Expert Opinion

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What is the role of particle morphology in pharmaceutical powder aerosols?

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Background: The aerosol performance of a powder for inhalation drug delivery is controlled by a number of physicochemical properties of the formulation, including particle size, density and morphology. *Objective*: The role of particle morphology in powder inhalers will be reviewed. *Methods*: Original research publications in the literature about the contribution of particle morphology to the aerosol performance of pharmaceutical powders have been selected, including both the lactose carriers and the drugs. *Results/conclusion*: Existing data showed that morphology of both the lactose carrier and drug particle can affect the aerosol performance of powders significantly, a factor which should be taken into consideration during the development of dry powder inhalation products.

Keywords: asthma, dry powder inhaler, inhalation therapy, particle morphology, respiratory diseases

Expert Opin. Drug Deliv. (2008) 5(8):909-914

1. Introduction

Research and development into pulmonary delivery systems of both small and large drug molecules have been a growing area of the past decade. Although recently inhaled insulin suffered the ill fate of having been removed from the market [1], there have been a number of inhalation aerosol products developed successfully over the last few years for the treatment of lung infection [2] and pulmonary hypertension [3], as well as for the diagnosis and therapeutic monitoring of airway hyper-reactivity such as asthma [4]. Inhalation aerosols using dry powder inhalers (DPIs) offer many advantages over the liquid formulation, including the delivery system, bioavailability and chemical stability [5]. However, DPIs are complex system depending on both the inhaler device and the powder formulation. There are many physicochemical factors, including particle size, density and morphology, that are critical for the dispersion of a powder formulation as aerosol [6]. Inhaler devices control the dispersion mechanisms which may be predominated by turbulence, collisions between agglomerates and collisions between agglomerates and device wall [7,8]. Since the agglomerate strength is influenced by the particle morphology (see below), it has a direct consequence on deagglomeration via any of these mechanisms. Particle morphology in general refers to the external shape and surface texture of a particle (**Figure 1**). In addition, it can refer to the internal structure if the particle is porous or contains voids.

The morphology of particles can affect the aerosol performance of a powder at various levels: molecular, particulate and aerosol. At the molecular level, different particle shapes of crystalline materials (i.e., crystal habits) will have different chemical functional groups on specific faces of the particles, leading to a variation in the surface energy, hygroscopicity (and the resulting capillary force)

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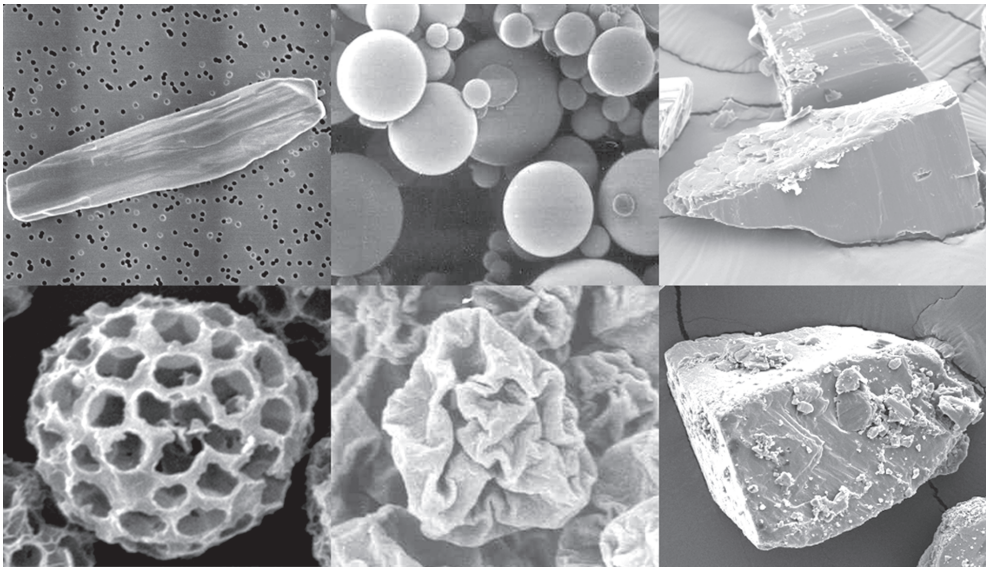

Figure 1. Examples of different particle morphology.

and electrostatic interactions. These differences will be manifested in the inter-particulate forces at the particulate level. Due to these forces, particles may become cohesive and exist as agglomerates in a powder. The agglomerate strength is given by:

$$\sigma = 15.6\Phi^4 \frac{W}{D} \quad (1)$$

Where ϕ is the packing fraction, W the non-equilibrium value of the work of adhesion and D the particle diameter. Particle morphology determines not only the particle packing in an agglomerate but also the specific surface area and friction (which affect flowability and powder emptying from a powder inhaler), as well as mechanical properties (which affect deformation and subsequent interaction for particles coming in contact). Once a particle becomes airborne, the aerodynamic diameter, D_a, is given by:

$$D_a = d_v \sqrt{\frac{1}{\chi} \cdot \frac{\rho}{\rho_o}} \quad (2)$$

Where d_v is the volume equivalent diameter of the particle, χ the dynamic shape factor, ρ particle density (with internal void included) and ρ_o unit density (1 g cm^{-3}).

Morphology affects D_a via the shape factor and density terms in the equation. For example, a large χ and small ρ would reduce D_a of a particle. This will be discussed in detail below. In this article, the influence of particle morphology on the aerosol performance of pharmaceutical powder formulations will be reviewed, with a focus first on the lactose carrier, then on the drug particles.

2. Particle morphology and aerosol performance

2.1 Lactose carriers: smooth, rough and elongated particles

The work of Ganderton and co-workers in the early 1990s is widely cited as a classic example to illustrate the effect of surface morphology (roughness or rugosity) of lactose carriers on the aerosol performance of blend formulations [9]. In this case, the rugosity was defined as the surface area of the lactose powder measured by gas permeametry relative to the theoretical surface area, assuming ideal spheres for the powder. Three lactose samples were used: regular lactose and spray-dried lactose with rough surfaces and smooth recrystallised lactose. There was a strong correlation between the surface roughness and the fine particle fraction (FPF, % mass particles < 5 µm) in the aerosol, with the smooth lactose showing a FPF of 20% compared with < 5% for the rough lactose carriers. What is seldom considered is that the smooth lactose also had a different particle shape compared with the rough lactose, which could additionally have affected the FPF, but the effect was unknown. Furthermore, rugosity is an indirect measurement which does not provide details about actual surface roughness. A decade later Young *et al.* (2002) used atomic force microscopy to quantify the surface roughness of two lactose samples, raw and smooth [10]. Raw lactose was shown to have a roughness of 108 ± 37 nm and smooth lactose 26.5 ± 7.4 nm. In contrast to the previous results, there was no difference in the aerosol performance between the two lactose carriers, except a larger error bar was reported in the fine particle dose of the drug (beclometasone dipropionate) using the raw (i.e., rough) lactose, implying a higher performance variation in this lactose formulation.

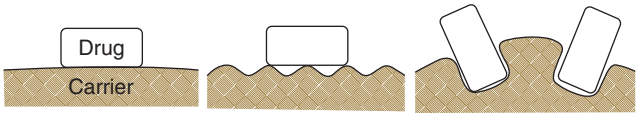

Figure 2. A schematic illustration of the interaction between drug particles and carrier surface with various levels of roughness. The adhesion of micron-sized drug particles to a nanoscopically rough surface is smaller than to smooth or microscopically rough surfaces. In practice, all forms of surface roughness are possible when the particles adhere to the carrier surface. The overall adhesion thus depends on the number of asperities of each type. To reduce particle adhesion, the carrier surface should possess nanoscopic roughness without microscopic asperities.

It could be argued that the lack of a performance difference is due to an insufficient variation in the degree of surface roughness between the two lactose samples. Consequently, a crucial question is: exactly how much surface roughness is necessary to make a difference in aerosol performance?

The quantitative answer to the above question is not yet known, but Kawashima *et al.* provided a qualitative account (**Figure 2**), which was based on three cases characterising the effect of surface roughness on particle adhesion described by Zimon [11]. Smooth surfaces allow close contact between the drug particle and lactose carrier, leading to increased interactions and a low FPF. In contrast, if the carrier surface is very rough with crevices and cavities (i.e., when their sizes are comparable with the dimensions of the drug particles), drug particles can be mechanically trapped and unable to come out, which would also lead to a low FPF. Thus, an optimal roughness level exists on the lactose surface that would cause minimal contact with the drug, leading to reduced interactions and a high FPF. A series of lactose was studied and the results indeed followed the expectation of exhibiting a maximum FPF at the intermediate roughness (**Table 1**). Unfortunately, the results were complicated by differences in the particle shape and/or polymorphic form, which could also have contributed to the variation in the FPF observed. It becomes necessary to take into consideration these confounding factors in any study. In practice, this may not be always possible as crystallisation is a highly perturbable process, and morphology changes may be accompanied by polymorphism.

The first study correlating both the surface roughness and particle shape of lactose carriers with FPF was undertaken by Zeng *et al.* (2000) [12]. They reported an empirical relationship: FPF = 6.56E + 24.5S – 13.9 ($r^2 = 0.901$), where E is the elongation ratio (i.e., length/width) and S the surface roughness measured by image analysis. Interestingly, the equation shows that 13.9% of the FPF cannot be explained by particle morphology alone, indicating the involvement of other factors contributing to the aerosol performance. Since only a narrow range of the elongation ratio (1.2 – 2.0) was employed in the study, it is not certain whether the correlation can be applied to longer needles.

2.2 Elongated carrier and elongated drug particles

Similar to the results of Zeng *et al.* (2000), Larhrib *et al.* (2003) found that elongated lactose carriers produced significantly higher FPFs of the drug, salbutamol sulfate (**Table 2**) [12,13]. In addition, the investigators studied elongated drug particles and found a much better performance (FPF 17.2%) compared with the commercial drug (FPF 5.5%). Elongated particles of a steroidal drug was previously studied by Ikegami *et al.* (2002) [14], who reported an eightfold increase in the FPF for the needle-like particles (FPF 39.3%) compared with the plate-like particles (4.7%). However, the results were complicated by the fact that these particles are also of different polymorphs (α-form, plates; β-form, needles) which could change the FPF via differences in the surface chemistry of the crystal faces.

2.3 Elongated drug particles without carriers

It has long been known that, despite their length, elongated particles like asbestos can be inhaled and deposited in the alveoli [15]. This is because the aerodynamic diameter of a fibre is determined mainly by the width rather than by the length of the particle. Gonda and Khalik (1985) showed that the ratio of the aerodynamic diameter to the physical diameter (width, D_f) of an elongated particle increases with the aspect ratio (i.e., length/width) of the particle and levels off at a value of about 2 – 2.5 when the aspect ratio is ≥ 15 – 20 (**Figure 3**) [16]. Chan and Gonda explored such an aerodynamic advantage in elongated particles of prophylactic drugs for asthma, including cromoglicic acid and nedocromil (**Figure 4**) [17,18]. These elongated particles revealed aerodynamic diameter values that matched the theoretical predictions [16,18].

2.4 Porous particles and 'solid' wrinkled particles

During the late 1990s, porous particles including the AIR™ particles and Pulmosphere™ were used for the development of DPI formulations. These particles have a low particle density (< 0.5 $g \cdot ml^{-1}$) which, according to Equation 2, will lead to a low Da. In addition, these porous particles can have an extensive surface area (> 50 m^2 g) which will further reduce Da via the dynamic shape factor in the equation. In contrast to the low density porous particles, we explored 'solid' wrinkled particles of bovine serum albumin (BSA), which were found to out-perform their smooth counterpart (**Figure 5**) [19]. Only a low degree of surface roughness (measured by surface fractal analysis using light scattering) was sufficient for the improved performance of the powder, which is attributed to not only the enhanced drag force on the wrinkled surface reducing the Da, but also the reduced cohesion of the powder, leading to better device emptying and dispersion [20]. Most recently, using focussed ion beam (FIB) milling, we observed the presence of an internal void

Table 1. Effects of different lactose carriers on aerosol performance.

Lactose	Spray dried amorphous	Spray dried crystallised	Fluidised bed granulated	DCL-11
Roughness	1.08	1.14	1.33	1.13
FPF (wt.%)	10	18	3.4	11
Emission (wt.%)	74	62	84	75
Shape	Spherical	Spherical	Irregular	Spherical
Solid-state	Amorphous	α and β	α	α and amorphous

Adapted from [24].

Table 2. Aerosol performance of elongated particles.

Salbutamol sulfate	Lactose	Content uniformity	Emission (%)	FPF (%)
Micronised	Commercial	98.2 ± 1.1	79.9 ± 5.1	5.5 ± 3.3
	Needle	97.6 ± 3.1	80.0 ± 2.9	23.3 ± 2.6
Needle	Commercial	98.6 ± 3.7	77.4 ± 3.9	17.2 ± 1.7
	Needle	96.7 ± 6.7	69.2 ± 4.0	29.1 ± 1.4

Adapted from [13].

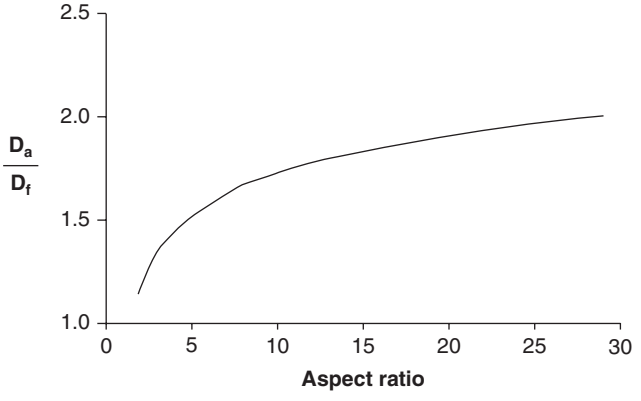

Figure 3. Influence of the aspect ratio of fibres on the aerodynamic diameter of the particles.

in some of these particles, mostly in smooth particles and those with a low degree of wrinkles [21]. In most cases, the effect of the void volume on the Da was minimal and only became significant (i.e., a 30% drop in the Da value) when it reached about 50% of the particle volume. Hence, the FIB findings did not negate the earlier conclusion but rather reinforced it, that is had these particles not contained a void, their Da would have been higher, hence a lower FPF, which would make an even bigger difference in the FPF between the smooth and wrinkled particles.

2.5 Recent developments on nanoparticles

When a suspension of nanoparticles is spray dried, the resulting micron-sized particles are spherical agglomerates with a corrugated surface and voids inside, leading to a high FPF [22]. Another recent development is to increase the surface roughness of drug particles by coating them with specifically engineered surface-modified nanoparticles of 5 – 10 nm, which was shown to be highly effective in improving the aerosol performance of the coated powder [23].

3. Determination of particle morphology

A number of techniques was mentioned in the preceding discussion to quantify particle morphology, including specific surface area, fractal dimension analysis, image analysis and atomic force microscopy. The technical details of each technique has been detailed in the original references and will not be repeated here. However, there is no single 'best' method which is suitable for all purposes, as each method will have its advantages and limitations. Depending on the objective of the study, some key considerations would be: is the objective to obtain data on the whole powder or individual particles? Is the prim ary interest the particle shape or surface roughness? Is two-dimensional information sufficient, or are three-dimensional data required? Does the method provide only indirect rather than direct measurement, and is the resolution of the method sufficient? All of these factors would impact on the effort and time required for the measurement. For example, measurement of the specific surface area can provide the particle surface roughness of the whole powder but it is only an indirect, low resolution technique, without taking the particle shape into account. In contrast, atomic force microscopy allows a direct measure of the surface roughness of individual particles at very high (nanometre) resolution,

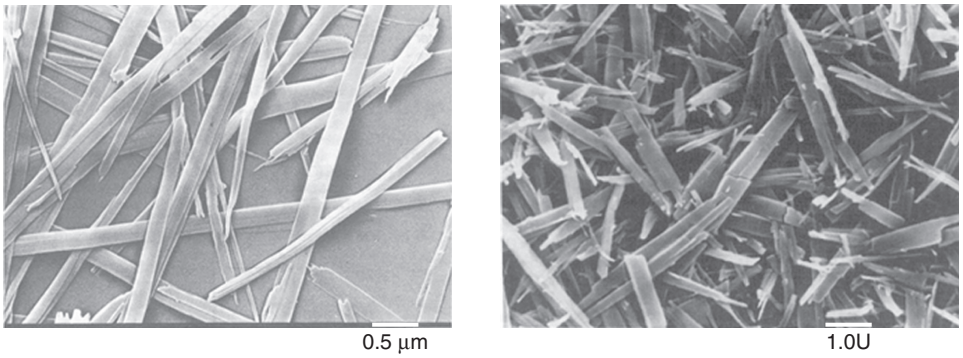

Figure 4. SEM images of elongated particles of cromoglicic acid (left) and nedocromil (right).

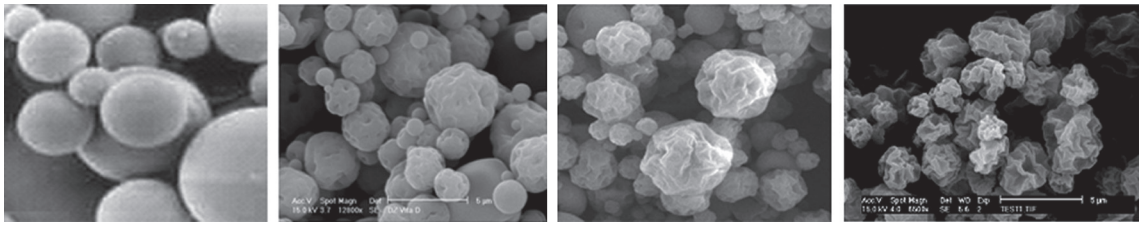

Figure 5. SEM images of bovine serum albumin particles with increasing surface roughness (from left to right).

but it will become practically impossible to measure the whole powder sample. The choice or suitability of a method will depend on factors such as the simplicity, robustness, skill level required, type of sample and data required, speed and cost of the method.

4. Expert opinion and conclusion

The existing literature shows that the shape and surface roughness of both the lactose carrier and the drug particle can affect the aerosol performance of powders significantly and needs to be taken into account when developing DPI products. An optimal roughness level was proposed to exist on the lactose carrier surface, which maximises the FPF in the aerosols. Similarly, lactose particles with a higher elongation ratio have been found to perform better. However, one must also consider the variability and not just the mean value of the FPF when using these morphology-engineered carriers. Needle-like drug particles have a low aerodynamic diameter and increase FPF in lactose blend formulations. Powders of wrinkled drug particles also enhanced the aerosol performance. The role of particle morphology is expected to change with inhaler efficiency and air flow. A highly efficient inhaler can readily aerosolise a powder, regardless of its particle morphology. Conversely, a poor efficiency inhaler may rely on the particle morphology to enhance aerosolisation of the powder. The role of particle morphology in powder inhalers is under-explored, and currently particle morphology is not vigorously controlled in DPIs. However, control of morphology is not trivial as it can impact every aspect of the manufacturing process, from particle production to characterisation and formulation. Furthermore, one has to decide exactly which morphology parameters are to be controlled and what characterisation techniques used. All of these issues have to be carefully considered before the manufacture of DPI products can capitalise on the control of particle morphology.

Acknowledgments

The author is grateful for the technical support provided by Herbert Chiou during the preparation of this manuscript.

Declaration of interest

The author states no conflicts of interest and has received no payment in the preparation of this manuscript.

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