Use of Solid Corrugated Particles to Enhance Powder Aerosol Performance

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Purpose. To study the dispersion performance of non-porous corrugated particles, with a focus on the effect of particle surface morphology on aerosolization of bovine serum albumin (BSA) powders.
Methods. The solid-state characteristics of the spray-dried BSA powders, one consisting of smooth spherical particles and another corrugated particles, were characterized by laser diffraction, X-ray powder diffraction, scanning electron microscopy, confocal microscopy, thermogravimetric analysis, surface area analyzer, and buoyancy method. The powders were dispersed using the Rotahaler® and the Dinkihaler® coupled to a four-stage liquid impinger operating at 30 to 120 L/min. Fine particle fraction (FPF) was expressed as the wt. % of BSA particles of size ≤5 μm collected from the liquid impinger.
Results. Apart from the morphology and morphology-related properties (specific surface area, envelope density), the corrugated particles and spherical particles of BSA had very similar solid-state characteristics (particle size distribution, water content, true density, amorphous nature). Using the Dinkihaler®, the FPFs of the corrugated particles were 10–20 wt. % higher than those of the smooth particles. Similar FPF differences were found for the powders dispersed by the Rotahaler®, but the relative changes were larger. In addition, the differences were inversely proportional to the air flows (17.3% at 30 L/min, 25.2% at 60 L/min, 13.8% at 90, 8.5% at 120 L/min). Depending on the inhaler, capsule and device retention and impaction loss at the impinger throat were lower for the corrugated particles.
Conclusions. Enhanced aerosol performance of powders can be obtained by surface modification of the particles. The surface asperities of the corrugated particles could lower the true area of contact between the particles, and thus reduce the powder cohesiveness. A distinct advantage of using corrugated particles is that the inhaler choice and air flow become less critical for these particles.

KEY WORDS: protein; dry powder aerosol; spherical; corrugated; spray drying.

INTRODUCTION

Dry powders are increasingly used for the aerosol delivery of small molecule drugs and therapeutic proteins to the lung (1–17). The generation of dry powder aerosols is influenced by many factors, including both the inhaler device and the particle characteristics (1). It has been demonstrated that particle morphology could be manipulated by the formulation and the method of preparation (2–5). Spray drying of compounds of different compositions (3,5–7) resulted in a change of particle morphology, which is potentially of importance in the development of therapeutic powder aerosol formulations.

To date, investigators have observed that large porous particles (~10–20 μm, specific surface area ~50–100 m^2/g) improved the amount of respirable particles both *in vitro* (5,6,8) and *in vivo* (9,10,18). Despite the large physical size, these porous particles showed excellent aerosol performance. This has been attributed to the low particle density (i.e., high porosity or voids), which gives rise to small aerodynamic size. On the other hand, French and co-workers found that the inclusion of protein rhG-CSF with mannitol resulted in a less dense powder with surface indentations leading to an increase in the surface area of the powder. The performance of the highly indented mannitol-rhG-CSF particles was better than the mannitol particles alone (19). The improvement was attributed to smaller interparticulate cohesive forces resulting from the surface indentation and reduced bulk density. However, the presence of protein in the mannitol particles may also attribute to the weaker cohesion through reducing the Hamaker constant (hence reduced van der Waals force).

In contrast to those porous particles, solid, non-porous corrugated particles containing no additives were obtained in the present study. Our aim was to compare the dispersion behavior of the corrugated particles with smooth, spherical particles of similar physical properties. The focus was on the effect of surface morphology on the dispersion of dry powders as aerosols, using bovine serum albumin (BSA) as a model compound. Studies were conducted at various air flows using two inhalers of different dispersion efficiencies.

MATERIALS AND METHODS

Powder Preparation

The powders were obtained by spray drying using a Buchi 191 spray dryer (Flawil, Switzerland). The feed solution containing BSA (Fraction V, minimum 98%, lot 97HO984, Sigma Chemical Co., St. Louis, MO) dissolved in deionized water was sprayed at following conditions: aspiration rate 57.6 m^3/h, feed rate 1.4 mL/min, inlet and outlet air temperatures 45 and 36°C, respectively, and atomizing air pressure 400 and 600 kPa for the corrugated and smooth spherical particles, respectively.

Solid-State Characterization

Particle Morphology

Powder samples were mounted onto metal sample plates and coated with platinum (~3 nm thick). The samples were then examined under a Jeol JSM 6000F scanning electron microscope (Tokyo, Japan), operating at 2–3 kV.

Particle Interior Structure

Powder (approximately 1–2 mg) was fixed on a glass slide using glutaraldehyde (0.1 v/v%, Sigma Chemical Co., St. Louis, Missouri), dried overnight, and viewed under a confocal microscope (Bio-Rad Radiance Plus scanning system, Hertfordshire, UK). Continuous sectioning along the z-axis of the specimen via the confocal microscope allowed the detection of void(s) in the particle (20).

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Particle Sizing

Particle size distribution of the powders was measured in suspensions using a Mastersizer S Laser Diffractometer (Malvern, Worcs, UK) as described previously (11–13). Chloroform was used as a dispersion medium. Particle size analysis was based on the refractive index (RI) of BSA (1.550), $RI_{imaginary}$ of BSA (1.000 for spherical particle; 1.200 for corrugated particle), and RI of chloroform (1.444). The size distribution was expressed by the volume median diameter (VMD) and span. VMD is related to the mass median diameter (MMD) by the density of the particles (assuming a size-independent density for the particles). Span is a measure of the width of the size distribution. Span = [D(v,90) − D(v,10)]/D(v,50)], where D(v,90), D(v,10), and D(v,50) are the equivalent volume diameters at 90, 10, and 50% cumulative volume, respectively.

Density Determination

True Particle Density. The true density of the spray-dried powders was determined by a validated buoyancy method (11,12). Powder samples (1–2 mg) were placed in a density gradient liquid (comprising bromoform and 1-hexanol) and centrifuged (Jouan CT422, Saint Herblain Cedex, France) at 3500 rpm (corresponding to 2359 g) and 5°C for 30 min. The particle density was equal to the density of the liquid when the particles remained suspended after centrifugation.

Density of the Corrugated Particle Viewed as a "Spherical Envelope". The Malvern laser diffraction provides results as the equivalent sphere diameter, thus the size of the corrugated particle was measured as a sphere that consists of void space (the "spherical envelope" described in Fig. 1a). The "spherical envelope" density, rather than the true density of the corrugated particles, would be required to calculate the mass median aerodynamic diameter from the MMD obtained from the laser diffraction.

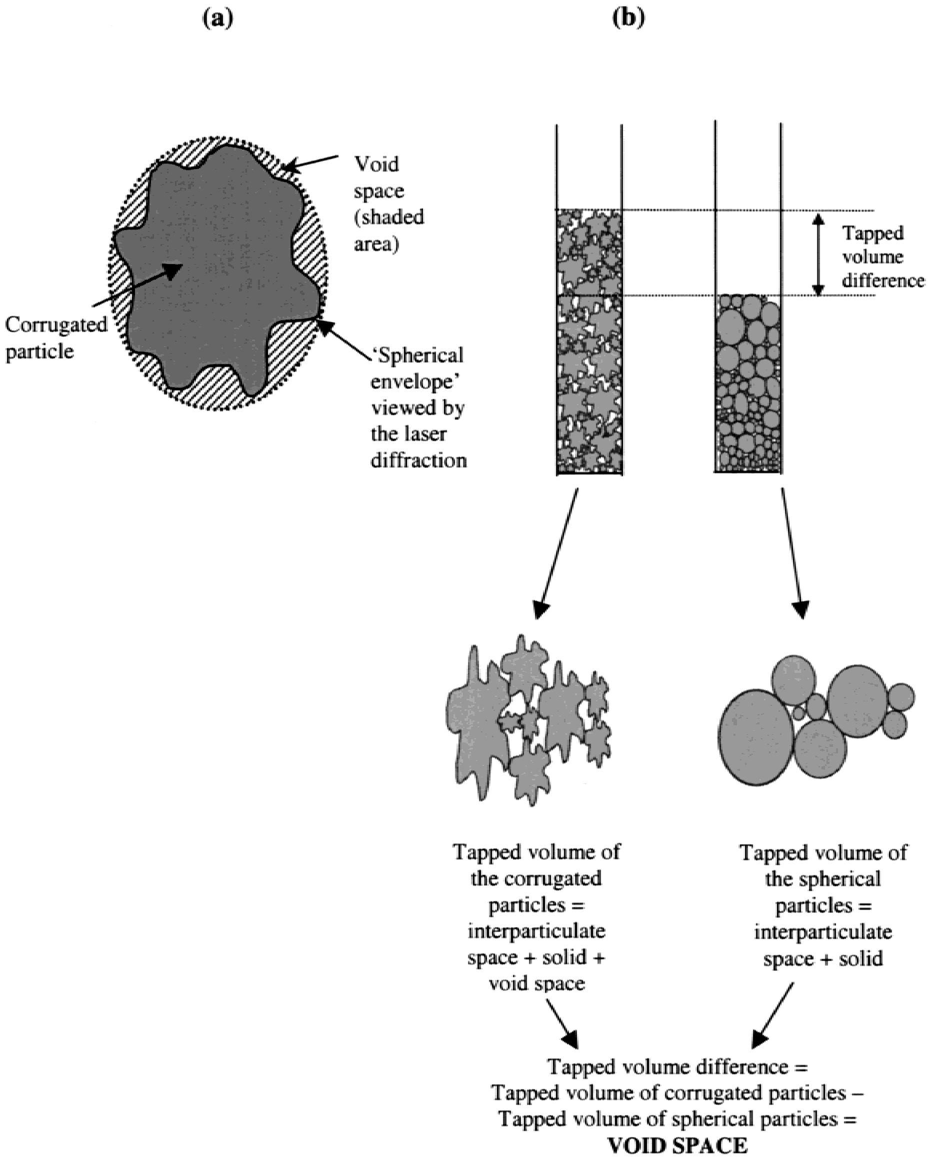

Fig. 1. (a) Schematic diagram of the corrugated particle viewed as a "spherical envelope" by the laser diffraction; (b) estimation of the void space in the "spherical envelope."

Experimentally, equal amounts of powder (~450 mg) of spherical particles and corrugated particles were filled into two separate glass tubes of the same diameter (~5 mm). The powder was subjected to tapping (step height 3 mm, 100 rpm) at room conditions (20°C, 50% RH), and the height of the powder bed was measured once the equilibrium was reached (after approximately 1000 taps). As an approximation, the tapped powder bed is assumed to have particles closely packed with minimal interparticulate space. The tapped volume of the spherical particles would be the sum of the solid and the interparticulate space, whereas for the corrugated particles, the tapped volume would be the sum of the solid, the interparticulate space and the void space (Fig. 1b). Because the spherical and corrugated particles had similar size and polydispersity (Table I), the volume difference (after tapping) between the two powders would approximately be the void space of the "spherical envelope" (Fig. 1b). In reality, polydispersity and interlocking of the particles would cause deviation from this ideal situation (6). However, at present there is no satisfactory experimental technique to quantify the degree of particle interlocking. The spherical envelope density in this study was calculated as the mass (g) of powder of corrugated particles (used for tapping) divided by the sum of the void space (mL) and the volume (mL) of powder (calculated from the true particle density) used for tapping.

Powder Crystallinity

Powder crystallinity was assessed by XRD. Samples were packed on a glass sample plate under the storage humidity (23% RH) and analyzed on a Siemens D5000 X-ray powder diffractometer (Hamburg, Germany) using CuK_α radiation generated at 40 kV and 30 mA, with an angular increment of 0.05°/s and a count time of 2.0 s.

Moisture Content

Samples (~10 mg) were placed in platinum pans and heated at a rate of 5°/min under a nitrogen purge (~30 mL/min) in a thermogravimetric analyzer (SDT 2960, TA Instruments, New Castle, DE) controlled by a TA thermal solutions controller 4000. Percent moisture was calculated as the weight loss between room temperature and 200°C where the profiles leveled off.

Surface Area Determination

The surface area of the spray-dried powders was determined by the Accelerated Surface Area and Porosimetry Analyzer (model ASAP 2000, Micromeritics, Norcross, GA) using nitrogen as the adsorbate gas. The powder materials (~0.3–0.7 g) were degassed for ~24 h under nitrogen at 45°C to remove the preadsorbed gases and vapors from the surface of the samples. The surface area was determined by the multipoint Brunauer, Emmett, and Teller (BET) method using the adsorption data in the relative pressure (P/Po) range of 0.07–0.22.

Aerosol Behavior of the Smooth Spherical vs. Corrugated Particles

The method details have been given elsewhere (11,12). Briefly, studies were conducted in an airtight perspex glove box (45 cm × 75 cm × 80 cm) at known temperature (23 ± 2°C) and relative humidity (23 ± 5%). The dispersion behavior (the breaking up of agglomerates to regenerate the primary particles) of the spray-dried powders was assessed by a Rotahaler® (Glaxo-Wellcome) and a Dinkihaler® (Aventis) coupled to a four-stage (plus filter) liquid impinger (Copley, Nottingham, UK) with a glass throat. Powder (20 mg) was filled into a capsule (which was pre-equilibrated over saturated potassium carbonate solution at 44%RH) just prior to the experiment and was then dispersed immediately. Four capsules were dispersed per experiment. BSA was assayed by ultraviolet spectrophotometry (Model U-2000, Hitachi, Tokyo, Japan) at 750 nm using the Bio-Rad DC protein assay kit (Bio-Rad, Hercules, CA). A calibration curve was constructed using standard solutions of BSA in deionized water: Absorbance = 1.5 * concentration (mg/mL) [n = 10, R^2 = 0.998]; linear at concentrations between 0.025 and 0.250 mg/mL.

Fine particle fraction (FPF) is defined as the mass fraction of particles ≤5 μm in the aerosol. FPF was obtained by interpolation to the cumulative percent undersize at 5 μm. Capsule and device retention is defined as the mass fraction of the powder remaining in the capsules and the device. Impaction loss is defined as the mass fraction of the powder collected at the throat and stage 1 of the impinger. FPF, retention, and impaction loss were all referenced against the

Table I. Solid-State Characteristics of the Spray-Dried BSA Powders

	Corrugated BSA	Spherical BSA
MMD (μm) (SD)	3.2 (0.0)	2.8 (0.0)
MMAD[a] (μm)	2.7	3.1
Span (SD)	1.5 (0.1)	1.5 (0.0)
Particle size distribution	Unimodal	Unimodal
True Density (g/cm^3) (SD)	1.2 (0.1)	1.2 (0.1)
Spherical envelope density (g/cm^3) (SD)	0.7 (0.1)	N/A
Voids	None (Fig. 2a)	None (Fig. 2b)
Water content (wt. %)	5.7	6.2
Surface area (m^2/g) (SD)	6.07 (0.11)	2.13 (0.01)
Crystallinity	Amorphous	Amorphous
Morphology	Corrugated particles (Fig. 3a)	Smooth, spherical particles (Fig. 3b)

[a] The MMAD of the powder was calculated from the product of MMD and the square root of true particle density for the spherical particles (14) and the product of MMD and the square root of "spherical envelop" density for the corrugated particles (see "density determination" in Methods and Materials section).

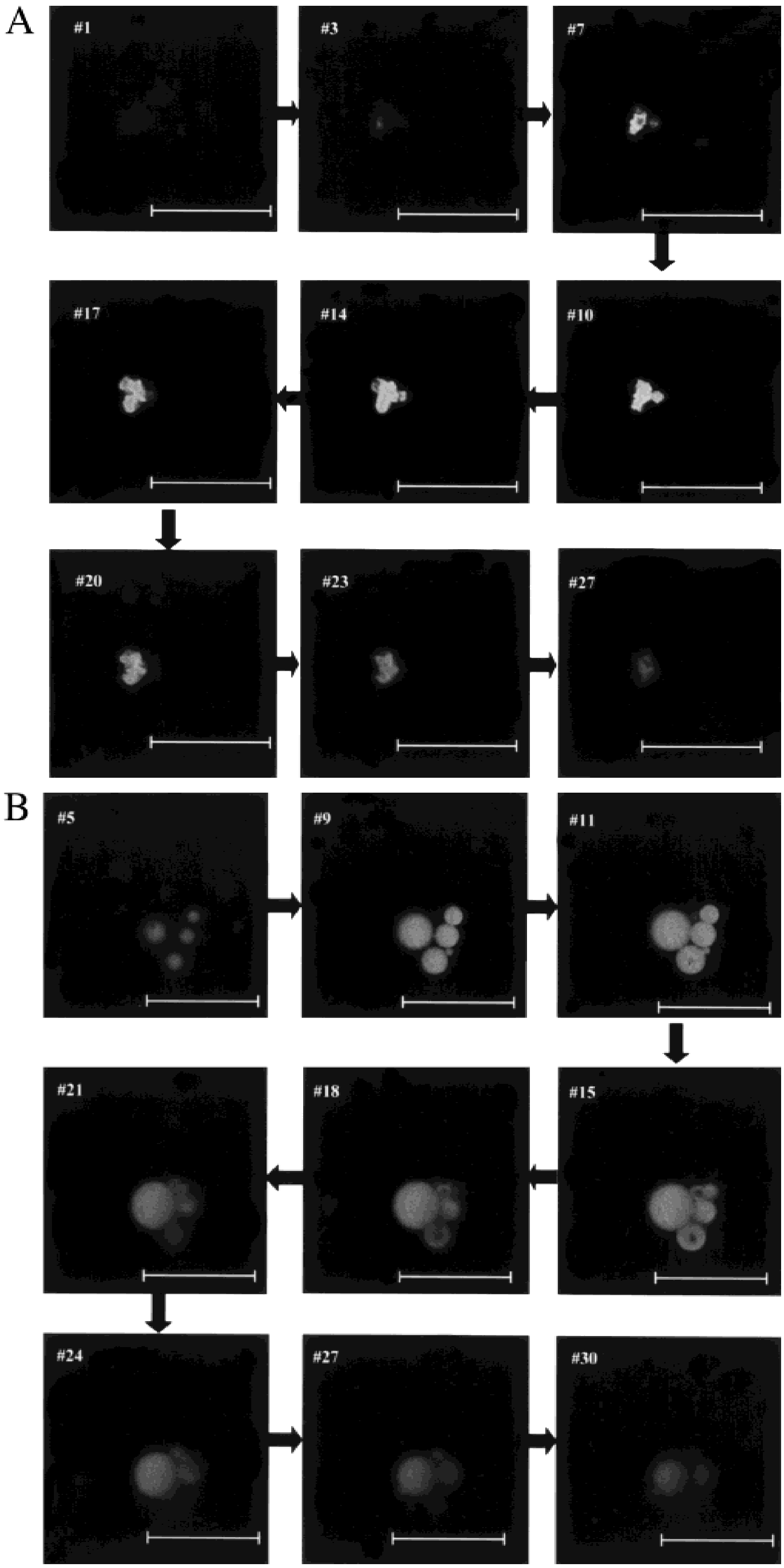

Fig. 2. (a) Confocal images of the corrugated bovine serum albumin particles: slicing particles from the top to bottom using approximately 0.10-μm thickness per slice for a total of 27 slices. Only slices 1, 3, 7, 10, 14, 17, 20, 23, and 27 are shown (scale bar-10 μm). (b) Confocal images of the spherical bovine serum albumin particles: slicing particles from the top to bottom using approximately 0.09-μm thickness per slice for a total of 35 slices. Only slices 5, 9, 11, 15, 18, 21, 24, 27, and 30 are shown (scale bar 10 μm).

recovery (i.e., total dose = emitted dose + device and capsule retention) and were expressed as the means of triplicate runs ($n = 3$). Data were subjected to analysis of variance (ANOVA) and Student's *t* test (Microsoft Excel version 97) with probability values of less than 0.05 considered as statistically significant.

RESULTS

Solid-State Characteristics

Table I summarizes the solid-state characteristics of the spray-dried BSA powders. The true density values and confocal images (Fig. 2) confirmed the non-porous nature of the particles. Apart from the morphology (Fig. 3) and morphology-related properties (specific surface area, envelope density), the corrugated particles and spherical particles of BSA had very similar solid state characteristics [particle size distribution, water content, true density, amorphous nature (XRD results not shown)].

Effect of Surface Morphology on the Aerosol Generation

Rotahaler®

The FPFs of the corrugated particles were significantly higher ($p < 0.05$) than those of the spherical particles at the same air flow (Fig. 4a), with the differences being greater at lower flows: 17.3 wt. % at 30 L/min; 25.2 wt. % at 60 L/min; 13.8 wt. % at 90 L/min; 8.5 wt. % at 120 L/min. Although the FPF of the smooth spherical particles increased proportionately with the air flow, with the maximum FPF (FPF_{max}) attained at 90 L/min (30 wt. %), such a trend disappeared with the corrugated particles. Increasing the air flow from 30 to 60 L/min almost doubled the FPF of the corrugated particles, which then rapidly leveled off at high flows.

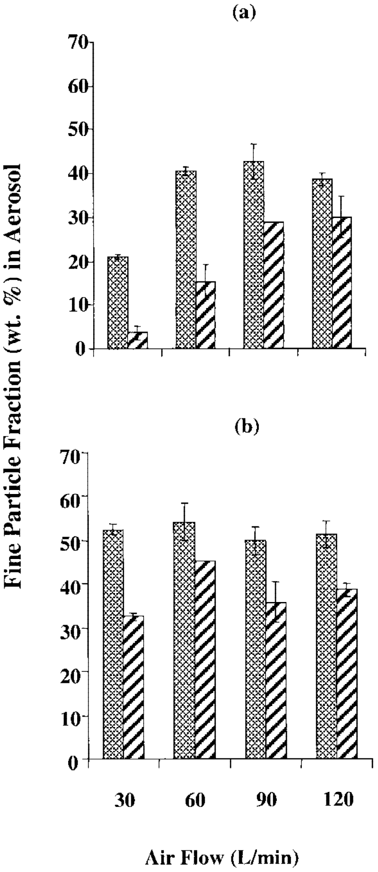

Fig. 4. Fine particle fraction of corrugated and spherical bovine serum albumin powders dispersed by (a) the Rotahaler® and (b) the Dinkihaler®.

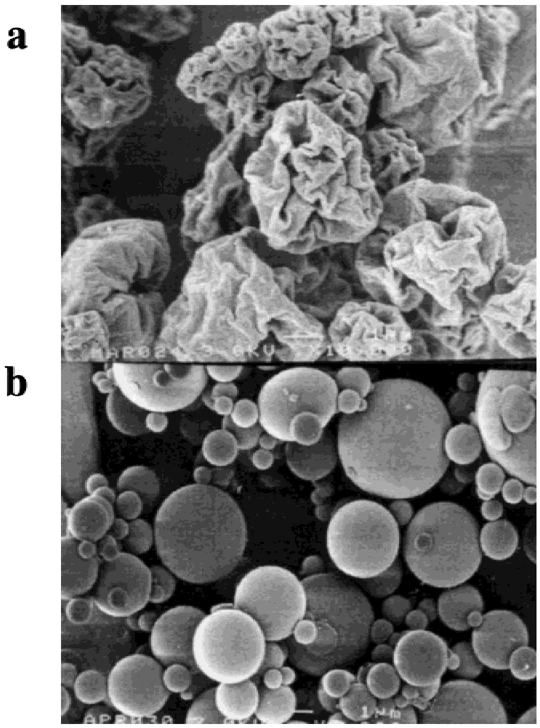

Fig. 3. Scanning electron micrographs of the spray-dried bovine serum albumin powders, (a) corrugated particles, (b) spherical particles (scale bar 1 μm).

Dinkihaler®

Both powders were more effectively dispersed by the Dinkihaler®, as shown by the higher FPFs, which was readily achieved at a low flow of 30 L/min with no flow dependence of the FPF (Fig. 4b). Similar to the Rotahaler® results, the FPFs of the corrugated particles were about 10–20 wt. % higher than those of the spherical ones.

Capsule and Device Retention

Retention of both spherical and corrugated particles in the Rotahaler® decreased with increase of air flow, and the retention values of both powders were similar at the same flow ($p > 0.05$, Fig. 5a). For the Dinkihaler®, retention also decreased with increase of air flow (Fig. 5b). However, the amount retained was lower ($p < 0.05$, except at 60 L/min) for the corrugated particles than the spherical particles.

Impaction Loss

Increasing the air flow through the Dinkihaler® increased the impaction loss for both spherical and corrugated particles to similar extents (Fig. 5b). The impaction loss also

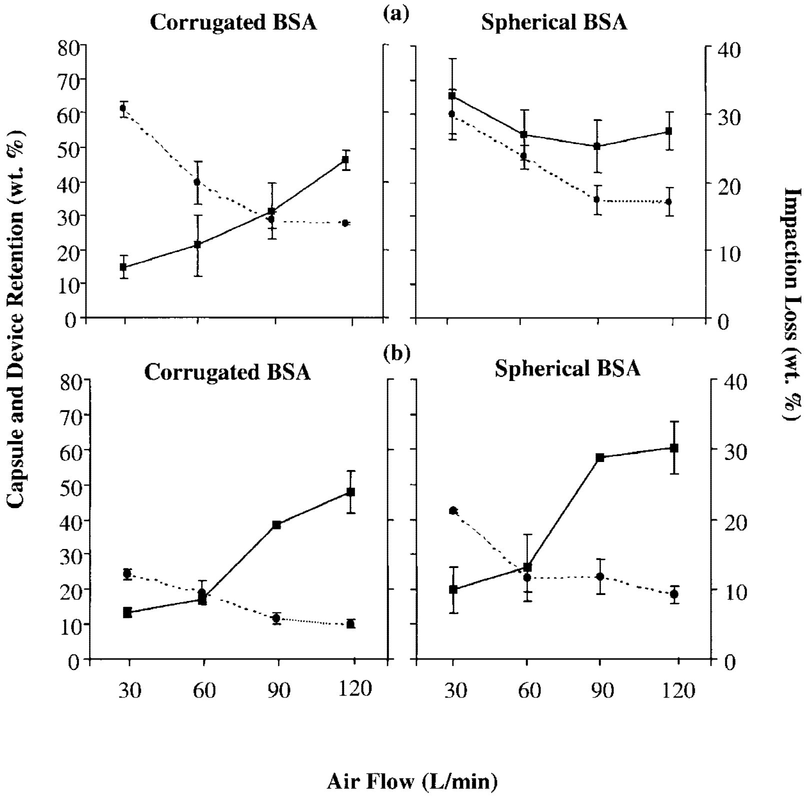

Fig. 5. Capsule and device retention ··●·· and impaction loss ━■━ of the spherical and corrugated bovine serum albumin powders dispersed by (a) the Rotahaler® and (b) the Dinkihaler®.

increased with the air flow through the Rotahaler® for the corrugated particles (Fig. 5a). In contrast, the impaction loss for the spherical particles was independent of the air flow through the Rotahaler®, and the loss was substantially higher ($p < 0.05$) than those of the corrugated particles at flows of 30–90 L/min (Fig. 5a).

DISCUSSION AND CONCLUSIONS

This study demonstrated that significantly enhanced amounts of fine particles in the aerosol could be obtained by using solid, non-porous, corrugated particles. It is well recognized that the amount of fine particles available in the aerosol is influenced by the air flow and the dispersion efficiency of the inhaler type (11,12,15,16), especially for powders that are cohesive and require high energy to disperse into fine particles (13,17). Flow dependence of FPF is thus commonly seen with cohesive powders and/or with low dispersion efficiency inhalers (11,12,16), as was also shown with the dispersion of the spherical BSA particles using the Rotahaler® in the present study. The lack of flow dependence of FPF for the corrugated particles (via the Rotahaler®) suggested that they were less cohesive than the spherical particles. The aerosol performance of these particles was thus less air flow and device dependent.

The improved dispersion of the corrugated particles was coupled to the reduced device retention and impaction loss for the Dinkihaler® and the Rotahaler®, respectively. The reduced powder retention in the Dinkihaler® indicated a better flow of the powder out of this particular device by the entrained air. Impaction loss is proportional to the air flow and square of the particle size (21). The lower impaction loss for the corrugated particles when dispersed by the Rotahaler® indicated that these particles were easier to disperse and the agglomerates formed during dispersion were much smaller (hence less inertia for impaction) than those of the spherical particles. This was confirmed by the impinger's particle size distribution which was shifted to a larger MMAD for the spherical particles (Fig. 6). The impaction loss stays nearly the same for spherical particles with the Rotahaler as the large agglomerates decrease in size with increasing air flow.

A practical advantage of using the corrugated particles is that, because of the significant improvement of FPF at low air flows, the inhaler choice and air flow become less critical for fine aerosol generation. Although the use of a high dispersion efficiency device (e.g., the Dinkihaler®) is required for dispersion of the spherical particles (to improve FPF and to minimize the flow dependency and impaction loss), acceptable FPFs can be obtained from the corrugated particles using the Rotahaler® at 60 L/min, and maximum FPF is achieved using the Dinkihaler® at flow as low as 30 L/min.

Although the corrugated particles have a higher specific surface area, not all the area is necessarily accessible for contact. As shown in the electron micrographs, the surface asperities of the corrugated BSA particles could have significantly reduced the true area of contact between particles, and thus lowered the cohesion (22). The reduced point-to-point contact would reduce the influence of van der Waals forces of cohesion by increasing the average distance between particles (19). This can explain why the corrugated particles were

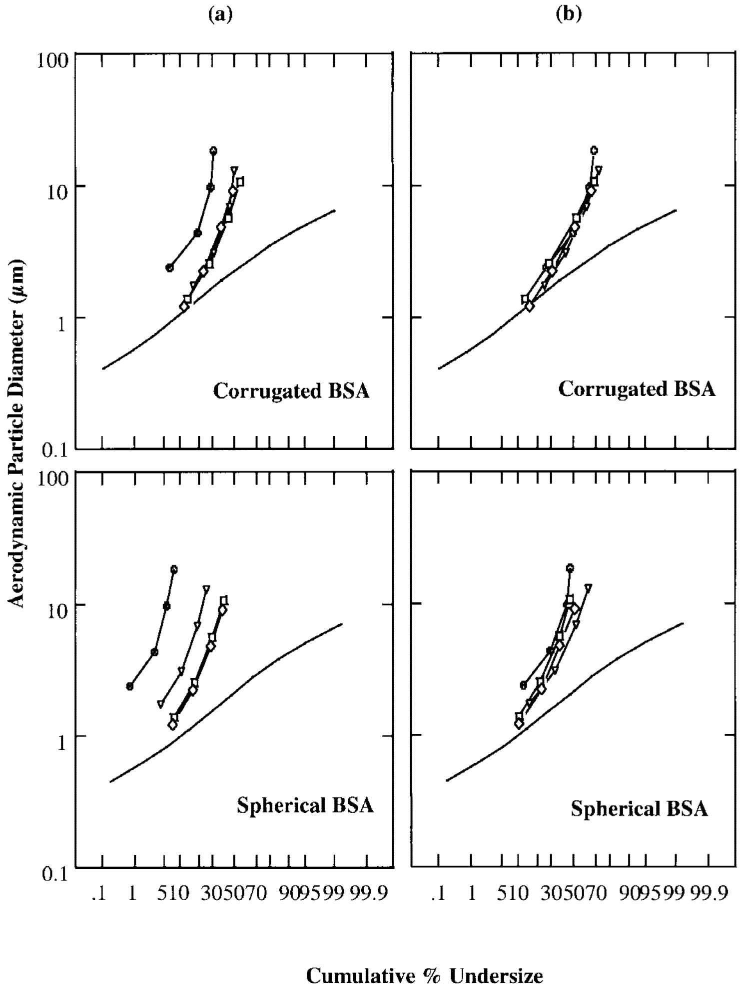

Fig. 6. Particle size distribution of the spray-dried powders before (solid line) and after dispersion using the Rotahaler® (a) and Dinkihaler® (b) at different air flow (—⊖— 30 L/min, —▽— 60 L/min, —⊟— 90 L/min, —◇— 120 L/min).

easier to disperse with less device and capsule retention. In the previous work by French *et al.* (19) protein-sugar particles were compared with pure sugar particles and hence direct comparison could not be made because of the complication due to different chemical compositions. The present study has utilized identical chemical entity for the smooth and wrinkled particles and confirmed the important role of surface morphology on dispersion of powders as aerosols.

In conclusion, solid, non-porous corrugated particles showed enhanced aerosol performance over the smooth spherical particles of otherwise similar physical properties. Depending on the inhaler, corrugated particles showed higher FPF, lower impaction loss, and less capsule and device retention. This can be attributed to the surface asperities which decrease the true surface area of contact between the particles and consequently, a reduction of cohesion. The lower dependence on the air flow and inhaler choice in achieving the same or higher FPF using corrugated particles emphasized the significance of surface morphology on powder aerosol generation.

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