Preparation of Dry Powder Inhalation by Surface Treatment of Lactose Carrier Particles

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An attempt was made to produce carrier particles for dry powder inhalations by the surface treatment of lactose particles with aqueous ethanol solution. Drug/carrier powder mixtures were prepared consisting of lactose carriers with different particle surface properties and micronized salbutamol sulfate. These powder mixtures were aerosolized by Spinhaler®, and *in vitro* deposition properties of salbutamol sulfate were evaluated by twin impinger. The degree of adhesion between drug particles and carrier particles was determined by the ultracentrifuge separation method. In addition, the air jet sieve method was used to evaluate characteristics of the separation of drug particles from carrier particles in airflow. The average adhesion force (F50) between the surface-treated lactose carrier and drug particles was significantly lower than that of powder mixed with the untreated lactose carrier, indicating that the degree of separation (T50) of drug particles from carrier particles was improved when surface-treated lactose carrier was used. This resulted in an improvement of *in vitro* inhalation properties.

Key words dry powder inhalation; carrier particle; surface treatment; ultracentrifuge separation method; air jet sieve method

As a route for local administration of anti-asthmatic drugs and systemic administration of peptide drugs by dry powder inhalation, the lungs are naturally the prime focus of attention. As a technique for delivering drugs to the lung, dry powder inhalation is considered one of the most promising[1—6] due to its many advantages, such as (1) absence of the need for propellants such as chlorofluorocarbon, (2) portability, and (3) relatively low cost.[7,8] For inhalation of a drug powder into the lungs and its deposition, efficiently dispersed drugs with an aerodynamic diameter of 1.0—6.0 μm are most effective for the delivery of particles.[9] Thus, dry powder inhalations have been formulated with micronized drug particles of about a few micrometers in size. However, micronized drug particles with a diameter of less than 10 μm are markedly adhesive and cohesive, and have poor dispersing properties. It is difficult to pack the adhesive and cohesive micronized drug particles uniformly into inhalation devices and capsules and uniform emission of these particles from devices and capsules is also difficult.

One delivery system for dry powder inhalations which might overcome these problems is a coarse-carrier particle system, such as one having lactose particles blended with micronized drug particles.[10] When mixed with carrier particles such as lactose, drug particles adhere to the surfaces of the carrier particles. Then, in airflow, the micronized drug particles have to be separated from the carrier particles, efficiently emitted from the capsule and inhalation device, and finally delivered to the lungs. Thus, it is important to consider the precise nature of the inhalation process for a drug/carrier mixture when designing dry powder inhalations using carrier particles.

We previously reported on the influence of surface-treatment of carrier particles on the flow properties of a drug/carrier (salbutamol sulfate/lactose) powder mixture and the emission of drug adhering to carriers from capsules and inhalation devices.[11] At that time, we suggested that when the flow properties of the drug/carrier powder mixture improved, the outflow of the powder mixture from capsules and devices, and consequently the emission of the drug, became easier. Presumably, drug/carrier adhesion force is closely related to the flow and emission behavior of a mixture; in addition, this adhesion force is likely to be critical in the separation of drug particles from carrier particles. However, there have only been a few studies in which the drug/carrier interparticle adhesion force was measured, and its relationship with inhalation properties investigated.[12] Therefore, we investigated adhesion properties to evaluate the drug particle separation characteristics from the surface of carrier particles in airflow.

Experimental

Materials As the model carrier particle for dry powder inhalation, α-lactose monohydrate was used (Pharmatose® 200M, DMV, The Netherlands).

Salbutamol sulfate was used as the 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 Co., Japan).

Physical Properties of Powders. Mean Particle Diameter The mean particle diameter (Heywood diameter) of lactose particles was determined using an image analyzer (Luzex-FS, NIRECO, Japan) connected to a microscope (OPTIPHOT, Nikon).[13]

Surface Roughness The surface roughness of single lactose particles was determined using a confocal scanning laser microscope (1LM-21, Lasertec Co., Japan). The surface roughness parameter Ra (the arithmetic mean roughness) was evalated according to JIS B 0601 (1994).

True Particle Density True particle density was obtained with a Shimadzu-Micromeritics helium-air pycnometer (Model-1302, Japan).

Preparation of Dry Powder Mixture. Sieving Lactose particles were sieved to obtain a uniform mean particle diameter using an Air Jet Sieve (HOSOKAWA MICRON, Japan). Each sieving time was 480 s and the vacuum pressure was 1500 Pa.

Surface Treatment of Lactose Powders Dissolution of Protuberances or Projections on the Particle Surfaces[14]: Lactose powders were treated with aqueous ethanol solution (70% v/v) to dissolve the protuberances or projections on the particle surfaces and produce particles with smooth surfaces.[11] Approximately 30 g of lactose particles was added to 200 ml of the aqueous ethanol solution in a beaker, and the mixture was stirred for 5, 10, or 20 min and then filtered; the residue was washed with fresh ethanol and dried for 6 h at room temperature using a silicagel desiccator attached to a rotary pump.

Preparation of Powder Mixture Powder mixtures of 2.5 w/w% salbu-

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tamol sulfate were prepared by mixing 1.0 g of salbutamol sulfate and 39.0 g of lactose in a glass bottle (diameter 3.5 cm, height 12 cm) with a vortex mixer (Vortex-Genie model K-550-G, U.S.A.) for 5 min.

Packing of Powder Mixture into a Capsule A total of 80 mg of powder mixture was packed into a No. 2 gelatin hard capsule (Shionogi Qualicaps Co., Ltd., Japan) and stored in a desiccator at 22±2 °C for 24 h.

***In Vitro* Deposition Property** The powder mixtures were aerosolized using a dry powder inhalation device (Spinhaler®, Fisons, U.K.). 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 stages 1 and 2, respectively. After the Spinhaler® was connected to the mouthpiece of the twin impinger, a capsule was placed in the holder of the Spinhaler®, which had a pin attached to pierce the capsule. An airstream 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. These determinations were carried out at 22±2 °C and 50±5% relative humidity.

In this study, since we focused on the separation of drug particles from the surface of a carrier emitted from a capsule and a device, we employed the respirable particle percent of emitted particles from the inhalation system (RP) to represent the *in vitro* deposition property. RP was proposed by Hino *et al.*[15] and Kawashima *et al.*[16] to evaluate inhalation behavior and expressed as:

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

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

Evaluation of Powder-Adhesion Properties. Ultracentrifuge Separation Method The adhesion force between drug particles and carrier particles was determined using an ultracentrifuge separation technique (Optima XL-90K, Beckman, U.S.A.). Samples of approximately 5 mg powder blend were studied at ultracentrifuge rotor speeds of 5000, 10000, 20000 and 30000 rpm. The percentage of drug particles remaining attached to the carrier, Rc, was calculated as follows:

$$Rc=(Ro-R_1)/Ro\times 100 \quad (2)$$

where Ro is the amount of drug adhering to the carrier particles before separation, and R_1 is the amount of separated drug after each centrifugation step. Salbutamol sulfate contents of sample solutions were determined by spectrophotometry (UV-160A, Shimadzu, Japan) at 224 nm. The separation force between the micronized drug and carrier particles during centrifugation was calculated as follows[17]:

$$F=(\pi/6)\cdot\rho\cdot d^3\cdot r\cdot\omega^2 \quad (3)$$

where F is the adhesion force between adhering drugs and carrier particles, ρ is the true particle density, d is the mean diameter of the drug particles, r is the distance between the center of the particle and the axis of rotation and ω is the angular velocity.

Air Jet Sieve Method The air jet sieve technique was used to assess the characteristics of separation of the micronized drug from the carrier particles in an air stream. Approximately 10.0 g of powder blend was sieved with a 325 mesh wire screen using an Air Jet Sieve (Model-200, HOSOKAWA MICRON, Japan) for 6, 16, 36, 120, or 440 s. The drug concentration in the mixture was determined by UV analysis of 50 mg samples taken from the mixture before and after sieving. The percentage of drug retained on the carrier was calculated as follows:

$$Rs=(R_2/Ro)\times 100 \quad (4)$$

where Rs is the percentage of drug retained on the carrier particles, Ro is the amount of drug particles adhering to the carrier particle surface before sieving and R_2 is the amount of drug retained on the carrier particles after each sieving step.

The experiments on the powder-adhesion properties were carried out at 20±5 °C and a relative humidity of 50±10%.

Results and Discussion

Particle Diameter of Lactose Carrier Particle diameters of the lactose carrier particles of the dry powder inhalation are shown in Table 1.

Table 1. Physical Properties of Lactose Carriers

Carrier	Surface treatment time (min)	Particle diameter[a] (μm)			Surface roughness[b] Ra (μm)
		D_{10}	D_{50}	D_{90}	
Lac-a	0	49	64	76	0.70±0.13
Lac-b	5	50	66	79	0.62±0.15[c]
Lac-c	10	49	64	76	0.42±0.07[d]
Lac-d	20	48	63	75	0.37±0.10[d]

a) Heywood diameter (n=100). *b*) Data are represented as mean±S.D. (n=30). *c*) $p<0.05$, significant difference compared to Lac-a by Student's unpaired t-test. *d*) $p<0.01$, significant difference compared to Lac-a by Student's unpaired t-test.

Table 2. Average Adhesion Force and Mean Separation Time

Carrier	F50×10^{-9} (N)	T50 (s)
Lac-a	7.5±1.2	130±30.5
Lac-b	5.1±0.9[a]	74.7±15.0[a]
Lac-c	4.0±0.6[a]	65.0±18.5[a]
Lac-d	4.9±1.1[a]	54.3±24.5[a]

Data are represented as mean±S.D. (n=3). *a*) $p<0.05$, significant difference compared to Lac-a by Student's unpaired t-test.

Table 3. *In Vitro* Deposition of Salbutamol Sulfate with Various Lactose Carriers

Carrier	RP (%)
Lac-a	17.9±2.4
Lac-b	24.4±0.4[b]
Lac-c	26.7±1.0[a]
Lac-d	24.5±2.0[b]

Data are represented as mean±S.D. (n=3). *a*) $p<0.01$, significant difference compared to Lac-a by Student's unpaired t-test. *b*) $p<0.05$, significant difference compared to Lac-a by Student's unpaired t-test.

Lac-a represents surface-untreated lactose, and Lac-b, -c, and -d, represent lactose particles surface-treated with aqueous ethanol solution for 5, 10, or 20 min, respectively. Mean particle diameters of the lactose carriers used were approximately uniform.

Surface Roughness of Lactose Carrier The surface roughness parameter Ra decreased with an increase in surface treatment time (Table 1). In our previous paper,[11] we showed that surface-untreated lactose particles have a rough surface with protuberances or projections, while surface-treated lactose particles have a smooth surface, exhibiting rounded protuberances and decreased overall surface roughness. These findings are consistent with the surface roughness parameter Ra (Table 1) determined in the present study.

Evaluation of the Characteristics of Adhesion between Drug Particles and Carrier Particles For dry powder inhalations with carrier particles, easy separation of drug particles from the carrier is important. Thus, the properties of adhesion between drug particles and carrier particles were examined by ultracentrifuge separation.

Table 2 shows the average adhesion force (F50) between drug particles and carrier particles. The F50 between drug particles and the surface-treated lactose particles was significantly lower than that between drug particles and untreated lactose particles.

Figure 1 shows scanning electron microphotographs of

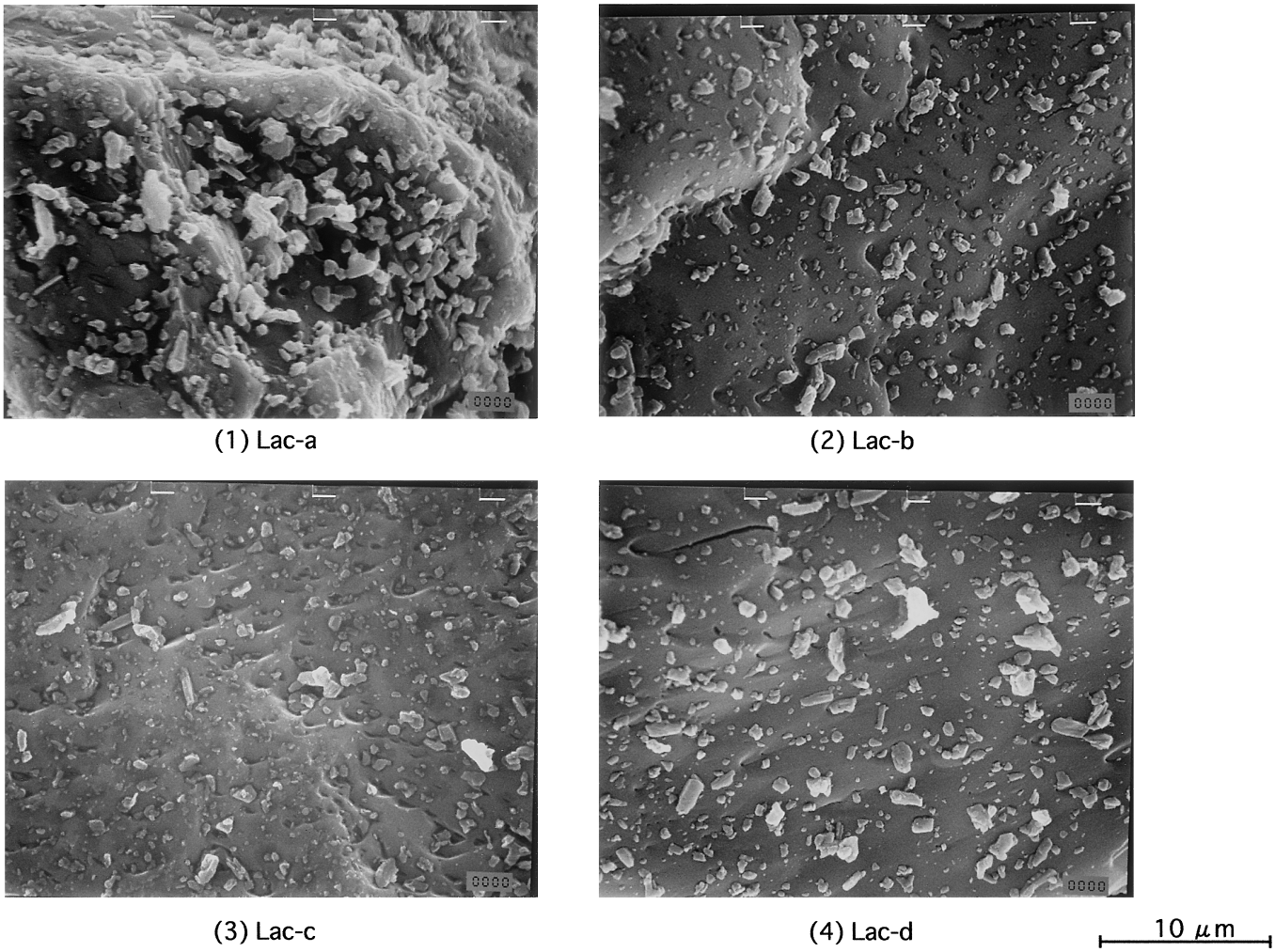

Fig. 1. Scanning Electron Microphotographs of Salbutamol Sulfate on the Surface of a Lactose Carrier
Carrier: (1) Lac-a, (2) Lac-b, (3) Lac-c, (4) Lac-d. Conditions: after air jet sieving for 440 s.

salbutamol sulfate on the surface of the lactose particles. When the untreated lactose carrier (Lac-a) was used, many drug particles were observed in macroscopic depressions on the carrier particle surface (Fig. 1). This was in agreement with the observation by Kawashima *et al.* that lactose particles with larger surface areas could carry higher amounts of drug particles on emission because of their greater capacity for deposition and stronger adhesion with drug particles.[16)]

In the case of the lactose carrier surface treated for the shortest time (Lac-b), the carrier particle surface became flat as the macroscopic roughness of the carrier particle surface decreased. Fine drug particles in the macroscopic depressions decreased in number, resulting in drug particle separation from the carrier particle surface. When the treatment time of the lactose particles was increased (Lac-c), F50 showed a further decrease. In the Lac-c case, it is possible that the particle surface possesses microscopic asperities, and the height of the projections is an order smaller than the drug particle dimensions. Here the drug/carrier surface contact area would be smaller, and adhesion force would accordingly be less. In the case of the lactose carrier receiving the longest surface treatment (Lac-d), the particle surface became smoother as the microscopic asperity decreased (Table 1). In the Lac-d case, an increase in adhesion force would take

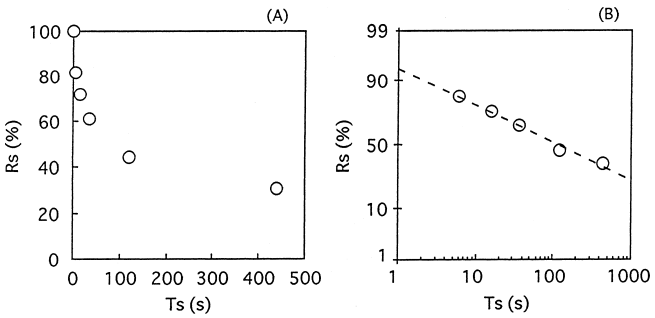

Fig. 2. Plots of Percentage of Drug Retained against Sieving Time
(A) normal plots, (B) logarithmic probability plots. Carrier: Lac-a.

place as a result of the smoother condition of the carrier surface. Possibly, the contact area between the drug particles and carrier surface again increased, and this led to an increase in adhesion force.[18)]

Evaluation of the Properties of Separation of Drug Particles from Carrier Particles in Dry Powder Inhalation The properties of separation of the drug particles from carrier particles were investigated by the air jet sieve method. A typical result from the air jet sieve method is shown in Fig. 2A. The percentage of drug retained (Rs) decreased as the

sieving time (Ts) increased. As shown in Fig. 2B, the logarithmic probability showed a linear relationship. Such linear relationships were obtained for all samples, and the mean separation time (T50) for each sample was determined using a graph.

The T50 was defined as the time point at which 50% of the drug particles had separated from the carrier particles. Table 2 shows the T50 of the four samples. Compared with that obtained using untreated lactose carrier, the T50 obtained by surface treatment was significantly shorter, indicating that drug separation from the carrier particle was facilitated by surface treatment.

Staniforth *et al.* reported that large lactose particles with a more porous surface structure formed stronger adhesion bonds with fine drug particles due to the entrapment of fine particles in surface indentations.[19] In the present study, when the surface treatment time of the lactose carrier was short (Lac-b), the amount of macroscopic roughness on the lactose carrier particle surface decreased, and therefore, drug particles entering macroscopic depressions and remaining there decreased, which facilitated separation of the drug particles from carrier particles. When the surface treatment time of the lactose carrier was prolonged (Lac-d), the microscopic asperity on the lactose carrier particle surface decreased further (Table 1). These results would demonstrate how the separation of fine drug particles from the carrier particles depended on the surface condition of the latter.

***In Vitro* Deposition Properties of Salbutamol Sulfate** Table 3 shows the *in vitro* inhalation index of salbutamol sulfate with various carriers, determined by twin impinger. Since we focused on the separation of drug particles from carrier particles emitted from capsules and inhalation devices, we employed RP as the *in vitro* inhalation property index. The RP of the powder mixed with the surface-treated lactose carrier was significantly higher than that of the powder mixed with the surface-untreated lactose carrier.

Many drug particles remaining in the macroscopic depressions of the untreated lactose carrier surface were observed in scanning-electron microphotographs (Fig. 1). Drug particles adhered in the deep concavity would become entrapped and relatively immobile in the macroscopic depressions.[20] The separation of drug particles from surface-untreated lactose carriers would be lower, resulting in lower RP values. With Lac-b, which was lactose carrier surface-treated for a short time, the amount of macrosopic roughness on the lactose particle surface was smaller than that with untreated lactose, and the carrier-particle surface was flatter. This decreased the number of drug particles remaining in macroscopic depressions and facilitated drug separation. When the treatment time of the lactose surface increased (Lac-c), the RP value further increased. A possible reason could be that the microscopic asperities reduced the contact areas between the drug and lactose surfaces.

Figure 3 shows the effect of the surface roughness of lactose particles (Ra) on the adhesion force between drug and lactose particles (F50) and the *in vitro* deposition properties of salbutamol sulfate (RP). When the surface roughness of lactose particles was compared with the F50 and RP, there was an optimal surface roughness with an F50 of 4.0×10^{-9} (N) and RP of 26.7 (%) (Fig. 3). Drug particles adhering to the microscopic projections reduced the van der Waals attractive forces, resulting in easier separation of the drug particles from the lactose surfaces and a higher RP.[6] When Lac-d, was used, the amount of surface microscopic asperity of the lactose particles was less, and the carrier-particle surface was smoother (Table 1). The adhesion force (F50) for Lac-d is greater than Lac-c because of the larger in-contact area between drug particles and lactose surface resulting in lower RP.

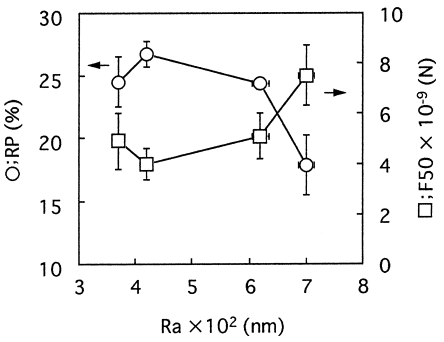

Fig. 3. Relationship between Ra, F50 and RP
□, F50; ○, RP. Data are expressed as mean±S.D. of three runs.

In summary, the present study demonstrated that short surface-treatment of a lactose carrier with aqueous ethanol solution contributed to overall reduction of adhesion force due to its surface-smoothing effect. While it allowed the drug and carrier mixture to be more flowable and, consequently, made the emission of the mixture particles easier,[11] this treatment of carrier particles also enhanced the separation of drug particles. These results suggested that while the drug particles adhering to the flat surface of the carriers worked as an anti-adherent until emission, the strength of the adhesion force was well balanced so that the drug particles could be emitted together with the carrier particles and efficiently separated in airflow after emission.

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