Preparation of Dry Powder Inhalation with Lactose Carrier Particles Surface-Coated Using a Wurster Fluidized Bed

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An attempt was made to produce carrier particles for dry powder inhalation with lactose carrier particles surface-coated using a Wurster fluidized bed. The lactose carrier particles were coated with lactose aqueous solution containing hydroxypropyl methyl cellulose (HPMC) as a binder using a Wurster coating apparatus. Drug/carrier powder mixtures were prepared consisting of micronized salbutamol sulfate and lactose carriers under various particle surface conditions. These powder mixtures were aerosolized by a Jethaler®, and the *in vitro* deposition properties of salbutamol sulfate were evaluated by a twin impinger. The *in vitro* inhalation properties of the powder mixture prepared using the coated lactose carrier differed significantly compared with those of the powder mixture prepared using the uncoated lactose carrier, indicating improvements in *in vitro* inhalation properties of sulbutamol sulfate. *In vitro* inhalation properties increased with the surface coating time. This surface coating system would thus be valuable for increasing the *in vitro* inhalation properties of dry powder inhalation with lactose carrier particles.

Key words dry powder inhalation; salbutamol sulfate; lactose carrier particle; surface coating; Wurster fluidized bed

In preparing dry powder inhalation (DPI), a pharmaceutical technique utilizing inactive and coarse carrier particles such as lactose is applied to improve inhalation properties of micronized drug particles with aerodynamic particle diameters of 1—6 μm.[1—6)] During inhalation, carrier particles help the emission of the drug from the device or capsules and improve its inhalation properties. Therefore, in designing DPI using carrier particles, it is important for drug particles to adequately separate from the surface of carrier particles in the inhalation air flow. The *in vitro* inhalation properties of DPI are reported to relate to the surface conditions of the carrier particles.[2,7—10)] We previously reported the effects of a lactose carrier prepared by dissolving the surface of lactose particles with a aqueous solution of ethanol (70 v/v%) on *in vitro* inhalation properties. This treatment allowed good separation of drug particles from carrier, leading to improvement of *in vitro* inhalation properties.[8)]

In the pharmaceutical field, the pharmaceutical technique in which core particles are coated with aqueous solution has been reported.[11—16)] In this study, we proposed a new particle design in which the lactose carrier particle surfaces are coated with lactose aqueous solution containing hydroxypropyl methyl cellulose (HPMC) as a binder using a Wurster coating apparatus. There has been no other report on the use of lactose surface-coated with lactose aqueous solution for DPI. Therefore, carrier particles were prepared by coating the surface of lactose particles, which are widely used as carriers for DPI. We performed basic investigation of the applicability of the lactose particles surface-coated by a Wurster coating technique as carrier particles for DPI.

Experimental

Powder Samples As the carrier particle for dry powder inhalation, α-lactose monohydrate was used (Pharmatose® 200M, DMV, The Netherlands). Salbutamol sulfate was used as a model drug, and was obtained from LEIRAS (Finland). Salbutamol sulfate was micronized by 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).

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 particle was observed by a scanning electron microscope (T-20, JEOL, Japan).

Surface Coating of Lactose Carrier Particles Table 1 shows the formulation of the aqueous coating liquid for surface coating of lactose carrier particles. Hydroxypropyl methyl cellulose (HPMC, TC-5E, Shin-Etsu Chemical Co., Ltd., Japan) as a binder was added to the lactose (Pharmatose® 200M, DMV, The Netherlands) aqueous solutions before coating. Lactose was coated using the Wurster coating apparatus (MP-01-SCP, Powrex Corporation, Japan). The operating conditions for lactose coating are listed in Table 2; this was reported previously.[17)] After coating, the lactose-coated powders were sieved using a 400-mesh wire screen by suction at an airflow pressure of 4000 kPa using an Air Jet Sieve (HOSOKAWA MICRON, Japan) for 10 min. The lactose particles were sieved into the range from 40 to 88 μm, which was used as a carrier for dry powder inhalation.

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 for 5 min.

Table 1. Formulation of Aqueous Coating Liquid

Component	Concentration (%)
Pharmatose® 200M	13.0
HPMC (TC-5F)	2.0
Distilled water	85.0
(Total)	100.0

Table 2. Operation Conditions for Lactose Coating

Operation conditions	
Lactose powder supplied (g)	700
Binder concentration (%)	2
Spraying rate (g/min)	5
Inlet temperature (°C)	75
Outlet temperature (°C)	28
Air flow rate (m^3/s)	6.9×10^{-3}
Atomizing air flow (m^3/s)	6.7×10^{-4}

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Table 3. Physical Properties of Lactose Carriers

Carrier	Surface coating time (min)	Particle diameter[a] (μm)			Shape factor[b] SF	Surface roughness[c] Ra (μm)	Specific surface area[d] Sw (m^2/g)
		D_{10}	D_{50}	D_{90}			
Lactose-0	0	55.8	71.7	85.5	1.35±0.24	0.95±0.12	0.148±0.001
Lactose-1	110	51.5	63.7	81.2	1.25±0.15	0.73±0.05**	0.132±0.001**
Lactose-2	180	53.2	68.5	81.8	1.23±0.15	0.61±0.03**	0.125±0.001**
Lactose-3	240	53.8	69.3	82.5	1.21±0.06	0.48±09.10**	0.121±0.001**

a) Data are represented mean (n=100). *b*) Data are represented as mean±S.D. (n=100). *c*) Data are represented as mean±S.D. (n=3). *d*) Data are represented as mean±S.D. (n=3). ** $p<0.01$, significant difference compared to lactose-0 by Student's unpaired t-test.

Packing of Powder Mixture into a Capsule Eighty milligrams 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 powder mixtures were aerosolized using a dry powder inhalation device (Jethaler®, Hitachi Unisia Automotive, Japan). The aerodynamic particle deposition was investigated using a twin impinger (Model TI-2, Copley) containing 7 and 30 ml of solvents (0.1 M hydrochloric acid) for stage 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 throughout 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, 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.*[2] to evaluate inhalation behavior and expressed as:

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

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

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 Shape The particle shape of lactose particles were determined by an image analyzer (Luzex-FS, NIRECO, Japan) connected to a microscope (OPTIPHOT, Nikon, Japan).[19] The shape factor (SF) is 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 the particle is a real sphere, SF becomes unit.

Results and Discussion

Physical Properties of Lactose Carrier Particles Table 3 shows the particle diameter, shape factor, surface roughness, and specific surface area. In the table, lactose-0 indicates surface-uncoated lactose particles, and lactose-1, lactose-2, and lactose-3 indicate lactose particles after surface coating with lactose aqueous solution by a Wurster fluidized bed for 110, 180, and 240 min, respectively.

The particle diameter was approximately the same among all lactose carrier particles prepared. The shape factor (SF) obtained by image analysis decreased with the surface coating time. The surface roughness and the specific surface area were lower for coated lactose particles than for uncoated lactose particles, because lactose aqueous solution containing HPMC as binder is considered to have made the surface of lactose particles smoother. HPMC has been used widely as a binder of aqueous coating.[20—23]

As for changes in the specific surface area by surface coating, the specific surface area of lactose-3 was 0.121 m^2/g, which was 18% smaller than 0.148 m^2/g of lactose-0. The specific surface area may have decreased with prolongation of the surface-coating time, as the frequency of adhesion of the coating liquid increased and more lactose was coated to the surface of lactose particles.

Figure 1 shows SEM photographs of the lactose carrier particles prepared for dry powder inhalation. The surfaces of uncoated lactose particles were rough, but the surfaces of coated lactose particles were smooth. In lactose-1 prepared with a short coating time, the surface of lactose particles coated with thin film. In lactose-3 prepared with a long coating time, more spraying liquid coated the surface of lactose particles and filled depressions and gaps on it. These results were in agreement with the values of the shape factor, the surface roughness, and the specific surface area shown in Table 3, suggesting that lactose particles became spherical after surface coating.

Effects of Surface Coating of Carrier Particles on *in Vitro* Inhalation Properties Table 4 shows *in vitro* inhalation indices of salbutamol sulfate mixed with various lactose carriers. EM was significantly lower in coated carriers than in the uncoated carrier. The lactose-0 particles 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 adhering. The lactose carrier having a larger surface area can carry higher amount of drug particles because of higher capacity of attaching and stronger adhesion with drug particles. The amount of drug emitted by lactose-1, lactose-2 and lactose-3 was not as high as that by lactose-0. However, ST2 values of drug deposited in stage 2 of the twin impinger was significantly higher for lactose-1, lactose-2 and lactose-3 than for lactose-0. This finding indicated that the surface area of the carrier particles affect drug particle adhesion. Drug particles deposited in depressions on the surface of lactose particles are less likely to be separated in the inhalation air flow because of the large contact area, which makes the adhesive force stronger. RP was significantly greater in coated carriers than in the uncoated carrier, indicating the *in vitro* inhalation properties of salbutamol sulfate were improved. Surface-coated of a lactose carrier with the aqueous lactose solution contributed to overall reduction of adhesion force due to its surface-smoothing, resulting in easier separation of the drug particles from the lactose surfaces and a higher RP.

Figure 2 shows the effect of the surface coating time on the *in vitro* inhalation properties (RP) of salbutamol sulfate

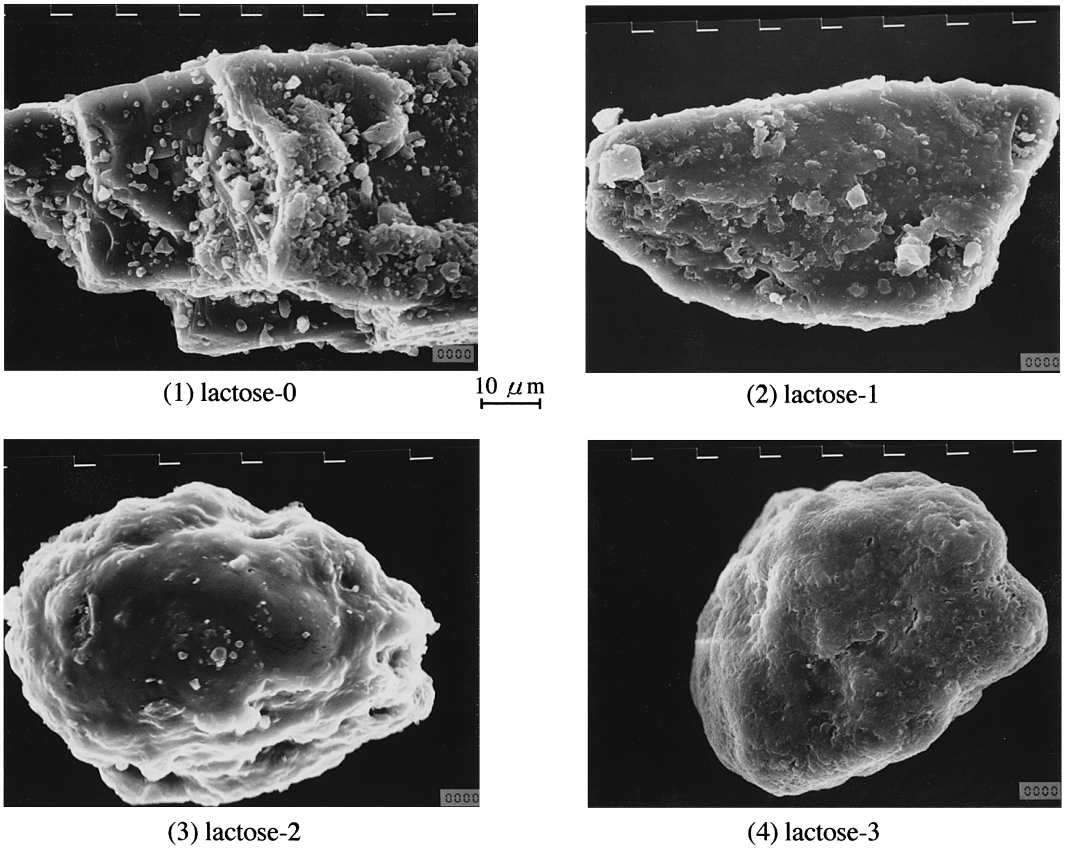

Fig. 1. Scanning Electron Microphotographs of Lactose Carrier Particles Used
Carrier: (1) lactose-0, (2) lactose-1, (3) lactose-2, (4) lactose-3.

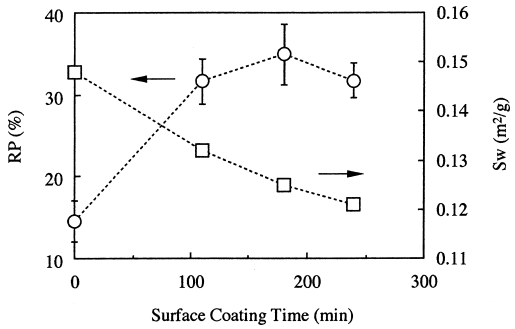

Fig. 2. Relationship between RP, Sw and Surface-Coating Time
○, RP; □, Sw. Data are expressed as mean±S.D. (n=3—5).

and the specific surface area (Sw) of lactose carrier particles. When the surface coating time was compared with the RP and Sw, the RP values increased with surface coating time. On the other hand, Sw decreased with prolongation of the surface-coating time. The RP of the drug powder mixed with the surface coated lactose carrier was significantly higher than that of the powder mixed with the surface uncoated lactose carrier. Drug particles adhered in the concavity would become entrapped and relatively immobile in the depressions on the carrier surface.[1,3] The separation of drug particles from surface uncoated lactose carriers would be lower, resulting in low RP values. Since uncoated lactose particles have a rough surface and a large surface area, drug particles are deposited in depressions on the surface and adhere tightly

Table 4. *In Vitro* Inhalation Indices of Salbutamol Sulfate Mixed with Various Lactose Carriers

Carrier	EM (%)	ST2 (%)	RP (%)
Lactose-0	93.6±2.1	13.6±2.1	14.6±2.5
Lactose-1	84.7±1.3**	26.8±2.7**	31.6±2.7**
Lactose-2	86.6±1.7**	30.2±2.7**	34.9±3.7**
Lactose-3	85.7±3.3**	27.1±2.2**	31.7±2.1**

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

to the lactose particles. Since the contact area between drug particles and lactose particles is large, the drug is emitted from the capsule by adhering tightly to the surface of lactose carrier, hence a high EM (emission property). However, as the drug remains captured in the depressions on the surface of carrier particles after emit from the capsule, it is deposited in stage 1 and is not transported to stage 2, resulting in a low RP. With lactose-3, which was lactose carrier surface coated for a long time, the amount of roughness on the lactose particle surface was lower than that with uncoated lactose, and the carrier-particle specific surface area was smaller. This decreased the number of drug particles remaining in depressions and facilitated drug separation. This was in agreement with the results by Kawashima *et al.* that lactose particles with larger surface areas could carry higher amounts of drug particles, whereas they held more firmly the drug particles in the inhaled air stream.[2] This would be explained by an increase in the adhesion forces between the micronized drugs and carrier particles as the roughness of lactose particle sur-

faces is increased.

In this study, the effects of surface coating of lactose carrier particles on *in vitro* inhalation properties of sulbutamol sulfate were investigated. RP obtained by surface coating with lactose aqueous solution were significantly better than that of uncoated lactose carrier. Preparing of carrier particles as well as drug particles is important for designing DPI. Surface coating of carrier particles may be an effective technique that may lead to improve the inhalation properties of DPI. In discussing the effects of surface coating of carrier particles on *in vitro* inhalation properties of DPI, there are many factors to be investigated including the surface coating technique and differences in the surface-coating material. We will further study the effects of surface coating technique and the quantity of the surface coating material used on *in vitro* inhalation properties of DPI with lactose carrier particles.

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