Effects of Surface Processing of Lactose Carrier Particles on Dry Powder Inhalation Properties of Salbutamol Sulfate

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The effects of the surface processing of lactose carrier particles on the dry powder inhalation properties of salbutamol sulfate were investigated. Lactose carrier particles were processed using a high-speed elliptical-rotor-type powder mixer (Theta-Composer®). In the present study, drug/carrier powder mixtures were prepared, consisting of micronized salbutamol sulfate and coarse lactose carriers with various particle surface conditions prepared by surface processing. These powder mixtures were aerosolized by a Jethaler®, and the *in vitro* inhalation properties of salbutamol sulfate were evaluated with a twin impinger. Compared with those of the powder mixed with unprocessed lactose carriers, the *in vitro* inhalation properties of the powder mixture prepared using the surface processed lactose carriers were significantly different, showing that the *in vitro* inhalation properties of salbutamol sulfate were improved. The *in vitro* inhalation properties increased with the rotor rotation rate. Using this surface processing system would thus be valuable for increasing the inhalation properties of dry powder inhalation with lactose carrier particles.

Key words dry powder inhalation; lactose carrier particle; salbutamol sulfate; surface processing; high-speed elliptical-rotor-type powder mixer

Dry powder inhalation therapy plays an important role in the treatment of bronchial asthma.[1,2] Inhaled drugs delivered to the bronchi are directly absorbed at their deposition sites, exerting effects. Therefore, dry powder inhalation therapy is effective at a low drug dose, reducing systemic side effects. For the preparation of dry powder inhalation, a coarse carrier particle (30—90 μm in diameter) system, such as lactose particles mixed with fine drug particles, has been developed.[3—7] this system, drug/carrier powder mixtures are prepared by mixing fine drug particles (aerodynamic particle diameter, 1—6 μm) with coarse inactive carrier particles such as lactose particles, and the fine drugs are re-separated from the carrier particles during inhalation. After emission of the powder mixtures from a capsule or inhalation device, the separation of the fine drugs from the carrier particles and their delivery to the targeted sites are important. However, the separation efficiency of fine drug particles from the carrier surface is low, and effective drug delivery to the targeted sites (bronchi) is very low.[8]

In a previous study,[9] we covered the lactose particle surface with sucrose tri-stearate (J-1803F), prepared lactose carrier particles that allow good separation of drug particles from carrier, and improved the *in vitro* inhalation properties. However, since sucrose tri-stearates are not approved as medical drug additives, their safety as excipients for dry powder inhalation remains to be clarified.

In the pharmaceutical field, some pharmaceutical mechanical techniques in which particles are processed in a dry phase without using organic solvents have been reported.[10—16] Frequently, these mechanical techniques have been used for composite covering of the core particle surface with fine particles for surface modification.[9—11,14]

In this study, we proposed a new particle design method in which the core particle surface is not covered with fine particles, but intermittent shear force is directly applied to the core particle surface for uniform surface processing. This mechanical technique is particle surface processing using mechanical energy by applying a strong shear force to the particle surface in a dry phase. Particle processing in a dry phase does not cause residual organic solvents, and is appropriate for environmental preservation. Therefore, carrier particles were prepared by processing the surface of lactose particles, which are widely used as carriers for dry powder inhalation, in a dry phase by a pharmaceutical mechanical technique. In this study, we performed a basic investigation of the applicability of surface-processed lactose particles prepared by the pharmaceutical mechanical technique as carrier particles for dry powder inhalation.

Experimental

Powder Samples As the carrier particle for dry powder inhalation, α-lactose monohydrate was used (Pharmatose® 200 M, DMV, The Netherlands). Salbutamol sulfate was used as the drug, and was obtained from LEIRAS (Finland). Salbutamol sulfate was micronized by at Spiral Jet Mill (100AS, HOSOKAWA MICRON, Japan). The cube-like fine crystals of the latter had a volume median diameter of 1.7 μm, as determined by laser diffraction (Lasermicronsizer, SEISHIN, Japan). β-Anhydrous lactose powder was supplied from DMV (The Netherlands).

Physical Properties of Lactose Carrier Particles The particle diameter (Heywood diameter) of lactose particles was determined using an image analyzer (Luzex-FS, NIRECO, Japan) connected to a microscope (OPTIPHOT, Nikon, Japan). The specific surface area of lactose particles was measured by an air permeametry method (SS-100, Shimadzu, Japan).

The surface condition of lactose particles was observed by a scanning electron microscope (SEM, T-20, JEOL, Japan).

Surface Processing of Lactose Carrier Particles The lactose powders were processed for 10 min with a high-speed elliptical-rotor-type powder mixer (Theta-Composer®; TC, Tokuju, Japan).[17] Figure 1 shows a schematic diagram of the Theta-Composer®. The rotor and the vessel are on the same axis, and rotate in reverse directions. At the site at which the distance between the rotor and vessel was the minimum (clearance), shear stress was applied to the powder for particle surface processing. Rotation of the vessel at a low rate in a direction reverse to that of rotor rotation allows intermittent application of shear stress to particles, which inhibits an increase in temper-

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ature. The lactose powder loading was 20.0 g. The clearance between the rotor and the vessel wall was 0.5 mm. Particle surface processing was performed at a vessel rotation rate of 35 rpm and a rotor rotation rate of 3500, 4000, and 4500 rpm, respectively. Preliminary experiments were performed on lactose powder loading, clearance, rotor rotation rate, vessel rotation, and processing time, and conditions for effective surface processing were determined. After particle surface processing, the lactose powders were sieved using a 350-mesh wire screen by suction at an airflow pressure of 4000 kPa using an Air Jet Sieve (HOSOKAWA MICRON, Japan) for 10 min, and fine particles were removed.

Preparation of Powder Mixture Powder mixtures of 2.5 w/w% salbutamol sulfate were prepared by mixing 1.0 g of salbutamol sulfate and 39.0 g of lactose carrier particles in a glass bottle with a vortex mixer (SCIENTIFIC INDUSTRIES, U.S.A.) for 5 min. In this study as well as our previous study, [5,9] SEM confirmed uniform attachment of the drug to carrier particles prepared under the same mixture conditions.

Packing of Powder Mixture into a Capsule A total of 80 mg of powder mixtures were packed into a No. 2 HPMC hard capsule (Shionogi Qualicaps, Japan) and stored in a desiccator with silica gel at 22±2 °C for 24 h.

***In Vitro* Deposition Property** The drug/carrier powder mixtures were aerosolized using a dry powder inhalation device (Jethaler®, Hitachi Unisia Automotive, Japan). The aerodynamic particle deposition was determined using a twin impinger (Model TI-2, Copley) containing 7 and 30 ml of solvents (0.1 M hydrochloric acid) for stages 1 and 2, respectively. After the Jethaler® was connected to the mouthpiece of the twin impinger, a capsule was placed in the holder of the Jethaler®, which had a pin attached to pierce the capsule. An air stream of 60 l/min was allowed to flow through the system by attaching the outlet of the twin impinger to a vacuum pump for 5 s. The drugs in stages 1 and 2, the capsule, and the device were collected by rinsing with fresh solvent. The rinsed solutions were diluted to appropriate volumes and the drug contents were determined by spectrophotometry (UV-160A, Shimadzu, Japan) at 224 nm.

In this study, since we focused on the separation of drug particles from the surface of a carrier emitted from a capsule or a device, we employed the respirable particle percent (RP) of emitted particles from the inhalation system to represent the *in vitro* deposition property. RP was proposed by Hino *et al*.[18] and Kawashima *et al*.[3] to evaluate inhalation behavior and is expressed as:

$$RP=(ST2)/(EM)\times 100 \quad (1)$$

EM is the amount (%) of drug particles emitted from the inhalation device or capsules, and ST2 is the amount (%) of drug deposited in stage 2 of the twin impinger.

Thermal Analysis Thermal analysis was carried out by differential scanning calorimetry (DSC) with a type DSC-60 apparatus (Shimadzu, Japan). Samples were placed in aluminum pans and scanned at a heating rate of 5 °C/min. The melting point of sample powders was obtained from the DSC curves.

Powder X-Ray Diffraction Powder X-ray diffraction analysis was performed with an X-ray diffractometer (RAD-II VC, Rigaku, Japan).[19]

The operating conditions were as follows: target, Cu$K\alpha$; voltage, 40 kV; current, 80 mA; and scan speed, 5°/min.

Surface Roughness The surface roughness of single lactose particles was determined using a violet laser color 3D profile microscope (VK-9500, KEYENCE, Japan). The surface roughness parameter Ra (the arithmetic mean roughness) was evaluated according to JIS B0601 (1994).

Particle Density The particle density was obtained using a helium–air pycnometer (Model-1302, SHIMADZU-MICROMERITICS, Japan).

Particle Shape The particle shape of lactose particles was determined using an image analyzer (Luzex-FS, NIRECO, Japan) connected to a microscope (OPTIPHOT, Nikon, Japan).[20] The shape factor (SF) was obtained by dividing the actual projected area of a particle, A, by the area of a circle having a circumference equivalent to the perimeter length of the projected image, PM, as shown in Eq. 2.

$$SF=(PM)^2/(4\pi A) \quad (2)$$

If SF approaches unity, there is increased particle sphericity.

Results and Discussion

Physical Properties of Lactose Carrier Particles Table 1 shows the conditions of the surface processing of lactose carrier particles. Lac-0 indicates surface-unprocessed lactose particles, and Lac-1, Lac-2, and Lac-3 indicate lactose parti-

Table 1. Conditions of Surface Processing of Lactose Carrier Particles

Carrier	Rotor (rpm)	Vessel	Time (min)
Lac-0	0	0	0
Lac-1	3500	35	10
Lac-2	4000	35	10
Lac-3	4500	35	10

Table 2. Physical Properties of Lactose Carrier Particles

Carrier	Particle diameter[a] (μm)			Particle density[b] (g/cm^3)	Melting point[c] (°C)	Shape factor[d] SF	Surface roughness[c] Ra (μm)	Specific surface area[e] Sw (m^2/g)
	*D*10	*D*50	*D*90					
Lac-0	42.9	71.4	148.6	1.53±0.00	211±0.3	1.35±0.17	0.69±0.13	0.140±0.001
Lac-1	46.2	76.4	174.8	1.53±0.00	211±0.3	1.28±0.11	0.45±0.02*	0.135±0.001**, ★
Lac-2	44.8	74.3	173.7	1.53±0.00	210±0.3	1.25±0.09	0.46±0.08*	0.126±0.001**, ☆
Lac-3	45.4	73.2	153.3	1.53±0.00	210±0.4	1.21±0.07	0.52±0.11	0.114±0.001**, ☆, ★

a) Heywood's diameter (n=100). *b*) Data are represented as mean±S.D. (n=5). *c*) Data are represented as mean±S.D. (n=3). *d*) Data are represented as mean±S.D. (n=100). *e*) Data are represented as mean±S.D. (n=5). * $p<0.05$, significant difference compared to Lac-0 by Student's unpaired t-test. ** $p<0.01$, significant difference compared to Lac-0 by Student's unpaired t-test. ☆ $p<0.01$, significant difference compared to Lac-1 by Student's unpaired t-test. ★ $p<0.01$, significant difference compared to Lac-2 by Student's unpaired t-test.

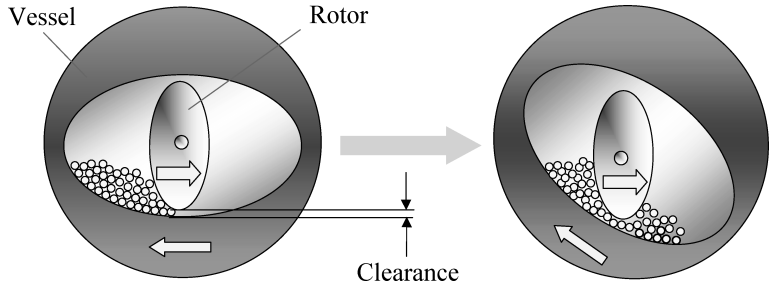

Fig. 1. Schematic Diagram of Mechanism of Surface Processing with Theta-Composer®

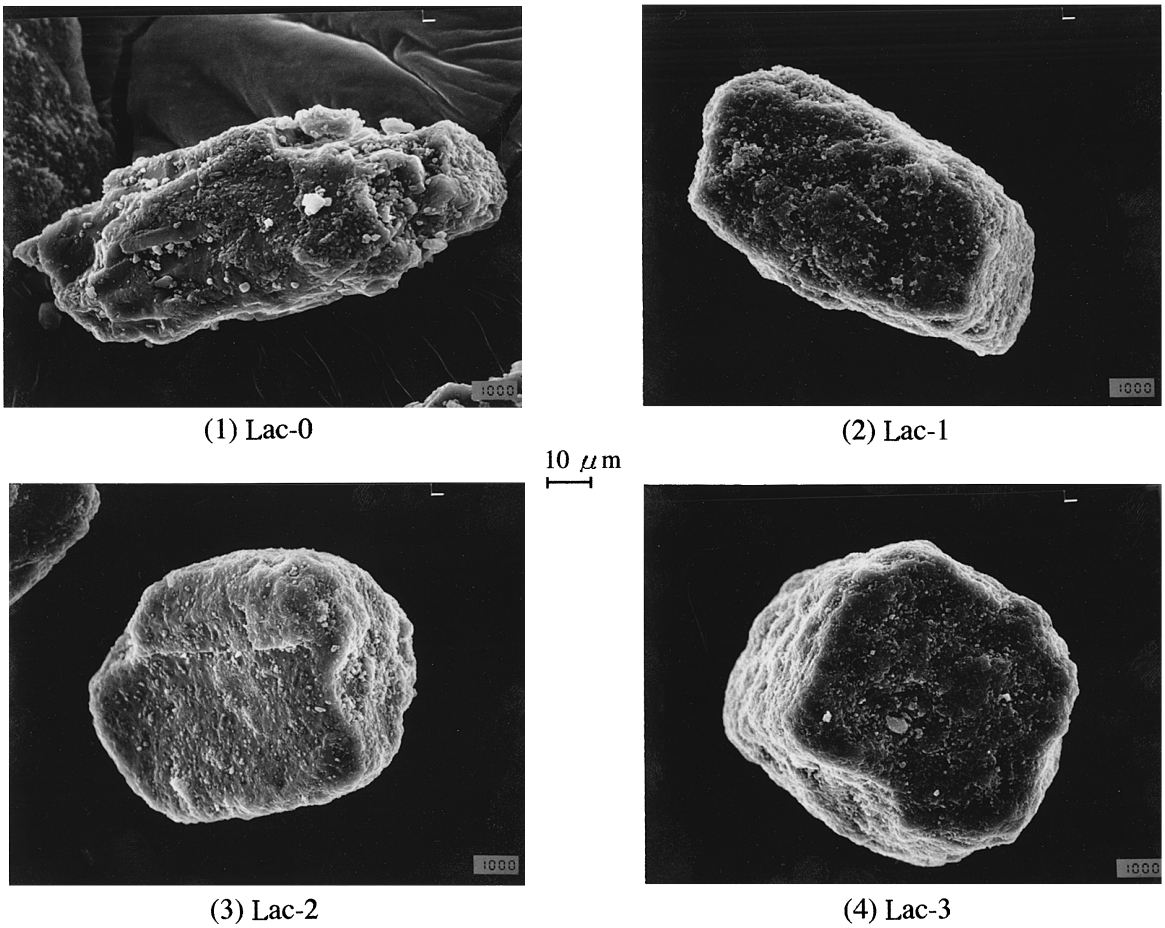

Fig. 2. Scanning Electron Microphotographs of Lactose Carrier Particles Used Carrier: (1) Lac-0, (2) Lac-1, (3) Lac-2, (4) Lac-3.

cles after surface processing at rotor rotation rates of 3500, 4000, and 4500 rpm, respectively.

Table 2 shows the particle diameter, particle density, melting point, shape factor, surface roughness and specific surface area. The particle diameter was approximately the same among all lactose carrier particles prepared.

The particle density and the melting point were similar among all lactose carrier particles. The shape factor (SF) obtained by image analysis increased with the rotor rotation rate. The surface roughness and the specific surface area were lower in processed lactose particles compared with those in unprocessed particles, because the surface processing of lactose particles made them smoother. No significant difference was observed in shape factor or surface roughness among Lac-1, Lac-2, and Lac-3.

Figure 2 shows SEM photographs of the lactose carrier particles prepared as carriers for dry powder inhalation. The surfaces of the unprocessed lactose particles were rough, but the surfaces of the processed lactose particles were smooth. These results were in agreement with the values of the specific surface area, surface roughness and shape factor shown in Table 2, suggesting that lactose particles became spherical after surface processing.

The specific surface area was smaller in surface-processed lactose than in surface-unprocessed lactose. Naito *et al*. reported that composite particle fabrication using a Mechanofusion system results in a decrease in the specific surface area of processed particles, compared with that of unprocessed particles.[21] In this study, after application of intermittent shear stress to lactose particles using a Theta-Composer®, the specific surface area of surface-processed lactose decreased. The mechanism of this decrease may be as follows. Macro-roughness on the lactose particle surface received friction force due to mechanical energy, and was worn down and decreased. Due to this decrease, the particle surface became smooth, which decreased the specific surface area. The surface roughness (Ra) of surface-processed lactose was lower than that of unprocessed lactose. Shear stress was applied using a Theta-Composer® to macro-roughness on the unprocessed lactose particle surface, and a decrease in surface roughness due to friction force may have decreased Ra.

Evaluation of Crystallinity of Lactose Particles Lactose particles are widely used as a carrier for dry powder inhalation.[22] In this study, lactose particles were processed under shear stress applied using a Theta-Composer®. However, the changes in the crystallinity of lactose due to friction heat caused by shear stress may occur. As lactose, there are α-monohydrate lactose, α-anhydrous lactose, and β-anhydrous lactose.[23] α-Anhydrous lactose is unstable and absorbs water in the air, immediately being changed to α-monohydrate lactose. β-Anhydrous lactose is obtained by re-crystallization of aqueous α-monohydrate lactose solution at 93 °C or higher.[23] Therefore, we performed DSC measurement and

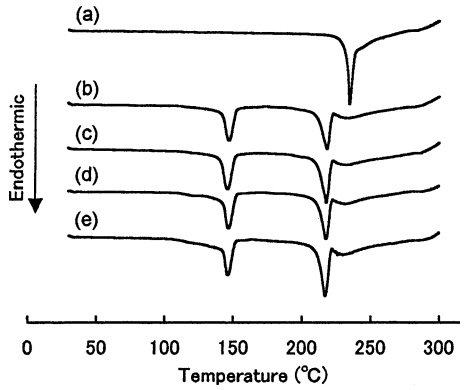

Fig. 3. Differential Scanning Calorimetry (DSC) Curves of Various Lactose Particles

(a) β-Anhydrous lactose, (b) Lac-0, (c) Lac-1, (d) Lac-2, (e) Lac-3.

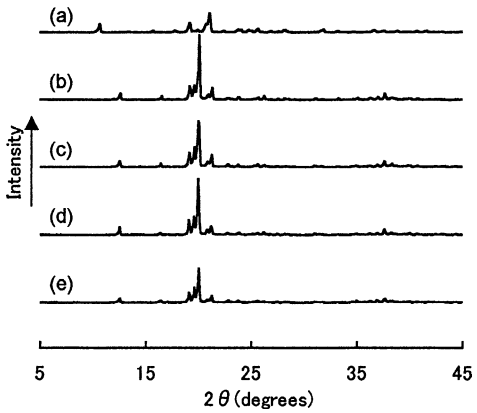

Fig. 4. Powder X-Ray diffraction patterns of Various Lactose Particles

(a) β-Anhydrous lactose, (b) Lac-0, (c) Lac-1, (d) Lac-2, (e) Lac-3.

powder X-ray diffraction measurement of the lactose particles used in this study to evaluate lactose crystallinity.

Figure 3 shows the results of DSC measurements of lactose particles. The DSC curve of unprocessed lactose (Lac-0) showed an endothermic peak due to dehydration of the water of crystallization at about 130 °C and an endothermic peak due to melting of α-monohydrate lactose at about 225 °C, suggesting that the unprocessed lactose is α-monohydrate lactose.[24] The DSC curve of each surface-processed lactose showed a pattern similar to that of the unprocessed lactose, confirming that the processed lactose is β-monohydrate lactose. For comparison, the DSC curve of β-anhydrous lactose is shown in Fig. 3(a). β-Anhydrous lactose had a characteristic endothermic peak due to melting at about 240 °C, but none of the lactose carriers in this study showed a peak at 240 °C.[25]

Figure 4 shows the results of the powder X-ray diffraction measurement of the lactose particles. Unprocessed lactose (Lac-0) showed a peak characteristic of α-monohydrate lactose at about 2θ=20, indicating that this lactose is α-monohydrate lactose.[25] Surface-processed lactose showed a pattern similar to that of unprocessed lactose, confirming that all the processed lactose carriers are α-monohydrate lactose. For comparison, the results of powder X-ray diffraction measurement of β-anhydrous lactose are shown in Fig. 4(a). β-Anhydrous lactose had a characteristic peak at about 2θ=10.4, but none of the lactose carriers used in this study showed such a peak.[25]

Table 3. *In Vitro* Inhalation Indies of Salbutamol Sulfate Mixed with Various Lactose Carriers

Carrier	EM (%)	ST2 (%)	RP (%)
Lac-0	93.6±2.1	13.6±2.1	14.6±2.5
Lac-1	82.4±1.8**	24.9±2.7**	30.2±2.7**
Lac-2	79.4±4.3**	26.7±1.1**	33.6±1.5**
Lac-3	80.1±1.7**	27.1±1.6**	33.8±1.4**

Data are represented as mean±S.D. (n=3—5). **p<0.01, significant difference compared to Lac-0 by Student's unpaired t-test.

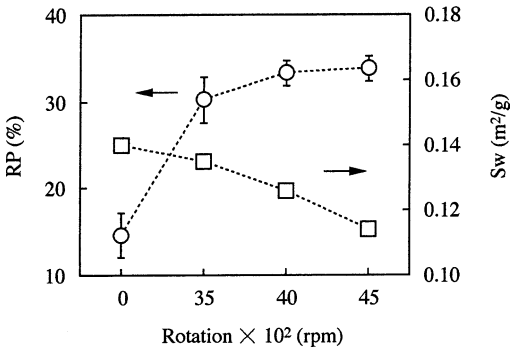

Fig. 5. Relationship between Rotor Rotation Rate and RP, Sw

○, RP ; □, Sw. Data are expressed as mean±S.D. (n=3—5).

We performed DSC measurement and powder X-ray diffraction measurement of the lactose particles used in this study to evaluate their crystallinity. Under the conditions for the use of the Theta-Composer® in this study, the crystallinity of lactose did not change after its processing.

Effects of Surface Processing of Lactose Carrier Particles on *In Vitro* Inhalation Properties Table 3 shows the *in vitro* inhalation indices of salbutamol sulfate mixed with various lactose carriers. EM significantly decreased in processed carriers compared to that in the unprocessed carrier. The Lac-0 carriers were the most effective for emitting the drug particles from the inhalation device and capsules, probably because of their higher available surface area for drug adhesion. Consequently, higher EM (%) was found with Lac-0. However, the ST2 values of drug deposited in stage 2 of the twin impinger were significantly higher for the Lac-1, Lac-2 and Lac-3, compared to the Lac-0. This was seen even though the amount of drug emitted by the Lac-1, Lac-2 and Lac-3 was not as high as that by the Lac-0. This finding indicated that the surface area of the carrier particles affects drug particle adhesion. RP was significantly greater in processed carriers than in the unprocessed carrier, indicating that the *in vitro* inhalation properties of salbutamol sulfate were improved.

Figure 5 shows the effect of the rotor rotation rate in the surface processing on the *in vitro* inhalation properties (RP) of salbutamol sulfate and the specific surface area (Sw) of lactose carrier particles. When the rotor rotation rate in the surface processing was compared with the RP and Sw, the RP values increased with the rotor rotation rate in the surface processing. On the other hand, the Sw decreased with increase in the rotor rotation rate in the surface processing. With a further increase in the rotor rotation rate, the difference in surface smoothing was negligible, suggesting negligi-

ble changes in RP and Sw. The RP of the powder mixed with the surface-processed lactose carrier was significantly higher than that of the powder mixed with the unprocessed lactose carrier. Drug particles adhered to the concavity become entrapped and relatively immobile in the depressions on the carrier surface.[4,22] The separation of drug particles from unprocessed lactose carriers would be lower, resulting in low RP values. With Lac-3, which was a lactose carrier surface processed at a high rotor rotation rate, the amount of roughness on the lactose particle surface was smaller than that of unprocessed lactose, and the carrier-particle specific surface area was smaller. This decreased the number of drug particles remaining in depressions and facilitated drug separation. Since smoothing of the surface of carrier particles decreased drug particles attached to macro-depressions of the carrier particle surface, the separation of drug particles from carrier particles may have improved.[26] This was in agreement with the results of Kawashima *et al*., who reported that lactose particles with larger surface areas could carry a larger amount of drug particles, since they held the drug particles more firmly in the inhaled air-stream.[3] This could be explained by the increase in the adhesion force between the micronized salbutamol sulfate and the carrier particles, as the macro-roughness of the lactose particle surfaces is increased.

In this study, we proposed a new particle design method in which the core particle surface is not covered with fine particles, but intermittent shear force is directly applied to the core particle surface for uniform surface processing, and the effects of the surface processing of lactose carrier particles on the *in vitro* inhalation properties of salbutamol sulfate were investigated. The RP obtained by surface processing was significantly better than that of the unprocessed lactose carrier. The surface processing of lactose carrier particles is a clean and simple technique. The design of carrier particles as well as of drug particles is important in the design of dry powder inhalation. The surface processing of carrier particles may be an effective technique that may lead to improvements in the inhalation properties of dry powder inhalation. In discussing the effects of the surface processing of carrier particles on the *in vitro* inhalation properties of dry powder inhalation, there are many factors to be investigated, including the surface processing technique and differences in the surface processing conditions. We will further study the effects of the surface processing technique and the conditions of the surface processing on the *in vitro* inhalation properties of dry powder inhalation with lactose carrier particles.

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