Pharmaceutical Research, Vol. 22, No. 1, January 2005 (© 2005)
DOI: 10.1007/s11095-004-9020-4

Research Paper

How Much Particle Surface Corrugation Is Sufficient to Improve Aerosol Performance of Powders?

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Received July 30, 2004; accepted September 14, 2004

Purpose. The current study aimed to quantify the different degree of particle surface corrugation and correlate it to the aerosol performance of powders.
Methods. Powders of different degree of surface corrugation were prepared by spray drying under varying conditions. The solid-state properties of the powders including particle size, morphology, crystal form, true density, and moisture content were characterized. The degree of surface corrugation was quantified by the surface fractal dimension (D_S) obtained by light scattering. The aerosol performance was studied by dispersing the powders using the Rotahaler at 60 L/min into a multi-stage liquid impinger. Fine particle fraction (FPF) was expressed as the wt% of BSA particles of size ≤ 5 μm in the aerosol.
Results. Four powders of increasing degree of particle surface corrugation were prepared, with D_S ranging from 2.06 for the least corrugated to 2.41 for the most corrugated. The powders had a similar size distribution (VMD 3 μm, span 1.4–1.5) and solid-state properties. Increasing the surface corrugation, $D_{S,}$ slightly from 2.06 to 2.18 enhanced the FPF significantly from 27% to 41%. This was explained by the reduced area of contacts and increased separation distance between the particles. Further increase of corrugation ($D_S \geq 2.18$) did not improve FPF.
Conclusions. Powders with varying degrees of corrugation were successfully obtained by spray drying with their surface roughness quantified by fractal analysis. It was shown that only a relatively small degree of surface corrugation was sufficient to accomplish a considerable improvement in the aerosol performance of the powder.

KEY WORDS: DPI; dry powder aerosols; fractal dimensions; inhalation drug delivery.

INTRODUCTION

During the rapid development of dry powder aerosols in the past decade, many attempts have been made using the powder formulation to optimize the delivery of drug particles into the lung. Due to the small size (hence large specific surface area) and other physicochemical nature such as being partly amorphous, the presence of moisture and electrostatic charge, fine particles are generally cohesive with poor ability to flow and disperse. A number of strategies are capable of improving the powder performance. A major focus has been on the engineering of particles with designed features to lower powder cohesion and increase dispersibility. Coated particles (1,2), needle crystals (3), AIR™ particles (4), aerogel powders (5), spray-freeze dried particles (6), and Pulmosphere (7) are examples. The effect of surface morphology on enhancing aerosol performance was explored using nonporous corrugated solid albumin particles (8). These particles were shown to produce significantly more fine particles in the aerosol than the noncorrugated spherical particles. A distinct advantage of these corrugated particles is that their dispersion behavior is less dependent on the inhaler device and air flow.

In the previous report (8), the degree of surface corrugation was not quantified, and there remain important questions unanswered: how much corrugation would be sufficient for improving the powder dispersion, and is there a quantitative relationship between the aerosol performance and degree of corrugation? In the current study, we have prepared corrugated particles with their degree of surface roughness quantified and correlated to the aerodynamic behavior.

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ABBREVIATIONS: Re, particle Reynolds number; ψ, sphericity, μ_L, viscosity of suspending fluid; ρ_L, density of suspending fluid; S_F, shape factor; χ, skin factor, d_A, equivalent projected area diameter; d_V, equivalent volume diameter; d_S, equivalent surface area diameter; U, particle terminal settling velocity; A_s, A_{ns}, surface area of spherical and nonspherical particles of equal volume and density, respectively; K_1, K_2, the Stokes' and Newton's shape factors, respectively; $V_{P,}$ ρ_P, volume and density of the particle, respectively; g, gravitational acceleration; A_A, projected area of the particle normal to the settling direction; d_{Aer}, aerodynamic diameter.

MATERIALS AND METHODS

Preparation of Particles with Different Degree of Corrugation

Bovine serum albumin (BSA) (Fraction V, minimum 98%, Sigma Chemical Co., St. Louis, MO, USA), as the model compound, was dissolved in water (MilliQ, Waters) and spray dried at an inlet temperature of 45°C (outlet temperature 36°C), feed rate of 1.4 ml/min and aspiration rate of 57.6 m^3/h using a spray dryer (Büchi 191, Flawil, Switzerland) to produce the powders. The feed concentration and atomisation rate were customised to obtain particles with varying degree of surface corrugation (Table I).

Physicochemical Properties of the Corrugated Particles

The equivalent volume diameter of the particles was determined by laser diffraction with the corresponding aerodynamic diameter calculated by the "spherical envelop" density method described previously for BSA (8). Moisture content of the powders was determined by a thermal gravimetric analysis (SDT 2960, TA Instruments, New Castle, DE, USA) by heating the powder sample (~10 mg) from room temperature to 200°C at a rate 5°C/min. Powder crystallinity was measured by an X-ray diffractometer (Siemens D5000, Hamburg, Germany) using Cu Kα radiation at 30 mA and 40 kV, with an angular increment 0.05°/s and count time of 2.0 s. Particle morphology was examined under an scanning electron microscope (JEOL JSM 6000F, Tokyo, Japan) operating at 2–3 kV on samples coated with platinum. True particle density was determined by a buoyancy method (8).

Quantification of Particle Surface Corrugation

The degree of particle surface corrugation was expressed by surface fractal dimension which was determined using the light scattering method. This method has been described in detail elsewhere (9–12). Briefly, particles are subjected to a light source, resulting in the scattering of light at different angles with reference to the incident light beam. The scattering momentum (q) is commonly used to characterize the incident and scattered beam in terms of the scattered angle (θ), the wavelength of light in vacuum (λ) and the refractive index of the surrounding medium (n) (13). Based on Rayleigh-Gans-Debye scattering theory, the intensity of scattered light, $I(q)$, can be related to surface fractal dimension based on the following (13):

$$I(q) \propto q^{-6+D_s} \tag{1}$$

The fractal dimension, D_s, can therefore be obtained from the slope of the plot of scattered intensity [$I(q)$] vs. scattering momentum (q), on a log-log scale.

Table I. Spray-Drying Parameters for Preparing Powders of Different Degree of Surface Corrugation

	Powder			
	1	2	3	4
Feed concentration (mg/ml)	75	50	25	10
Atomisation rate (L/h)	600	550–600	550	300

Experimentally, particles were suspended in chloroform at ~0.1% (w/w), which was found to be an appropriate concentration with minimal multiple scattering. The determination of surface fractal dimension was based on the refractive index (RI) of both the BSA powder and solvent using the following parameters values: RI of BSA: 1.550; $RI_{imaginary}$ of BSA: 1.000 and 1.200 for smooth and corrugated particles, respectively; RI of chloroform: 1.444. Each sample was repeated 10 times in the measurement to ensure reproducibility. Numerically surface fractal of "2" corresponds to a perfectly smooth surface, while "3" corresponds to a very rough surface (14–16).

Determination of Aerosol Performance

Twenty milligrams of powder were dispersed from gelatine capsules (two per experiment) as an aerosol by Rotahaler (GlaxoSmithKline) as described previously (8,17). The Rotahaler was connected to a 90°-angle USP stainless steel throat of a 4-stage liquid impinger (Copley, Nottingham, UK) operating at 60 L/min. The amount of powders collected at the impinger stage, throat, capsules and device was determined using a Bio-Rad DC protein assay kit (Bio-Rad, Hercules, CA, USA) followed by UV absorption at 750 nm on a

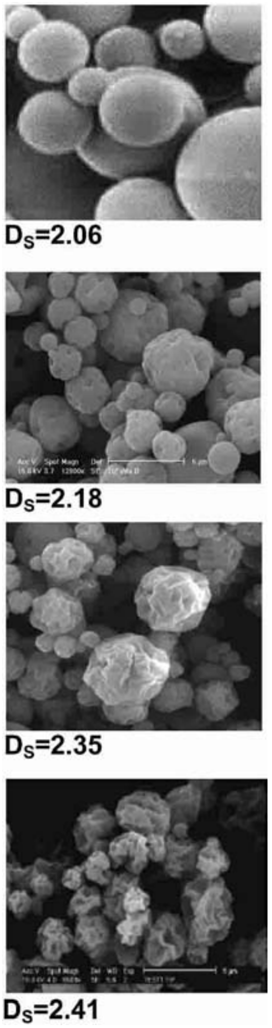

Fig. 1. SEM photos of the spray dried powders with different degrees of surface corrugation.

Table II. Physical Particle Size, Span, Fractal Dimensions, and Aerodynamic Size of Spray-Dried Powders

Powder	Degree of corrugation	Volume median diameter (μm)	Span	Fractal dimension (D_s)	Envelop density (g/cm^3)	Aerodynamic particle size[b] (μm)	Aerodynamic particle size[c] (μm)
1	Least	2.69 (0.02)[a]	1.41 (0.02)	2.06 (0.05)	1.20 (0.00)	2.95 (0.05)	2.75 (0.10)
2	↓	2.78 (0.00)	1.41 (0.01)	2.18 (0.05)	1.13 (0.02)	2.92 (0.00)	2.56 (0.26)
3		2.96 (0.00)	1.53 (0.01)	2.35 (0.05)	0.86 (0.02)	2.81 (0.00)	2.46 (0.36)
4	Most	3.21 (0.06)	1.51 (0.03)	2.41 (0.05)	0.68 (0.02)	2.69 (0.00)	2.61 (0.38)

[a] Values in parenthesis indicate standard deviation (n = 3).

[b] Calculation based on "spherical envelop" density method (8).

[c] Calculation based on a recent computational model (Appendix and Ref. 23).

spectrophotometer at (Model U-2000, Hitachi, Tokyo, Japan).

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. FPF and retention were all referenced against the recovery (i.e., total dose = emitted dose + device and capsule retention) and were expressed as the mean 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 AND DISCUSSION

The current study aims to quantify the degree of particle surface corrugation and correlate it to aerosol performance. Four powders with varying particle surface corrugation as shown by SEM (Fig. 1) were obtained by carefully controlling the spray drying conditions (Table I). In general, a higher degree of corrugation was obtained using lower BSA concentrations and air atomization rates (i.e., larger droplets but at a lower protein concentration). Being a macromolecule with a slight surface activity, BSA will stay preferentially on the droplet surface forming an initial dry crust with the droplet core containing relatively less protein as drying proceeds. The corrugated morphology is formed as the protein-enriched crust collapses and invaginates into the protein-depleted interior. These powders were prepared so that they had a similar particle size, as well as size distribution as depicted by the span (Table II). The slight increase in VMD with increasing corrugation is necessary to keep the aerodynamic diameters similar due to the increased drag force and decreased envelope density. In addition, all powders were amorphous with a similar moisture content of 7.4 ± 0.3 wt% and true particle density of 1.2 ± 0.1 g/cm^3. Keeping these physical parameters constant was crucial to allow an unambiguous assignment of the effects of particle surface morphology to the aerosol performance.

Surface fractal dimensions, D_S, of the spray dried BSA particles were successfully obtained from light scattering. Figure 2 shows the scattering curves for the smoothest particles with D_S 2.06 and the roughest particles with D_S 2.41. The scattering patterns show typical linear fractal regions from which D_S was obtained using Eq. 1. The scattering intensity (q) for the fractal region to represent individual particle surface roughness has to be higher than 1/particle diameter. Using the volume median diameter values shown in Table II, the minimum q value to obtain D_S for the BSA particles is 3.12×10^{-4} nm^{-1}. Figure 2 shows that the fractal regions indeed exist for $q > 3.12 \times 10^{-4}$ nm^{-1} and hence scattering exponents represent the surface fractal dimension.

Powder dispersion (FPF) was previously found to improve with corrugated particles (8), but it remains unknown if a quantitative relationship exists between the FPF and corrugation, and how much corrugation is needed to bring forth the improvement. The present results showed that a small degree of surface roughness (D_S = 2.18) was sufficient to elicit a large improvement of the aerosol performance (FPF = 40.6 ± 1.7) compared with the noncorrugated particles (FPF =26.9 ±

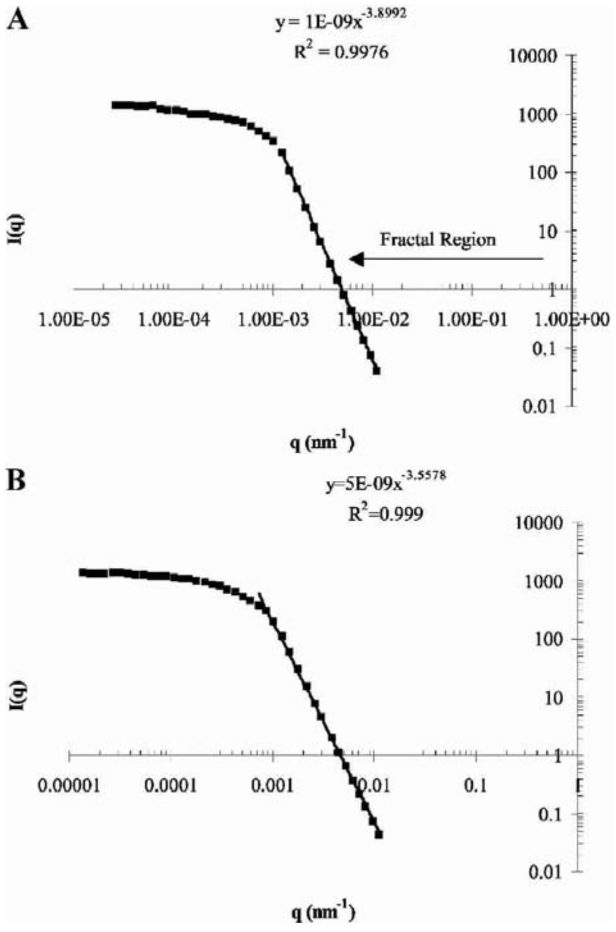

Fig. 2. Scattering curves obtained from light scattering of BSA particles with surface fractal dimension, D_S 2.10 (top) and 2.44 (bottom).

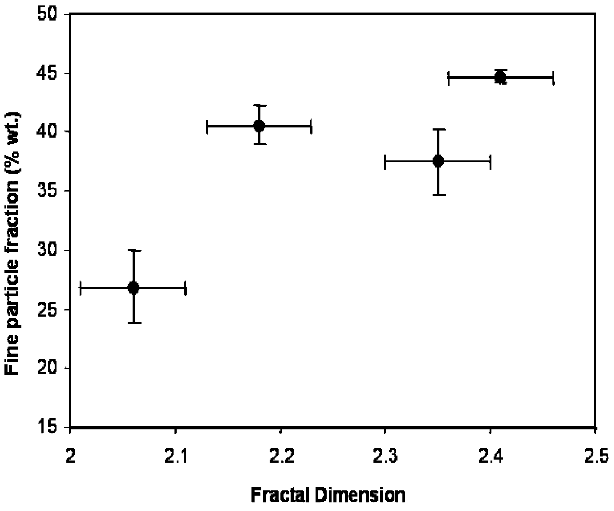

Fig. 3. Effect of particle corrugation (surface fractal dimension) on the aerosol performance (fine particle fraction) of the powders.

3.0) (Fig. 3). Further increase of the surface roughness (i.e., higher D_S values) did not improve the FPF. The improvement of FPF was due to i) reduction in the capsule and device retention of the corrugated particles and/or ii) increase in the powder dispersibility, that is, the amount of fine particles in the aerosol cloud per *emitted* dose (Table III). The results indicate that the corrugated particles tend to be less adhesive to the device surface and/or less cohesive to each other.

Once a powder is dispersed, the FPF is determined by the aerodynamic diameter of the particles in the aerosol. It is thus possible that the difference in FPF was simply due to a smaller aerodynamic diameter of the corrugated particles arising from a higher drag force on the rough surface (hence a lower sedimentation velocity). However, similar aerodynamic diameters were obtained among the different powders using theoretical calculations based on two independent methods (8,21; Table II). The results thus support surface roughness being the major determinant for the increased FPF of the corrugated particles.

Surface corrugation would decrease particle-particle interactions in two ways. First, the asperities prevent close contact between particles, which effectively increases the interparticulate distance (H), and since van der Waals force (F_{vdw}) of attraction is inversely related to H^2, a lower F_{vdw} is resulted [Based on $F_{vdw} = AR/12H^2$ between two identical spherical particles, where A is the Hamaker constant and R the particle radius (18–20)]. Second, the asperities may reduce the total area accessible for interaction. It is important to note that even though the corrugated particles have a higher specific surface area, it does not necessarily be fully accessible because of the asperities. In addition, the true contact area will be determined by elastic and/or plastic deformation (21,22) which may vary differently depending on the surface roughness and possibly particle size (VMD). Thus, as the surface corrugation increases, a balance between the interparticulate distance and contact area may exist, leading to a plateau in the F_{vdw} and the aerosol performance.

It is worth to point out that over the last decade there has been a significant focus on using "porous" particles to improve the aerosol performance of powders (4,6,7). While these particles have a small aerodynamic diameter due to the low particle density, the particle surface is also "rough." Therefore, the effect of surface roughness on the drag and van der Waals forces discussed in this study can be equally applicable to those "porous" particles to help explain their dispersion and aerodynamic behavior. The surface fractal dimension described can potentially be useful as an independent descriptor for these rough particles.

In conclusion, powders with varying degrees of corrugation were obtained by spray drying under carefully controlled conditions. The surface roughness was quantified by fractal analysis. It was shown that only a relatively small degree of surface corrugation was sufficient to accomplish a considerable improvement in the aerosol performance of the powder.

Nomenclature

Re	Particle Reynolds number
ψ	Sphericity
μ_L	Vicosity of suspending fluid
ρ_L	Density of suspending fluid
S_F	Shape factor
χ	Skin factor
d_A	Equivalent projected area diameter
d_V	Equivalent volume diameter
d_S	Equivalent surface area diameter
U	Paticle terminal settling velocity
A_s, A_{ns}	Surface area of spherical and non-spherical particles of equal volume and density, respectively.
K_1,K_2	The Stokes' and Newton's shape factors, respectively
V_P, ρ_P	Volume and density of the particle, respectively.
g	Gravitational acceleration
A_A	Projected area of the particle normal to the settling direction.
d_{Aer}	Aerodynamic diameter

ACKNOWLEDGMENTS

The project was funded by the Australia Research Council (ARC Project DP 0208175).

Table III. Aerodynamic Properties of Spray-Dried Powders Dispersed at 60 L/min Using the Rotahaler

Powder	Degree of corrugation	Fractal dimension (D_s)	Fine particle fraction (% wt)	Capsule and device retention (% wt)	Dispersibility[b]
1	Least	2.06 (0.05)	26.9[a] (3.0)	51.4 (4.7)	60.2 (4.0)
2	↓	2.18 (0.05)	40.6 (1.7)	40.1 (4.8)	69.5 (2.1)
3		2.35 (0.05)	37.5 (2.8)	50.2 (3.0)	77.3 (0.3)
4	Most	2.41 (0.05)	44.7 (0.6)	37.1 (0.6)	72.5 (0.7)

[a] Significantly different from the other powders. Values in parenthesis indicate standard deviation (n = 3).

[b] Mass fraction of particles ≤5 μm in the aerosol per emitted dose (24).

APPENDIX 1

The aerodynamic diameter of the particles was obtained by the following computational method using iteration procedure described schematically as:

$$\begin{tikzcd}
\mathrm{U}_1 \arrow[r] & \mathrm{Re} = \dfrac{U\rho_L d_V}{\mu_L} \arrow[r] & \mathrm{C_D} \arrow[r] & U_2 = \sqrt{\dfrac{2[V_P(\rho_P - \rho_L)g]}{A_A \rho_L C_D}} \arrow[d] \\
 & & & U_2 - U_1 = 0 \arrow[lllu, "\text{No}"] \arrow[d, "\text{Yes}"] \\
 & & & d_{Aer} = \sqrt{\dfrac{18U\mu_L}{g}}
\end{tikzcd}$$

The aerodynamic diameters in Table II are mean values of results calculated using the three different drag coefficients, C_D, formulated by:

1. Ro and Neethling (25):

$$C_\mathrm{D} = \frac{24\chi}{\mathrm{Re}} + 3.6 S_F^{\,2}\,\mathrm{Re}^{-0.313} \qquad S_F = \frac{d_A}{d_V} \quad \chi = \frac{d_S}{d_V}$$

2. Ganser (26):

$$\frac{C_D}{K_2} = \frac{24}{\mathrm{Re}\,K_1K_2}\{1 + 0.1118(\mathrm{Re}\,K_1K_2)^{0.06567}\} + \frac{0.4305}{1 + \dfrac{3305}{\mathrm{Re}\,K_1K_2}}$$

$$K_1 = \left[\left(\frac{1}{3}\right) + \left(\frac{2}{3}\right)\psi^{-0.5}\right]^{-1}$$

$$K_2 = 10^{1.8148(-\log\psi)^{0.5743}}$$

$$\Psi = \frac{A_s}{A_{ns}}$$

3. Haider and Levenspiel (27):

$$C_D = \frac{24}{\mathrm{Re}}[1 + \exp(2.3288 - 6.4581\,\psi + 2.4486\,\psi^2)\mathrm{Re}^{(0.0964+0.5565\psi)}] + \frac{\mathrm{Re}\cdot\exp(4.905 - 13.8944\psi + 18.4222\psi^2 - 10.2599\psi^3)}{\mathrm{Re} + \exp(1.4681 + 12.2584\psi - 20.7322\psi^2 + 15.8855\psi^3)}$$

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