Novel Approach to DPI Carrier Lactose with Mechanofusion Process with Additives and Evaluation by IGC

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The effect of lactose carrier surface property on the inhalation profile of dry powder inhaler (DPI) was evaluated using a micronized drug (Compound A) by inverse gas chromatography (IGC). Mechanofusion with magnesium stearate (Mg-St) or sucrose stearate increased the fine particle fraction (FPF), considered to be due to decrease in the interaction between Compound A and the lactose carrier. The effect of Compound A concentration on FPF was smaller in mechanofusion-processed lactose compared to intact lactose, especially when processed with Mg-St. The relationship between the IGC parameters of the lactose and FPF was also investigated. FPF increased as both the dispersive component of the surface energy and acidity similarity between the lactose carriers and Compound A increased. Although further investigation is necessary, it could be suggested that acidity similarity decreases the interaction between Compound A and lactose, thus contributing to the increase in the FPF. In conclusion, (1) mechanofusion with Mg-St or sucrose stearate could be an effective method to improve FPF of a DPI drug formulation; (2) IGC would be a valuable method to investigate the interaction between a drug and the DPI carrier; and (3) a relationship between surface acidity and inhalation profile was suggested.

Key words dry powder inhaler; mechanofusion; inverse gas chromatography; lactose; magnesium stearate; sucrose stearate

Dry powder inhaler (DPI) has drawn great attention in recent years. With the development of powder technology, various DPI formulations have been reported.[1—3)] A mixture of small drug particles with a large particle lactose carrier is a typical formulation.[4,5)]

Some surface modifications of carrier particles have been reported to improve inhalation performance of DPI.[6,7)] Mechanofusion is a powder-processing technology through which lactose particles receive shearing stress. Yamamoto *et al.*[8)] reported that the mechanofusion process changed the surface property of powder particles. As a part of DPI formulation investigation, carrier property has been studied in various ways.[9)] And various factors have been reported to affect the inhalation property of DPI formulations, for example, humidity,[10,11)] air flow,[12)] inhaler design,[4,13)] particle size[14)] and carrier surface property.[6,7,15)] Among these properties, carrier surface property would be considered preferable to apply pharmaceutical ideas to improve the inhalation property. Modification of carrier surface property might change the surface energy and there are various reports based on the theory that high energy binding sites on the carrier surface affects the inhalation property.

As DPI formulation study has proceeded, various techniques have been applied to characterize DPI powder formulations, and inverse gas chromatography (IGC) is one of them. IGC is a unique technique that can measure the surface energy of powder particles. The basic concept of IGC is that of gas chromatography (GC). Different from conventional GC, IGC measures the unknown surface of a sample powder that is packed into a column and known vapor is injected into the column as probes. The surface energy of the powder is calculated from the retention time of the probes. This method also can evaluate the acidity of the particle surface using non-polar and polar gases as probes. Recently, utilization of IGC is growing rapidly and evaluation of pharmaceutical materials such as mannitol, lactose monohydrate, trehalose and albuterol has been reported.[16—19)] Though it is said more research is required for the fundamental understanding of this technique, IGC is considered to be a powerful tool to characterize powder surface.[20)]

In this study, we evaluated mechanofusion-processed lactose as a carrier for DPI containing Compound A, and evaluated the surface property of the lactose by IGC.

Experimental

Materials Three α-lactose monohydrates, Lactohale 100 (Friesland Foods Domo, The Netherlands), Pharmatose 325M (DMV, The Netherlands) and SorboLac 400 (Meggle, Germany), were used. Magnesium stearate (Mg-St) was purchased from Taihei Chemical Industrial Co., Ltd. (Japan) and sucrose stearate (S370F) was purchased from Mitsubishi-Kagaku Foods Corporation (Japan). Compound A was synthesized by Sankyo Co., Ltd. (Japan).

Lactose Carriers Three grades of lactose, Lactohale 100, Pharmatose 325M and SorboLac 400, and their surface modified lactose particles were used as DPI carriers. Surface modified lactose was prepared by mechanofusion using a rotor-type powder mixer, Mechanofusion® AMS (Hosokawa Micron Corporation, Japan).

Preparation of Powder Formulation Compound A was milled with a Jet Mill Co-Jet system (Seishin Enterprise Co., Ltd., Japan). Lactose carrier and milled Compound A were gently blended with a mortar and pestle in the ratios of 2 : 98, 4 : 96 and 10 : 90, w/w. Twenty-five milligrams ($\pm$1 mg) of each blend was loaded into size 2 HPMC capsules (Qualicaps Co., Ltd., Japan).

Mechanofusion Process The mechanofusion process was conducted with the Mechanofusion® AMS.[8)] Figure 1 shows a schematic diagram of the Mechanofusion® AMS. Mg-St and sucrose stearate were used as coating materials. The gap between the press head and the rotor wall surface was 1 mm. The rotation speed was between 1000 and 1500 rpm. Mechanofusion process was conducted for 15 min except mechanofusion of Pharmatose 325M without additive and SorboLac 400 without additive. Those two exceptions showed little change of surface morphology of SEM observation after 15 min of mechanofusion process. And the process time was extended up to 30 min for Pharmatose 325M without additive and 90 min for SorboLac 400 without additive. Through the process, lactose or a mixture of lactose and coating materials received compression and shear force simultaneously, and the mechanical energy triggered alteration of the particle morphology or a physicochemical reaction at the particle surface. Additives were selected from the commonly used materials for improvement of powder properties. The mixing ratios of the additives were as follows: in the case for mechanofusion of Lactohale 100 and Pharmatose 325M, sucrose

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stearate/lactose=1/99 (w/w) and Mg-St/lactose=3/97 (w/w); and in the case for mechanofusion process of SorboLac 400, sucrose stearate/lactose=1/99 (w/w) and Mg-St/lactose=1/99 (w/w).

Characterization of Physicochemical Properties of Micronized Compound A and Carrier Lactose The particle size of micronized Compound A and lactose carrier was measured with a laser diffraction particle size distribution analyzer (Helos & Rodos, Sympatec GmbH, Germany). The specific surface area of carrier lactose was measured by the BET adsorption method with nitrogen gas. The surface morphology of the lactose carrier particles was examined under a scanning electron microscope (SEM). For SEM observations, lactose particles were fixed on a piece of carbon tape and coated with platinum–palladium. SEM observation was conducted with a Hitachi microscope S-350N (Hitachi, Ltd., Tokyo, Japan) at 5 kV.

Cascade Impactor Test The inhalation properties of the DPI formulations were evaluated using an Andersen Cascade Impactor (ACI, Copley, U.K.) with an inhalation device, Jethaler (dual chamber type, Hitachi Unisia Automotive, Ltd., Japan). A capsule filled with formulated powder was set in the Jethaler and pierced before inhalation. The powder in the capsule was inhaled into ACI as air flowed through the device. The cascade impactor study was conducted at the flow rate of 30 l/min. The amount of Compound A deposited on each part of the ACI was quantified by HPLC analysis.

Fine particle fraction (FPF) is defined as the mass fraction of particles smaller than a certain size in the aerosol. Numerically, FPF is the percentage of powder collected from Stage 2 to Stage 7 and a filter at 30 l/min. FPF is given by Eq. 1:

$$\text{FPF}\,(\%)=(\text{Compound A collected from Stage 2 to Stage 7})/(\text{entire dose})\times 100 \quad (1)$$

Drug Analysis Compound A was analyzed by HPLC employing a mixture of acetonitrile and 0.1 mol/l potassium phosphate buffer (pH 3.0) (30 : 70%, v/v) as the mobile phase running at a flow rate of *ca.* 1 ml/min and UV detection of 230 nm. The HPLC system consisted of a pump (Shimadzu Corporation, Japan), a UV detector (Shimadzu Corporation, Japan) and L-column ODS (25 cm×4.6 mm i.d., particle size 5 μm, Chemicals Evaluation and Research Institute, Japan), which was maintained at 30 °C.

Measurement of Surface Property with Inverse Gas Chromatography (IGC) Experiments were performed using IGC (Surface Measurement Systems Ltd., U.K.). Samples of 100—300 mg were packed into a silanised glass column (Surface Measurement System Ltd., U.K.) of size of 6 mm o.d., 3 mm i.d. and 300 mm length, by vertical tapping. Tapping continued until there were no visible cracks, hollows or channels in the body of the powder. Both ends of the column were loosely stoppered with silanised glass wool. The conditioning of the column packed with the sample powder was carried out at 303 K and 0% RH, and the experiment was performed under the same conditions. Methane was used for the inert reference; *n*-decane, *n*-nonane, *n*-octane and *n*-heptane were used to determine the alkane line; and chloroform, ethyl acetate, acetone and ethanol were employed as polar probes. The gas flow rate used was 10 ml/min and helium gas was used as the carrier gas. Each probe was injected twice to give a measure of the reproducibility.

Powder surface energy can be calculated from the retention time of nonpolar and polar probes. The methodology is described by Schultz *et al.*[21] As Grimsey *et al.* reported,[22] the basic relationship employed is:

$$RT\ln V_n = 2N(\gamma_s^D)^{1/2}a(\gamma_l^D)^{1/2}+C \quad (2)$$

where R is the gas constant, T is the temperature (K), V_n is the net retention volume of the probe, N is Avogadro's number, a is the molecular surface area of the probe, γ_s^D is the dispersive component of the surface energy of the sample powder, γ_l^D is the dispersive component of the surface energy of the probe and C is a constant. Plotting $RT\ln V_n$ *vs.* $a(\gamma_l^D)^{1/2}$ for the nonpoler probes yields a straight line. The dispersive component of the solids is calculated from the slope in Eq. 2. The value of V_n was obtained from the retention times of the probes, and the values of a and γ_l^D were obtained from the literature.[21,23]

The retention times for a homologous series of alkane probes and polar probes were used to calculate the acid-base parameters. The retention behavior of polar probes on the $RT\ln V_n$ *versus* $a(\gamma_l^D)^{1/2}$ plot results in responses that are located above the line drawn through the alkane probe results, and the vertical distance between the data points of polar probes and the alkane line gives the specific energy of adsorption of a polar probe for a solid material ($-\Delta G^{AB}$). The value of $-\Delta G^{AB}$ is related to the acid or electron accepting parameter (K_A) and the base or electron donating parameter (K_D) as described in Eq. 3:

$$-\Delta G^{AB}=K_A DN+K_D AN^* \quad (3)$$

where DN is an electron donor or base number characterized according to Gutmann[24] and AN^* is an electron acceptor or acid number.[25]

By measuring the value of $-\Delta G^{AB}$ for polar probes, a linear plot of $-\Delta G^{AB}/AN^*$ *versus* DN/AN^* was obtained. The values of K_A and K_D of the sample powders were determined from the gradient and intercept of the line, respectively. The acid-base property was evaluated with the distance between plotted points of Compound A and each lactose on the K_A *vs.* K_D graph (Fig. 5). The distance between Compound A and the lactose was defined as "distance from Compound A" and calculated as described in Eq. 4:

$$\text{distance from Compound A}=\sqrt{(K_{AD}-K_{AL})^2+(K_{DD}-K_{DL})^2} \quad (4)$$

where K_{AD} and K_{AL} are acid parameters and K_{DD} and K_{DL} are base parameters of Compound A and the lactose.

Results and Discussion

Characterization of DPI Carrier Lactose The diameters of intact Lactohale 100, Pharmatose 325M and SorboLac 400 are about 150, 60 and 10 μm, respectively. The mechanofusion process was used to prepare lactose particles with different surface properties of three particle size groups, *i.e.* 150, 60 and 10 μm. Through the mechanofusion process, compression and shearing energy is added to the lactose particles when they go through the narrow gap between the rotor and press head of the mechanofusion apparatus, Mechanofusion® AMS (Fig. 1). Scanning electron micrographs (SEMs) showed that the mechanofusion process made the surfaces of Lactohale 100 and Pharmatose 325M smoother and their shape rounder (Fig. 2). But those changes were not observed

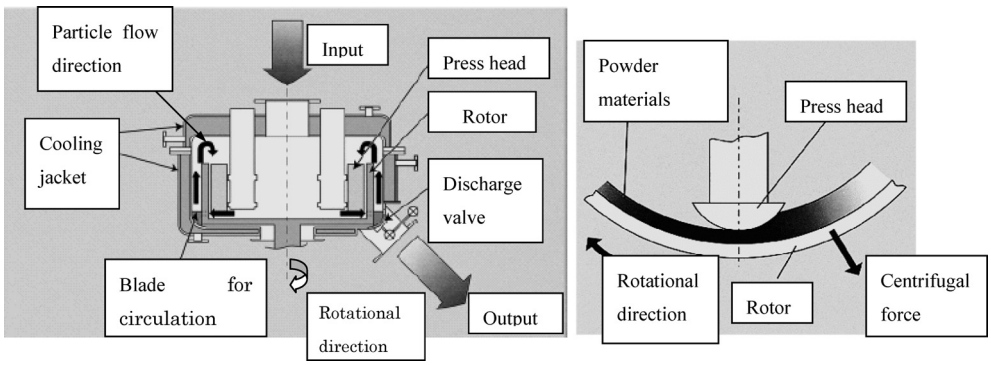

Fig. 1. Structure and Basic Mechanism of Mechanofusion System

Outline of the instrument (left) and magnified view of upper side of press head and rotor (right).

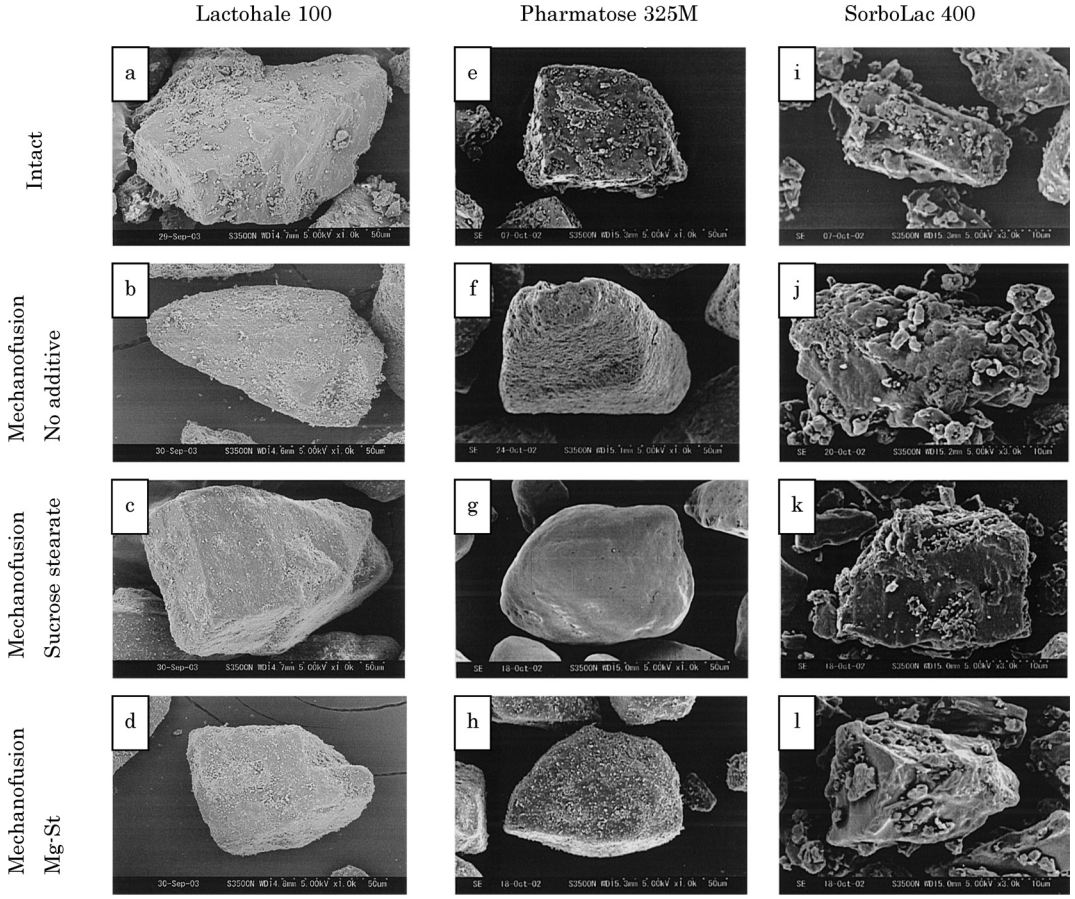

Fig. 2. Scanning Electron Micrograph Images of Lactose Particles

(a, e, i) Intact. (b, f, j) Mechanofusion processed with no additive. (c, g, k) Mechanofusion processed with sucrose stearate. (d, h, l) Mechanofusion processed with Mg-St.

for SorboLac 400. The sizes of the lactose particles showed little change through the mechanofusion process by laser diffraction analysis, however, the surface areas of Lactohale 100 and Pharmatose 325M changed greatly (Table 1). The size of the SorboLac 400 particles seemed to be too small for morphological conversion through the mechanofusion process. SEMs showed the mechanofusion process reduced the roughness of the surface but the microscopic asperity increased when the process was conducted with Mg-St. The BET measurement showed the mechanofusion process without additive or with Mg-St increased the surface area. On the other hand, the mechanofusion process with sucrose stearate decreased the surface area of Pharmatose 325M significantly.

Inhalation Properties of DPI of Compound A and Lactose Effects of Mechanofusion Process: The DPI formulations of Compound A and the lactose carriers were studied using an Andersen Cascade Impactor (ACI). Compound A was milled to a diameter of 2—3 μm. Three different sizes of lactose particles, Lactohale 100 (particle size: 150 μm), Pharmatose 325M (particle size: 60 μm) and SorboLac 400 (particle size: 10 μm), and mechanofusion-processed lactose of each of them were used as carriers. The effect of mechanofusion processing on the inhalation properties of Compound A for each carrier size is shown in Fig. 3. Lactose mechanofusion processed with Mg-St showed the highest FPF and moreover the deposition ratio at the lower stages (Stages 4 and 5) of the ACI was relatively high. In contrast, the deposition ratios at the throat and/or pre-separator were low. Lactose mechanofusion processed with sucrose stearate showed the second highest inhalation property. The deposition profile implies that mechanofusion with Mg-St or sucrose stearate decreases the interaction between the Compound A particles and the lactose carrier surface. As particle size is one of the principle factors influencing the inhalation profile, 2—3 μm Compound A particles were supposed to be deposited at the lower part of the ACI compared to the lactose particles. And the larger and heavier lactose particles were supposed to be deposited at the upper part of the ACI, especially on the pre-separator. Therefore, if interaction be-

Table 1. Sizes and Surface Areas of Carrier Lactose

Lactose	Mechanofusion process	Mean diameter[a)] (μm)	BET surface area (m^2/g)
Lactohale 100	Intact	145 (1.3)	0.12
	No additive	165 (1.2)	0.21
	Sucrose stearate	148 (5.0)	0.17
	Mg-St	139 (4.6)	0.31
Pharmatose 325M	Intact	63 (1.6)	0.22
	No additive	48 (1.0)	0.27
	Sucrose stearate	61 (1.6)	0.09
	Mg-St	58 (0.4)	0.78
SorboLac 400	Intact	7 (0.5)	1.02
	No additive	8 (0.4)	0.91
	Sucrose stearate	8 (0.1)	0.83
	Mg-St	8 (0.3)	0.72

a) Data are represented as mean (S.D.) (n=3).

tween Compound A and the lactose carrier decreases, Compound A would detach from the lactose more easily in the air stream and be deposited at the lower part of the ACI.

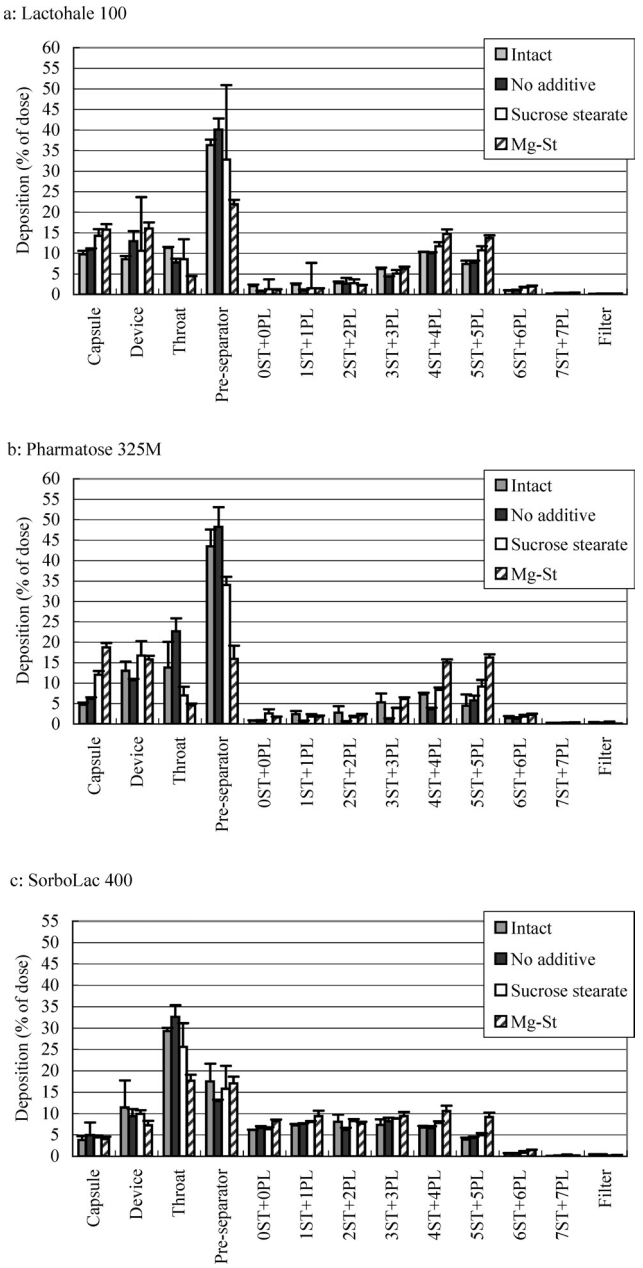

Fig. 3. Cascade Impactor Deposition Profile of Compound A DPI Formulation

(a) Compound A was mixed with Lactohale 100 or mechanofusion-processed Lactohale 100 in the ratio of 2 : 98 (w/w). (b) Compound A was mixed with Pharmatose 325M or mechanofusion-processed Pharmatose 325M in the ratio of 2 : 98 (w/w). (c) Compound A was mixed with SorboLac 400 or mechanofusion-processed SorboLac 400 in the ratio of 2 : 98 (w/w). Error bars denote standard deviation, $n=3$.

Decrease in the interaction was also suggested by the increase in the residual ratio in the capsule and device. Compound A particles are small and relatively adhesive. Therefore, the weaker the interaction, the greater the number of Compound A particles remaining in the capsule. This FPF increase with the increase of remaining in the capsule is considered to be a dilemma of DPI formulation with carriers. The balanced point between increase of FPF and remaining in a capsule seems to be considered at the development of DPI with carriers.

Effect of Lactose Carrier Size: The difference in inhalation property according to the mechanofusion condition, *i.e.* no additive, sucrose stearate additive or Mg-St additive, was the most significant for particle diameter of 60 μm (Fig. 3b) compared to smaller or larger carrier particle size (Figs. 3a, c).

As mentioned above, particle size of 10 μm was considered to be too small to conduct mechanofusion processing sufficiently. Therefore, the mechanofusion process might have little effect on the inhalation property of lactose carriers of such small particle size. Comparison of lactose particle sizes of 60 μm (Fig. 3b) and 150 μm (Fig. 3a) suggested that the effect of surface property on the inhalation profile was higher for the carrier particle size of 60 μm. The inhalation profile is the overall outcome of various factors such as particle size or particle surface properties. Therefore, it would be better to select one particle size to simplify the system. Based on this, the more detailed inhalation profile was shown below using lactose of particle size of 60 μm.

Effect of Compound A Concentration: The Compound A concentration of the DPI formulation had an effect on the inhalation profile (Fig. 4, Table 2). For DPI formulation containing intact lactose and lactose mechanofusion processed without additives and with sucrose stearate, the higher the Compound A concentration, the greater the number of Compound A particles deposited at the lower part of the ACI. And when lactose mechanofusion processed with Mg-St was used as a carrier, the effect of Compound A concentration was insignificant. The increase in the FPF with Compound A concentration would be caused by saturation of the high energy binding sites. Various studies on high binding energy sites where drug particles preferably adhered have been reported.[26—29] Covering these binding sites with adhesive fine particles would increase the dispersibility of drug particles from the carrier surface and enhance the FPF of the DPI. When high energy binding sites become saturated, the excess drug particles would be more dispersible from the carrier surface than the particles entrapped by those binding sites. But in the case of lactose carrier mechanofusion processed with Mg-St or sucrose stearate, the interaction between the drug and lactose would be weak even at these binding sites.

Table 2. Effect of Compound A Concentrations on FPF of DPI with Pharmatose 325M or Mechanofusion-Processed Pharmatose 325M

Compound A concentration	Intact	Mechanofusion process		
		No additive	+Sucrose stearate	+Mg-St
2%	20.8 (1.77)	13.2 (0.27)**	25.7 (2.48)*	42.4 (1.30)**
4%	25.1 (3.07)	20.4 (3.74)	35.2 (0.26)**	42.7 (3.15)**
10%	34.1 (1.81)	34.8 (0.45)	39.7 (1.59)*	44.2 (1.97)**

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

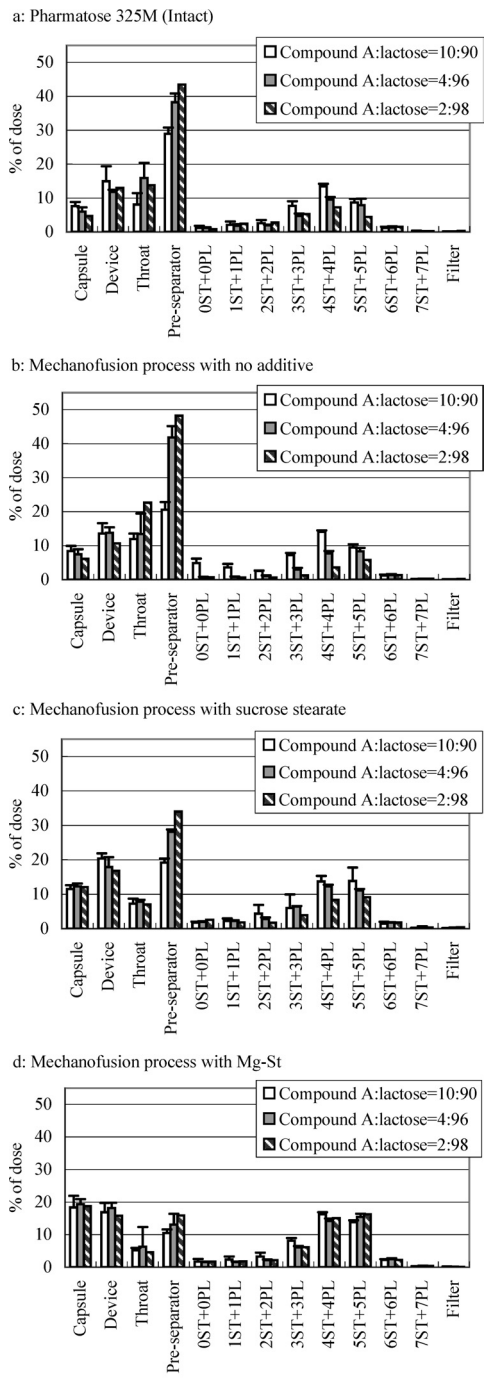

Fig. 4. Effect of Compound A Concentration on Cascade Impactor Deposition Profile of Compound A DPI Formulation

The carrier lactose was Pharmatose 325M or mechanofusion-processed Pharmatose 325M. (a) Intact; (b), mechanofusion processed with no additive; (c), mechanofusion processed with sucrose stearate; (d), mechanofusion processed with Mg-St. Error bars denote standard deviation, $n=3$.

The drug particles would detach from the lactose surface easily and the dependency on the concentration would not be detectible. Independence of concentration seems to be valuable for the design of DPI formulation for different drug concentrations. If the inhalation property changes depending on the drug concentration, it would be difficult to estimate the actual amount of drug deposited in the lungs based on the administered dose. Therefore, lactose mechanofusion processed with Mg-St would seem to be a good carrier for DPI formulation.

Effect of Surface Area: Carrier surface roughness is reported to be relevant to the inhalation performance of DPI.[5,15,30—32] When there are cavities where drug particles might find shelter, the inhalation performance would decrease. On the other hand, asperity on a micro scale would decrease the contact area between particles and consequently increase dispersibility. In this study, the mechanofusion process changed the surface asperity greatly but no clear relationship between the surface area of lactose and FPF was found. Moreover, mechanofusion-processed lactose with Mg-St at various conditions showed high FPF around 40—50% of the dose throughout the BET surface area of 0.21—0.78 m^2/g (data not shown). Further investigation is required on this point, but it could be suggested that surface properties other than the surface roughness might have equal or more effect on the interaction between Compound A and lactose particles.

IGC Measurement The IGC parameters of Pharmatose 325M and its mechanofusion-processed lactose are shown in Table 3. The data suggested that the mechanofusion process had an effect on both the dispersive component of the surface energy (γ_s^D) and the acid-base parameters of the lactose carrier surface (K_A, K_D). The mechanofusion process increased the dispersive component of the surface energy and decreased the K_D/K_A ratio. The decrease in the K_D/K_A ratio was mainly due to a change in K_D as K_A stayed almost constant. The decrease in the K_D/K_A ratio indicated increase in the acidity.

The acid-base property was evaluated by the distance between the plotted points of Compound A and each lactose on the K_A *vs.* K_D graph ("distance from Compound A" in Fig. 5).

The relationship between inhalation property and energetic surface property is shown in Figs. 6 and 7. In the case of Lactohale 100 and Pharmatose 325M, when the carrier was mechanofusion processed, FPF increased as the surface energy became higher (Fig. 6). And as the distance from Compound A on the K_A *vs.* K_D plot became shorter, FPF increased (Fig. 7). The possibility of optimum value of distance from Compound A was suggested in case of Lactohale 100 (Fig. 7). In both Figs. 6 and 7, the relationship between

Table 3. IGC Parameters of Compound A and Carrier Lactose

Sample name	Mechanofusion processing	γ_s^D (mJ/m^2)	K_A	K_D	K_D/K_A	Distance from Compound A
Compound A	—	52.0[a] (1.1)	481	495	1.03	—
Pharmatose 325M	Intact	46.9[a] (2.6)	324	86.3	0.27	438
Mecanofusion-processed Pharmatose 325M	No additive	50.6[b] (7.2)	419	30.8	0.07	469
	Sucrose stearate	64.9[b] (0.8)	467	51.3	0.11	444
	Mg-St	76.3[b] (1.6)	510	65.3	0.13	431

a) Data represented as mean (S.D.) ($n=3$). *b*) Data represented as mean (S.D.) ($n=2$).

the FPF and IGC parameters is unclear in case of SorboLac 400. This was in agreement with the results of SEM and BET that mechanofusion did not convert the surface properties of SorboLac 400 very much. An increase in FPF with an increase in carrier surface energy has also been reported.[18] An increase in lactose carrier surface energy would increase the interaction between Compound A and the lactose carrier. Cline and Dalby[18] supposed a certain minimum surface energy interaction between a drug and lactose particles is needed to pull highly cohesive micronized drug particles apart and increase FPF. This appears to conflict with the following two observations. One is the increase in detachment observed in the ACI profile (Fig. 3b) as the γ_s^D value of the lactose carrier increased. And the other is that Compound A and lactose DPI showed high FPF at high Compound A concentration (Fig. 4). Further investigation is required on the effect of the dispersive component of surface energy on particle-particle interaction to clarify this contradiction between increasing dispersive component and FPF dependency on drug particle detachment from lactose. The shorter the distance from Compound A to the lactose on the K_A *vs.* K_D plot, the more similar the surface property of the electron donation between Compound A and the lactose. Moreover, similarity in electron donation property would decrease the interaction between the particles and the dispersibility of Compound A from the lactose surface would be affected.

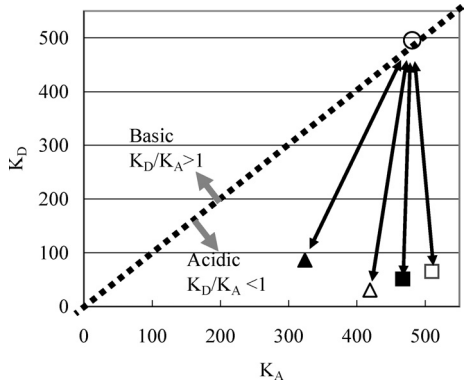

Fig. 5. Illustration of Distance from Compound A

○: Compound A, ▲: intact, △: mechanofusion processed with no additive, ■: mechanofusion processed with sucrose stearate, □: mechanofusion processed with Mg-St.

Regarding intact lactose, the inhalation property would be affected by other factors such as morphology or cavities providing shelter to drug particles. As shown in SEMs of Fig. 2, intact lactoses were more rugged and adhered fine lactose particles to intact lactoses were larger than those to mechanofusion lactoses. And intact lactose particles are considered to have more cavities those worked as a shelter for drug particles from detachment than mechanofusion-processed particles. This might be the reason that the inhala-

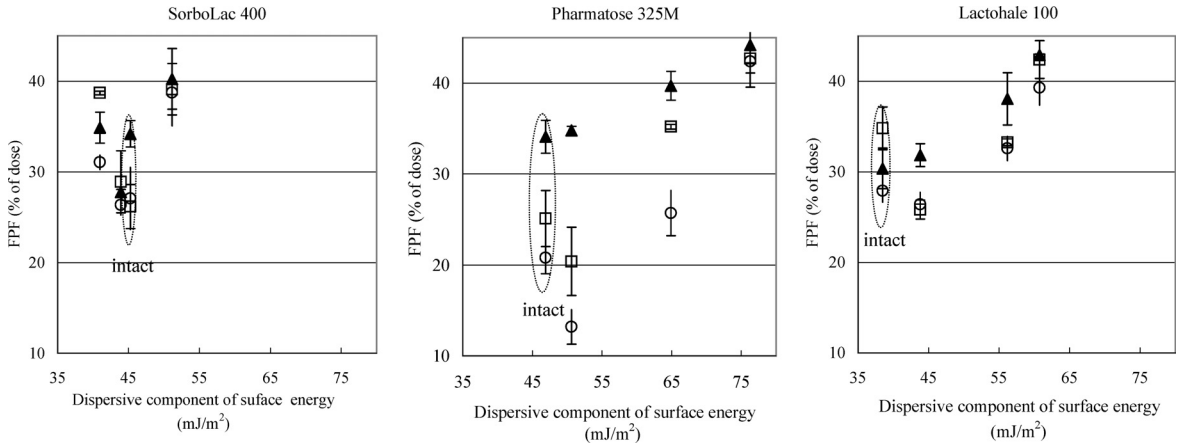

Fig. 6. Plot of Dispersive Component of Lactose Surface Energy *vs.* FPF

Compound A was mixed with lactose of each γ_s^D in the following ratios: ○, Compound A : lactose=2 : 98; □, Compound A : lactose=4 : 96; ▲, Compound A : lactose=10 : 9.0.

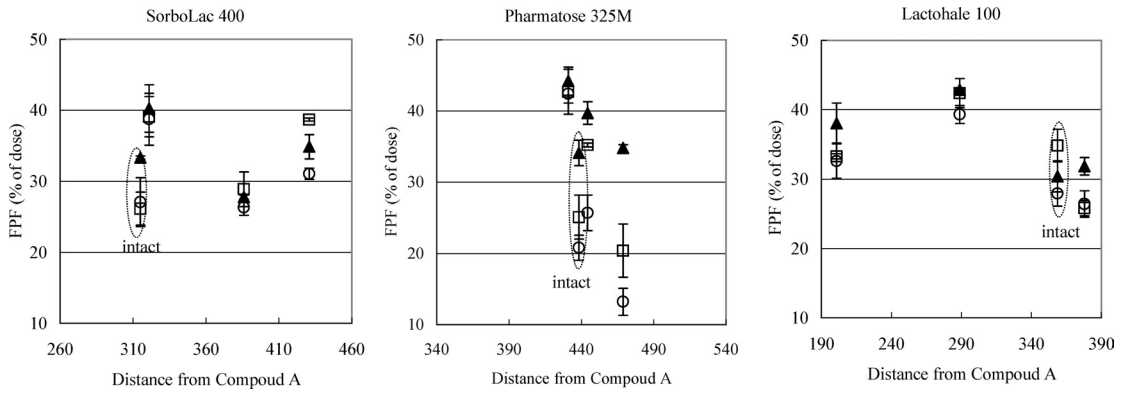

Fig. 7. Plot of Distance from Compound A *vs.* FPF

Compound A was mixed with lactose of each distance from Compound A in the following ratios: ○, Compound A : lactose=2 : 98; □, Compound A : lactose=4 : 96; ▲, Compound A : lactose=10 : 90.

tion property of Compound A with intact lactose varied from the tendency of that with the mechanofusion-processed lactose (Figs. 6, 7). Parameters those properly suggest whether IGC could be applicable to evaluate the drug-carrier interaction are currently studied.

The relationship between IGC parameters and FPF was more significant when the concentration of Compound A was lower. Decrease in Compound A concentration increased the interaction between Compound A and the lactose carrier; therefore, the inhalation profile would reflect the surface property of the carrier more clearly. This also could be related to sites with higher binding energy as described in Results and Discussion: "Effect of Compound A Concentration." At the lower concentration of Compound A, most of the drug particles bound to the high-energy sites and the effect of these sites on the surface property of the inhalation profile became more significant.

The IGC technique selectively detects high-energy sites under infinite conditions.[19] Therefore, IGC could be a preferable method to evaluate surface property that might affect the interaction between a drug and carriers that can actually be used define the inhalation profile.

Conclusion

Mechanofusion process with Mg-St or sucrose stearate decreased the interaction between Compound A and the lactose carrier. This consequently improved the inhalation profile of the DPI containing Compound A. Lactose mechanofusion processed with Mg-St seemed to be a good DPI carrier with high FPF and less dependency on the Compound A concentration.

The inhalation property seemed to be strongly affected by surface property at the lactose size of 60 μm. At this size of lactose, correlation was observed between the IGC parameters of the lactose carrier and the FPF. Although the effects of surface energy on FPF should be investigated further, similarity in acidity between Compound A and the lactose carrier is necessary to decrease interaction and increase the FPF. These findings also show IGC could be a useful tool to investigate the interaction between a drug and the DPI carrier.

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