A New Powder Design Method to Improve Inhalation Efficiency of Pranlukast Hydrate Dry Powder Aerosols by Surface Modification with Hydroxypropylmethylcellulose Phthalate Nanospheres

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Purpose. A new particle design method to improve the aerosolization properties of a dry powder inhalation system was developed using surface modification of hydrophobic drug powders (pranlukast hydrate) with ultrafine hydrophilic particles, hydroxypropylmethylcellulose phthalate (HPMCP) nanospheres. The mechanism of the improved inhalation properties of the surface-modified particles and their deposits on carrier particles (lactose) was clarified *in vitro*.

Methods. Drug particles were introduced to aqueous colloidal HPMCP dispersions prepared by emulsion-solvent diffusion techniques followed by freeze- or spray-drying of the resultant aqueous dispersions. The surface-modified powders obtained with HPMCP nanospheres and their mixture with lactose powders were aerosolized by Spinhaler and their mode of deposition in lung was evaluated *in vitro* using a twin impinger. To elucidate the inhalation mechanism of these surface modified particles, we measured their modified micromeritic properties, such as surface topography, specific surface area, dissolution rate, and dispersibility in air.

Results. Dramatically improved inhalation properties of the surface modified powder, i.e. a two-fold increase in emission and a three-fold increase in delivery to deep lung, were found *in vitro* compared with the original unmodified powder. Improved inhalation was also found with the surface-modified drug deposited on lactose particles. Those improvements were attributed to the increased surface roughness and hydrophilicity of the surface-modified particles, and the resultant increased dispersibility in air.

Conclusions. Surface modification of hydrophobic drug particles with HPMCP nanospheres to improve hydrophilicity was extremely useful in increasing the inhalation efficiency of the drug itself and the drug deposited on carrier; this was attributed to increased dispersibility in air and emission from the device, for spray- and freeze-dried particles, respectively.

KEY WORDS: dry powder inhalation; powder design; surface modification; inhalation efficiency *in vitro*; hydroxypropylmethylcellulose phthalate nanosphere; pranlukast hydrate.

INTRODUCTION

Pressurized metered-dose inhalation (PMDI) has been widely used for local and systemic delivery of drugs. However, due to the drawbacks associated with the use of chlorofluorocarbon propellants and the need for coordinated administration with inspiration, dry powder inhalations (DPIs) have become a possible alternative to PMDIs for local (1) and systemic administration of peptide and protein drugs (2,3).

Many trials to develop ideal DPIs, which can deliver the drug accurately to the targeted region of the lung, have been conducted by designing powders and constructing inhalers to permit their complete emission, dispersion, and inhalation (4). For this, drug particles are preferably micronized to an aerodynamic diameter of 1–6 μm for deep penetration into lung; then they are transformed into agglomerates or deposited on carrier particles (e.g., lactose) to improve their flowability for capsule filling (4). On emission from the capsule, they should be completely disintegrated into the original micronized particles or separated from the carrier particles to allow the desired aerosolization and inhalation.

In the present study, a new powder method, surface modification, was proposed to improve the micromeritic properties of micronized drug particles for aerosolization. In this process, the micronized drug particles were adsorbed on ultrafine surface modifier (hydrophilic polymeric nanoparticles) to reduce their aggregation. Pranlukast hydrate (PH), an antiasthmatic drug and cohesive hydrophobic powder, was used as model drug. Hydroxypropylmethylcellulose phthalate (HPMCP) nanospheres were used as the hydrophilic surface modifier because of the characteristic pH-dependent solubility, soluble at pH > 5.5, which should improve the affinity of drug particles for the lung mucosa at pH = 5.7 to 7.5 (5).

In this paper, we discuss how the surface of micronized drug particles was modified and how these modified particles were dispersed and inhaled *in vitro*.

MATERIALS AND METHODS

Materials

Pranlukast hydrate, 4-oxo-8-[4-(4-phenylbutoxy)benzoylamino]-2-(tetrazol-5-yl)-4H-1-benzopyran hemihydrate (abbreviated PH), a leukotriene antagonist for bronchial asthma (6,7), was supplied in micronized powder form from Ono Pharmaceutical Co., Japan. The PH particles were smaller than 9.3 μm with mean diameter of 2.1 μm and were strongly cohesive due to their hydrophobicity (solubility in water; 1.2 μg/ml). α-lactose monohydrate (Pharmatose 325M, DMV, Netherlands) was used as a carrier without modification. Hydroxypropylmethylcellulose phthalate (HPMCP, HP-55) was used as a surface modifier and obtained from Shin-Etsu Chemical Co., Japan.

Preparation of Surface-Modified Drug Particles

The surface-modifying nanosphere system with aqueous colloidal HPMCP dispersion was prepared by the 'emulsion-solvent diffusion technique' developed by Kawashima and coworkers (8,9). HPMCP (0.5 g) was dissolved in a mixture of ethanol (48 ml) and water (12 ml) and the resultant solution was added to water (200 ml) in a cylindrical vessel, stirring at 400 rpm with a 4-blade propeller-type agitator. By this process, ethanolic quasi-emulsion droplets of HPMCP were produced spontaneously (8). The mean diameter of the droplets was 51.6

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nm, measured by dynamic light scattering (LPA 300 and LPA 3100, Otsuka Electronics Co., Japan). After completing the addition of HPMCP solution, PH powder (24.5, 9.5 and 4.5 g) was dispersed in the system with a surface-modifier content of 2, 5, and 10%, respectively. This dispersion was warmed at 50°C and stirred under reduced pressure for 2 h to remove ethanol from the dispersed HPMCP droplets. Then, an aqueous dispersion of solidified HPMCP nanospheres and PH particles was produced. The surface-modified PH powder obtained with HPMCP nanospheres was prepared by freeze-drying (FD) or spray-drying (SD) the resultant aqueous dispersion. The freeze-dryer (Neocool, Yamato Co., Japan) was operated for 3 days or longer after prefreezing at −100°C. The operating conditions of the spray-dryer (Pulvis Basic Unit Model GB-21, Yamato Co., Japan) were: inlet air temperature, 105°C, outlet air temperature, 55°C, drying air rate, 350 l/min, atomizing air pressure, 314 kPa, atomizing nozzle diameter, 406 μm, and spray rate, 5 ml/min. The spray droplet diameter was measured by a laser diffraction size analyzer (LDSA-2400A, Tohnichi Computer, Japan). According to the HPMCP content, i.e. 2, 5, and 10%, the surface-modified particles were named FD 2, FD 5, FD 10 for the freeze-dried product and SD 2, SD 5, SD 10 for the spray-dried product, respectively.

The drug carrier system for inhalation was prepared by depositing surface-unmodified or surface-modified drug particles on lactose particles (Pharmatose 325M), weight ratio 1:9, by manual vortex mixing for 5 min.

In Vitro Inhalation Test

In vitro inhalation properties of surface-modified PH particles were evaluated using a twin impinger (Copley Instruments, UK) in two stages containing 7 and 30 ml collecting solvent (50 mM sodium bicarbonate solution/ethanol = 1/1), respectively. A dry powder inhalation device (Spinhaler, Fisons, UK) was equipped with a No. 2 hard gelatin capsule (Japan Elanco, Japan) loaded with 20 mg powder. The hard capsule was pierced to give two holes to release powder from the capsule. The inhalation assembly was connected to the twin impinger and was subjected to a vacuum to produce an air stream of 60 l/min for inhalation for 5 s. After actuation, the drug in the capsule, device, and stages 1 and 2 was collected by rinsing with collecting solvent. The rinses were diluted to appropriate volumes and the drug content was determined spectrophotometrically at 260 nm (UV-160A, Shimadzu, Japan). The mean aerodynamic cut-off diameter between stages 1 and 2 of the twin impinger was approximately 6.4 μm (10,11). The particles captured in stage 2, i.e. the finer particle fraction, were considered to be the respirable particle fraction in deep lung.

Two indices, i.e. the effective index, (EI; Eq. 1) and the respirable particle percentage of emitted dose (RP; Eq. 2) were employed to describe the inhalation of DPIs with respect to the rates (%) of drug emitted from the capsule and device (Em), and those of drug collected in stage 2 (St2), as defined in the previous paper (12).

$$EI\ (\%) = \sqrt{Em \times St2} \quad (1)$$

$$RP\ (\%) = (St2/Em) \times 100 \quad (2)$$

When ideal inhalation was achieved, both indices were 100 %.

Characterization of Micromeritic Properties of Surface-Modified Drug Particles

The surface topography of particles was investigated by scanning electron microscopy (JSM-T330A, JEOL, Japan). The content of surface modifier (HPMCP) was calculated by gravimetry, i.e. subtracting the amount of drug determined spectrophotometrically from the weight of surface-modified powder. The specific surface area of particles was determined by BET adsorption using nitrogen gas (Gemini, Micromeritics, USA). Tapped density of the particles was determined using a tap density tester (RHK type, Konishi Seisakusyo, Japan).

The dissolution rate of surface-modified drug particles was determined using the paddle method specified in JP XIII.

Dispersibility of particles into an air stream was evaluated using a dry powder disperser (PD-10S, Tohnichi Computer, Japan) and a laser diffraction size analyzer (LDSA-2400A, Tohnichi Computer, Japan). Powder was dispersed in the air stream by the disperser using compressed air at 19.6 and 294 kPa, and the particle size distribution of the aerosols was determined at the nominated dispersing pressure. The dispersing pressures, i.e. 19.6 and 294 kPa, were respectively the minimum and maximum required pressures to achieve complete dispersion. The dispersing ratio (DR) was defined by Eq. 3.

$$DR\ (\%) = F_P/F_{294} \times 100 \quad (3)$$

where, F_P and F_{294} are the cumulative fractions smaller than 6.6 μm determined at a dispersing pressure of P (<294 kPa) and 294 kPa, respectively. When the particles were ideally dispersed at pressure, P, this ratio was 100%.

RESULTS AND DISCUSSION

In Vitro Inhalation Properties of Surface-Modified PH Obtained Using HPMCP Nanospheres

In vitro inhalation properties of surface-modified PH using FD and SD are shown in Fig. 1 (A) and (B), respectively, and Table I. Original surface-unmodified powder (ORG) remained mostly in the capsule and device after actuating, reducing the stage 2 fraction (13.4%) and EI (22.3%). Surface modification by FD markedly reduced the remaining drug in the capsule and device (as shown in FD 2, FD 5, FD 10) and increased the stage 2 fraction. Consequently, the EI values were significantly increased, up to 56.3% for FD 10. Surface-modification effects with SD depended on the content of modifier in the system. At lower levels, the percent remaining in the capsule increased more than the percent trapped in stage 2, resulting in a reduction in the EI of SD 2. The SD 10 improved inhalation efficiency, having a high EI, as did the particles modified by FD. The increase in EI produced by FD was higher than that by SD when the amount of modifier formulated was low (2%).

The inhalation properties of the original PH, FD 10, and SD 10 deposited on lactose carrier are shown in Fig. 2 and Table I. The stage 2 fractions were significantly increased by formulating the surface-modified PH, particularly SD 10. FD 10 had smaller values for the capsule and device fractions. Consequently, a significantly increased EI was found with both FD and SD formulations.

These findings suggest that the physicochemical properties of PH were successfully modified for aerosolization by HPMCP

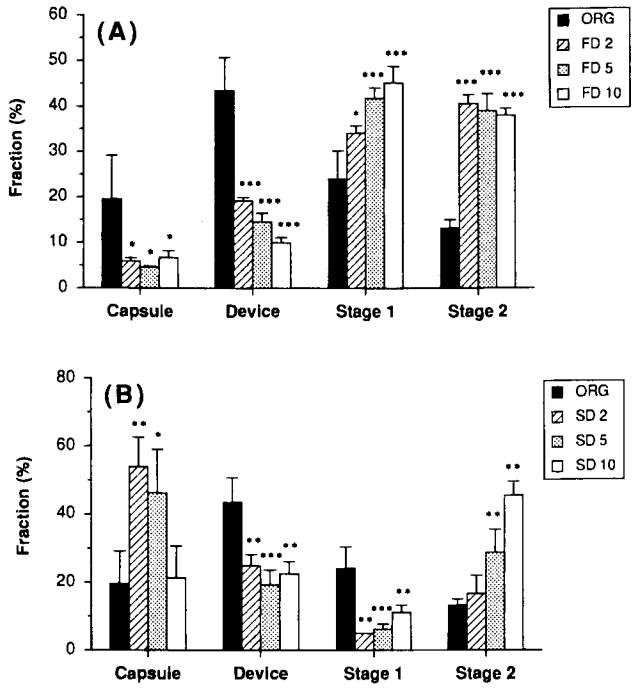

Fig. 1. *In vitro* inhalation properties of surface-modified PH using (A) FD and (B) SD. The data are the means ± sd of 3–5 runs. Significantly different compared with the original powder (ORG) at $p < 0.05$ (*), $p < 0.01$ (**) and $p < 0.001$ (***) using Student's t-test.

nanospheres, depending on the process, i.e. FD or SD. How the surface of PH was modified with to improve inhalation is discussed in the following paragraph.

Modification of Micromeritic Properties of PH with HPMCP Nanospheres

Typical scanning electron microphotographs of original and surface-modified particles obtained by FD and SD are shown in Fig. 3 (A), (B) and (C), respectively. The original PH particles are elongated plate-like crystals with a smooth surface compared with modified particles adsorbed on HPMCP

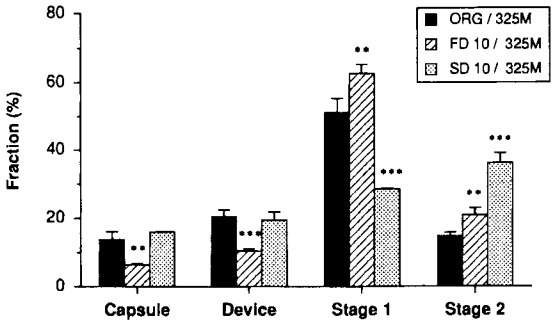

Fig. 2. *In vitro* inhalation properties of surface-modified PH deposited on carrier lactose (Pharmatose 325M). The data are the means ± sd of 3–5 runs. Significantly different compared with the original powder (ORG)/325M at $p < 0.01$ (**) and $p < 0.001$ (***) using Student's t-test.

nanospheres. On the surface of FD 10 particles, the modifier particles are arrayed randomly and some are multilayered, forming an aggregate. Their surface topographies were more quantitatively described by the specific surface area and nanosphere content of the modified particles. The modifier content of FD particles (%) was higher than that of SD particles, resulting in increased specific surface area as shown in Table I. With FD, HPMCP nanospheres should be condensed in the interparticle space and forced into close contact around the surface of the PH particles with ice during freezing. With SD, HPMCP nanospheres are monolayered and partly fused on the surface of PH particles during drying in the spray-drying chamber. It was assumed that a spray droplet contains only single or few PH particles, because the diameter of the spray droplet was about 0.5 to 18.6 μm. This size range covered approximately that of PH particles, i.e. 0.6 to 9.3 μm.

Improved Dispersion and Dissolution Rate of Surface-Modified PH in Aqueous Media

The original PH particles were water-repellant and floated on the surface of aqueous solutions due to their strong hydrophobicity. However, the surface-modified PH particles were

Table I. Inhalation Indices and Micromeritic Properties of Surface-Modified PH

Formulation	EI (%)	RP (%)	Modifier content (%)	Specific surface area (m^2/g)	Tapped Density (g/cm^3)	DR at 19.6 kPa[a] (%)
ORG	22.3 ± 2.5	36.2 ± 5.7	—	5.01	0.398	14.3
FD 2	55.1 ± 1.5***	54.3 ± 2.4**	1.18 ± 0.49	5.82	0.300	36.7***
FD 5	56.1 ± 3.3***	48.2 ± 3.7**	5.62 ± 0.29	7.42	0.273	33.1**
FD 10	56.3 ± 1.0***	45.7 ± 3.0*	9.05 ± 0.18	10.3	0.232	19.7*
SD 2	18.8 ± 5.5	76.2 ± 5.1***	0.38 ± 0.26	5.73	0.395	90.9**
SD 5	31.5 ± 7.5*	82.4 ± 0.6***	3.00 ± 0.44	6.14	0.382	95.8***
SD 10	50.7 ± 5.0**	80.7 ± 2.1***	6.77 ± 0.68	6.91	0.396	96.8***
ORG / 325M	31.1 ± 1.4	22.5 ± 2.4	—	—	—	—
FD 10/325M	44.3 ± 3.0††	36.2 ± 2.4††	—	—	—	—
SD 10/325M	47.1 ± 3.3†††	53.6 ± 4.9††	—	—	—	—

[a] Dispersing ratio calculated from Eq. 3 at 19.6 kPa.
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$: significant difference compared with ORG using Student's *t* -test.
†† $p < 0.01$, ††† $p < 0.001$: significant difference compared with ORG/325M using Student's *t* -test.

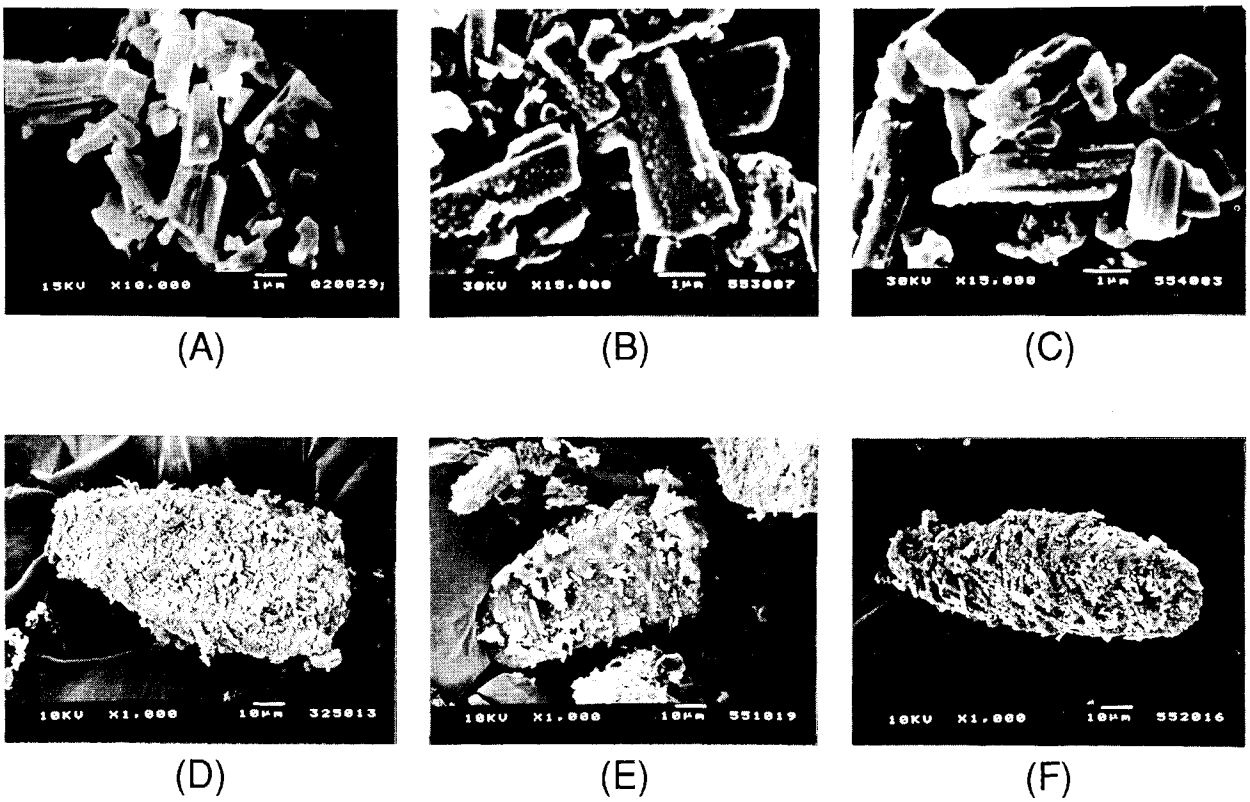

Fig. 3. Scanning electron microphotographs of (A) original PH, (B) FD 10, (C) SD 10, (D) original PH/lactose (Pharmatose 325M), (E) FD 10/lactose (Pharmatose 325M) and (F) SD 10/lactose (Pharmatose 325M).

instantly and uniformly dispersed in aqueous medium. This indicates that the surface of PH had become hydrophilic due to HPMCP nanospheres. This hydrophilic modification was clearly shown by the improved dissolution rate of surface-modified PH particles on dispersion in pH 6.5 phosphate buffer as shown in Fig. 4. The difference in dissolution rate between FD and SD products was caused by the amount of modifier deposited and the specific surface area (Table I). These results also suggest that the drug particles deposited on lung mucosa would dissolve rapidly, leading to improved drug bioavailability.

Improved Dispersibility of Surface-Modified PH

The dispersing ratio (DR) of surface-modified PH with 2% modifier increased with increasing dispersing air pressure (Fig. 5). The DRs at 19.6 kPa for other formulations are given in Table I. As expected, there was a correlation between RP and DR (Fig. 6, $r^2 = 0.980$). The surface-modified PH obtained by SD was ideally dispersed in air even at a low dispersing pressure, with values of DR (P = 19.6 kPa) higher than 90%. Consequently, this indicates higher values of RP. However, the dispersibility of the surface-modified PH obtained by FD was moderately improved as reflected in the values of DR and RP (Figs. 5 and 6). On increasing the amount of HPMCP

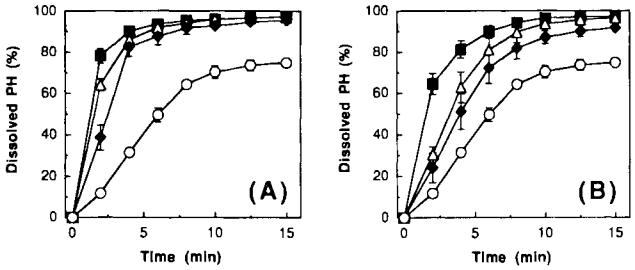

Fig. 4. Dissolution profiles of surface-modified PH prepared by (A) FD and (B) SD. ○: Original PH, amount of surface modifier ◆: 2 %, △: 5%, ■: 10%. The data are the means ± sd of 3 runs.

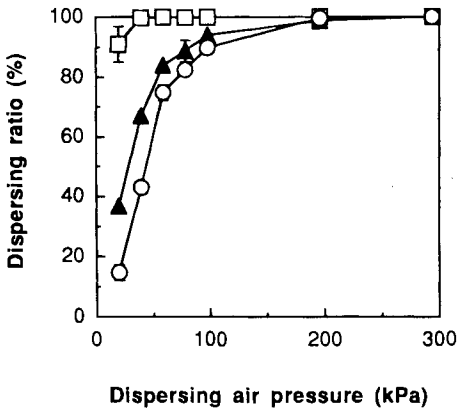

Fig. 5. Dispersion ratio as a function of dispersing air pressure. ○: Original PH, ▲: FD method, □: SD method. Amount of surface modifier was 2%. The data are the means ± sd of 3 runs.

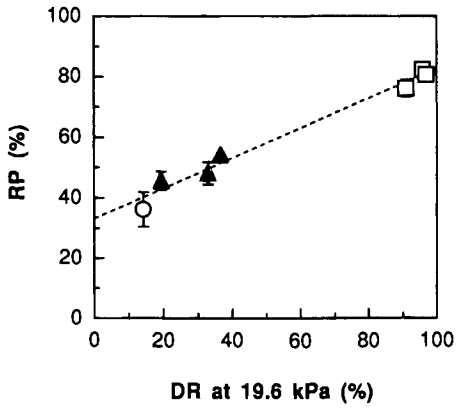

Fig. 6. Relationship between respirable particle percentage of emitted dose (RP) and dispersion ratio (DR) at 19.6 kPa. Symbols as in Fig. 5.

nanospheres, the RP and DR of FD particles decreased, while those of SD particles increased. With FD particles, aggregated HPMCP nanospheres were produced on the surface or in the interspace of PH particles on increasing the amount (Fig. 3). Consequently, the cohesive properties increased as reflected in the reduction in tapped density (Table I). With SD particles, the HPMCP nanospheres were monolayered and partly fused on the surface of PH particles (Fig. 3), resulting in a smoother surface and higher tapped density than FD particles. In fact, the average diameter of FD 10 and SD 10 aerosols dispersed at 19.6 kPa dispersing air pressure was 15.3 and 2.7 μm, respectively. Although, the dispersibility of FD particles was not greatly improved, the EI was significantly higher than that of SD particles. The lower % of FD particles remaining in capsule and device (Fig. 1), was responsible for the increased EI. Due to the moderate cohesion of FD particles, they entrapped air in the powder bed in the capsule. The air released from the powder bed on actuation could promote continuous emission and regulate the powder in the air stream passing through the holes of the capsule during actuation. SD particles were fluidized even in the capsule, and the dispersed particles adhered to the capsule wall on actuation.

Scanning electron microphotographs of original and surface-modified particles using FD and SD deposited on carrier particles (lactose) are shown in Fig. 3 (D), (E) and (F), respectively. With the carrier system, the adhesion of drug to carrier and the dispersibility of drug particles detached from carrier were key factors in determining RP. SD particles might be more easily separated from carrier particles and dispersed in a turbulent air stream than original particles, due to their loose adhesion to the carrier particles as found in Fig. 3 (D) and (F). FD particles were not uniformly deposited on the carrier particles and some aggregates were found (Fig. 3 (E)). Such heterogeneous mixtures were effectively sucked out of the capsule on actuation, reducing the percentage drug remaining in the capsule (Fig. 2). This was preferable to increasing the EI of PH (Fig. 2 and Table I).

In conclusion, surface modification of PH particles with HPMCP nanospheres rendering them hydrophilic was extremely useful in improving the inhalation efficiency of PH itself and deposited PH on the carrier. The nature of the modification with HPMCP nanospheres depended on the method of deposition on the PH particles, i.e. spray-drying or freeze-drying. Spray-drying improved the dispersibility of the modified particles and separated them from the carrier particles in an air stream. Freeze-drying enhanced significantly the emission efficiency of surface-modified PH even at low HPMCP nanosphere levels and of the carrier system from the capsule and inhalation device.

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