Evaluation of Flow Properties of Dry Powder Inhalation of Salbutamol Sulfate with Lactose Carrier

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The effects of the flow and packing properties of a drug/carrier powder mixture on emission of drug adhering to the carrier from capsules and inhalation devices were investigated. Model powder mixtures were designed consisting of lactose carriers with different particle shapes were prepared by surface treatment and micronized salbutamol sulfate. These powder mixtures were aerosolized by a Spinhaler®, and *in vitro* deposition properties of salbutamol sulfate were evaluated by a twin impinger. The flow properties of the mixed powders were evaluated by the Carr's flowability index (FI) and Hausner's ratio (HR). The packing properties of the mixed powders were determined employing the tapping method. Compared with the powder mixed with the untreated lactose carrier, the FI, HR, and the constant *K* in Kawakita's equation of the powder mixture prepared using the surface-treated lactose carrier were significantly different, showing that the flow and packing properties of the drug/carrier powder mixture were improved. Using this surface-treated system, the handling of the powder mixture when packing into capsules is improved, which is desirable for handling dry powder inhalants. The fraction (%) of drug emitted from capsules and devices (EM) and the FI of the powder mixture were correlated. As the flow properties improved, the outflow of the powder mixture from capsules and devices became easier, and emission of drug adhering on the carrier from capsules and devices improved. Improvement of the inhalation process, such as the drug particles emitted from the inhalation system, is valuable for increasing inhalation properties of dry powder inhalation.

Key words dry powder inhalation; carrier particle; flow property; Carr's method; Hausner's ratio

Dry powder inhalations are employed for the delivery of drugs to the lungs for the treatment of pulmonary and systemic diseases. It has been reported that in aerosol inhalation therapy, the effect of a drug on respiratory diseases is closely related to the aerodynamic diameter of the inhaled drug particles.[1)] For the treatment of asthma and alveobroncholitis, in particular, drug particles with an aerodynamic diameter of 1—6 μm are most effective.[2)] Thus dry powder inhalations are formulated with micronized drug particles. However, micronized drug particles are very adhesive and cohesive with poor flow properties, and cause problems in packing micronized drug particles into capsules and inhalation devices.

To solve these problems, a coarse carrier particle system in which drug particles are physically mixed with coarse carrier particles such as lactose is commonly used. Carrier particles are used to improve the flow of fine drug particles or to obtain uniform filling of fine drug particles into inhalation devices and capsules. Carrier particles also decrease the residual fine drug particles that adhere to inhalation devices and capsules upon inhalation of fine drug particles. With the use of carrier particles, drug particles are emitted from capsules and devices more easily, and the inhalation efficiency increases. Therefore both the design of the carrier particle and the design of drug particles are important for the development of dry powder inhalations. In the design of dry powder inhalations with carrier particles, it is important to consider how to obtain good flow, the packing properties of the drug/carrier powder mixture, and how to obtain a good outflow from capsules and devices. Therefore the evaluation of the flow and packing properties of dry powder inhalations are necessary. However, only a few studies reported on comparison of mechanical properties such as the flow and packing properties with the inhalation properties in dry powder inhalations using carrier particles.[3)]

For dry powder inhalations with carrier particles, first, reliable emission of the drug adhering to carrier particles from the capsule and inhalation device, and second, easy separation of drug particles from the carrier emitted are important. Thus it is important to consider these inhalation processes of drug/carrier mixture in designing dry powder inhalations using carrier particles. In this study, the effects of the flow and packing properties of the drug/carrier powder mixture on the emission of drug adhering to carrier particles from capsules and inhalation devices are investigated.

Otsuka *et al.*[4)] reported that the effect of particle shape and surface asperity on the adhesive force between surface-treated particles and a glass substrate was investigated by the impact separation method. The surface-treated particles were prepared to dissolve the protuberances on the particle surface. For this purpose, carrier particles with different particle shapes are prepared by treating the surface of lactose carrier particles. Our purpose was to prepare carrier particles with good flow and packing properties by surface treatment of lactose particles, and we investigated the possibility of designing a dry powder inhalation using surface-treated carrier particles.

Experimental

Materials Salbutamol sulfate used as a model drug was obtained from LEIRAS (Finland). The cube-like fine crystals had a volume median diameter of 1.7 μm as determined with laser diffraction (Lasermicronsizer, SEISHIN Co., Japan).

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

Mean Particle Diameter and Particle Shape The mean particle diameter (Heywood diameter) of lactose particles was determined using an image

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analyzer (Luzex-FS, NIRECO, Japan) connected to a microscope (OPTIPHOT, Nikon, Japan). The particle shape of lactose particles was determined using a scanning electron microscope (JSM-T20, JEOL, Japan), and evaluated by an image analysis method.[4] The shape factor (SF) is obtained by dividing the actual projected area of a particle, A, by the area of a circle having a diameter equivalent to the maximum projected length, ML, as shown in the following equation.

$$SF=(4A)/\pi\cdot(ML)^2 \quad (1)$$

Therefore the value of the SF ranges from zero to 1, and as SF approaches unity, there is increased particle sphericity.

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 the same mean particle diameter using an Air Jet Sieve (Hosokawa Micron, Japan). The sieving time for each sieve was 480 s and the vacuum pressure was 1500 Pa.

Surface Treatment of Lactose Powders Removal of Protuberances from Particle Surface[4]: Lactose powders were treated with aqueous ethanol solution (70% v/v) to dissolve the protuberances on the surface. About 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, 20, and 30 min, respectively and then filtered; the residue was washed with fresh ethanol and dried at room temperature.

Preparation of Powder Mixture Powder mixtures of 2.5% salbutamol sulfate were prepared by weighing 1.0 g of salbutamol sulfate and 39.0 g of lactose into a glass bottle (diameter 3.5 cm, height 12 cm) and mixing with a vortex mixer (Vortex-Genie model K-550-G) 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.

Carr's Flowability Index The flow properties of a dry powder inhalation were measured by the Carr's method,[5] in which the following four tests were involved: 1) Angle of repose; 2) compressibility; 3) angle of spatula; and 4) uniformity coefficient, using the POWDER TESTER[6] (PT-D, Hosokawa Micron, Japan). The flowability index (FI) was calculated with the point scores for evaluation of flowability of dry solids by Carr.

Hausner's Ratio Hausner's ratio[7] (HR) was determined from the minimum and maximum bulk density values with the tapping method by Eq. 2.

$$HR=\rho_t/\rho_b \quad (2)$$

where ρ_t is the maximum bulk density (n=1000) and ρ_b is the minimum bulk density (n=0).

Packing Properties of Dry Powder Inhalation The packing properties of the powder mixture were determined with the tapping method by means of Kawakita's equation for indicating porosity.[8—10]

$$1/(\varepsilon_n-\varepsilon_f)=K\cdot n+1/(\varepsilon_o-\varepsilon_f) \quad (3)$$

where ε_o, ε_n, and ε_f are the porosity of powder bed at the initial, nth, and final tapping, respectively, and n is the number of taps. The constant K is expressed as the packing rate constant.

***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 the twin impinger (Model TI-2, Copley) containing 7 and 30 ml of collecting solvents (0.1 M hydrochloric acid) for stage 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 was pinned to pierce the capsule. An air stream of 60 l/min was produced 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, capsule, and device were collected by rinsing with fresh solvent. The rinsed solutions were diluted to appropriate volumes and the drug contents were determined by a spectrophotometer (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 emission of drug adhering to the carrier from the capsule and device, we employed the fraction (%) of drug emitted from capsule and device (EM) to represent the *in vitro* deposited property. EM was proposed by Hino *et al.*[11] to evaluate inhalation behavior and expressed as :

$$EM=\{(\text{stage 1}+\text{stage 2})/(\text{stage 1}+\text{stage 2}+\text{capsule}+\text{device})\}\times 100 \quad (4)$$

where stage 1, stage 2, capsule, and device are expressed by the fraction (%) of drug deposited in stage 1, stage 2, capsule, and device, respectively.

Results and Discussion

Physical Properties of Lactose Carrier Particle diameters and the SFs of the carrier lactose particles of the dry powder inhalation are shown in Table 1. Lactose-0 represents nonsurface-treated lactose, and lactose-5, -10, -20, and -30 represent lactose particles surface-treated with aqueous ethanol solution for 5, 10, 20, and 30 min, respectively. Mean particle diameters of the lactose carriers used were approximately the same. Therefore the effects of the particle diameter of the carrier on the inhalation properties and the mechanical properties of the powder of the dry powder inhalation could be ignored.

The SF obtained by image analysis tended to increase as the treatment time of the particle surface was prolonged, showing changes in the particle shape of lactose. Figure 1 shows scanning electron microphotographs of the lactose particles prepared as carriers for the dry powder inhalation. The nontreated lactose had many asperities on the particle surface, and large protuberances formed angular edges. In contrast, the surface protuberances were round in the surface-treated lactose particles, and the lactose particles became spherical as asperities decreased, which corresponded well to the SFs shown in Table 1. The SF increased with prolonged treatment time. The SF increased with the decreasing ratio of the actual projected area of a particle, A, to the area of a circle with a diameter equivalent to the maximum projected length, ML.

Evaluation of the Flow Properties of the Dry Powder Inhalation Using Carrier Particles The advantage of dry powder inhalations prepared using carrier particles is good flow property of the powder mixture. Using lactose carriers with various shapes prepared by surface treatment, our aim was to design a dry powder inhalation. Table 2 shows the FIs obtained from the four parameters of powder mechanical properties (angle of repose, compressibility, angle of spatula, and uniformity coefficient) and the HR of the five powder

Table 1. Physical Properties of Lactose Carrier Used

Carrier	Treatment time (min)	Mean particle diameter[a] (μm)	Shape factor[b]
Lactose-0	0	64.3±10.4	0.526±0.031
Lactose-5	5	64.8±10.2	0.585±0.034
Lactose-10	10	63.7± 9.6	0.621±0.039
Lactose-20	20	64.1± 8.7	0.635±0.045
Lactose-30	30	62.7± 8.9	0.658±0.049

a) Heywood diameter. *b*) Shape factor represents sphericity of particles (when particles are spherical, SF=1.0). Data are represented as mean±S.D. (n=100).

Table 2. Results of Flowability Index by Carr's Method, Hausner's Ratio, and Constant K of Kawakita's Equation

Carrier	Flowability index	Hausner's ratio	K
Lactose-0	67.8±0.3	1.34±0.02	1.02±0.17
Lactose-5	73.3±0.6[a]	1.26±0.05[b]	2.64±0.75[b]
Lactose-10	71.7±0.3[a]	1.28±0.02[b]	2.10±0.28[b]
Lactose-20	72.2±1.2[a]	1.29±0.01[b]	1.67±0.35[b]
Lactose-30	69.5±0.9[b]	1.30±0.01[b]	1.88±0.69

Data are represented as mean±S.D. (n=3). *a*) $p<0.01$, significant difference compared to lactose-0 by Student's unpaired t-test. *b*) $p<0.05$, significant difference compared to lactose-0 by Student's unpaired t-test.

mixtures.

The FI and HR of the powder mixed with the surface-treated lactose particles were significantly higher than those of the powder mixed with the nontreated lactose particles, showing that the flow properties of the powder mixture increased. Good flow properties are desirable for handling dry powder inhalation. However, although the surface treatment time of the lactose particles increased, the FI was shown to reach a limit. In the lactose carrier surface treated for the shortest time (lactose-5), the angular edges of particles became rounded as the protuberances and asperities on the particle surface decreased, which may have reduced geometric interlocking among the carrier particles and improved the flow properties of the powder mixture.

When the nontreated lactose carrier was used, many drug particles were observed adhering to hollows and pits on the

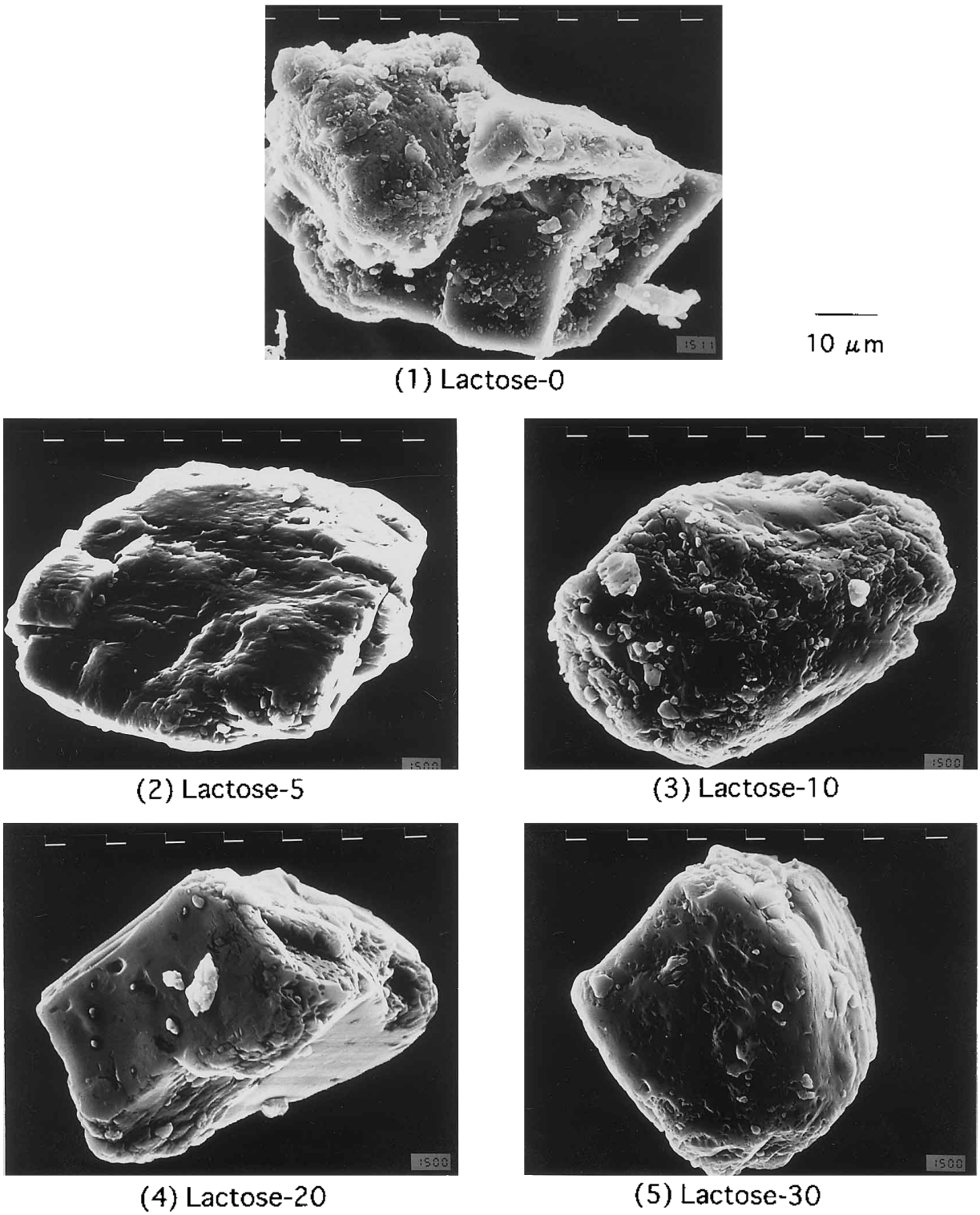

Fig. 1. Scanning Electron Microphotographs of Lactose Carrier Particles Used

Carrier: (1) Lactose-0, (2) lactose-5, (3) lactose-10, (4) lactose-20, (5) lactose-30.

carrier particle surface by electron microscopy. In the lactose carrier surface treated for a prolonged time (lactose-30), the particle shape became more rounded as the surface asperity decreased (Fig. 1). When the lactose carrier with fewer protuberances and less asperity on the particle surface was used, fine drug particles adhered and cohered to the flat region of the carrier particle surface. The results showed that the frequency of adhesion between the fine drug particles increased, the frequency of direct contact between the carrier particles decreased, and the flow properties may have reached a limit.

Evaluation of the Packing Property of the Dry Powder Inhalation using Carrier Particles Packing processes of the powder mixture were determined using the tapping method to evaluate the packing property of the dry powder inhalation. Figure 2 shows an example of the measured values plotted by Kawakita's equation.[8—10] There was a linear relationship between n and $1/(\varepsilon_n-\varepsilon_f)$, and the constant K was obtained from the slope of this line. Table 2 shows the constant K values of the five powder mixtures. Compared with the powder mixed with the nontreated lactose particles, the constant K of the powder mixed with the surface-treated lactose particles significantly increased, showing that the packing property of the powder mixture was improved. Good packing properties are also desirable for the handling of dry powder inhalation. However, the constant K may have reached a limit when the treatment time of the lactose surface increased, and a tendency similar to the flow properties (FI and HR) was observed. When lactose-30 surface treated for a prolonged time was used, the surface asperity of the lactose particles decreased and the carrier particle became spherical. As the flat region increased on the lactose particle surface, fine drug particles adhered and cohered in it. Thus the frequency of adhesion and cohesion between fine drug particles increased, and the interactive force, such as the van der Waals attractive force between the mixed powder particles, increased.

***In Vitro* Deposition Property of Salbutamol Sulfate** Table 3 shows the *in vitro* inhalation index of salbutamol sulfate with various carriers measured using a twin impinger. Since we focused on the emission of the drug particles from capsules and inhalation devices in this study, we employed the EM as the index of the *in vitro* inhalation property. The EM of the powder mixed with the surface-treated lactose carrier was significantly higher than that of the powder mixed with the nontreated lactose carrier, showing that emission of drug particles was improved.

Under the microscope, the emitted drug particles from the capsule and device were observed as nonaggregated particles. The emission of the adhered drug powder mixture using the surface-treated lactose carrier from capsule and inhalation device was improved, showing that mixing with a surface-treated lactose carrier may be useful for improving the inhalation properties of dry powder inhalations. However, the EM value did not change markedly even when the treatment time of the lactose surface increased, and the EM became constant and reached a limit. Using lactose-5, which was surface treated for a short time, the surface asperity of the lactose particles decreased, and edges were rounded, and the particles became spherical, which may have increased the flow properties of the powder mixture and improved emission of the drug particles from the capusule and inhalation device. When lactose-30 surface treated for a prolonged time was used, the surface asperity of the lactose particles decreased and the carrier particles became spherical. As the flat region increased on the lactose particle surface, fine drug particles adhered and cohered on it. Thus the frequency of adhesion and cohesion between fine drug particles increased and the interactive force such as the van der Waals attractive force between the mixed powder particles increased, which may have interfered with the flow properties of the powder mixture and resulted in emission of the drug particles from capsules and inhalation devices reaching a limit.

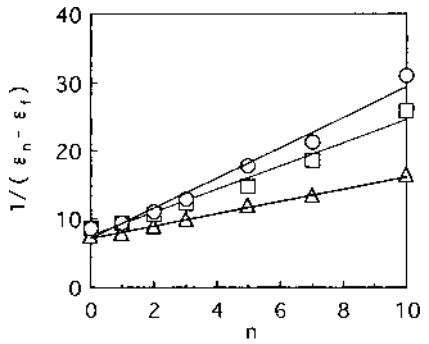

Fig. 2. Relationship between $1/(\varepsilon_n-\varepsilon_f)$ and n in Kawakita's Equation
Carrier: △, Lactose-0; ○, lactose-5; □, lactose-10.

Table 3. *In vitro* Deposition Results of Salbutamol Sulfate with Different Shaped Lactose Carriers

Carrier	EM (%)
Lactose-0	75.2±1.7
Lactose-5	81.0±1.9[a)]
Lactose-10	80.3±2.7[a)]
Lactose-20	78.7±1.4[a)]
Lactose-30	78.9±1.3[a)]

Data are represented as mean±S.D. (n=3). *a*) $p<0.05$, significant difference compared to lactose-0 by Student's unpaired t-test.

Effect of Flow Properties of the Powder Mixture on the Emission of Drug Adhering to Carrier from Capsule and Inhalation Device When a dry powder inhalation using carrier particles is packed in capsules and inhalation devices, first, reliable emission of drug adhering to carrier from capsules and inhalation devices is necessary, and it is important that dry powder inhalation is designed with due consideration of this inhalation process. Thus we investigated the effect of the flow properties of the powder mixture on the emission of drug adhering to carrier from capsules and inhalation devices. Figure 3 shows the relationship between the EM and the FI of the powder mixture. EM and FI showed a good correlation. EM tended to increase as FI increased.

Kawashima *et al*.[3] prepared powder mixtures using lactose particles with various specific surface areas. The emission (%) of drug was proportionally correlated to the specific surface area was reported. We prepared carrier particles with difference shapes by treating the surface of lactose particles in the present study. When the flow properties of the drug/carrier powder mixture increased, the outflow of the powder mixture from capsules and devices became easier, and the emission of drug increased. In this study, our aim was to design a dry powder inhalation with good flow and

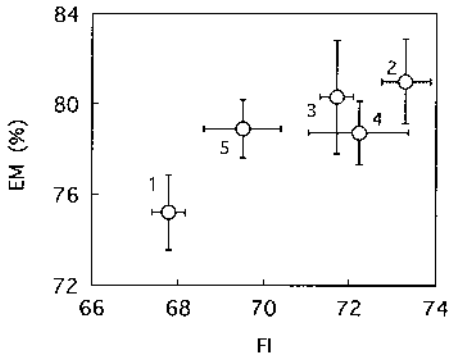

Fig. 3. Relationship between EM and FI

Carrier: 1, Lactose-0; 2, lactose-5; 3, lactose-10; 4, lactose-20; 5, lactose-30. Data are expressed as mean±S.D. of three runs.

packing properties using surface-treated lactose particles as the carrier, and we found that the emission of drug from capsules and devices increase using this system. We found that the flow properties of the powder mixture markedly affect drug emission from the capsule and device. Furthermore, the inhalation of drug/carrier mixture is probably related not only to the particle shape of the carrier, but also to the surface properties of the carrier particles and the adhesiveness between fine drugs and carrier particles.

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