Effect of Surface Covering of Lactose Carrier Particles on Dry Powder Inhalation Properties of Salbutamol Sulfate

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The effect of the surface covering of lactose carrier particles on the dry powder inhalation properties of salbutamol sulfate was investigated. Lactose carrier surfaces were covered with sucrose tristearate (J-1803F) by 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 lactose carriers with various particle surface conditions prepared by surface covering. These powder mixtures were aerosolized by a Jethaler®, and the *in vitro* inhalation properties of salbutamol sulfate were evaluated by a twin impinger. Compared with the powder mixed with uncovered lactose carrier, the *in vitro* inhalation properties of the powder mixture prepared using the surface covering lactose carrier were significantly different, showing that the *in vitro* inhalation properties of salbutamol sulfate were improved. *In vitro* inhalation properties increased with the percentage of J-1803F added. Using this surface covering 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 covering; sucrose tristearate

Dry powder for inhalation (DPI) is generally formulated as a powder mixture of coarse carrier particles and micronized drug particles with aerodynamic particle diameters of 1—6 μm.[1—6)] Inhaled drug particles with aerodynamic particle diameters of 1—6 μm defined as respirable particles are assumed to be deposited on the bronchi or alveoli.[7—10)] Carrier particles larger than respirable sizes are generally deposited on the upper respiratory tracts such as throats by the inertial impaction. During inhalation, carrier particles may help the emission of the drug from the device or capsules and improves its inhalation properties such as the delivery of the drug particles to the bronchi or alveolus. Therefore, in designing a DPI using carrier particles, it is important for drug particles to be adequately detached from the surface of carrier particles for inhalation. The *in vitro* inhalation properties of DPI are reported to be related to the surface properties of the carrier particles.[1,11—13)] In this study, we covered the surface of coarse lactose particles, which have been used as an inhalation carrier, with sucrose tristearate (J-1803F) from vegetable oil, which is widely used as a lubricant in the food industry. Recently, in the pharmaceutical field, there is a trend to limit the use of biological products and to substitute them with vegetable excipients.[14,15)] We, therefore, carried out basic investigations on the effects of surface covering of lactose carrier particles with sucrose tristearate (J-1803F) on DPI properties of salbutamol sulfate.

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 the 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). Sucrose tristearate (J-1803F, SURFHOPE® SE PHARMA) with mean diameter of 17.1 μm was obtained from MITSUBISHI-KAGAKU FOODS CORPORATION (Japan).

Physical Properties of Lactose Carrier Particles 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, 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 Covering of Lactose Carrier Particles J-1803F was added to lactose powder at 2, 5, and 10 w/w%, respectively. The premixed powders were further mixed for 10 min with a high-speed elliptical-rotor-type powder mixer (Theta-Composer®, Tokuju, Japan). The powder loading was 20 g. The clearance between the rotor and vessel wall was 0.5 mm. The rotor and vessel were rotated counter revolution at 3000 and 35 rpm, respectively. After mixing, J-1803F that did not deposit to the surface of the lactose particles and J-1803F that was easily detached from the surface of lactose particles were removed by suction at an airflow pressure of 4000 kPa using an Air Jet Sieve (HOSOKAWA MICRON, Japan) for 10 min.

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.

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 at 22±2 °C for 24 h.

***In Vitro* Inhalation 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 detachment of drug particles from the surface of a carrier emitted from a capsule and a device, we employed the respirable particle percent (RP) of emitted particles from the inhalation system to represent the index of the *in vitro* inhalation property. RP was proposed by Hino *et al.*[7)] and Kawashima *et al.*[1)] 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 capsule, and ST2 is the amount (%) of drug deposited in stage 2 of the twin impinger.

Quantitative Analysis of Sucrose Tristearate Sucrose tristearate (J-1803F) was quantified by the HPLC systems with peak area measuring

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method (LC-10AD, Shimadzu, Japan) described in the Japanese Pharmacopoeia (JP XIV).[16]

Percentage of Surface Covering The percentage of the mass of sucrose tristearate (J-1803F) covered on the surface of lactose particles relative to the mass of surface covered lactose particles was calculated and expressed as the percentage of surface covering defined by Eq. 2.

$$\text{percentage of surface covering} = (\text{sucrose tristearate cover})/(\text{surface covered carrier}) \times 100 \quad (2)$$

Where, sucrose tristearate cover is the mass of sucrose tristearate covered on the surface of lactose particles that was calculated by quantitative analysis of HPLC. The surface covered carrier is the mass of lactose carrier particles covered with sucrose tristearate (J-1803F).

Results and Discussion

Physical Properties of Lactose Carrier Particles Table 1 shows the mean particle diameter, specific surface area, and percentage of surface covering. In the table, lac-0 represents uncovered lactose particles, and lac-1, lac-2, and lac-3 represent lactose particles with 2, 5, and 10 w/w% of sucrose tristearate (J-1803F), respectively. The mean particle diameter was approximately the same among all lactose carrier particles prepared. The specific surface area was smaller in covered lactose particles compared with uncovered lactose particles, because J-1803F covering the surface of lactose particles made them smoother by covering depressions. Sucrose tristearate (J-1803F) has been widely used as a lubricant in the food industry because of its excellent lubricating effect. It has also been reported to have a marked tendency to deposit on the surface of larger particles and cover them.[17] We quantified sucrose tristearate (J-1803F) and calculated the percentage of J-1803F in the covered lactose particles as the percentage of surface covering (Eq. 2). As shown in Table 1, the percentage of surface covering is considered to have increased with percentage of J-1803F added, because collision and friction between particles were repeated under shear force applied in the Theta-Composer® and more J-1803F pressed against and covered the surface of lactose particles

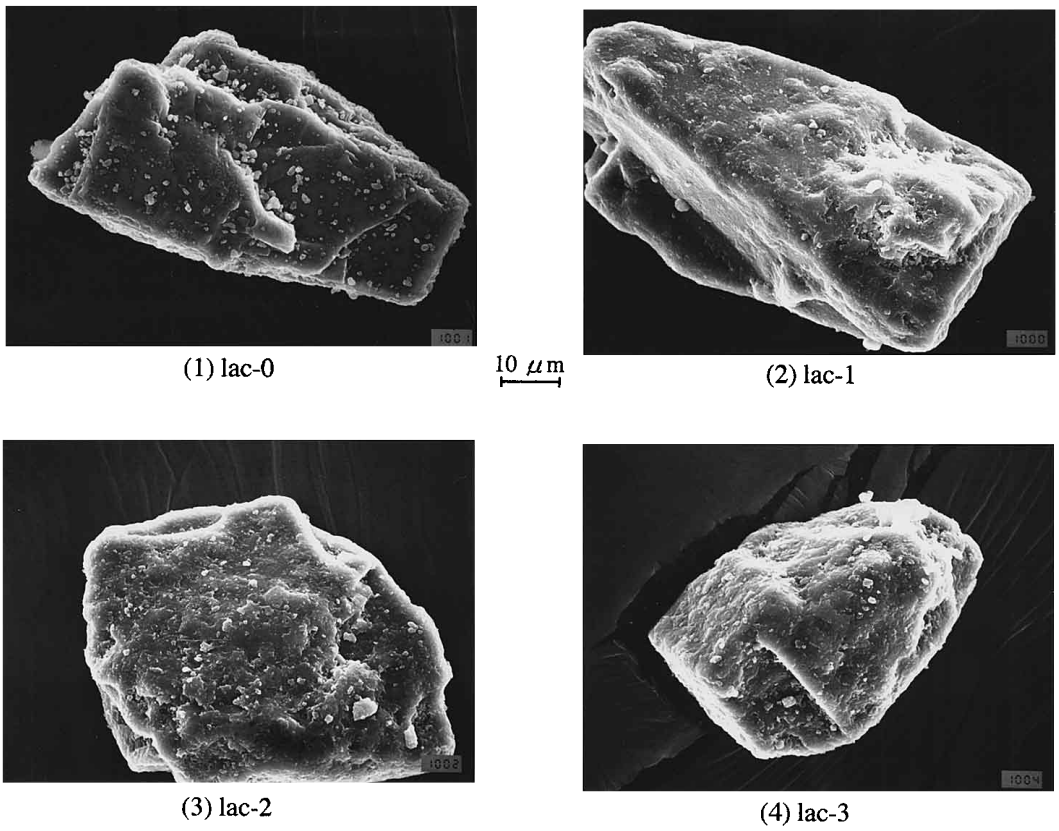

Fig. 1. Scanning Electron Microphotographs of Lactose Carrier Particles Used
Carrier: (1) lac-0, (2) lac-1, (3) lac-2, (4) lac-3.

Table 1. Physical Properties of Lactose Carriers and *in Vitro* Deposition Results of Salbutamol Sulfate with Various Lactose Carriers

Carrier	Percentage of J-1803F added (w/w%)	Mean particle diameter[a] (μm)	Specific surface area[b] (m^2/g)	Percentage of surface covering[c] (w/w%)	RP[d] (%)
lac-0	0	71.2±18.7	0.148±0.001	0	17.4±0.5
lac-1	2.0	70.8±19.2	0.134±0.002**	1.11±0.14	33.1±8.9*
lac-2	5.0	72.3±15.6	0.130±0.002**	2.81±0.41	37.0±5.5**
lac-3	10.0	71.9±17.5	0.128±0.002**	8.70±0.46	46.8±1.5**

a) Data are represented as mean±S.D. (n=100). *b*) Data are represented as mean±S.D. (n=3). *c*) Data are represented as mean±S.D. (n=3). *d*) Data are represented as mean±S.D. (n=3—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.

with percentage of J-1803F added.[18—23)]

Figure 1 shows SEM photographs of the lactose carrier particles prepared. The surfaces of uncovered lactose particles were irregular, but the surfaces of covered lactose particles were smooth. In lac-1 prepared with 2.0 w/w%, J-1803F covered the surface of lactose particles. In lac-3 prepared with 10.0 w/w%, more J-1803F covered them, filling depressions and gaps on the surface of lactose particles. These results were in agreement with the values of the specific surface area, and percentage of surface covering shown in Table 1.

Effects of Surface Covering of Carrier Particles on *in Vitro* Inhalation Properties Table 1 shows the *in vitro* inhalation property (RP) of salbutamol sulfate. RP was significantly greater in covered carriers than in the uncovered carrier, indicating the *in vitro* inhalation properties of salbutamol sulfate were improved.

When the percentage of J-1803F added was compared with the RP and the specific surface area (Sw) of lactose carrier particles, the RP values increased with the percentage of J-1803F added. On the other hand, Sw decreased with increased in the percentage of J-1803F added.

The RP of the powder mixed with the surface covered lactose carrier was significantly higher than that of the powder mixed with the surface uncovered lactose carrier. Fine drug particles cohered in the concavity would become entrapped and relatively immobile in the depressions on the carrier surfaces.[2,3)] Detachment of drug particles from surface uncovered lactose carriers would be lower, resulting in low RP values. With lac-3, which was lactose carrier surface covered with 8.70 w/w% of J-1803F, the amount of roughness on the lactose particle surface was smaller than that with uncovered lactose, and the carrier-particle specific surface area was smaller. This decreased the number of drug particles remaining in depressions and facilitated drug detachment. This was in agreement with the results by Kawashima *et al.* that lactose particles with larger surface areas could carry higher amount of drug particles, whereas they held more firmly the drug particles in the inhaled air stream.[1)]

In this study, the effects of surface covering of lactose carrier particles on the *in vitro* inhalation properties of sulbutamol sulfate were investigated. RP obtained by surface covering with J-1803F under shear with a Theta-Composer® were significantly better than that of uncovered lactose carrier. Surface covering of lactose carrier particles may be an effective technique that may lead to improvements in the inhalation properties of DPI using lactose carrier particles.

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