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Design of inhalation dry powder of pranlukast hydrate to improve dispersibility by the surface modification with light anhydrous silicic acid (AEROSIL 200)

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Abstract

A new particle design method was proposed for dry powder inhalation of hydrophobic cohesive drug particles (pranlukast hydrate, $D_{50} = 2.1$ μm) by the surface modification with hydrophilic colloidal silica (AEROSIL, $D_{50} = 16$ nm). The surface of drug particle was modified by compounding AEROSIL (2–10%) under shear with a manually operating mortar (PM method) or a high-speed elliptical-rotor-type mixer (Theta-Composer®, TC method). The surface modifications were also conducted by lyophilizing (FD method) or spray drying (SD method) the aqueous dispersions of the drug and AEROSIL. The surface modified particles were aerosolized through a Spinhaler® and their inhalation behaviors were evaluated by a twin impinger in vitro. The inhalation behaviors were evaluated by the coefficient of inhalation efficiency (EI) defined as the geometric mean of the drug % emitted from the device and delivered % in respirable fraction of the twin impinger. The EI of modified particles with TC, FD and SD methods were dramatically increased up to 66.9, 52.7 and 47.7%, respectively, with increasing AEROSIL content compared with that of (22.4%) original powder. The surface modification to hydrophilic with AEROSIL reduced the cohesive force between the drug particles, owing to the decrease in van der Waals and electrostatic forces, improving the dispersibilities of emitted particles from the Spinhaler®.

Keywords: Inhalation dry powder; In vitro evaluation; Surface modification; Respiratory deposition; Light anhydrous silicic acid

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1. Introduction

Dry powder inhalation aerosols (DPIs) have become an attractive alternative to the metered dose inhalation aerosols because the DPIs need not to use chlorofluorocarbon propellants and their administration is easily synchronized with patient's inspiration. Many applications of DPIs have been tried for asthma, chronic bronchitis, emphysema, cystic fibrosis and pulmonary infections (Smith and Bernstein, 1996). Recently, pulmonary administration of peptide and protein drugs into systemic circulation have been also investigated extensively by DPIs (Komada et al., 1994; Niwa et al., 1995).

The deposition site in the respiratory tract and the biological efficiency of inhaled particles 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 due to inertial impaction and expelled succeedingly from the respiratory pathways, and particles less than 0.5 μm are exhaled without deposition. The particles with aerodynamic diameters between 1.0 and 6.0 μm, termed 'respirable particles', have been reported to be most effectively deposited on the respiratory tract (Timsina et al., 1994). Consequently, micronized drug particles of about a few μm in diameter are formulated preferably for inhalation. However, micronized particles are frequently met difficulties in formulation process such as powder filling in inhalation container, e.g. capsule, because of their poor flowabilities. Moreover, fine particles are apt to adhere to the capsule and inhalation device walls on actuation, causing unreliable dosing.

To solve these problems, fine drug particles are granulated (granulation method, Kassem et al., 1991; Hino et al., 1998) or deposited on coarse carrier particles, e.g. lactose (carrier method, Bell et al., 1971). These two methods can improve flowing properties and reduce the adhesion of drug particle on the capsule and device walls. However, it is often to meet difficulties in disintegrating them in the air stream to regenerate 'respirable' drug particles, when inhaled.

In the present study, a third new particle design method for DPIs was proposed to reduce the drug amount remained in the capsule and device, and to increase respirable fraction after administration by surface modification of drug particles. With this technique, the surface of micronized drug particles were deposited with hydrophilic ultrafine particles to improve their inhalation properties. Pranlukast hydrate, selective active leukotriene antagonist for bronchial asthma (Nakagawa et al., 1992; Taniguchi et al., 1993), was chosen as a model DPI drug particles, because of their poor micromeritic properties for inhalation desired. Light anhydrous silicic acid (AEROSIL) was employed as a surface modifier due to its highly hydrophilic and adsorbing properties. The surface modifying particles were deposited on the drug particles by mechanically sheared mixing and by freeze or spray drying their aqueous dispersions. In this article, how the surface of drug particle is modified and how the modified particles are dispersed and inhaled in vitro test, are discussed to develop ideal DPIs.

2. Materials and methods

2.1. Materials

Pranlukast hydrate abbreviated PH (4-oxo-8-[4-(4-phenylbutoxy)benzoyl amino]-2-(tetrazol-5-yl)-4*H*-1-benzopyran hemihydrate) with mean diameter of 2.1 μm was supplied from Ono (Japan). They were highly adhesive, cohesive and hydrophobic powders (solubility in water; 1.2 μg/ml). Light anhydrous silicic acid (AEROSIL® 200, $D_{50} = 16$ nm) was obtained from Nippon AEROSIL (Japan). It was reported in the technical bulletin published by the Nippon AEROSIL. that AEROSIL is harmless in inhaling to human lung due to its amorphous form (Bode et al., 1967)

Ethanol and sodium bicarbonate used for dispersing and collecting media were analytical grade.

2.2. Preparation of surface modified drug particles

The surface modification of drug particles were carried out by following four methods. The AEROSIL content compounded in all products was 2, 5 or 10%.

1. PM (physical mixing) method; The PH and AEROSIL particles taken in a glass vessel were premixed with a vortex mixer, and they were compounded manually in a mortar under shear with a pestle (PM products).
2. TC (Theta-Composing) method; The premixed materials were further mixed for 30 min with a high-speed elliptical-rotor-type mixer (Theta-Composer®, Tokuju, Japan) shown in Fig. 1. The powder loading was 5 g. The clearance between the rotor and vessel wall was 1 mm. The rotor and vessel were rotated counterwise at 2500 and 30 rpm, respectively (TC products).
3. FD (freeze drying) method; The PH and AEROSIL particles were dispersed into water/ethanol (9/1) mixed solvent and sonicated with a bath sonicator. The resultant dispersion was lyophilized by using a Neocool (Yamato, Japan) for 3 days or longer after prefreezing under ethanol system at −100°C (FD products).
4. SD (spray drying) method; The PH particles and AEROSIL were dispersed into water/ethanol (9/1) mixed solvent and homogenized with a high speed homogenizer (Physcotron® NS-50, Nition, Japan) and resultant dispersion was spray dried (Pulvis Basic Unit Model GB-21, Yamato, Japan). The operating conditions were; inlet air temperature: 105°C, outlet air temperature: 55°C, drying air volume: 350 l/min, atomizing air pressure: 314 kPa, atomizing nozzle diameter: 406 μm, spray rate: 5 ml/min (SD products).

2.3. In vitro inhalation property

The in vitro inhalation properties of surface modified PH particles were evaluated by using a twin impinger (Copley, UK). 7 and 30 ml of 50 mM sodium bicarbonate solution/ethanol (1/1) mixed solvent was used as collecting solvent in the stage 1 and 2 of twin impinger, respectively. A dry powder inhalation device (Spinhaler®, Fisons, UK) installed with a No. 2 gelatin hard capsule (Japan Elanco, Japan) pierced two pores, loading 20 mg of powder was connected with the twin impinger and was vacuumed to produce air streams of 60 l/min for 5 s. After actuation, the drugs in the capsule, device and the stages 1 and 2 were collected by rinsing with the solvent. The rinsed solutions were then diluted to proper volumes and their drug contents were determined spectrophotometrically at 260 nm (UV-160A, Shimadzu, Japan). The mean aerodynamic cut-off diameter between the stage 1 and 2 of twin impinger was approximately 6.4 μm under the present operating condition (Hallworth and Westmoreland, 1987; Hino et al., 1997). The particles

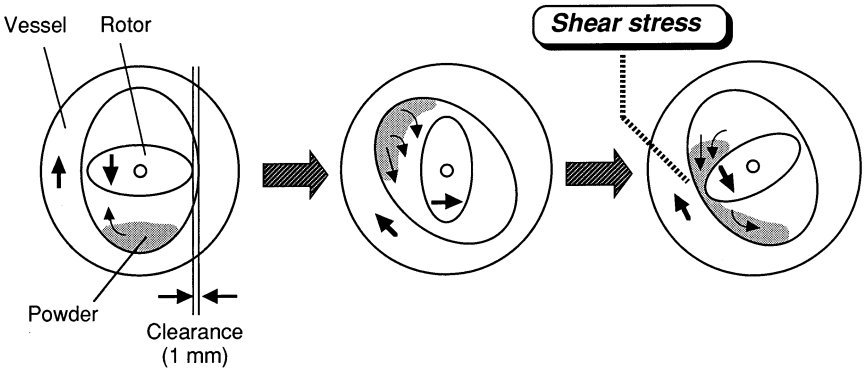

Fig. 1. Mechanism of surface modification with Theta-Composer®.

captured in the stage 2, i.e. finer particle fraction, was assumed as 'respirable' particle fraction.

To describe the inhalation properties of DPIs, two indices, i.e. the effective index (EI) and the respirable particle percent of emitted particles (RP), were used as defined by Eqs. (1) and (2), respectively.

$$\mathrm{EI} = \sqrt{\mathrm{EM} \times \mathrm{St2}} \quad (1)$$

$$\mathrm{RP} = \left(\frac{\mathrm{St2}}{\mathrm{EM}}\right) \times 100 \quad (2)$$

where EM is the % of drug emitted from capsule and device and St2 is the stage 2 fraction (%). The EM was introduced intentionally to describe the reliability of DPIs dosing. For ideal DPIs, both indices become 100%, indicating complete emission and delivery to targeted site in lung.

2.4. Micromeritic characterization

The surface topography of particles was observed with scanning electron microphotographs taken by a JSM-T330A (JEOL, Japan).

The surface modified PH particles were compressed into a tablet by an Autograph (AG-5000D, Shimadzu, Japan) at 196 MPa. A small droplet (15 μl) of water was placed on the tablet surface using a microliter syringe. Contact angle was measured directly by taking photographs.

Contact potential difference of surface modified particles was measured by the apparatus developed by Masuda et al. (1995).

Tapped density of the particles was measured by using a tap density tester (RHK type, Konishi Seisakusyo, Japan). A powder of about 20 ml was carefully placed gradually into a 25 ml graduated cylinder. The cylinder was tapped more than 1000 times to obtain the closest packed densities.

The dispersibility of surface modified particles into air stream was evaluated with a dry disperser (PD-10S, Tohnichi Computer, Japan) and a laser diffraction size analyzer (LDSA-2400A, Tohnichi Computer, Japan). A powder sample was dispersed by the dry disperser with compressed air at 19.6 and 294 kPa, and the particle size distribution of aerosols was measured. Dispersing ratio (DR) was defined by Eq. (3).

$$\mathrm{DR} = \left(\frac{P_{19.6}}{P_{294}}\right) \times 100 \quad (3)$$

where, $P_{19.6}$ and P_{294} are weight-based cumulative percentages of particles under 6.6 μm in diameter determined under the pressures of 19.6 and 294 kPa, respectively. When the particles were ideally dispersed, the DR of particles became 100%.

3. Results and discussion

3.1. Inhalation behaviors of surface modified PH particles

With the PM products, the surface modification was useless to reduce the remained drug % in capsule and device and to increase St2, unless AEROSIL was compounded at higher level, e.g. 10% as shown in Table 1. The TC products improved significantly the inhalation properties with increasing the amount of AEROSIL compounded in Table 1, compared to PM products. The FD method, as indicated in Table 1, was favorable to lowering the remained % of drug in capsule and device, as well as to improve fairly delivering the drug particles in the St2, with compounding AEROSIL even at 2%, compared to other methods. The SD method also improved the inhalation properties of drug at higher compounding of AEROSIL, e.g. 10% as found with PM method (Table 1).

The overall inhalation manners of surface modified PH particles are summarized in Table 2. Inhalation processes of DPIs are; (1) emission of drug particles from container (capsule) represented by EM values, (2) dispersing to respirable particles in air stream on passing through the inhalation device evaluated by RP values and (3) deposition in the respiratory tract represented by St2 values. The overall inhalation efficiency was described by EI values.

The EM values of surface modified PH particles were increased generally with increasing AEROSIL content. The FD and TC methods were the most effective to enhance emitting the drug particles by surface modification, compared with other methods.

Table 1
Remained % in capsule and device, and in in vitro deposition % in twin impinger of modified powder

Formulation	Capsule (%)	Device (%)	Stage 1 (%)	Stage 2 (St2) (%)
Original	18.9 ± 8.4	43.8 ± 6.3	24.0 ± 5.4	13.4 ± 1.7
PM				
2%	17.5 ± 3.9	41.4 ± 4.2	23.4 ± 0.6	17.7 ± 2.0*
5%	14.1 ± 0.8	38.2 ± 1.4	20.8 ± 0.4	27.0 ± 0.4**
10%	6.5 ± 2.0	33.3 ± 7.9	22.5 ± 3.3	37.7 ± 3.9***
TC				
2%	34.4 ± 3.3*	31.6 ± 3.3*	9.2 ± 0.6***	24.9 ± 0.7**
5%	7.4 ± 0.9*	27.1 ± 2.8***	13.6 ± 0.6*	52.0 ± 1.4**
10%	5.2 ± 1.4*	19.2 ± 2.7**	16.4 ± 0.3*	59.3 ± 2.3**
FD				
2%	9.4 ± 1.4	34.3 ± 2.2	23.5 ± 1.6	32.8 ± 2.6***
5%	12.4 ± 1.5	23.3 ± 3.0***	27.2 ± 1.7	37.0 ± 3.4***
10%	6.3 ± 1.4*	16.1 ± 0.3**	41.7 ± 2.8***	35.8 ± 3.4***
SD				
2%	39.9 ± 3.0***	34.4 ± 1.7*	6.2 ± 0.1***	19.6 ± 1.6***
5%	29.9 ± 2.0	31.0 ± 1.9*	11.5 ± 0.3	27.6 ± 0.1**
10%	11.5 ± 3.2	36.4 ± 4.6	8.4 ± 1.2***	43.7 ± 3.0**

Data are represented with mean ± S.D. ($n = 3–5$).
* $p < 0.05$,
** $p < 0.001$,
*** $p < 0.01$, significant difference compared to original powder by Student's unpaired t-test.

The RP values were significantly increased by TC and SD methods with lower loading of AEROSIL even at 2%, suggesting that the TC and SD products were preferably dispersed in air stream for trapping in the stage 2 of twin impinger.

The overall inhalation efficiencies (EI) were generally increased with AEROSIL content for all surface modification methods. The TC and FD methods were extremely useful to improve the inhalation manner of drug by surface modification with AEROSIL compounded at 5% or more.

3.2. Surface property of modified particle

The surface topographies and wettabilities of surface modified particles were investigated to clear how the surface of particles was modified in determining inhalation properties.

Scanning electron microphotographs of original and modified PH particles are shown in Fig. 2. The original PH crystals were aggregated with plate-like fine crystals with smooth surface, contacted face to face. Such morphology indicated their strong cohesive properties, leading to poor inhalation properties as found in Table 1 (Visser, 1989). The PM products are rather discrete particles deposited irregularly with AEROSIL particles. The TC products were discrete particles deposited more uniformly with AEROSIL particle under shear force applied in the Theta-Composer®. Such modification should decrease the cohesion force exerted between particles, as demonstrated in decreasing the adhesion force of potato starch adsorbed with AEROSIL particles to glass plate by Otsuka et al. (1985). This finding might be explained by the decrease in van der Waals force exerting between particles due to the decrease in contact area of particle. The FD products were loosely aggregated particles deposited randomly with AEROSIL particles. The SD products exhibited a similar morphology like PM products.

The original PH particles were water repelled and floated on the surface of aqueous medium when dispersed. The surface modified PH particles, however, were uniformly and immediately dispersed by mixing gently as shown in Fig. 3, indicating successful modification of hydrophobic surface of original PH particles to hydrophilic with AEROSIL particles. This was proved more quantitatively with decreased contact angle of surface modified particles. The effect of AEROSIL content on the contact angle of surface modified particles is shown in Fig. 4. The contact angle of surface modified PH particles was linearly decreased with increasing AEROSIL content, irrespective of modification method used ($r = -0.922$, $n = 45$, $p < 0.001$). These findings indicated that PH and AEROSIL particles were intermixed randomly on the surface of compact. Consequently, the contact angles of compact were predominantly determined by the PH/AEROSIL ratio, which were independent of the modification methods.

The hydrophilic modification with AEROSIL particles at 10% by TC method decreased significantly the apparent contact potential difference of PH particles (-0.366 V) compared with original unmodified PH (-5.570 V). The increased hydrophilicity reduced the electrostatic force due to the reduction of contact area as shown in Fig. 2 and the discharge through water sorption layer formed on the particles (Führer, 1996). The reduction in electrostatic force reduced the cohesion force of particles, improving the dispersibilities of particles emitted into the air stream.

3.3. Micromeritic properties determining inhalation behavior

The bulk density and DR of the original PH particles were higher and lower than those of modified particles, respectively (Table 2), because they formed strong aggregates as found in Fig. 2, due to their strong cohesive properties. The FD

Table 2
Inhalation indices and micromeritic properties of modified powder

Formulation	EM[a] (%)	RP[a] (%)	EI[a] (%)	Bulk density[b] (g/cm^3)	DR[c] (%)
Original	37.4 ± 5.7	35.8 ± 5.7	22.4 ± 2.5	0.398 ± 0.001	14.7
PM					
2%	41.1 ± 1.6	43.1 ± 3.3	27.0 ± 2.0*	0.412 ± 0.016	26.5
5%	47.8 ± 0.7*	56.5 ± 0.2**	35.9 ± 0.5***	0.361 ± 0.018	47.1
10%	60.2 ± 6.1**	62.7 ± 3.1***	47.7 ± 4.7**	0.284 ± 0.006	48.9
TC					
2%	34.0 ± 0.2	73.1 ± 1.9***	29.1 ± 0.4**	0.311 ± 0.008	75.0
5%	65.6 ± 1.9***	79.3 ± 0.4***	58.4 ± 1.7***	0.276 ± 0.015	96.2
10%	75.6 ± 2.3***	78.4 ± 0.7***	66.9 ± 2.3***	0.250 ± 0.013	98.6
FD					
2%	56.4 ± 1.8**	58.3 ± 3.3***	43.0 ± 2.3***	0.323 ± 0.014	32.2
5%	64.3 ± 1.7***	57.6 ± 3.8**	48.8 ± 2.9***	0.290 ± 0.003	30.0
10%	77.6 ± 1.5***	46.2 ± 3.9*	52.7 ± 2.8***	0.290 ± 0.011	22.2
SD					
2%	25.8 ± 1.5*	76.1 ± 1.9***	22.5 ± 1.6	0.333 ± 0.016	81.3
5%	39.1 ± 0.4	70.6 ± 0.5***	32.9 ± 0.2***	0.330 ± 0.010	58.7
10%	52.1 ± 3.9**	84.0 ± 1.5***	47.7 ± 3.4**	0.291 ± 0.024	96.1

[a] Data are represented with mean ± S.D. ($n = 3$–5)
[b] Data are represented with mean ± S.D. ($n = 2$)
[c] Data are represented with mean of three runs.
* $p < 0.05$,
** $p < 0.01$,
*** $p < 0.001$, significant difference compared to original powder by Student's unpaired t-test.

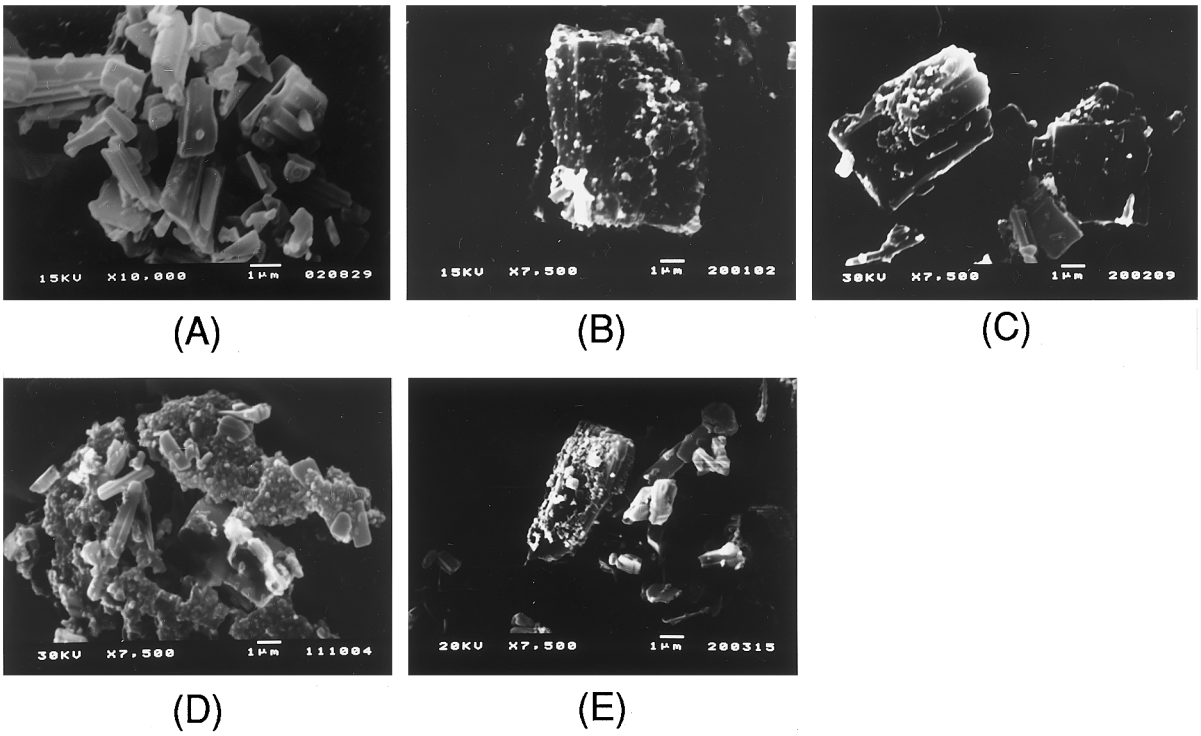

Fig. 2. SEMs of original and surface modified particles. (a) original PH, (b) PM 10%, (c) TC 10%, (d) FD 10%, (e) SD 10%.

method reduced moderately the cohesive properties of PH, forming bulky aggregates in Fig. 2. Their bulk density and DR were not altered significantly. Whereas, the TC and SD methods significantly reduced the cohesive properties of PH particles, forming discrete fine particles as shown in Fig. 2. Their bulk densities decreased and DRs increased, respectively. They were compacted loosely in a container (capsule) and easily dis-

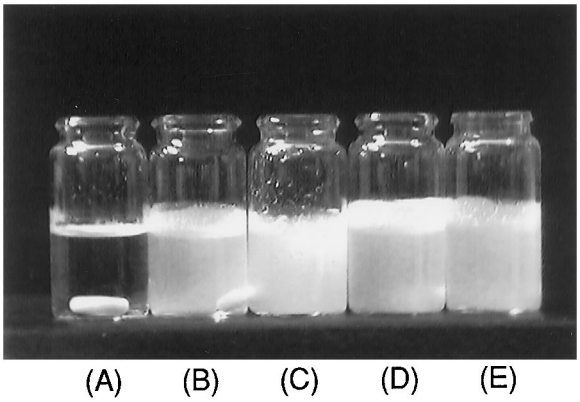

Fig. 3. Dispersibility of powders in water after stirring for 5 min. Symbols as in Fig. 2.

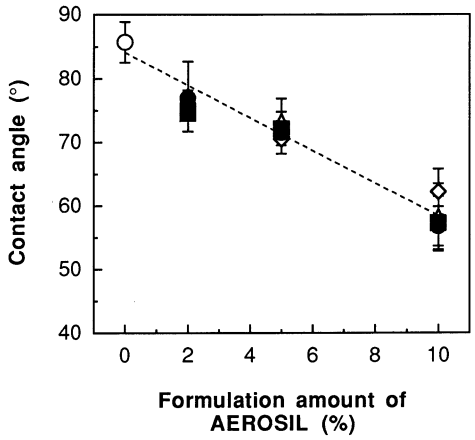

Fig. 4. Effect of AEROSIL content on contact angle. (○) original PH; (●) PM method; (■) TC method; (△) FD method; (◇) SD method. The values are represented as mean ± S.D. ($n = 6$).

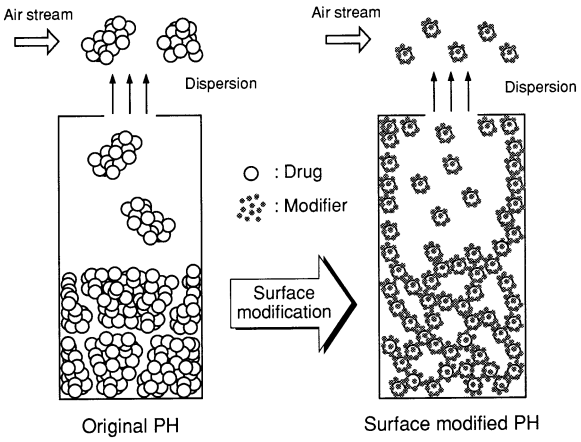

Fig. 5. Schematic representation of improvement of inhalation property by the surface modification of PH particles with AEROSIL.

persed even in the capsule as well as in the air stream on emitting due to their reduced cohesive properties owing to reduced electrostatic force. The image of dispersing behaviors of surface modified particles with TC and SD methods are illustrated in Fig. 5. Lots of adhesions of dispersed particles to the capsule wall were found, resulting in increasing remained % in the capsule particularly at lower compounding with AEROSIL, e.g. 2%. With increasing the compounding %, the remained % in capsule reduced for the TC products, whereas the SD products were still adhered as shown in Table 1. The mechanism of adhesion was remained undissolved.

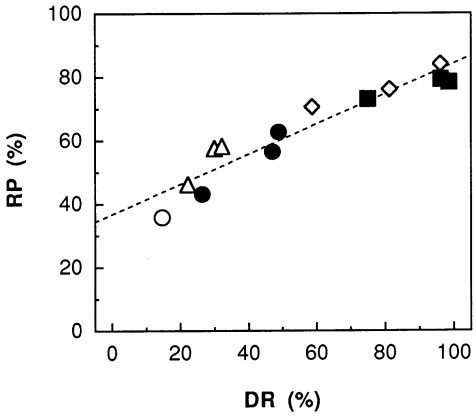

Fig. 6. Relationship between dispersing ratio (DR) and respirable particle percent of emitted particles (RP). (○) original PH; (●) PM method; (■) TC method; (△) FD method; (◇) SD method.

It was found that a proportional correlation between RP and DR was obtained ($r = 0.949$, $n = 13$, $p < 0.001$) as shown in Fig. 6. The increased dispersibility, i.e. RP, of TC products contributed to improve their inhalation properties, with higher EI values, as well as due to their higher emission % as shown in Table 2. The SD method did not provide as high EI values as expected, because of lower EM values than TC method. Whereas, the FD method desirably improved the inhalation manner, although the RP was not so improved as the SD products. The increased emitting % (EM) was responsible for increasing EI values (Table 2).

4. Conclusion

The surface modification of hydrophobic drug particles (PH) to hydrophilic with AEROSIL dramatically improved the inhalation behaviors of drug particles in vitro, depending on the manner of decreasing cohesive properties with the TC, FD or SD methods. The FD and TC methods with a lower and moderately higher compounding with AEROSIL, respectively, are recommendable to modify desirably the drug particles to improve their inhalation properties, with increasing the dispersibilities in inhaled air stream and emission efficiency, respectively.

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References

Bell, J.H., Hartley, P.S., Cox, J.S.G., 1971. Dry powder aerosols I: a new powder inhalation device. J. Pharm. Sci. 60, 1559–1564.

Bode, R., Ferch, H., Fratzscher, H. 1967. Technical Bulletin AEROSIL, No. 4. Nippon AEROSIL, p. 4.

Führer, C., 1996. Interparticulate attraction mechanisms. In: Alderborn, G., Nystoröm, C. (Ed.), Pharmaceutical Powder Compaction Technology. Marcel Dekker, New York, pp. 1–15.

Gupta, P.K., Hickey, A.J., 1991. Contemporary approaches in aerosolized drug delivery to the lung. J. Control. Release 17, 127–147.

Hallworth, G.W., Westmoreland, D.G., 1987. The twin impinger: a simple device for assessing the delivery of drugs from metered dose pressurized aerosol inhalers. J. Pharm. Pharmacol. 39, 966–972.

Hino, T., Serigano, T., Yamamoto, H., Takeuchi, H., Kawashima, Y., 1997. Assessment of inertial separation techniques used for pressurized metered dose inhalers to evaluate respiratory deposition of aerosolized Wogon extract dry powder in vitro. S.T.P. Pharma Sci. 7, 307–314.

Hino, T., Serigano, T., Yamamoto H., Takeuchi, H., Kawashima, Y., 1998. Particle design of Wogon extract dry powder for inhalation aerosols with granulation method. Int. J. Pharm. 168, 59–68.

Kassem, N.M., Shamat, M.A., Duval, C., 1991. The inspirable property of a carrier free dry powder aerosol formulation. J. Pharm. Pharmacol. 43, 75P.

Komada, F., Iwakawa, S., Yamamoto, N., Sakakibara, H., Okumura, K., 1994. Intratracheal delivery of peptide and protein agent: Absorption from solution and dry powder by rat lung. J. Pharm. Sci. 83, 863–867.

Masuda, H., Itakura, T., Gotoh, K., Takahashi, T., Teshima, T., 1995. The measurement and evaluation of the contact potential difference between various opowders and a metal. Adv. Powder Technol. 6, 295–303.

Nakagawa, N., Obata, T., Kobayashi, T., Okada, Y., Nambu, F., Terawaki, T., Aishita, H., 1992. In vivo pharmacologic profile of ONO-1078: A potent, selective and orally active peptide leukotriene (LT) antagonist. Jpn. J. Pharmacol. 60, 217–225.

Niwa, T., Takeuchi, H., Hino, T., Kawashima, Y., 1995. Aerosolization of lactide/glycolide copolymer (PLGA) nanospheres for pulmonary delivery of peptide drugs. J. Pharm. Soc. Jpn. 115, 732–741.

Otsuka, A., Iida, K., Danjo, K., Sunada, H., 1985. Measurement of the adhesive force between particles of powder organic substrate and glass substrate be means of the impact separation method. II. Effect of addition of light anhydrous silicic acid on the adhesive force of potato starch. Chem. Pharm. Bull. 33, 4054–4056.

Smith, S.J., Bernstein, J.A., 1996. Therapeutic uses of lung aerosols. In: Hickey, A.J. (Ed.), Inhalation Aerosols. Marcel Dekker, New York, pp. 233–269.

Taniguchi, Y., Tamura, G., Honma, M., Aizawa, T., Maruyama, N., Shirato, K., Takishima, T., 1993. The effect of an oral leukotoriene antagonist, ONO-1078, on allergen-induced immediate bronchoconstriction in asthmatic subjects. J. Allergy Clin. Immunol. 92, 507–512.

Timsina, M.P., Martin, G.P., Marriott, C., Ganderton, D., Yianneskis, M., 1994. Drug delivery to the respiratory tract using dry powder inhalers. Int. J. Pharm. 101, 1–13.

Visser, J., 1989. Van der Waals and other cohesive forces affecting powder fluidization. Powder Tech. 58, 1–10.