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Effect of surface morphology of carrier lactose on dry powder inhalation property of pranlukast hydrate

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Abstract

The effects of surface morphology of carrier lactose on dry powder inhalation (DPI) property of pranlukast hydrate (PH) were investigated. The PH was mixed with 9-fold weights of carrier lactose, i.e. pharmatose 325M, 200M, DCL-11, DCL-21, spray dried amorphous (SDGa), -crystallized (SDGc) lactoses and fluidized bed granulated lactose (FBG) with various surface morphologies. These mixed powders were aerosolized by a Spinhaler® and in vitro deposition properties were evaluated by a twin impinger. Carrier lactose with higher specific surface area, i.e. surface roughness, like FBG emitted effectively PH particles from the inhalation device, whereas they reduced the respirable fraction captured in the twin impinger, resulting in lower inhalation efficiency, due to strong adhesion of PH to the carrier lactose. The SDGc having lots of microscopical projection on the surface increased the respirable particle percent of the emitted particles, improving the inhalation efficiency. The SDGa, smoothed sphere particle, did not so improve the inhalation efficiency as expected, owing to fairly strong adhesion between PH and lactose particles. Those finding indicated that the separation of drug particles from carrier lactose was a determining step to improve inhalation process for DPIs, as far as lactose particles emitted satisfactorily PH particles from the inhalation device. The surface morphology designed like SDGc, having fairly large surface area with microscopically increased surface roughness was desirable to improve inhalation property of DPI.

Keywords: Powders for inhalation; Carrier lactose; Particle morphology; Crystalline form

1. Introduction

Dry powder inhalation aerosols (DPIs) for pulmonary delivery of anti-asthmatic agent (Smith and Bernstein, 1996) and peptide like agent (Niven et al., 1994; Kobayashi et al., 1996) have

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been developed as an alternative to the pressurized metered dose inhalation aerosols (pMDIs) because of their advantages to avoid the use of chlorofluorocarbon propellants and the coordinated administration with inspiration required for pMDIs.

The deposition site and the efficiency of inhaled aerosols in the respiratory tract are critically influenced by their aerodynamic diameter, size distribution, shape and density (Gupta and Hickey, 1991). It has been reported that inhaled particles larger than 10.0 μm are generally deposited in the upper respiratory tract because of its inertial impaction, and less than 0.5 μm are exhaled without deposition. Aerodynamic diameter between 1.0 and 6.0 μm are thought to be most effective to deliver inhaled particles to targeted region of the lung (Timsina et al., 1994). Consequently, micronized drug particles of about a few micrometers in size are formulated in the DPIs. However, strong adhesive and cohesive properties of such fine drug particles lead to their unreliable filling into inhalation device (e.g. capsule) because of their poor flowing properties. They tend to adhere and remain in the capsule and inhalation device during emission process, resulting in lower and unreliable dosing.

To dissolve these problems, coarse carrier particle (30.0–90.0 μm in diameter) system such as lactose particles loading fine drug particles has been originally developed for DPIs by Bell et al. (1971). The carrier particles have following three roles for the DPIs; (1) improvement of flowability of drug particles into inhalation device (capsule) during filling process (2) increase in dispersing property of cohesive drug particle during emission and (3) diluent of drug on lower dosing.

Lactose has been known to have various crystalline forms. Cartilier and Tawashi (1993) reported the flow and packing properties of lactose were much influenced by the crystalline forms or product grades, depending on particle morphology. However, the detailed effects of physicochemical properties of lactose on inhalation mechanism of drug and carrier have not been well discussed except the report of Kassem and Ganderton (1990). In the present paper, the effect of surface morphology of lactose particles on the inhalation property of the drug deposited on them were investigated in vitro by using a twin impinger. As a model drug micronized pranlukast hydrate particles (D_{50}: 2.1 μm) were employed because of their poor inhalation and micromeritic properties due to their strong adhesiveness, although they have been desired to develop pulmonary delivery system for asthma as an alternative P.O. system.

2. Materials and methods

2.1. Materials

Pranlukast hydrate, abbreviated PH, (4-oxo-8-[4-(4-phenylbutoxy)benzoylamino]-2-(tetrazol-5-yl)-4*H*-1-benzopyran hemihydrate) is a leukotriene antagonist (Nakagawa et al., 1992; Taniguchi et al., 1993), leading to anti-asthmatic effect. The PH particles with 0.6–9.3 μm in diameter, and plate-like fine crystals, were supplied from Ono (Japan). Lactoses employed to design carrier with various morphologies were supplied from DMV (The Netherlands).

2.2. Preparation of carrier lactose

Commercially available carrier lactose for DPIs, pharmatose 325M, (abbreviated 325M, DMV, The Netherlands) was used as supplied. Pharmatose 200M (abbreviated 200M), DCL-11, DCL-21 (DMV, The Netherlands) were sieved to have the same mean diameter as 325M (about 60 μm). Fluidized bed granulated lactose (FBG) was prepared with a fluidized bed granulator (LAB-1, Powrex, Japan), using 200 g of pharmatose 450M (DMV, The Netherlands). The operating conditions were; inlet air temperature: 80°C, air flow rate: 85 m^3/h, binder: 20% lactose solution, spray rate: 10 ml/min. After granulation, agglomerates were sieved to coincide their size to 325M (about 60 μm in diameter). Spray dried granules (amorphous lactose) were prepared with a rotary atomizing spray dryer (OC-16, Ohkawara Kakoki, Japan). 30% lactose solution was spray dried with following operating conditions; inlet air temperature: 180°C, outlet air temperature: 94°C, revolu-

tion speed of atomizer: 10000 rpm, spray rate: 7 kg/h. The spray dried product was sieved coincide their size to that of 325M and stored in a desiccator with silica gel (SDGa). The spray dried amorphous lactose was stored to be crystallized under ambient condition. The resultant cake of spray dried crystalline lactose was dispersed manually in a mortar, and sieved to coincide their size to that of 325M (SDGc).

2.3. Characterization of physicochemical properties of carrier lactose

Particle size distribution of carrier lactose was measured with a laser diffraction size analyzer (LDSA-2400A, Tohnichi, Japan) equipped with a dry disperser (PD-10S, Tohnichi, Japan). The crystalline form of carrier lactose was determined by an X-ray diffractometer (RAD-1, Rigaku Denki, Japan). The specific surface area of carrier lactose was measured by an air permeametry method (SS-100, Shimadzu, Japan) and BET adsorption method with nitrogen gas (Gemini, USA). The surface morphology of carrier lactose was observed by a scanning electron microscope (JSM-T330A, JEOL, Japan), and evaluated by means of an image analysis method (Hino et al., 1997). Surface roughness, SR, was described by Eq. (1).

$$\mathrm{SR} = \frac{\mathrm{PERIM}}{\mathrm{CPERIM}}$$

$$\mathrm{CPERIM} = \frac{1}{32}\sum_{1}^{32}(\text{Feret diameter}) \times \pi \qquad (1)$$

where, PERIM is the perimeter of particle determined by image analyzer. If the particle is a real sphere, SR becomes unit.

2.4. Preparation and packing property of drug/carrier mixture for DPIs

A total of 2 g of PH and 18 g of carrier lactose were weighed in a glass bottle (35 mm i.d., 125 mm height). These powders were mixed with a vortex mixer for 5 min (MT-31, Yamato, Japan). The PH/carrier mixing ratio was chosen to produce ordered mixture as described by Hersey (1975).

Packing properties of PH/carrier mixture were evaluated with a tapping method, by means of Kawakita's equation (Kawakita and Lüdde, 1970) Eq. (2).

$$\frac{N}{C} = \left(\frac{1}{a}\right)N + \frac{1}{(ab)} \qquad C = \frac{(V_0 - V_n)}{V_0} \qquad (2)$$

where, N is the number of taps, C is the degree of volume reduction of packed powder at nth tapping and V_0 and V_n are the bulk volume of powder bed at initial and nth tapping respectively. The parameter 'a' is the degree of volume reduction at the closest packing ($n = \infty$), describing flowing properties.

2.5. In vitro deposition property

A total of 20 mg of PH/carrier mixture were filled into a No. 2 gelatin hard capsule (Japan Elanco, Japan), and the capsule was installed to a dry powder inhalation device (Spinhaler®, Fisons, UK). The Spinhaler. was connected with a twin impinger (Copley, UK) containing 7 and 30 ml of collecting solvents (50 mM sodium hydrogen carbonate solution/ethanol = 1/1) for stages 1 and 2, respectively. Then the capsule was pierced to produce two emitting pores for dispersing particles and the system was vacuumed to produce air streams of 60 l/min for 5 s. After actuation, the drugs in the capsule, device and stages 1 and 2 were collected by rinsing with the collecting liquid. The rinsed solutions were then diluted to proper volumes and the drug contents were determined spectrophotometrically at 260 nm (UV-160A, Shimadzu, Japan). The aerodynamic cutoff diameter between stages 1 and 2 of the twin impinger was 6.4 μm (Hallworth and Westmoreland, 1987; Hino et al., 1997). The particles captured in the stage 2, i.e. finer particle fraction termed respirable fraction, was expected to be deposited on the lung lobe or trachea after inhalation.

Two indices, the effective inhalation index (EI; Eq. (3)) and the respirable particle percent of emitted particles from the inhalation system (RP; Eq. (4)), were introduced to describe the

inhalation properties of DPIs by referring to the fraction (%) of particles emitted from the inhalation system, i.e. capsule and device (Em) and the stage 2 fraction (%), St2, which were defined in the previous paper (Hino et al., 1998).

$$EI = \sqrt{Em \times St2} \quad (3)$$

$$RP = \left(\frac{St2}{Em}\right) \times 100 \quad (4)$$

For ideal DPIs, EI and RP become 100%.

2.6. Inhalation property of carrier lactose

PH/325M mixture (20 mg) were inhaled in the twin impinger containing ethanol as capturing solvent. After five intermitted actuations (for 25 s), the fractions of capsule and device, stages 1 and 2 were rinsed with ethanol to dissolve preferentially PH. Lactose suspended in the ethanol solution was filtered through a 1.0 μm PTFE membrane filter (Advantec, Japan). The lactose collected on the filter was dried and dissolved in distilled water. The concentration of lactose dissolved was determined by the phenol–sulfuric acid method (Fukumori et al., 1987).

3. Results and discussion

3.1. Micromeritic properties and inhalation behaviors of carrier lactose

Crystalline form and particle size of carrier lactose prepared are tabulated in Table 1. All carrier lactoses were approximately same in particle size (60–65 μm) and particle size distribution, corresponding to commercially available carrier lactose, 325M. Consequently, the effects of particle size of carrier on inhalation property reported previously (Kassem et al., 1989; Byron et al., 1990) were cancelled.

The crystalline forms of DCL-11 and DCL-21 were the mixtures of α-monohydrate (85%) and amorphous lactoses (15%), and of β-anhydrate (80%) and α-anhydrate lactoses (20%), respectively (Lerk, 1993). Spray dried lactose (SDGa) was formed to be amorphous. Whereas, SDGc was a mixture of α-monohydrate and β-anhydrate (content ratio was undetermined).

The morphologies of carrier lactose are shown in their scanning electron microphotographs (Fig. 1). The differences in morphologies were clearly shown, depending on the production method. The surface topographies of carrier lactose were described more quantitatively with specific surface

Table 1
Physicochemical property of carrier lactose employed

Grade	Crystalline form	Particle size (μm)			Specific surface area (m^2/g)		Surface roughness[c]
		D_{16}	D_{50}	D_{84}	Permeametry method[a]	Adsorption method[b]	
325M	α-Monohydrate	40.4	63.5	89.4	0.202 ± 0.002	0.233 ± 0.007	1.13 ± 0.01
200M	α-Monohydrate	44.1	64.8	88.6	0.206 ± 0.003	0.234 ± 0.012	1.16 ± 0.03
DCL-11	α-Monohydrate/amorphous	43.4	60.4	79.5	0.242 ± 0.015	0.232 ± 0.003	1.13 ± 0.02
DCL-21	β-Anhydrate/α-anhydrate	41.4	62.4	86.7	0.265 ± 0.002	0.286 ± 0.014	1.16 ± 0.03
FBG	α-Monohydrate	40.3	63.0	90.3	0.348 ± 0.001	0.362 ± 0.029	1.33 ± 0.08
SDGa	Amorphous	41.1	62.9	87.1	0.146 ± 0.010	0.139 ± 0.002	1.08 ± 0.01
SDGc	α-Monohydrate/β-anhydrate	40.5	61.2	89.7	0.174 ± 0.005	0.230 ± 0.004	1.14 ± 0.02

[a] Data are represented with mean $\pm$ S.D. ($n = 2$).
[b] Data are represented with mean $\pm$ S.D. ($n = 3$).
[c] Data are represented with mean $\pm$ S.D. ($n = 10$).

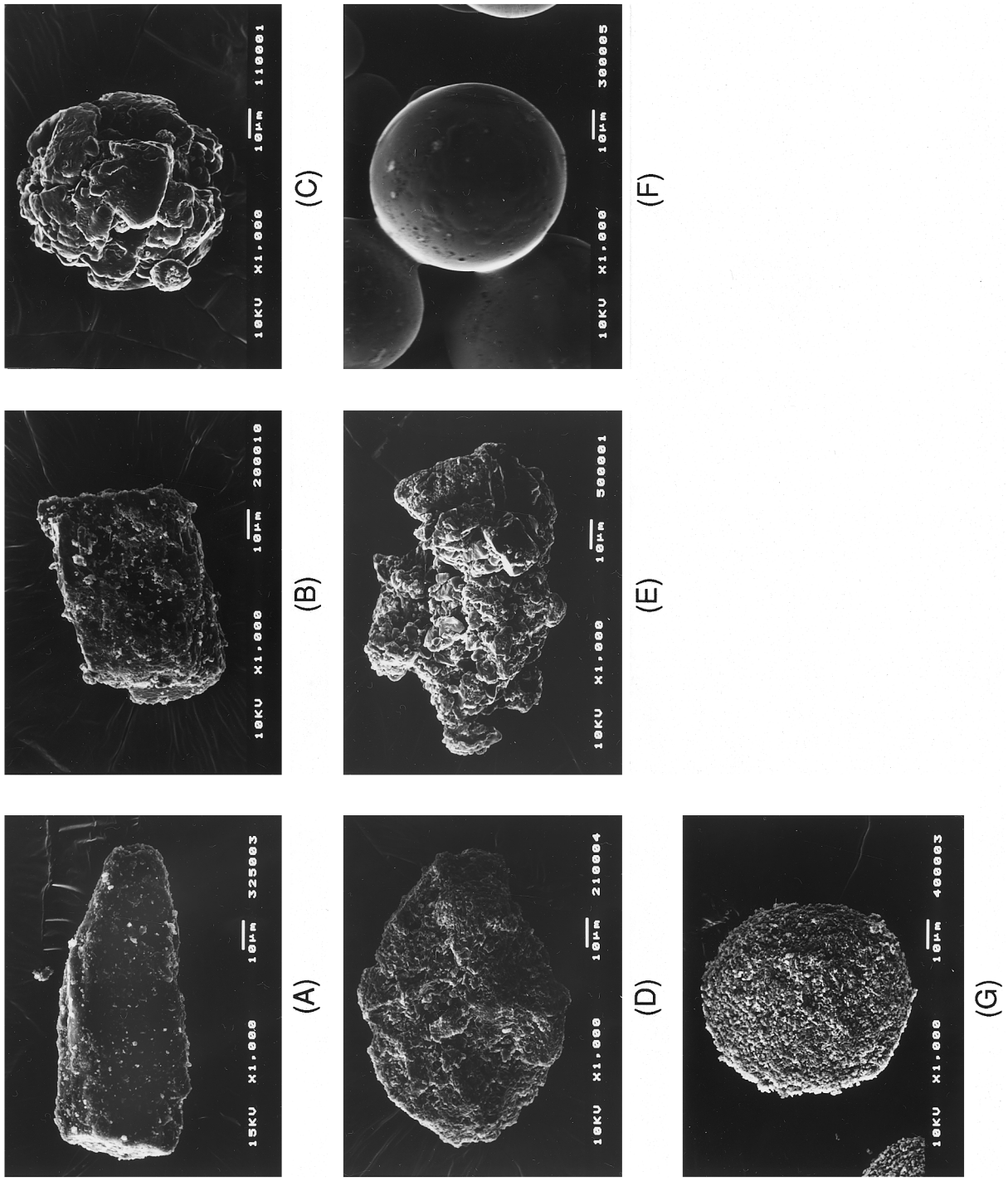

Fig. 1. Scanning electron microphotographs of carrier lactose employed. (A) 325M, (B) 200M, (C) DCL-11, (D) DCL-21, (E) FBG, (F) SDGa, (G) SDGc.

Table 2
Inhalation property of 325M after emission from Spinhaler

Part	Fraction[a] (%)
Capsule and device	1.6 ± 0.7
Stage 1	98.4 ± 0.7
Stage 2	0.0 ± 0.0

Data are represented with mean ± S.D. ($n = 3$).

area and surface roughness in Table 1. The specific surface areas determined by gas adsorption method were slightly larger than those by permeametry method. This finding indicated that the surface area of carrier lactose was determined dominantly by the surface topography rather than intraparticle surface. As expected, the specific surface areas of SDGc and SDGa were smaller than the others, whereas that of FBG was largest among the carrier lactoses. The order of surface roughness of carrier lactose was well corresponded to that of specific surface area.

It was confirmed that all lactose particles were ideally inhaled as a carrier, which were almost completely emitted from the device and were trapped in the stage 1, as shown in the inhalations of 325M on actuation (Table 2).

3.2. In vitro deposition property of PH inhaled with lactose carrier

In vitro deposition patterns and inhalation indices of PH deposited on various carrier lactose inhaled are shown in Fig. 2 and Table 3, respectively. The emission of drug particles were significantly improved from the capsule and device by depositing them on carrier lactose compared to without using carrier lactose system exhibiting the highest drug remain % in capsule and the lowest Em % (Fig. 2 and Table 3). The FBG particles were the most effective for emitting the drug as shown in Fig. 2, probably because of their higher available surface area for drug depositing as shown in Fig. 1 and Table 1. Consequently, higher Em (%) was found with FBG, followed to DCL-11, DCL-21. These Em values were smaller than that of carrier lactose (98.4% in Table 2). It was assumed that the drug particles were separated even in the capsule and some resultant particles adhered in the capsule wall during actuation. The St2s (%) of drug particles were not significantly increased, except SDGc, resulting in lowering RP (%) as represented with an extremely low value of FBG (Table 3). This finding indicated that the adhesion of drug on FBG was extremely strong preventing the separation of

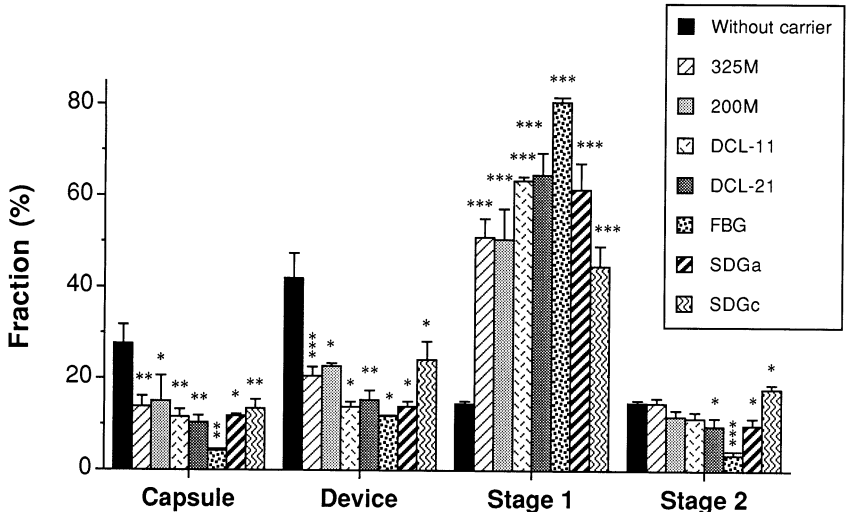

Fig. 2. In vitro deposition properties of PH deposited on various carrier lactoses. Data are expressed as mean ± S.D. of three runs. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$: significant difference compared to without carrier by Student's unpaired t-test.

Table 3
Inhalation indices of PH mixed with various carrier lactose

Carrier	Em (%)	St2 (%)	EI (%)	RP (%)
Without	29.2 ± 1.1	14.8 ± 0.5	20.8 ± 0.7	50.5 ± 0.3
325M	65.7 ± 3.8***	14.7 ± 1.1	31.1 ± 1.4***	22.5 ± 2.4***
200M	62.3 ± 5.3***	11.8 ± 1.4	27.0 ± 0.4***	19.2 ± 4.0***
DCL-11	74.8 ± 2.1***	11.4 ± 1.4	29.1 ± 2.1*	15.2 ± 1.4***
DCL-21	74.4 ± 3.1***	9.7 ± 1.8*	26.8 ± 2.0*	13.2 ± 3.0***
FBG	84.0 ± 0.1***	3.4 ± 0.9***	16.9 ± 2.2	4.1 ± 1.1***
SDGa	74.3 ± 0.7***	9.9 ± 1.5*	27.1 ± 2.0*	13.4 ± 2.1***
SDGc	62.4 ± 3.7**	17.8 ± 1.0*	33.3 ± 0.8***	28.5 ± 3.1***

[a] Data are represented with mean ± S.D. ($n = 3$).
* $p < 0.001$,
** $p < 0.05$,
*** $p < 0.01$; significant difference compared to without by Student's unpaired t-test.

drug from carrier in the air stream. The SDGc increased significantly the EI value, indicating the drug particles were preferentially separated from the carrier on actuation, although the loaded amount of drug on carrier was not so much as FBG. The 325M also reasonably increased the EI value as expected in Table 3. The EI of FBG was rather reduced compared to the non-carrier system, attributed to lowering extremely the RP.

3.3. How the inhalation process of drug/carrier system determined by the surface morphology of carrier lactose

The inhalation process of drug/carrier system was assumed as composed of (1) emission of drug deposited on carrier from the inhalation device, (2) separation of drug from carrier emitted and dispersion of separated drug in the air stream inhaled and (3) delivery of dispersed drug particle to targeted site of lung (stage 2 in the twin impinger in vitro).

The emission % of PH (Em) was proportionally correlated to the specific surface area measured by permeametry (Fig. 3) and gas adsorption method except spray dried lactose (SDGa). This finding indicated that the lactose particle having larger surface area can carry higher amounts of drug particles on emitting because of higher capacity of depositing and stronger adhesion with drug particles.

The carrier lactose with larger surface area after depositing drug particles provided better flowability, described in terms of smaller parameter 'a' in Kawakita's equation (Eq. (2)) on tapping. It was found that the Em was inversely proportional to the 'a' as shown in Fig. 4. The drug/carrier mixture flew and packed easily into the capsule was highly emitted, which was desirable for improving reliability of inhalation process.

The specific surface area of carrier lactose was well correlated to RP (Fig. 5) and St2 (data are not shown) except SDGa. The carrier particles with higher specific surface area separated few drug particles from their surface under shear force

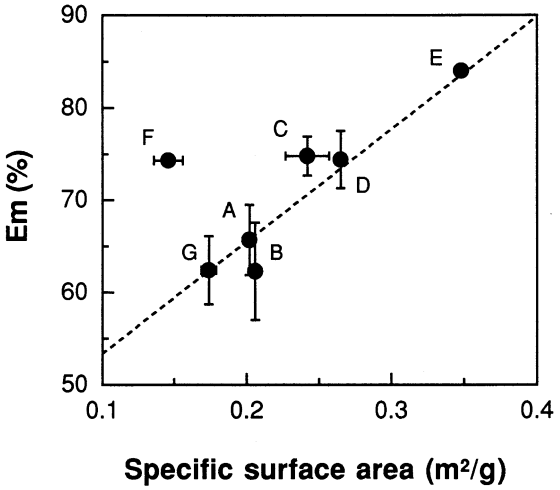

Fig. 3. Relationship between specific surface area of carrier lactose determined by permeametry method and % of drug particles emitted from the inhalation system (Em). Data are expressed as mean ± S.D. of two or three runs. Symbols as in Fig. 1.

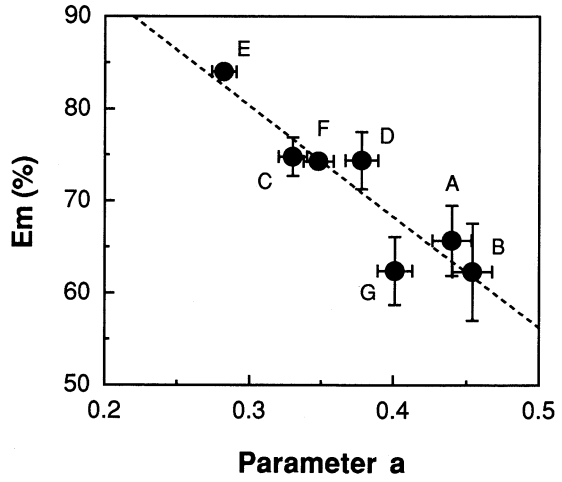

Fig. 4. Relationship between parameter a of drug/carrier mixture in Kawakita's equation and % of drug particles emitted from the inhalation system (Em). Data are expressed as mean ± S.D. of two or three runs. Symbols as in Fig. 1.

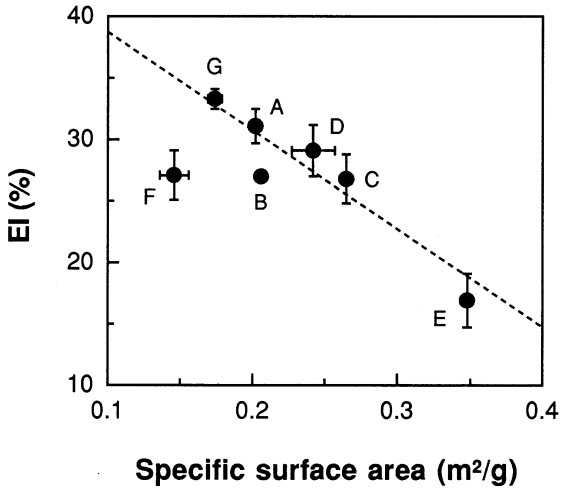

Fig. 6. Relationship between specific surface area of carrier lactose determined by permeametry method and effective index (EI). Data are expressed as mean ± S.D. of two or three runs. Symbols as in Fig. 1.

in the air stream, suggesting stronger adhesion force applied between drug and carrier lactose particles.

Effective index of inhalation (EI) decreased with increasing the specific surface area and surface roughness of carrier lactose as shown in Figs. 6 and 7, respectively. Carrier lactoses with larger specific surface area, i.e. surface roughness carried higher amount of the drug particles (Fig. 3), whereas they held more firmly the drug particles in the inhaled air stream (Fig. 5). Therefore, the effects of surface morphology, i.e. surface roughness, offset to improve inhalation process. In the present system, the separation of drug particles

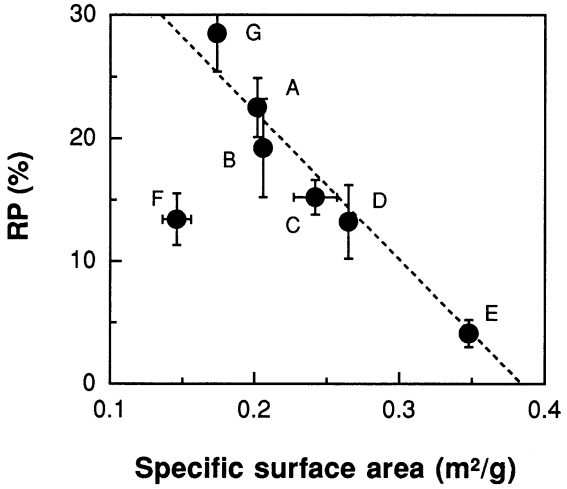

Fig. 5. Relationship between specific surface area of carrier lactose determined by permeametry method and respirable particle fraction of emitted dose (RP). Data are expressed as mean ± S.D. of two or three runs. Symbols as in Fig. 1.

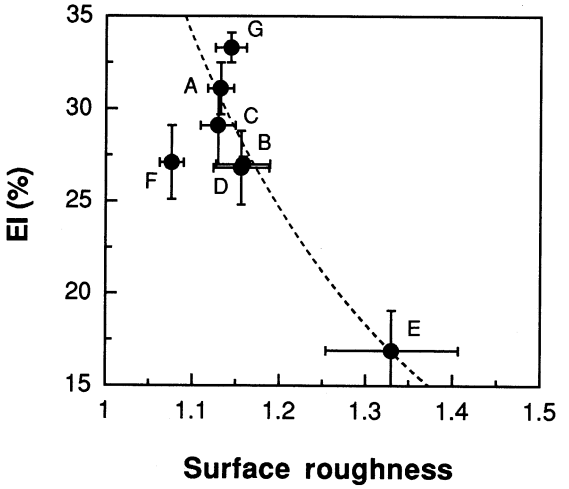

Fig. 7. Relationship between surface roughness of carrier lactose (SR) and effective index (EI). Data are expressed as mean ± S.D. of three or ten runs. Symbols as in Fig. 1.

from the carrier particles was a determining step to improve inhalation process, as found in Fig. 6 and Table 3.

The inhalation behavior of amorphous spray dried lactose (SDGa) was exceptional as shown in Figs. 3 and 5–7. Although, the specific surface area of SDGa was the smallest, the Em and EI, RP were higher and lower than those expected from the findings on the other products, respectively. The smooth surface morphology of SDGa as shown in Fig. 1 should be responsible for enhancing preferably van der Waals attractive force exerted between deposited drug and SDGa due to larger intimate contact area between them compared to other lactose particles, e.g. 325M, 200M and DCL-21 (Visser, 1989). Further, their higher surface energy due to amorphism might make more drug particles to be deposited for lowering the surface energy levels (Chan et al., 1997). Whereas, the surface of SDGc was covered with submicronized crystals, characterized by lots of microscopical projection in Fig. 1. Such surface topography might reduce the contact areas between particles and increase the distance between them. Consequently, the van der Waals attractive force exerted between contacted particle reduced, resulting in easier separation of deposited PH particles from the surface of lactose when the inertial force applied in the air stream inhaled.

From the view point of adhesion of PH particles to carrier lactose found for detaching them in the air stream for inhalation in the present study, the surface morphologies of lactose were classified into three groups: (1) micrometered topography as appeared on FBG, providing strong adhesive force to the drug (2) smooth surface with fairly adhering to the drug like SDGa and (3) nanometered topography of SDGc as described above. The rank order of adhesive property of carrier lactose and the image of its interaction with PH particles are illustrated in Fig. 8, with referring to Zimon (1969).

In conclusion, the design of surface morphology, like SDGc, having fairly large surface area with microscopically increased surface roughness, was found to be desirable to improve the inhalation efficiency of DPIs, which should be testified in a pharmacological test awaited to compare P.O. system.

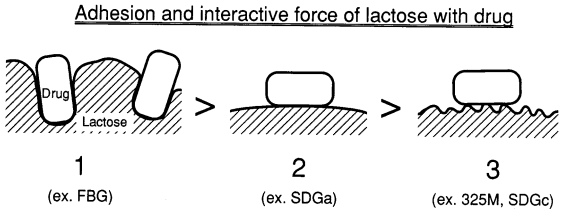

Fig. 8. Rank order of adhesion and interactive force of carrier lactose with drug depending on surface roughness.

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