performance using the lactose-MgSt systems. The amount of MgSt was set at 1% because it was most effective for improving the flowability, as mentioned below. The variable focused on in each test is stated in the section, and the other operating conditions used were 20%

charging in a 35-mL vessel and 1000 rpm for 10 min. The flowability of the processed powders was assessed entirely using the AOR and the aerated bulk density.

Figure 1 shows the change of the AOR as a function of time when the PCM was operated at various processing speeds. When the operation speeds were from 400 to 800 rpm, the AOR decreased with an increase of the processing time from 1 to 30 min, indicating improvement in the flowability of the lactose powders. An increase in processing time improved the flowability of the lactose powder since the MgSt powder was more de-agglomerated and better dispersed. At a speed of 1000 rpm, however, the AOR value reached a plateau at 10 minutes, indicating that additional improvement did not occur subsequently. As shown in Figure 1, the aerated bulk density also increased with operation time. The change was evident for the aerated bulk density as well as for the AOR.

The influence of the operation speed was also evaluated from the results shown in Figure 1. At one minute of operation, the AOR were 49.9, 50.0, 47.5, and 44.5°, at speeds of 400, 600, 800, and 1000 rpm, respectively. A high speed tended to provide high flowability for a short duration. In general, at the first step of ordered mixing, self-agglomerates of MgSt need to be dispersed to adhere the lactose powder immediately (16). High-speed operation seemed to cause rapid de-agglomeration owing to a higher mechanical force. At 30 minutes of operation, the AOR were 42.0, 40.6, 40.8, and 39.5, at speeds of 400, 600, 800, and 1000 rpm, respectively. At operation speeds from 600 to 1000 rpm, good flowability was obtained within 30 minutes. A higher operation speed tended to cause de-agglomeration of the MgSt and more uniform surface coverage, resulting in better flowability. Similar influences of operation speed and time were observed by Zhou et al. (17) when Pharmatose450M was coated with 1% MgSt using mechanofusion. In the present study, adequate operational conditions seemed to be 1000 rpm for more than 10 minutes.

Effect of charging rate

Charging rate in the vessel is one of the most important variables affecting coating performance (18). The AOR and the aerated bulk density of powders processed at the various charging rates are summarized in Table 3.

The AOR increased with an increase of charging rate, as shown in Table 3. This suggested that the efficiency of powder coating was impaired. In general, a higher charging rate of powders caused a reduction in the area for the free movement of the powders. As a result, effective coating was not achieved because of a reduction in collisions between particles (19). Therefore, a lower charging rate in the vessel was recommended to improve the flowability in the PCM.

Effect of vessel size

In this study, we examined three sizes of vessel: 24 mL, 58 mL, and 100 mL. The AOR and the aerated bulk density of the processed lactose powders are summarized in Table 4. There was no significant difference in both the AOR and the aerated bulk density among the three kinds of vessel, indicating that vessel size did not influence the coating performance.
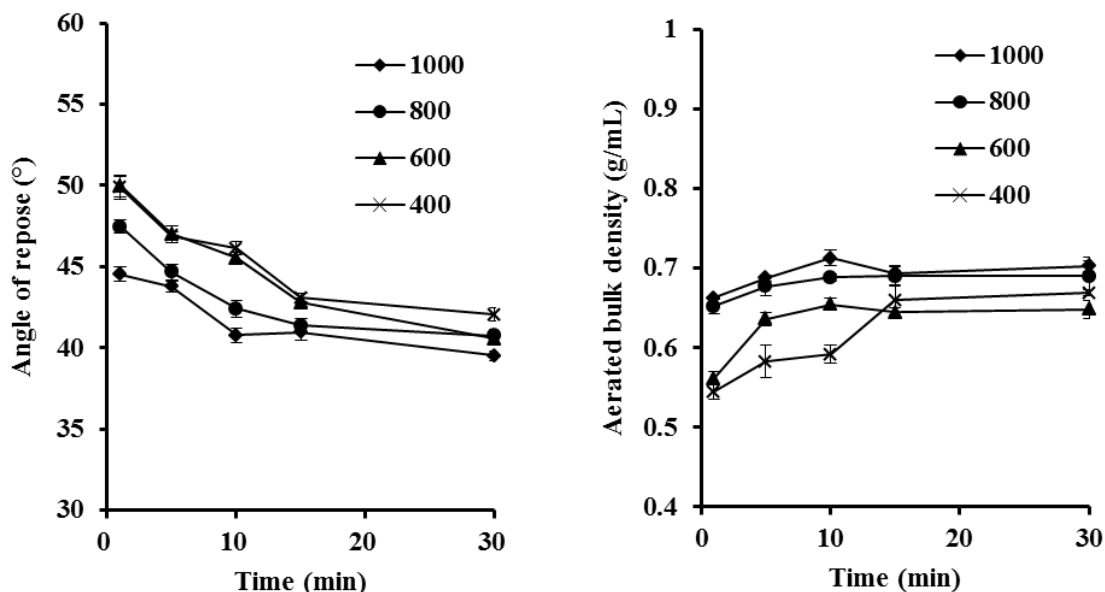

Figure 1. Change in angle of repose and aerated bulk density of the coated lactose powders as a function of processing time, using various operation speeds (400-1000 rpm). The values presented as the mean ± S.D. ($n = 3$).

Table 3. Effect of charging rate on angle of repose and aerated bulk density of processed lactose powders with 1% magnesium stearate

Charging rate	Angle of repose (°)	Aerated bulk density (g/mL)
20%	40.8 ± 0.45**	0.713 ± 0.0010**
30%	43.1 ± 0.24†	0.671 ± 0.0060
40%	44.7 ± 0.81	0.675 ± 0.0087

The values are presented as the mean ± S.D. ($n = 3$). The asterisks show significant differences from the others at ** $p < 0.01$. The dagger shows a significant difference from the 40% sample at † $p < 0.05$.

Table 4. Effect of vessel size on angle of repose and aerated bulk density of processed lactose powders with 1% magnesium stearate

Vessel size	Angle of repose (°)	Aerated bulk density (g/mL)
24 mL	41.7 ± 0.90	0.687 ± 0.014
58 mL	41.3 ± 0.39	0.692 ± 0.0076
100 mL	42.5 ± 0.90	0.678 ± 0.0036

The values are presented as the mean ± S.D. ($n = 3$). No significant differences were detected ($p < 0.05$).

II. Effect of magnesium stearate amount on coating performance

Lactose powders were processed with various contents of MgSt using a 35-mL vessel with 20% charging rate at 1000 rpm for 10 min. Initially, surface morphologies of original host and guest powders, and of the resultant powders after processing were examined using SEM. Figure 2 shows representative SEM micrographs of unprocessed lactose (a), unprocessed MgSt (b), and processed lactose with 0-5.0% MgSt (c-f).

The unprocessed lactose powders showed irregularly angular and sharp-edged shapes (Figure 2a). MgSt tended to form agglomerates, approximately 15 μm in diameter, as shown in Figure 2b. It is worth mentioning that the shape and appearance of the processed lactose without MgSt were rarely altered (Figure 2c). On the other hand, the lactose powders with 0.1% MgSt showed round-edged shapes and flat surfaces (Figure 2d). The lactose powders coated with 1% MgSt appeared to be almost the same shape as the 0.1% MgSt samples (Figure 2e). However, smaller powder was found on the surface of the lactose powders as well as around the large particle in Figure 2e. These observations indicated that agglomerates of MgSt were broken and dispersed over the surface of the lactose powders. Then, the lactose powders with 5% MgSt showed a rough surface with many pits (Figure 2f), suggesting that MgSt formed a multi-layered film. Similar observations have been reported by Zhou et al. (18) with regard to lactose powders (Pharmatose450M) coated with MgSt using mechanofusion. It was suggested that 1% MgSt was sufficient for a uniform thin-film coating of Pharmatose450M and excess MgSt seemed to form overlapping and flaking layers at the 5% level of MgSt.
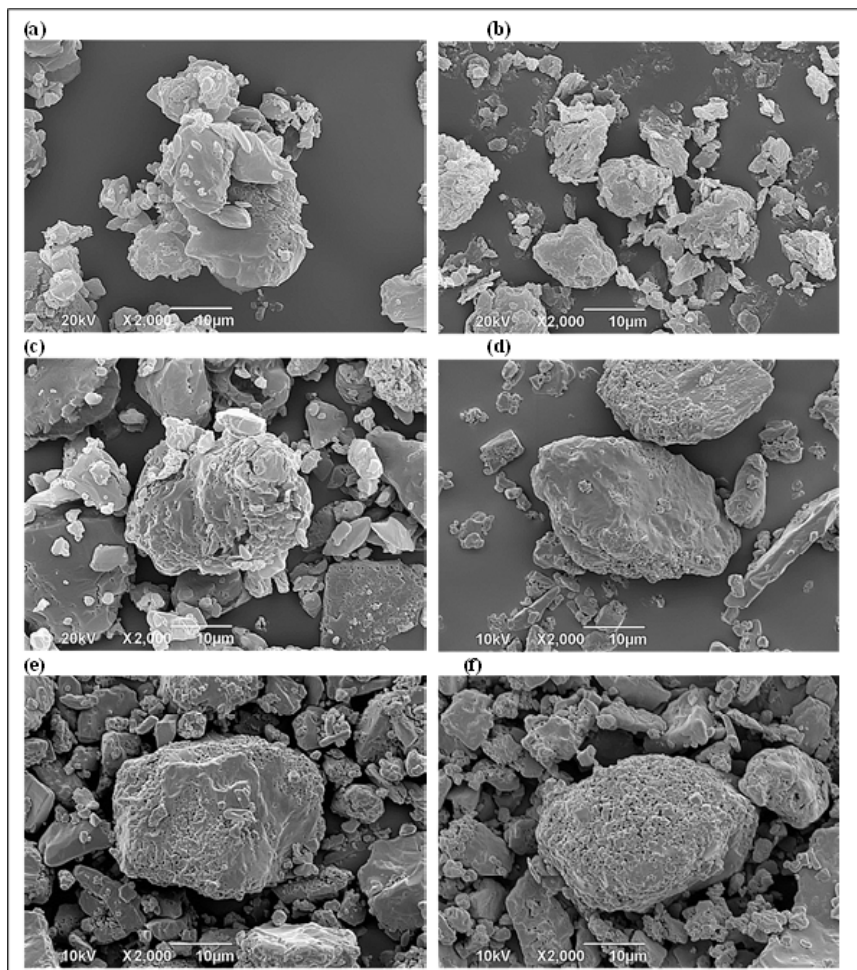

Figure 2. Images of scanning electron microscope (magnification: 2000×) of lactose (a), Magnesium stearate (MgSt) (b), processed lactose (c), lactose coated with 0.1% MgSt (d), lactose coated with 1.0% MgSt (e), and lactose coated with 5.0% MgSt (f).

Particle size distribution

The particle size distributions of the MgSt-coated lactose powders after processing at 1000 rpm for 10 minutes were compared with the unprocessed lactose powders to determine whether appreciable host particle attrition or agglomeration had occurred. Figure 3 shows the particle size distribution of the samples. The median size of the lactose powders used in this study is reported to be 20 μm by the manufacturer. There was no substantial size change for each lactose sample before and after the PCM process. This indicated that the PCM did not cause attrition and fragmentation of the host powders. It was considered that the mechanical stress of the PCM was relatively low compared with that for high-energy mixers. There was also no appreciable change in the powder size of the lactose powders coated with MgSt after processing (Figure 3). It appeared that MgSt spread over the surface of the host powder as a thin film (10).

On the other hand, the powders with a size of about 3 μm increased with increasing content of MgSt (Figure 3). The fraction seemed to be excess MgSt, which was unused for coating.

Flowability of the coated lactose

The flowability of the coated powders was characterized through measuring AOR, to evaluate the coating efficiency by means of improving flow properties. Figure 4 shows the results of the AOR measurements. The lactose powder has poor flowability because of its high cohesiveness. By increasing the amount of MgSt from 0 to 0.1, 0.5, and 1.0%, the corresponding AOR is reduced from 51.2 to 48.3, 44.1, and 40.8°, respectively. According to Carr (21), the flowability of coated lactose powders changes from "poor" to "passable". These results indicate that effective coating was achieved with the PCM because simple mixing did not improve the AOR in the Pharmatose450M-MgSt system (10). On the other hand, the AOR for the lactose powders coated with 5% MgSt slightly but significantly increased to 42.8°. It seemed that excess MgSt influenced the flowability of the powder mixture as a whole.

In this study, tapped density could not be determined because the coated powders often did not reach a constant value. Morin and Briens (22) also reported that the Hausner ratio and Carr's index did not provide sufficient resolution regarding change in flowability. Therefore, we examined aerated bulk density of the powders in the present study. Aerated bulk density indicates the porosity of powders, and reflects their cohesiveness. High aerated bulk density means a high tendency to cohere.
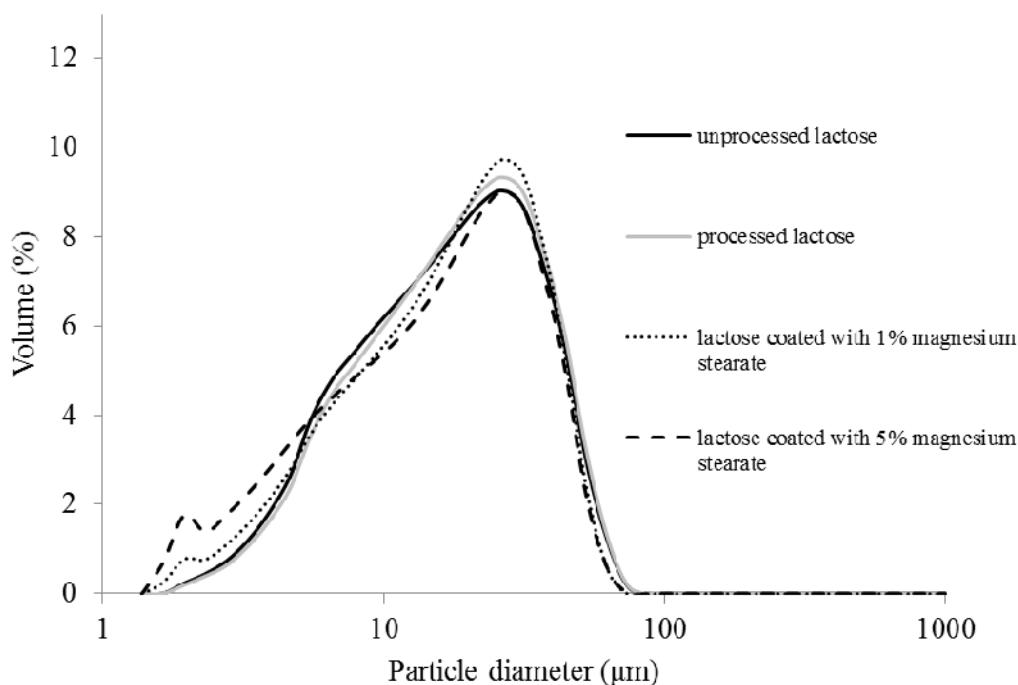

Figure 3. Particle size distribution of unprocessed, processed, and coated lactose powders

The results of the aerated bulk density are shown in Figure 5. The aerated bulk density of the coated lactose increased compared with that of the uncoated lactose, with an increase in MgSt content. There were significant differences in the aerated bulk density between the samples of 0% and 0.1%, and the samples of 0.5, 1, and 5% ($p < 0.01$). The aerated bulk density increased from the lowest value of 0.521 g/mL for the untreated lactose powder to the highest value of 0.713 g/mL for the sample of 1% MgSt (Figure 5). This was also because the level of MgSt decreased upon direct contact of the lactose particles with one another (23).

Wettability of the coated lactose
Wettability tests were performed for the uncoated and coated lactose powders to confirm the state of coating. Since MgSt is hydrophobic, the coating with MgSt should make the hydrophilic lactose surface become hydrophobic. Therefore, effective coating leads to reduction of the affinity between lactose and water, showing a high contact angle. Figure 6 shows photos taken just after contact between the water drop and the sample powder bed. It can be seen that the water drop disappears instantaneously from the surface of uncoated and 0.1% MgSt-coated powders because of the high affinity between lactose and water (Figures 6a and b). After coating with 0.5, 1, and 5% MgSt (Figures 6c-e), the water drop is not absorbed and remains on the surface of the coated lactose powders.

Zhou et al. (20) reported that simple mixing of Pharmatose450M and MgSt could not change the hydrophilicity of the materials. These results clearly proved that the surface of the lactose powders was coated by the MgSt powders and that the affinity of the lactose powder with water was reduced by dry coating. Then, we compared the wettability of the coated powders by measurement of the contact angle between the coated powders and water. The results of the lactose powders treated with 0.5-5% MgSt are listed in Table 5. The contact angle of the lactose powders coated with 0.5-5% MgSt was over 90°, indicating hydrophobicity. The contact angle increased with increasing content of MgSt. A higher level of MgSt seemed to form a more seamless film coating. As a result, the hydrophobicity of the coated lactose powders improved. It was previously observed that, when the surface coverage of silica particles with MgSt obtained after treatment in high shear mixer was uniform, the wettability measurements led to similar results as for the PCM (13).
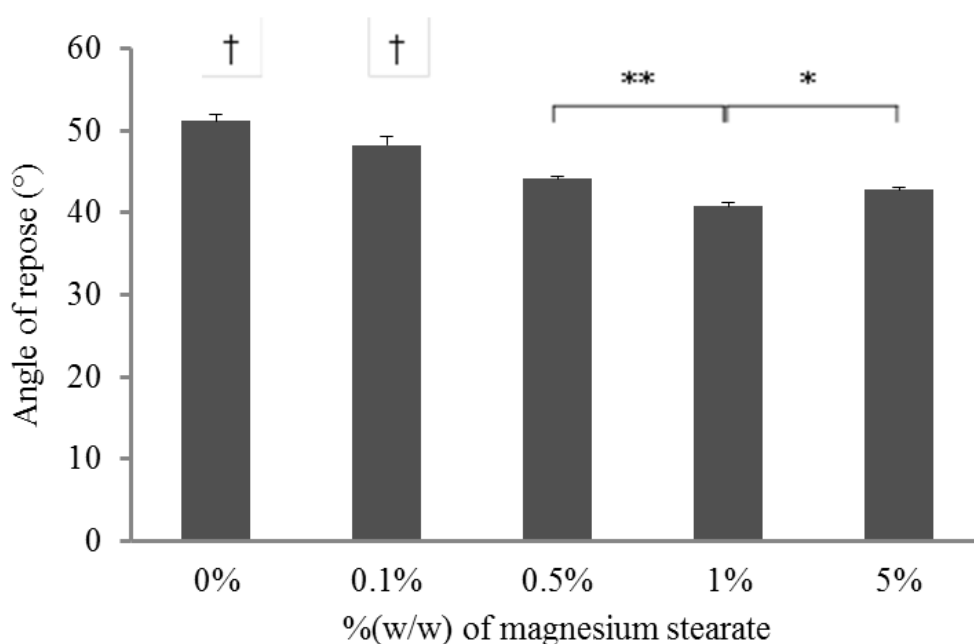

Figure 4. Angle of repose of the lactose powders processed with 0-5% magnesium stearate
The values are presented as the mean ± S.D. ($n = 3$). Samples of 0 and 0.1% were significantly different from the others ([†] $p < 0.01$). The asterisks show significant differences between them at * $p < 0.05$ and ** $p < 0.01$.
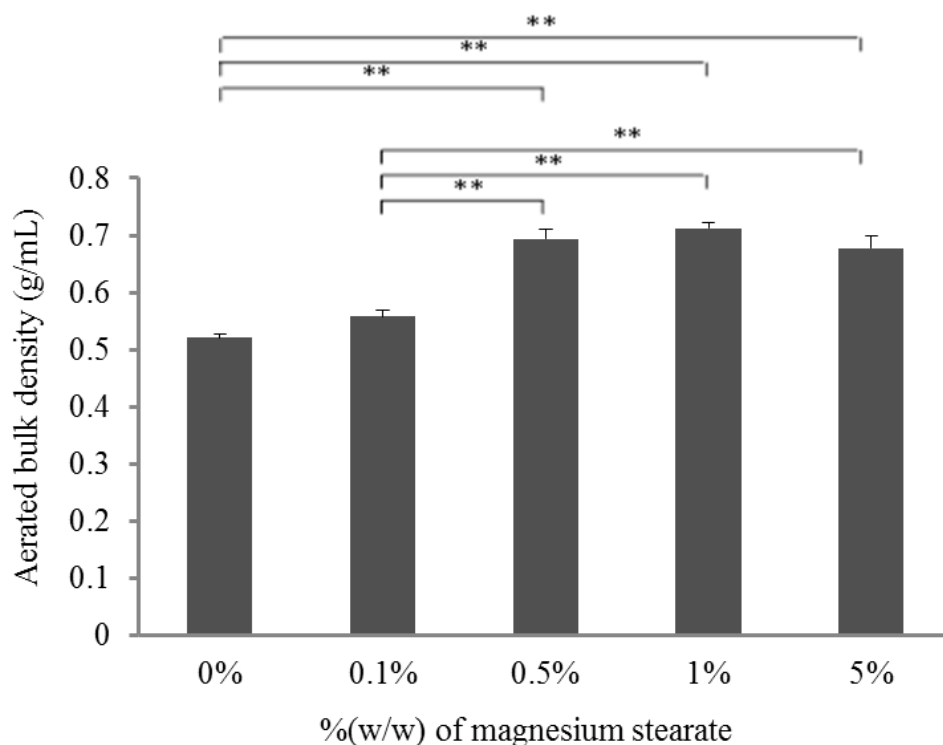
Figure 5. Aerated bulk density of the lactose powders processed with 0-5% magnesium stearate
The values are presented as the mean ± S.D. ($n = 3$). The asterisks show significant differences between them at ** $p <$ 0.01.
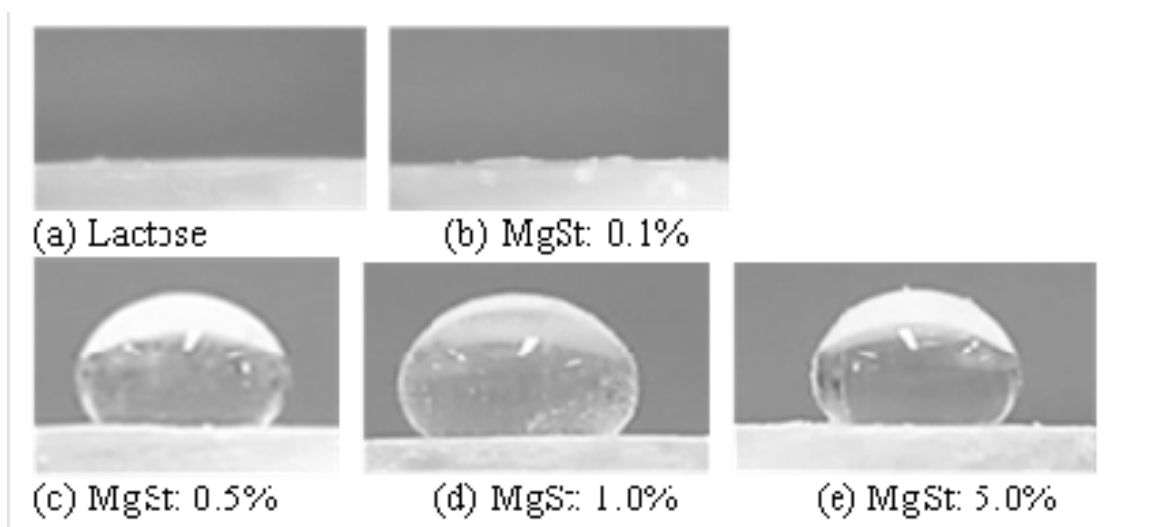

Figure 6. Wettability of the lactose powder before and after coating with magnesium stearate (MgSt)
Photos show the profile of a 10-μL of water drop immediately after dropping. In a and b, a water drop did not appear.

Table 5. Effect of magnesium stearate content on the contact angle

Magnesium stearate content (%)	0.5	1	5
Contact angle (°)	106 ± 5.4**	121 ± 1.8**	133 ± 2.5**

The values are presented as the mean ± S.D. ($n = 5$). The asterisks show significant differences from the others at ** $p < 0.01$.

III. In the ibuprofen-lubricant systems

It is well known that ibuprofen particles are highly cohesive and low-water-soluble materials. Therefore, it is necessary for their flowability to be improved in the process of pharmaceutical manufacturing. We examined dry coating of IBU with various lubricants using PCM. Operational conditions were fixed at operation speed: 1000 rpm, operation time: 10 min, vessel size: 35 mL, and charging ratio: 20%, according to the results of the lactose-MgSt systems and preliminary studies (data not shown). The amount of each lubricant added to the drug powder was defined from the following equations to achieve an optimal monolayer coating (23). The weight percentage of guest particles (W) is:

$$W = (Nd^3\rho_d)/(D^3\rho_D + Nd^3\rho_d) \times 100, \quad (1)$$

where D and d are host and guest particle sizes, respectively. ρ_D and ρ_d are host and guest densities, respectively. The number N of guest particles per host particle is given by the equation:

$$N = 4(D+d)^2/d^2 \quad (2)$$

From these equations, the percentages of Aerosil 200, Aerosil 300, Aerosil R973, and MgSt were assumed to be about 1.5, 1.0, 2.0, and 1.0%(w/w), and then the resultant powders were named IBU-Aerosil 200, IBU- Aerosil 300, IBU- Aerosil R973, and IBU-MgSt, respectively.

AOR and aerated bulk density of the ibuprofen particles coated with various lubricants are shown in Figure 7. All of the coated particles showed smaller AOR values and higher aerated bulk density than the drug particle, indicating improved flowability. These results suggest that the drug particles were successfully coated with the lubricants.

Furthermore, wettability was assessed using a sessile water drop method to confirm the completeness of the coating. The contact angle is summarized in Table 6. In the use of hydrophilic lubricants, IBU- Aerosil 200 and IBU- Aerosil 300, a water drop did not form on the samples, indicating that the hydrophobic surface of the drug had changed to a hydrophilic one. On the other hand, the contact angle increased when the hydrophobic lubricants, IBU- Aerosil R973 and IBU-MgSt, were used. These results suggest that the lubricants covered the surface of the drug particles.
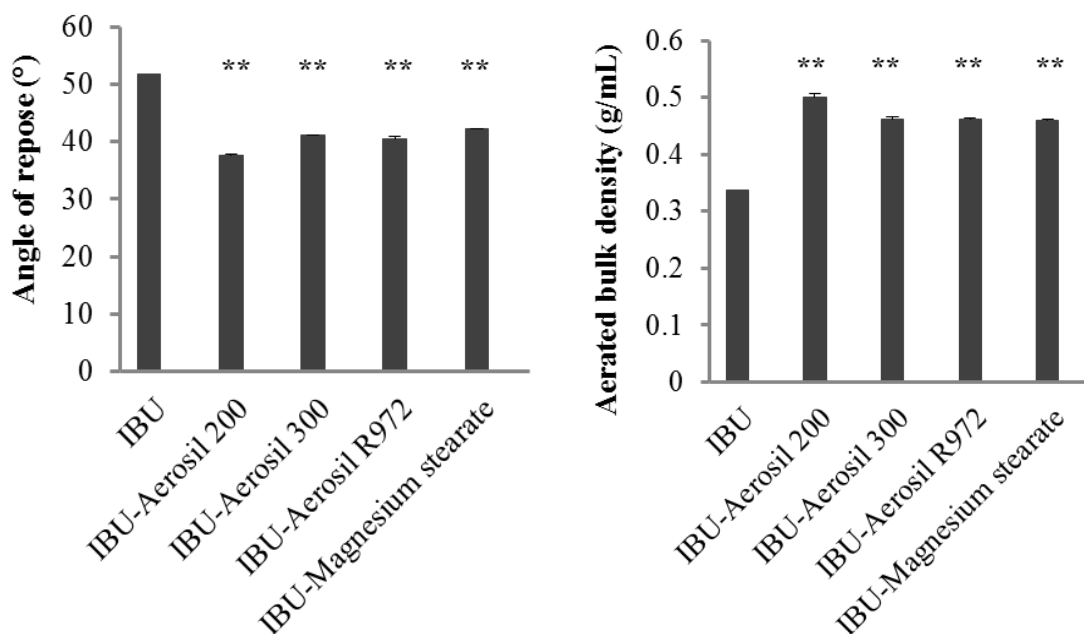

Figure 7. Angle of repose and aerated bulk density of the ibuprofen (IBU) particles coated with various lubricants
The values are presented as the mean ± S.D. ($n = 3$). The asterisks show significant differences from IBU at * $p < 0.05$ and ** $p < 0.01$.

In addition, we investigated the dissolution profile of the drug because IBU is needed to improve water solubility. As shown in Figure 8, all coated particles dissolved more rapidly than the drug powder.

The times required for 70% dissolution (T70%) to occur were 4.0, 6.1, 22, 36, and 46 min for IBU-Aerosil 300, IBU-Aerosil 200, IBU-MgSt, IBU-Aerosil R973, and IBU, respectively. Using the hydrophilic lubricants, T70% decreased to 9-13% of the values of IBU. This was due to

alteration of the wettability. Although the hydrophobicity of the particle surface was increased by using the hydrophobic lubricants, IBU-Aerosil R972 and IBU-MgSt showed 78 and 48% shorter times than IBU, respectively.

To investigate the reason for this, we examined the sample powders in terms of their dispersability in water. Table 7 shows the turbidity of the water suspension of the sample powders using absorbance at 660 nm.

Table 6. Effect of lubricant on the contact angle

Sample	IBU-Aerosil 200	IBU-Aerosil 300	IBU-Aerosil R973	IBU-Magnesium stearate	IBU
Contact angle (°)	-	-	125 ± 0.64**	122 ± 0.13**	117 ± 0.061

The values are presented as the mean $\pm$ S.D. ($n = 5$). The asterisks show significant differences from ibuprofen (IBU) at ** $p < 0.01$. A water drop did not appear on IBU- Aerosil 200 and IBU- Aerosil 300.
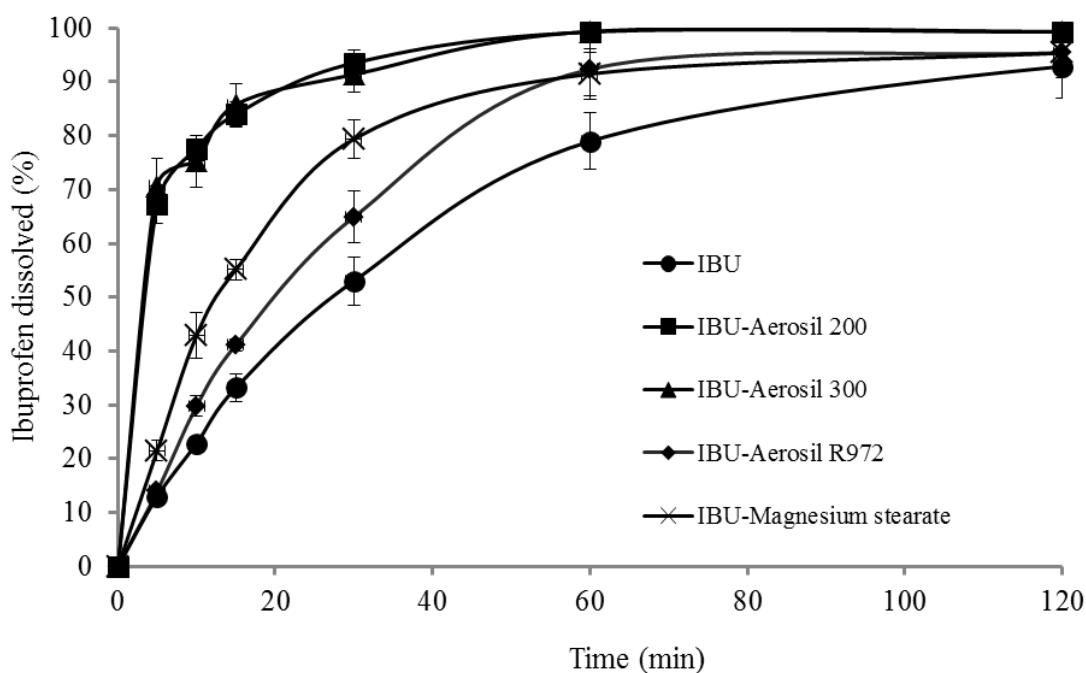

Figure 8 Dissolution profiles of ibuprofen from various composite particles

Table 7. Effect of lubricants on the dispersability in water

Sample	IBU-Aerosil 200	IBU-Aerosil 300	IBU-Aerosil R973	IBU-Magnesium stearate	IBU
Absorbance	2.41 ± 0.028*	2.37 ± 0.012*	1.18 ± 0.022*	1.08 ± 0.094*	0.566 ± 0.0098

The values are presented as the mean $\pm$ S.D. ($n = 3$). The asterisks show significant differences from ibuprofen (IBU) at * $p < 0.01$.

All coated particles showed higher turbidity than IBU, improving dispersability. Lefebvre et al. reported that, for Aerosil R973 amounts from 0 to 4%(w/w) in the talc-Aerosil R973 system, a higher amount of Aerosil R973 led to an increase in the rate of dispersion owing to a decrease in the work of adhesion (24). Since the coated IBU particles dispersed well, the surface area contributing to drug dissolution increased.

Drug crystallinity of the composite particles
In the dry coating process, it is possible that high mechanical stress may lead to change in the form of

drugs (25). Therefore, it was necessary to evaluate the effect of the PCM process on drug crystallinity. PXRD measurements were performed to assess the impact of the processed drug powders. The results, as presented in Figure 9, show nearly the same patterns and peak positions, suggesting that the dry coating process does not lead to change into an amorphous form of IBU.

FT-IR measurements were also conducted and are presented in Figure 10. The results show nearly the same spectrums, suggesting that the dry coating process did not cause transition of the crystalline forms.
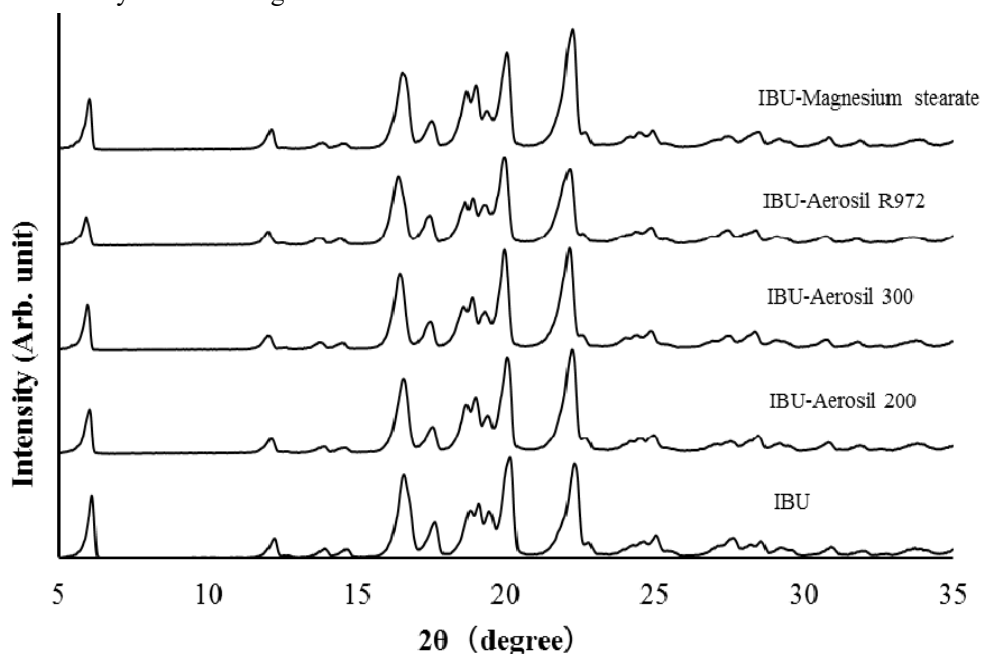

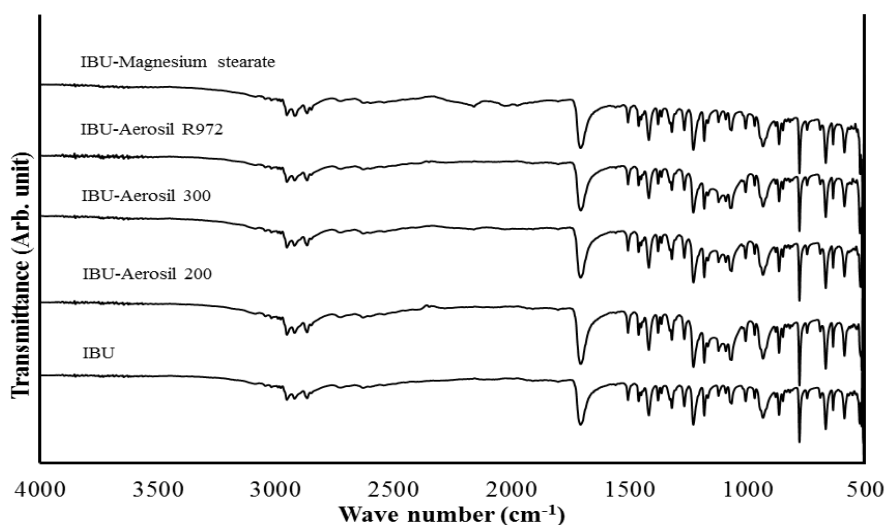**Figure 9.** Powder X-ray diffraction patterns of ibuprofen (IBU) and composite particles

Figure 10. Fourier-transform infrared spectra of ibuprofen (IBU) and composite particles

DISCUSSION

The present study was conducted to clarify the potential of the PCM, which is pharmaceutical compounding equipment for ointment blending, as a dry powder coating apparatus. Two model systems, lactose-MgSt and IBU-lubricant, were examined for flowability, wettability, or drug dissolution of the PCM processed powders as indicators of the dry coating performance of the PCM. The PCM could improve the flowability of the host powders processed with the lubricants (Figures 4 and 7). Then, the processed powders with hydrophobic lubricants showed good hydrophobicity (Figure 6 and Table 6). In contrast, the powders coated with hydrophilic lubricants obtained excellent wettability (Figure 6). Moreover, IBU could be coated with several lubricants having different properties. As a result, drug dissolution from the coated powders differed depending on the property of the lubricants (Figure 8). These results suggest that the selection of appropriate lubricants provides desired functions, such as preventing access of light and moisture as well as taste masking, to host powders. Additionally, PXRD and FT-IR assessments revealed that the crystallinity of IBU was not changed after the dry coating process (Figures 9 and 10). This benefited the method because pharmaceutical products are formulated to contain a drug in the stable crystalline form for storage stability. Thus, we revealed that the PCM is an effective apparatus for dry powder coating.

Pharmacists or compounders just change the formulation of unswallowable medicines (26), involving crushing tablets into a powder (27). At that time, the powder should retain the original functions of the tablets in terms of the stability of the API (28). At present, there is no apparatus applied to dry powder coating in pharmacies. The PCM could coat the cohesive powders until 10 min (Figure 1). In addition, the vessel size did not affect the coating performance (Table 4). Furthermore, the PCM is a type of vessel rotating mixer without mixing blades, so the process is completely free from cross-contamination by using disposable containers (29). These are a great advantage for pharmacists or compounders to dispense medicines.

The purpose of this study was to reveal the feasibility of dry powder coating using the PCM. Our next goal, therefore, will be to optimize the process parameters of PCM simultaneously, because factors affecting the coating efficiency may interact. It is also still necessary to assess several factors and issues for the establishment of dry powder coating using the PCM. Although caking, charging, or heat generation of materials was not observed in this study, these issues are important for dry powder coating.

In conclusion, the PCM could be successfully applied for the dry powder coating of cohesive powders with conventional lubricants. The PCM could coat the host particles without causing major changes in the material shape, size, and crystallinity. Study on dry powder coating using the PCM is still at its initial phase. Hereafter, we will make a continuous effort to clarify the coating performance of the PCM with respect to crushed tablets and opened capsules. Our final objective is to formulate better medicines for children through sophisticated pharmaceutical compounding. This challenge will be achieved by dry powder coating using PCM in the future.

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