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Influence of size and surface roughness of large lactose carrier particles in dry powder inhaler formulations

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ABSTRACT

The objective of this study was to determine the effect of both carrier particle size and surface roughness on the aerosol performance of dry powder formulations. Two morphologically distinct grades of lactose, anhydrous (AN) and granulated (GR), were fractionated into 11 discreet sizes up to 300 μm, and separately employed as carriers in 2% (w/w) budesonide blends. *In vitro* deposition studies were performed at 60 L min^{-1} with an Aerolizer® DPI. It was found that large carriers can improve dispersion performance, although the effect is more pronounced with greater surface roughness. AN carriers exhibited minimal surface roughness and generally behaved as predicted from the literature, with the smaller carriers outperforming their larger counterparts. In contrast, GR carriers had a high degree of surface roughness, and the dispersion performance of larger carriers exceeded that of the smaller size fractions. Comparing the two lactose grades, AN carriers deposited a greater fraction of the total dose up to the 90–125 μm size range, when they were surpassed in performance by the GR carriers. These results suggest that the mechanism of drug detachment varies with the physical properties of the carrier particle population, where surface roughness can alter the predominant detachment mechanism to favor larger carrier particle diameters.

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1. Introduction

Therapeutic formulations administered via dry powder inhalers are typically interactive mixtures, comprised of the active pharmaceutical ingredient and a coarse carrier material blended together to produce a homogeneous powder. Delivery to the deep lung requires drug particles possessing aerodynamic diameters between 1 μm and 5 μm (Hickey, 2004). However, given the high surface area-to-volume ratio of particles in this size range, van der Waals forces dominate the interactions, producing highly cohesive powders that flow poorly and are resistant to dispersing into primary particles during inhalation (Visser, 1989; Finlay, 2001).

To improve powder flow and dispersion, a population of coarse particles (50–100 μm) are incorporated into the formulation to serve as carriers onto which the drug particles adhere during blending (Hickey, 2004). Carrier particles must be inert, possess a physical and chemical stability compatible with the drug substance, and be readily available and inexpensive (Steckel and Bolzen, 2004). While a variety of materials, primarily sugars, have been evaluated for their suitability to serve as carrier particles, α-lactose monohydrate is the only material currently in marketed products approved by the FDA for inhalation purposes (French et al., 1996; Tee et al., 2000; Steckel and Bolzen, 2004; Hooton et al., 2006).

Production of a stable and homogeneous powder blend requires a balanced interaction between drug and carrier particles, with forces strong enough such that drug preferentially adheres to the carrier during mixing, yet sufficiently tenuous to facilitate redispersion of drug particles during inhalation (Begat et al., 2004; Saleem et al., 2008). Studies focused on the physical properties of carriers have examined the particle size, size distribution, morphology, surface roughness, surface area, and surface energy of carrier particle populations, with a consensus that increasing the diameter of the carrier particle population generally hinders drug dispersion performance (Podczeck, 1997; Steckel and Muller, 1997; Kawashima et al., 1998; Cline and Dalby, 2002; Louey et al., 2003; de Boer et al., 2003b; Islam et al., 2004; Dickhoff et al., 2005; Hickey et al., 2007).

To account for this observation, various explanations have been proposed in the literature. Studies have cited both the diminishing specific surface area of larger carriers, inducing drug aggregation, and the increased surface roughness of larger particles, allowing drug to be shielded within carrier surface asperities from detachment forces (Steckel and Muller, 1997; Cline and Dalby, 2002; de Boer et al., 2003b). Additionally, as carrier particle size fraction increases, the concentration of fine lactose particles (<10 μm) is reduced (Islam et al., 2004). This is relevant to dispersion as the role of fine lactose particles in improving aerosol performance is well established and believed to occur via passivation of high energy sites on the carrier surface, or through the formation of aggregates between fine lactose and drug particles that facilitate detachment

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(Lucas et al., 1998; Srichana et al., 1998; Karhu et al., 2000; Louey and Stewart, 2002).

Previous studies investigating the physical properties of lactose carriers have generally been limited to broad particle size distributions, and/or carrier particle fractions below 200 μm (Steckel and Muller, 1997; Podczeck, 1997; Louey et al., 2003) In addition, examination of larger carrier particles have focused primarily on a single particle morphology, α-lactose monohydrate, while studies investigating the role of surface roughness are restricted to a single particle size range (Kawashima et al., 1998; Zeng et al., 2000; Dickhoff et al., 2005). Therefore, it was aim of the present study to address these long standing gaps in experimental design and concurrently examine the influence of carrier particle size and surface roughness on the aerosol performance of binary dry powder formulations. To this end, 2% (w/w) budesonide blends were prepared incorporating 11 carrier particle size fractions ranging up to 300 μm, derived from two morphologically distinct lactose grades (anhydrous and granulated). *In vitro* drug deposition was used to assess the aerosol performance of the dry powder formulations.

2. Materials and methods

2.1. Materials

Micronized budesonide (EP) was purchased from Spectrum Chemicals (CA, USA) and used as received. Analytical grade ethanol was supplied by Sigma Chemical Company (MO, USA). As inhalation grade lactose is processed to yield particles predominately below 200 μm, lactose grades typically employed in tablet preparation were used as carrier particles. Samples of anhydrous (SuperTab® 22AN), and granulated (SuperTab® 30GR) lactose were provided by DMV-Fonterra (New Zealand). Size 3 gelatin capsules were obtained courtesy of Capsugel® (NJ, USA).

2.2. Fractionation of lactose carrier particles

Samples of each lactose batch were fractionated on a vibrating sieve shaker (Gilson Company Inc., OH, USA) for 5 min through the following sieves: 300 μm, 250 μm, 212 μm, 180 μm, 150 μm, 125 μm, 90 μm, 75 μm, 63 μm, 45 μm, and 32 μm. Following the initial fractionation, the lactose carriers were again sieved for an additional 5 min to obtain narrow particle size distributions.

2.3. Preparation of budesonide/lactose binary blends

Budesonide and lactose were mixed in a ratio of 1:50 (w/w) via geometric dilution to obtain 500 mg of a 2% binary blend. The formulations were blended with a Turbula® orbital mixer (Glen Mills, NJ, USA) for 40 min at 46 RPM. Samples were stored in a desiccator at least 5 days prior to use. Blend uniformity was determined by randomly selecting eight 20-mg samples from each mixture and assessing the drug content in the powder. Formulations were considered well blended if the coefficient of variation (% CV) between the samples for a given blend was below 5%.

2.4. Scanning electron microscopy

Carrier particle size and surface roughness were visually assessed by scanning electron microscopy (SEM; Supra 40VP, Zeiss, Germany). Prior to SEM, approximately 20 nm of platinum were deposited onto the particles via sputter coating.

2.5. Surface area analysis

Specific surface areas of the lactose carrier particle populations were determined via nitrogen adsorption with a single-point BET method using a Monosorb® surface area analyzer (Quantachrome, FL, USA).

2.6. Atomic force microscopy

Atomic force microscopy was performed on a Multimode SPM NanoScope IIID (Veeco Instruments, CA, USA) in tapping mode using RTESP cantilevers with a nominal spring constant of 40 N/m. AFM settings were tuned to provide the best topographical image. Image processing and analysis was done in NanoScope Analysis software (v1.10, Veeco Instruments).

2.7. Density of lactose carriers

The true densities of the lactose carrier particles were determined with a helium multi-pycnometer (Quantachrome, FL, USA).

2.8. In vitro drug deposition

Size 3 gelatin capsules filled with 20 (±1) mg of powder were dispersed through an Aerolizer® DPI (Plastiape S.p.A., Italy) into a next generation cascade impactor (Copley Scientific, UK) at a volumetric flow rate of 60 L min^{-1} actuated for 4-s intervals. Prior to each actuation the pre-separator was loaded with 15 mL of ethanol, which was collected following powder dispersion from each capsule. Additionally, the drug deposited in the capsule, inhaler, adaptor mouthpiece, throat, and NGI stages was collected by rinsing with ethanol. Drug content was assessed via UV–vis absorption spectroscopy at 244 nm. The emitted fraction was calculated as the ratio of the drug mass depositing in the throat, pre-separator, and impactor stages over the cumulative mass of drug collected following actuation (total drug deposited in the capsule, inhaler, mouthpiece, throat, pre-separator and stages). The fine particle fraction (FPF) of each dose was the ratio of the drug mass depositing on stages 3 through 8 of the impactor (corresponding to an aerodynamic diameter less than 4.46 μm) over the emitted dose. The respirable fraction was the ratio of the drug mass deposited on stages 3–8 over the entire dose recovered following each actuation.

2.9. Statistics

Statistical significance between performance values was determined with one-way ANOVA with Post Hoc tests between groups according to the Bonferroni method ($P < 0.05$).

3. Results

3.1. Physical characterization of lactose carrier particles

Narrow lactose carrier particle fractions were generated by the double-sieving technique (Fig. 1). Although studies examining binary dry powder formulations are generally restricted to α-lactose monohydrate carriers, different grades of lactose have been employed as carrier particles in the literature. These include both granulated lactose and anhydrous lactose (Kawashima et al., 1998; Larhrib et al., 1999; Dickhoff et al., 2005). Granulated lactose is α-lactose monohydrate generated via fluidized bed granulation, producing particles with extensive surface rugosity (Figs. 1 and 2). Anhydrous lactose is a form of β-lactose, absent the water of crystallization of the monohydrate form, and characterized by relatively flat particle surfaces. The increased surface roughness of the granulated lactose carriers is most pronounced at the larger particle size ranges, though at the smaller fractions the contrast between anhydrous and granulated carriers is less striking (Fig. 2).

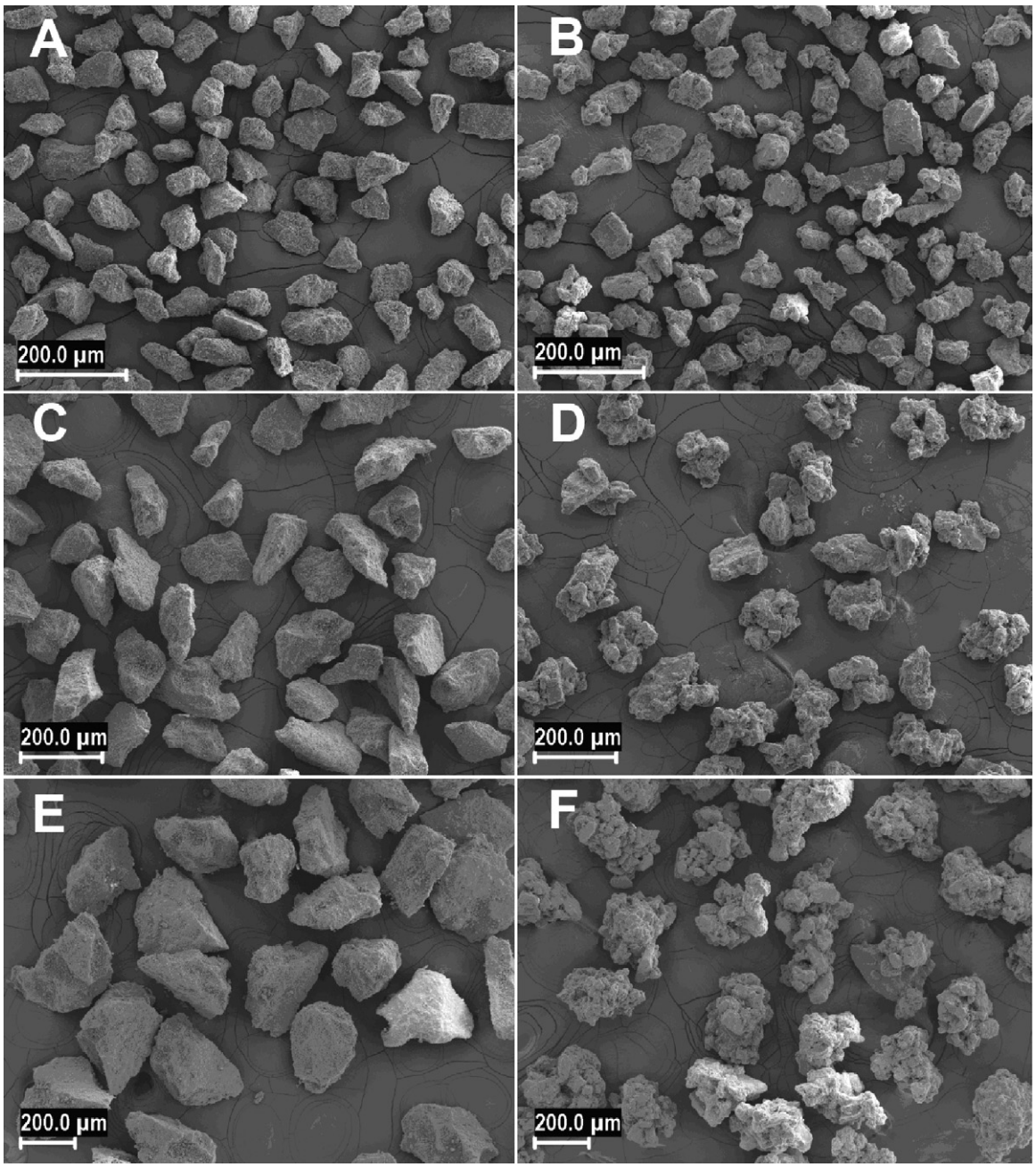

Fig. 1. SEM micrographs of uncoated (A) 45–63 µm anhydrous lactose, (B) 45–63 µm granulated lactose, (C) 90–125 µm anhydrous lactose, (D) 90–125 µm granulated lactose, (E) 212–250 µm anhydrous lactose and (F) 212–250 µm granulated lactose sieve fractions. Scale bars denote 200 µm.

The specific surface areas (SSA) of all 11 carrier fractions, for both lactose populations, are listed in Table 1. The extensive surface roughness of the granulated particles yielded SSA values up to 4-fold higher than the anhydrous particles. Additionally, the SSA of the granulated particles does not diminish with increasing carrier particle size to the same extent as the anhydrous carriers.

3.2. Surface roughness of carrier particles

Theoretically, given the higher surface area-to-volume ratio of smaller particles, the specific surface area (SSA) of a carrier powder diminishes as the diameter of the particles is increased. For a constant mass of carrier particles (e.g. 20 mg), the surface area available for drug binding is reduced for larger carriers, potentially leading to drug–drug particle agglomeration. Practically, surface area may

Table 1
Specific surface areas (SSA) of anhydrous and granulated lactose carrier particles by sieve fraction. The right column lists the SSA ratio of the granulated particles ($SSA_{(GR)}$) over anhydrous particles ($SSA_{(AN)}$) for a specific size range.

Carrier size fraction (µm)	Anhydrous lactose (m^2/g)	Granulated lactose (m^2/g)	$SSA_{(GR)}/SSA_{(AN)}$
<32	0.94	1.87	2.0
32–45	0.48	1.71	3.6
45–63	0.38	1.62	4.3
63–75	0.43	1.64	3.8
75–90	0.37	1.52	4.1
90–125	0.41	1.56	3.8
125–150	0.38	1.81	4.8
150–180	0.38	1.73	4.6
180–212	0.40	1.44	3.6
212–250	0.42	1.67	4.0
250–300	0.36	1.46	4.1

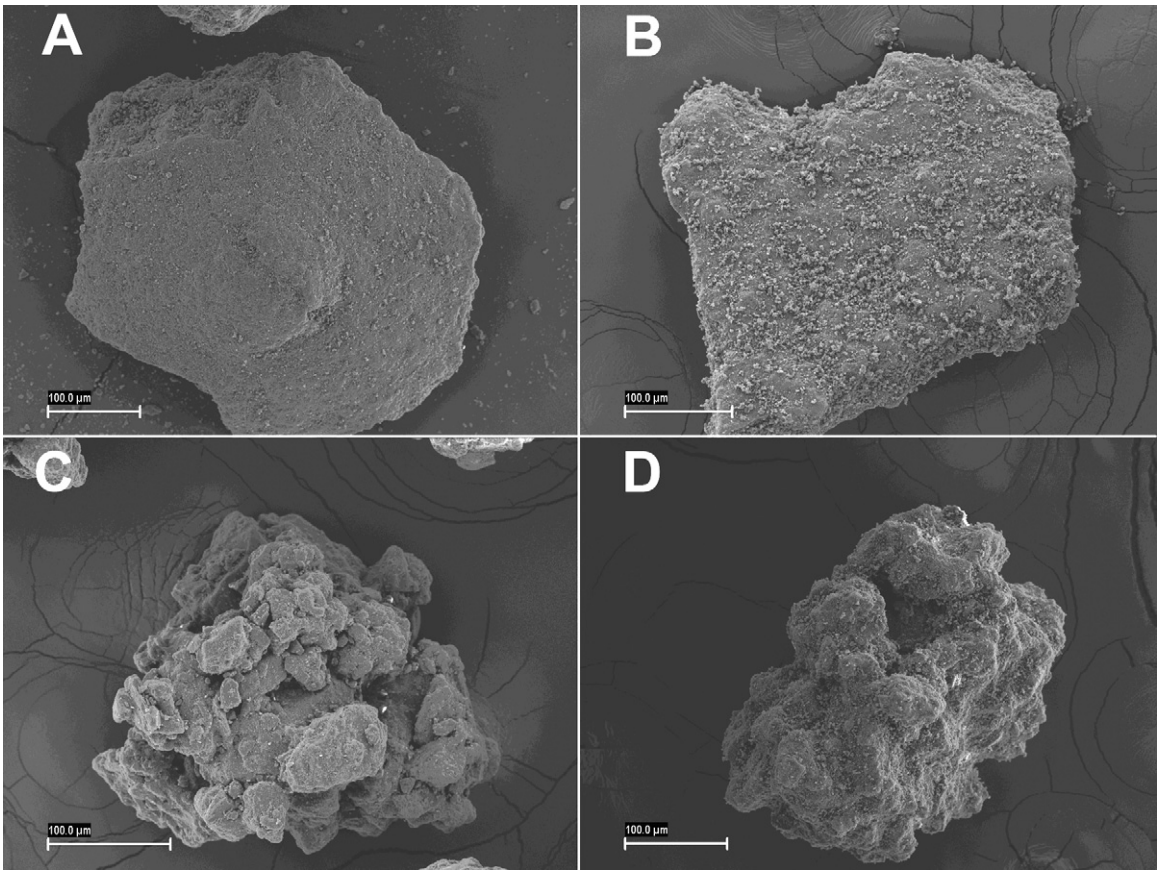

Fig. 2. SEM micrographs of 250–300 μm (A) anhydrous lactose carrier particles without drug, (B) anhydrous lactose carrier particles with 2% (w/w) budesonide, (C) granulated lactose carrier particles without drug, and (D) granulated lactose with 2% (w/w) budesonide. Scale bars denote 100 μm.

be significantly influenced by the extent of surface roughness, particularly as the carrier particle size is varied (de Boer et al., 2003b; Dickhoff et al., 2005). Therefore, surface area can be effectively used as a relative measure of surface roughness for a series of size fractions of the lactose carriers. The experimentally observed SSA for each size fraction of each lactose grade was determined and compared to the theoretical SSA for equivalent sized spheres possessing a diameter corresponding to the mean particle diameter of the sieve fraction. To facilitate comparison, the SSA was normalized to that of the smallest size fraction of each population (spherical, anhydrous, and granulated); the SSA of each subsequent carrier particle fraction (CPF) was divided by that of its smallest size fraction (<32 μm):

$$\frac{SSA_{CPF}}{SSA_{<32}}$$

Fig. 3 depicts the decline in SSA as particle diameter is increased. This plot allows the direct comparison of how closely each lactose grade follows the theoretical relationship between particle size and surface area, providing insight into the degree of surface roughness. The theoretical SSA of the perfectly spherical particles declines as a cubic function. However, in reality lactose has significant surface roughness coupled with the presence of fine particles. Thus, the observed decline in SAA of the lactose particles is not as severe as that of the spherical particles (Fig. 3). For anhydrous lactose, the SSA begins to noticeably deviate from theoretical at the 45–63 μm carrier fraction, and converges to approximately 40% of the <32 μm SSA value over the remaining size ranges. By contrast, the SSA of the granulated lactose is within 80%, and in a few instances over 90%, of the <32 μm fraction despite large increases in particle size. Accordingly, given the higher rugosity of granulated particles relative to their anhydrous counterparts, increasing carrier particle size does not severely diminish the surface area available for drug attachment during blending. This difference may be important for limiting the extent of drug–drug particle agglomerate formation that occurs during blending for formulations with granulated carriers relative to anhydrous.

To supplement SSA data on surface roughness, atomic force microscopy (AFM) studies were performed on selected lactose size fractions. Fig. 4 shows representative examples of the surface

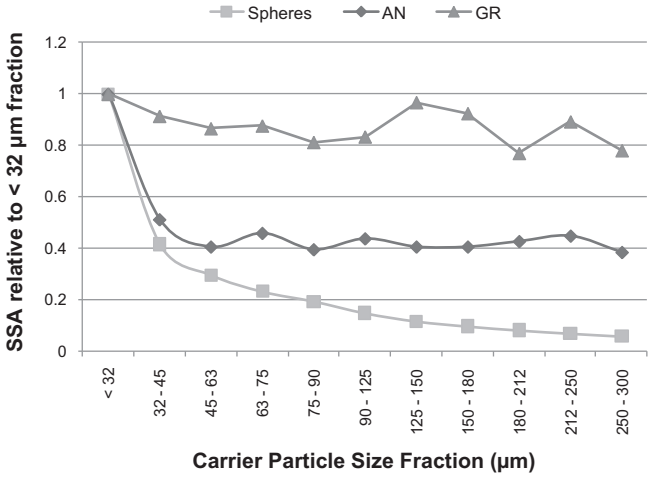

Fig. 3. Reduction in specific surface area (SSA) with increasing carrier particle size for anhydrous (AN) and granulated (GR) lactose carrier particles, as compared to populations of mono-disperse spherical particles.

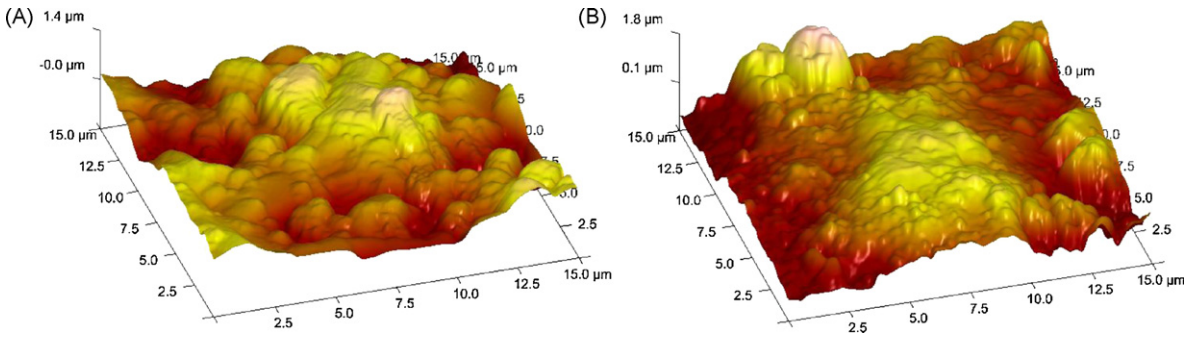

Fig. 4. Surfaces of uncoated (A) 75–90 µm and (B) 250–300 µm anhydrous lactose particles determined by tapping mode atomic force microscopy.

topography of both small anhydrous carrier particles (75–90 µm) and larger anhydrous carrier particles (250–300 µm). Statistical differences in surface roughness were identified in the root mean square (RMS) value of the roughness between large and small carriers. RMS surface roughness values of the 250–300 µm anhydrous samples was 568 (±31) nm compared to 385 (±60) nm for the 75–90 µm samples for three replicates. The surface roughness of granulated lactose was difficult to measure using AFM due to the large and abrupt changes in the surface structures, particularly in the *z*-direction. Therefore, AFM results for granulated lactose should be interpreted with caution, as the successful imaging attempts will bias the results in favor of smoother surfaces.

3.3. *In vitro* aerosol performance

Aerosol performance is governed by the combined influence of both carrier particle size and surface roughness, and the results of the present study reveal that poor dispersion performance is not a property inherent to larger carrier particles. For anhydrous carriers, performance did not progressively decline with carrier size (Fig. 5). Three distinct plateaus in RF values were noted as the size of the carriers was increased, with performance abruptly dropping off as carrier size increased to 32–45 µm (RF decreased from 18.4% to 13.7%), and once more at the transition to the 63–75 µm size range (14.6% compared to 10.4%) (Table 2). Additionally, following a drop in performance at the 150–180 µm size range (RF = 7.5%), a slight but statistically significant improvement was noted as RF values climbed for the three largest carrier size fractions, ranging from 8.7% to 9.9%. The observation that performance did not continually decline with carrier size, but rather exhibited a minor resurgence at the largest size ranges, was unexpected in the context of the current literature. In contrast to anhydrous formulations, aerosol performance of granulated carriers exhibited a distinct overall trend (Fig. 6). Although the smallest three fractions declined in performance, with RF values progressively dropping from 11.2% to 6.6%, dispersion improved markedly for larger carriers. A progressive increase in RF was observed beginning with the 90–125 µm size range, eventually surpassing the performance of even the <32 µm carrier population, such that the three largest carriers significantly outperformed all but the 125–150 µm size fraction.

4. Discussion

The influence of carrier particle surface roughness on drug dispersion performance has been previously examined in the literature (Podczeck, 1998; Kawashima et al., 1998; Zeng et al., 2000; de Boer et al., 2003b; Dickhoff et al., 2005). However, previous work specifically examining the influence of surface roughness has generally been limited to a single carrier size range. Accordingly, the effect of surface roughness on aerosol performance over a wide range of carrier particle sizes had to be extrapolated in previous

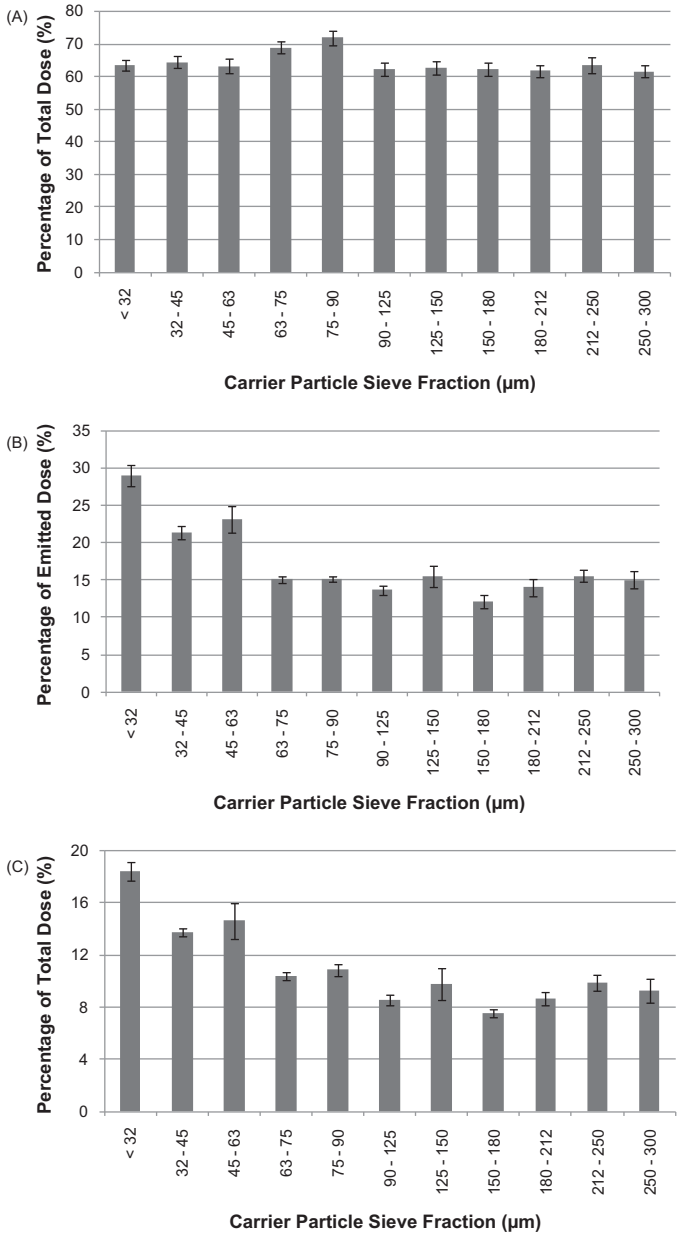

Fig. 5. *In vitro* drug deposition results for 2% (w/w) budesonide formulations employing anhydrous lactose carrier particles. (A) Emitted fraction, (B) fine particle fraction, and (C) respirable fraction. Values are given as the mean of $N = 3$ replicates, and error bars represent the standard deviation for $N = 3$ replicates.

Table 2
Emitted fraction, fine particle fraction (FPF), and respirable fraction (RF) for 2% (w/w) budesonide formulations employing anhydrous and granulated lactose carrier particles. Values are given as the mean of $N = 3$ replicates, and values within parentheses represent the standard deviation for $N = 3$ replicates.

	Anhydrous (AN) lactose			Granulated (GR) lactose		
Carrier sieve fraction (μm)	% Emitted	FPF	RF	% Emitted	FPF	RF
>32	63.5 (1.6)	29.1 (1.4)	18.4 (0.7)	57.0 (1.4)	18.5 (1.2)	11.2 (1.6)
32–45	64.5 (1.8)	21.3 (0.9)	13.7 (0.3)	69.1 (3.7)	11.1 (0.6)	7.7 (0.1)
45–63	63.2 (2.2)	23.1 (1.8)	14.6 (1.4)	74.4 (4.1)	8.9 (1.2)	6.6 (0.6)
63–75	68.9 (1.8)	15.1 (0.4)	10.4 (0.3)	73.9 (3.7)	12.7 (1.4)	9.3 (0.6)
75–90	71.9 (2.4)	15.2 (0.3)	10.9 (0.5)	73.9 (6.6)	9.7 (2.1)	7.1 (1.1)
90–125	62.3 (1.9)	13.7 (0.6)	8.5 (0.4)	77.8 (1.8)	11.6 (0.9)	9.0 (0.5)
125–150	62.7 (2.1)	15.6 (1.4)	9.8 (1.2)	71.3 (4.2)	18.9 (1.5)	13.4 (0.3)
150–180	62.3 (2.0)	12.1 (0.8)	7.5 (0.3)	73.8 (2.5)	14.2 (1.3)	10.5 (0.7)
180–212	61.8 (1.9)	14.1 (1.1)	8.7 (0.5)	72.6 (3.2)	20.8 (1.1)	15.1 (0.8)
212–250	63.5 (2.3)	15.5 (0.8)	9.9 (0.6)	68.7 (5.4)	20.2 (1.5)	13.8 (0.7)
250–300	61.6 (1.7)	15.0 (1.1)	9.3 (0.9)	68.5 (4.5)	20.2 (1.5)	14.5 (0.6)

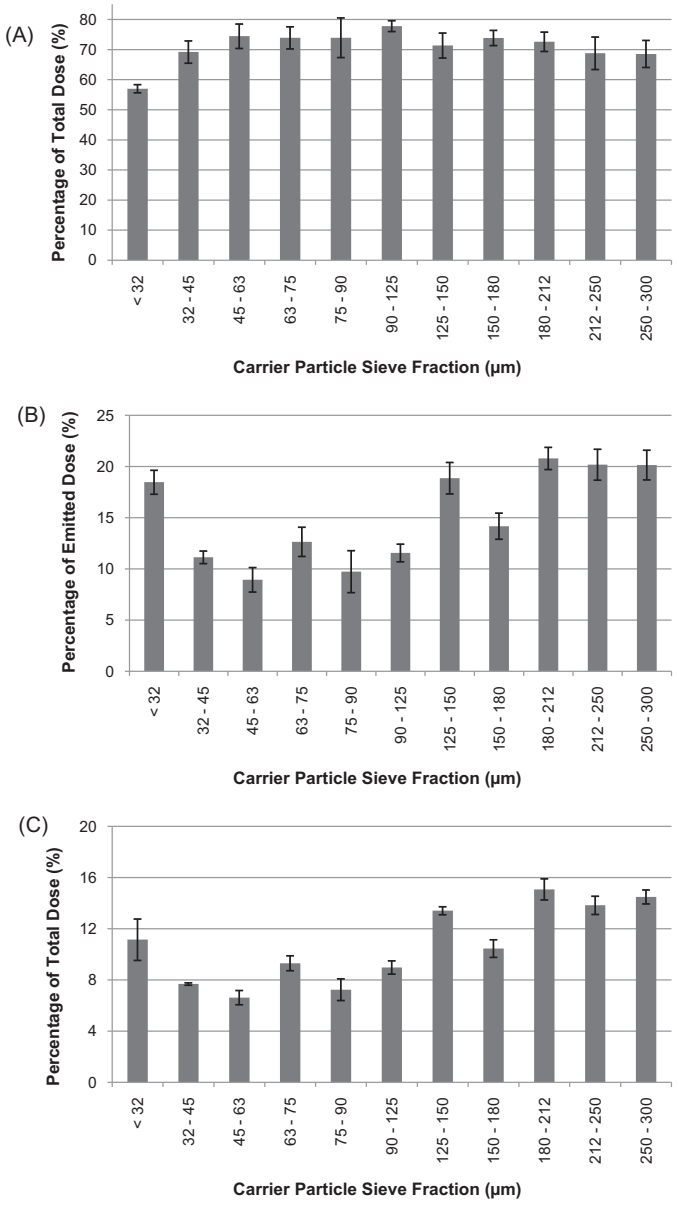

Fig. 6. *In vitro* drug deposition results for 2% (w/w) budesonide formulations employing granulated lactose carrier particles. (A) Emitted fraction, (B) fine particle fraction, and (C) respirable fraction. Values are given as the mean of $N = 3$ replicates, and error bars represent the standard deviation for $N = 3$ replicates.

studies, with speculation that the greater degree of surface roughness on larger carriers was a major contributor to their reduced dispersion performance relative to smaller carriers (Kawashima et al., 1998; Podczeck, 1998; de Boer et al., 2003b). Our results indicate that surface roughness influences performance by altering the relative contributions of the mechanisms governing drug detachment from carrier particles. Moreover, as the detachment potential of these mechanisms vary with carrier size, the view that large carrier particles are detrimental to aerosol performance is re-evaluated in light of the present study.

4.1. Mechanisms of drug detachment from carrier particles

Drug detachment and dispersion from carrier particles during inhalation is thought to proceed through two major mechanisms: detachment by the flow stream (fluid forces) and detachment by impaction (mechanical forces) (Voss and Finlay, 2002; de Boer et al., 2003a). Detachment by flow requires a relatively flat carrier particle surface, with minimal asperities, allowing the flow stream an unobstructed path to access and remove the drug. Additionally, detachment by flow is facilitated for larger drug particles (either drug agglomerates or primary particles) due to the increased surface area available for interaction with the flow stream (de Boer et al., 2003b).

Mechanical forces arise from the abrupt momentum transfer that occurs when a carrier particle contacts the inhaler wall (Finlay, 2001; de Boer et al., 2003a). As momentum is dependent on particle mass, detachment by mechanical forces are proportional to the cube of the carrier particle diameter, such that large particles will generate greater detachment forces (assuming constant velocity between carrier particle size fractions) (Donovan and Smyth, 2009). Moreover, detachment by mechanical forces is not inhibited by carrier particle surface roughness to the same degree as detachment by flow (de Boer et al., 2003a). However, only those drug particles for which the detachment force both exceeds the adhesive interaction with the carrier, and is in a direction favorable to detachment, will be dislodged from the carrier.

4.2. Surface roughness and particle size influence the predominant mechanism of detachment

Fig. 7 schematically illustrates the distinction between detachment by flow and mechanical forces in carriers with different surface roughness. For carriers with minimal surface roughness, the drug is readily exposed to the flow stream, and detachment by flow is likely the dominant mechanism. With increasing carrier surface roughness drug is sheltered within asperities, and drug detachment is more reliant on mechanical forces. Accordingly, when examining the carriers from the two lactose grades, it is speculated that

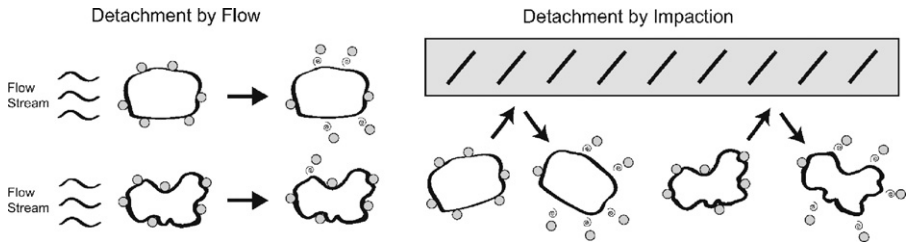

Fig. 7. Drug detachment occurs by the flow stream, or from mechanical forces arising from impactions between the carriers and inhaler as the particles exit the device during inhalation. The relative influence of the two mechanisms varies with surface roughness.
Adapted from de Boer et al. (2003b).

detachment by flow will predominate for the relatively smoother anhydrous particles while mechanical forces will dominate for the granulated carriers (e.g. Fig. 2).

The wide disparity in aerosol performance between the lactose types is therefore attributed to their diverse surface roughness characteristics. The influence of surface roughness on aerosol performance is evidenced by the divergent trends in RF values between the two lactose types as carrier size is increased (Fig. 8). Anhydrous lactose exhibits a decline in overall performance with increasing particle size, whereas the granulated carriers yielded the opposite trend. The overall reduction in performance observed in the formulations with anhydrous carrier particles is consistent with detachment by flow. From the literature, it has been noted that smaller carrier particles possess smoother surfaces relative to larger size fractions (Podczeck, 1998; de Boer et al., 2003b). It is then proposed that more drugs are sheltered within asperities on larger carriers, and thus less susceptible to detachment by the flow stream. Additionally, the reduction in available surface area for larger carriers would lead to more extensive drug agglomeration, hindering aerosol performance (Table 1). Thus, with larger anhydrous carriers not only are fewer drug particles dislodged from the surface, much of the detached drug is aggregated (as measured by MMAD and discussed below). Consequently, most of the drug that can be removed by the forces generated within a given inhaler at a specific flow rate is likely detached rapidly by the initial fluid forces, and a limited number of drug particles remain available for detachment by the mechanical forces that occur subsequent to the flow forces.

Conversely, detachment from granulated particles was primarily dependent on mechanical forces. As the magnitude of mechanical detachment forces increases with carrier size, the larger granulated carriers significantly outperformed the smaller size fractions (Fig. 8). The relatively high performance of <32 μm granulated particles can be attributed to the small surface roughness of this size fraction, which enabled detachment by flow to predominate.

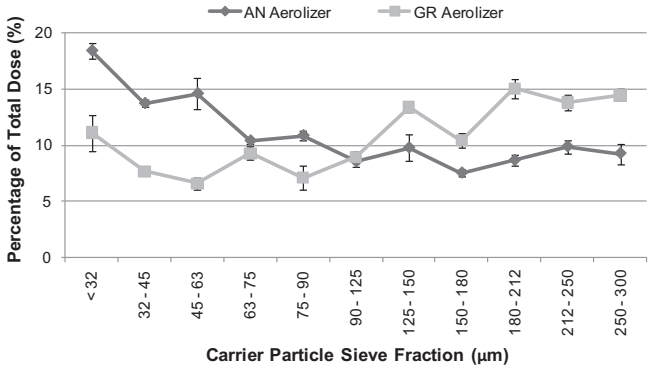

Fig. 8. Respirable fractions (RF) of 2% (w/w) budesonide formulations with anhydrous (AN) and granulated (GR) carrier particles following dispersion at 60 L min^{-1}. Values are given as the mean of $N = 3$ replicates, and error bars represent the standard deviation for $N = 3$ replicates.

4.3. Evidence for mechanical detachment mechanisms for larger carrier particles: flow rate dependent detachment

Mechanical detachment forces rely on the abrupt momentum transfer generated by carrier–inhaler collisions (Finlay, 2001). Accordingly, the influence of flow velocities on the performance of large carrier particles is an area that remains to be fully explored. However, while only a single volumetric flow rate was examined in this study, evidence for improved drug detachment from large carriers with increasing flow can be found in the literature. In studies with α-lactose monohydrate carrier particles, doubling the flow from 30 Lpm to 60 Lpm caused large carrier particles to outperform their smaller counterparts even though the smaller size fraction performed better at 30 Lpm. (Dickhoff et al., 2003). The observation that larger, rougher particles outperformed the smaller, smoother carriers at 60 Lpm provides evidence for additional detachment mechanisms other than flow forces (Dickhoff et al., 2003).

4.4. Relationship between carrier particle size fraction and detached drug particle size

Given their increased detachment potential due to mechanical forces, larger carriers may dislodge drug particles that are resistant to detachment by the flow stream. These "detachment-resistant" drug particles may be smaller particles (less susceptible due to their small surface area) or drug particles attached to high energy sites on the carriers. In addition, drug particles located within small surface asperities in a depth sufficient to obstruct their interaction with the flow stream would have more potential for mechanical detachment. Indeed, a study examining the relationship between impact forces and particle detachment revealed that greater impaction magnitudes were required to separate particles from a surface as the diameter of the particles decreased (Concessio et al., 1999). It follows that the diameter of drug particles depositing in the cascade impactor would be smaller from formulations with larger carriers, as they may generate greater detachment forces. Our observations are consistent with this theory (Fig. 9), for both anhydrous and granulated carriers, where the mass median aerodynamic diameter (MMAD) of the deposited drug exhibited a decreasing trend with increasing carrier size.

Examining only the MMAD values for the carrier fractions, it might be concluded that large carriers would demonstrate the best performance across both lactose types. This was true for granulated lactose, but for anhydrous lactose the large reduction in surface area likely induced drug aggregation. Indeed, with the exception of the 45–63 μm size range, the SSA plateau is also reflected in the respirable fractions (Table 2), where values initially decline significantly from the smallest particle size range, and again following the 45–63 μm fraction.

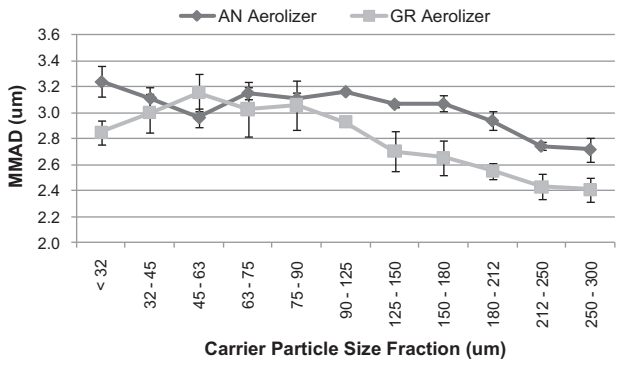

Fig. 9. Mass median aerodynamic diameters (MMAD) of budesonide particles deposited from anhydrous (AN) and granulated (GR) carriers. Values are given as the mean of $N = 3$ replicates, and error bars represent the standard deviation for $N = 3$ replicates.

4.5. Transition from flow detachment to mechanical detachment

To reconcile the opposing trends of MMAD and overall drug deposition performance for anhydrous carriers with particle size, it is proposed that drug aggregates formed during blending are readily detached by the flow stream due to their augmented surface area, but not dispersed into primary particles (accounting for the diminished RF values). However, larger carriers increased the mechanical detachment forces arising from stronger particle–inhaler collisions, and drug particles impervious to detachment by flow were consequently dislodged. As these are believed to be smaller primary drug particles, detachment correlates with deep lung deposition, contributing to the RF values. At precisely what size range this shift in detachment mechanism occurs is unclear, but from Fig. 5, aerosol performance of anhydrous particles deviates from the declining trend at the 180–212 μm carrier fraction, where a slight but significant improvement in RF value is observed, coinciding with the carrier fraction when MMAD trends to smaller values (Table 3).

An alternative explanation for the MMAD decline is the ability of larger carriers to comminute drug aggregates during blending. It has been observed that two types of drug agglomerates exist in dry powder formulations: natural agglomerates present in the pure drug powder, and mixing agglomerates that arise when drug and carrier particles are blended (Dickhoff et al., 2005). While the lower SSA of larger carriers can induce mixing agglomerates, their greater mass and flowability improves their potential to breakup natural agglomerates. Whether disruption of natural agglomerates surpasses the formation of mixing agglomerates depends not only on formulation conditions such as drug (% w/w) concentration, blending time and batch size, but also on the drug itself. For the beneficial aggregate-disruption to dominate, the interaction between drug and carrier must be stronger than that amongst drug particles, such that drug dislodged from agglomerates will adhere to the lactose. Conversely, aggregate formation prevails when the drug possesses a high cohesive tendency (Begat et al., 2004).

Begat et al. (2004) have previously demonstrated the cohesive nature of budesonide. Accordingly, it is speculated that agglomerate formation may predominate during blending, accounting for the decline in aerosol performance for larger anhydrous carriers. However, the reduction in MMAD is also observed with granulated lactose, where the high surface rugosity would shelter drug particles and inhibit the breakup of natural drug agglomerates. This supports the view that larger carriers can potentially dislodge smaller primary drug particles that would generally resist fluid detachment, as the increased amount of natural agglomerates with larger granulated carriers would be expected to shift MMAD values higher, but are instead compensated by a greater number of smaller detached drug particles, such that MMAD actually trends lower with carrier size. The difference between the two lactose types may be explained by the greater SSA of granulated particles, which can limit the extent of drug–drug particle interaction relative to the anhydrous carriers, inhibiting formation of blending agglomerates.

Table 3
Mass median aerodynamic diameters (MMAD) of budesonide particles detached from anhydrous and granulated lactose carriers as determined by *in vitro* drug deposition. Values are given as the mean of $N = 3$ replicates, and values within parentheses represent the standard deviation for $N = 3$ replicates.

Carrier sieve fraction (μm)	Anhydrous (AN) lactose MMAD (μm)	Granulated (GR) lactose MMAD (μm)
<32	3.24 (0.12)	2.85 (0.09)
32–45	3.11 (0.09)	3.00 (0.15)
45–63	2.96 (0.07)	3.15 (0.14)
63–75	3.15 (0.05)	3.03 (0.21)
75–90	3.11 (0.04)	3.06 (0.19)
90–125	3.16 (0.01)	2.93 (0.03)
125–150	3.07 (0.02)	2.70 (0.15)
150–180	3.07 (0.06)	2.66 (0.13)
180–212	2.94 (0.07)	2.55 (0.06)
212–250	2.74 (0.03)	2.43 (0.10)
250–300	2.72 (0.09)	2.41 (0.09)

4.6. Effects of increasing carrier particle diameter and mass

Aerosol performance can be improved by increasing the size of the carrier particles, although the improvement imparted by large carrier particles will not continue indefinitely, as the mass of the carriers (and gravitational and drag forces acting upon them) eventually become prohibitively large. The benefit to momentum that is conferred by the increased carrier mass will be countered by a reduced particle velocity. In our studies, the RF values of the 250–300 μm formulations for both lactose types were not significantly different from those of the size fraction immediately preceding them (212–250 μm) (Table 2). Therefore it is unclear precisely when the mass of carrier begins to inhibit drug dispersion. The maximum particle size employed in this study was limited to 300 μm, as at the next largest size range a fraction of the carrier particles were retained within the capsules following actuation from the Aerolizer®. It is speculated that the performance of size ranges larger than 300 μm would not increase significantly from those of the 250–300 μm fractions given the density of the carrier particles (between 1.54 g/cm^3 and 1.56 g/cm^3, data not shown).

5. Conclusions

The prevailing theories in the literature have been proposed to account for a relatively narrow carrier particle size distribution, and have focused primarily on a single particle morphology; the 'tomahawk' shape of α-lactose monohydrate. Indeed, for anhydrous lactose carrier particles with relatively flat surfaces, the results in our studies generally followed the expected trend with dispersion performance diminishing with increasing carrier particle diameter. However, improvements in aerosol performance were observed with larger size fractions in the formulations with granulated carrier particles, which were characterized by a high degree of surface roughness. Additionally, even the largest anhydrous carrier sizes were also seen to improve drug dispersion, possibly by dislodging smaller primary drug particles that were less susceptible to detachment by the flow stream, as indicated by the decline in MMAD of deposited budesonide. The present study strongly suggests that surface roughness may influence aerosol performance by

shifting the detachment mechanism to rely heavily on the mechanical forces generated from collisions between the carrier particle and the inhaler walls. Given that mechanical forces can potentially increase with larger carrier particles, the role of carrier particle size on dispersion performance was shown to vary markedly with surface roughness.

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