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Does carrier size matter? A fundamental study of drug aerosolisation from carrier based dry powder inhalation systems

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ABSTRACT

There is plenty of evidence supporting the notion that the size of the carrier influences the aerosolisation performance of drug from a drug–carrier blend. Interestingly, that evidence is contradictory in places and the study of such mechanisms is fraught by the compounding variables associated with comparing crystalline powders (e.g. as size is varied so may the shape, surface chemistry, roughness and the amount of fine excipients). To overcome these limitations, a series of model polystyrene spheres were used to study the influence of size on aerosol performance. Three polystyrene sphere carriers (TS-80, TS-250 and TS-500, describing their approximate diameters) were characterised using laser diffraction, atomic force microscopy, colloid probe microscopy, electron microscopy, true density and dynamic vapour sorption. The model carriers were blended with micronized salbutamol sulphate (67.5:1 ratios) and the aerosolisation performance was tested using a multistage liquid impinger at a range of flow rates (40–100 l min^{-1}). Physico-chemical analysis of the carriers indicated that all carriers were spherical with similar roughness and densities. Furthermore, the adhesion force of drug to the carrier surfaces was independent of carrier size. Significant differences in drug aerosolisation were observed with both flow rate and carrier size. In general, as carrier size was increased, aerosol performance decreased. Furthermore, as flow rate was increased so did performance. Such observations suggest that higher energy processes drive aerosolisation, however this is likely to be due to the number of impaction events (and associated frictional and rotational forces) rather than the actual collision velocity (since the larger carriers had increased momentum and drag forces). This study shows that, in isolation of other variables, as carrier size increases, a concurrent decrease in drug aerosolisation performance is observed.

1. Introduction

Dry powder drug particles, designed for respiratory delivery, require a small aerodynamic diameter (<6 μm) to avoid impaction in the throat and upper airways (Pritchard, 2001). Particles of this diameter have a high surface area to mass ratio and are therefore cohesive and have poor flow, making powder device filling and aerosolisation difficult. Furthermore, most pharmaceutical formulations have therapeutic doses in the microgram range (e.g. 6–12 μg for formoterol and 200–400 μg for salbutamol sulphate) and cannot be metered without the addition of a diluent. The most common excipient diluent used in dry powder inhalation (DPI) devices is lactose. Lactose (generally in the monohydrate form) comes in a variety of sizes (Edge et al., 2009) with the size used being specific to the formulation type. Many formulations utilise lactose particle sizes that have median diameters at least one order of magnitude greater than the drug particulates (>50 μm). These formulations are generally referred to as carrier-based formulations and the powder blend contains an ordered mix of drug particles, uniformly adhered to the larger carrier, throughout the powder bed (Hersey, 1975). Upon aerosolisation, the drug particles should be liberated from the carrier so that they can pass into the respiratory tree while the carrier material impacts in the throat and is swallowed. To complicate matters, the carrier may have a wide size distribution and contain excipient particles with a similar diameter to the drug material. In these cases the physics of a simple ordered mix is complicated as 'fine' excipient particles may alter the effective lactose surface and/or form complex multi-particulate agglomerated systems (Islam et al., 2004b; Jones and Price, 2006; Young et al., 2005).

The mechanism of drug–carrier blend formation and drug liberation during powder fluidisation/aerosolisation is poorly understood. Empirical observations and theoretical models for drug aerosolisation in these systems are complicated by the plethora of physico-chemical variables of the carrier. For example, carrier roughness (Kawashima et al., 1998; Young et al., 2009), carrier shape (Kawashima et al., 1998) and surface energy (Traini et al.,

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2008) are just a few variables that have been shown to influence aerosol performance. Inevitably the study of one physico-chemical property in isolation is difficult, since the modification of one variable generally results in a change in other variables in the system (e.g. changing carrier size alters roughness or changing polymorphic form alters both surface chemistry and shape, etc.). Previous studies have reported carrier size to be a dominating factor for drug aerosol performance.

For example, Dickhoff et al. (2003) reported larger lactose carriers (250–355 μm) to perform poorly when compared to smaller lactose carriers (32–45 μm), attributing this to carrier–drug (budesonide and sodium cromoglycate) kneading processes during blending. Interestingly, the group also reported that such observations were dose dependent and attributed this to variations in roughness and variations in 'force distribution' on the carrier. In another study, Islam et al. (2004a) studied the aerosolisation of salmeterol xinafoate from lactose carriers across a range of diameters (22–157 μm median diameters) and observed that aerosol performance decreased with increased lactose size. The team attributed their observations to the presence of excipient fines in the carrier system and confirmed this via 'decantation' of the lactose carriers (whose blends showed no variation with respect to the median diameters studies). Guenette et al. (2009) studied a range of multimodal carrier size distributions whose size distributions spanned 2–200 μm and using, principle component analysis, reported fine and course fine distributions influenced performance of the drug salbutamol sulphate. More recently, Donovan and Smyth (2010) studied the influence of carrier size on the aerosolisation behaviour of budesonide from blends across a wide range of size classifications (30 μm–300 μm). The group found that the aerosol performance was dominated by both size and roughness. For example, anhydrous lactose samples showed a rank decrease in performance as size was increased, while granulated lactose showed a rank increase in performance over the same size range. The authors attributed such observations to carrier fluid drag and impaction forces that could be related to the carrier morphology. While this study goes someway to defining the mechanism for drug detachment (as with the other studies), compounding variables appear in the study design (for example, the roughness of the 75–90 μm anhydrous carrier was 385 nm compared to 568 nm for 250–300 μm carrier fraction and the specific surface area for the size ranges studied did not follow that of a theoretical sphere of equivalent diameter).

The limitations of using organic crystalline carriers to study the fundamental processes encountered during powder fluidisation and drug detachment may be overcome by using an alternative model carrier. While not truly representative of a 'real' drug–carrier system, the use of a model carrier (where physico-chemical properties can be tightly controlled) may provide significant data that will advance knowledge in the field. To study the mechanism of drug detachment and aerosolisation the authors chose polystyrene spheres as a model carrier. Polystyrene can be prepared in a wide range of sizes, as spherical particles of similar density and surface morphology. These model carriers were characterised in terms of their physico-chemical properties and evaluated when combined with the drug salbutamol sulphate.

2. Materials and methods

2.1. Materials

The model polystyrene sphere carriers (Dynoseeds® TS-80, TS-230 and TS-500) were supplied by Microbeads AS (Skedsmokorset, Norway). Salbutamol sulphate (SS) was supplied by S & D Chemicals (Sydney, Australia) and was micronized using an air jet mill prior to use (Trost Air Impact Pulveriser, Trost Equipment Corporation, USA; feed pressure 280 kPa, grinding pressure of 680 kPa). Prior to testing the powders were stored at 45% RH and 25 °C, in tightly sealed containers, for >1 week to allow material relaxation post milling. Water was purified by reverse Osmosis (MilliQ, Molsheim, France). All solvents were analytical grade and supplied by Sigma (Sydney, NSW, Australia).

2.2. Particle size analysis

The micronized salbutamol sulphate and polystyrene carrier particle size distributions were measured by laser diffraction (Malvern Mastersizer 2000, Malvern, Worcestershire, UK). Approximately 10 mg samples of salbutamol sulphate or polystyrene carrier were dispersed in 15 ml isopropyl alcohol or water and sonicated for 5 min prior to analysis. An aliquot of the suspension was then transferred to the small dispersion cell of the Malvern particle sizer until an obscuration between 2% and 5% was achieved. Particle size was measured using refractive indices of 1.52 for salbutamol sulphate, 1.39 for isopropyl alcohol, 1.59 for polystyrene and 1.33 for water, respectively. Each measurement was based on 2000 sweeps and all samples were analysed in triplicate.

2.3. Scanning electron microscopy

The morphology of the micronized salbutamol sulphate, polystyrene samples and their respective blends was studied using scanning electron microscopy (Zeiss Ultra plus, Carl Zeiss Pty Ltd., Sydney, Australia). Prior to imaging samples were dispersed onto carbon sticky tabs and sputter coated with gold to a thickness of approximately 15–20 nm.

2.4. Density

The true density of each polystyrene sample was measured using helium pycnometry (Accupyc 1340 Gas Pycnometer, Micromeritics). Samples (ca. 30 g) were prepared using the same method as for the surface area measurements. During each analysis the temperature was maintained at 27 °C. Each sample was run ten times.

2.5. Dynamic vapour sorption

Moisture sorption profiles of the micronized salbutamol sulphate and polystyrene carriers were conducted using dynamic vapour sorption (DVS, DVS-1 Surface Measurement Systems, London, UK). Approximately 50 mg of powder was weighed into the sample pan of the DVS and subjected to a 0–90% relative humidity (RH) cycle (over 10% increments). Equilibration at each humidity was determined via a dm/dt of 0.005% min^{-1}.

2.6. Atomic force microscopy

The surface topography of the micronized salbutamol sulphate and polystyrene particles was analysed using atomic force microscopy (AFM) operating in tapping mode. Samples were mounted on carbon sticky tabs and imaged with a high aspect ratio silicon probe (MicroMasch tips, Group Scientific Ltd., Adelaide, Australia) at a scan rate of 1.0 Hz, using a commercially available AFM (Multimode AFM, Nanoscope IIIa controller, Veeco Inc., CA, USA). Five 10 μm × 10 μm areas were studied for each sample.

2.7. Colloid probe microscopy

The force of interaction between micronized salbutamol sulphate and each polystyrene carrier was studied using colloid probe

microscopy. Individual particles of micronized salbutamol sulphate were mounted onto the apex of tipless AFM cantilevers (0.58 N m^{-1} spring constant, NP-OW, Veeco, Cambridge, UK), using methods and validation described elsewhere (Young et al., 2003). Prior to measurement, samples of each polystyrene carrier were mounted on carbon sticky tabs and attached to AFM sample stubs. The force of adhesion between each salbutamol sulphate drug probe and the three polystyrene carriers was investigated using Force Volume 'imaging' (Multimode AFM, Nanoscope IIIa controller, Veeco Inc., CA, USA). Briefly, 4096 individual force curves were conducted over 10 μm × 10 μm areas with the following settings: approach–retraction cycle, 2 μm; cycle rate, 8.33 Hz; constant compliance region, 60 nm. Data analysed using custom-built data analysis software and represented as a spatial 3-dimensional force map and cumulative force histogram. Three salbutamol sulphate tips were studied on each carrier at 45% RH and 25 °C.

2.8. Preparation of blends

Salbutamol sulphate was blended geometrically with the polystyrene carrier at a ratio of 1:67.5 followed by mixing in a Turbula at 46 rev min^{-1} for 30 min (Bachofen AG Maschinenfabrik, Basel, Switzerland). After blending samples were stored in tightly sealed containers at 45% RH and 25 °C, for a minimum of 24 h prior to analysis. Content uniformity of each blend was tested according to the British Pharmacopoeia 2010. Ten 50 ± 1 mg samples were taken from each blend, diluted appropriately in water and individually assayed by HPLC. All four preparations were found to be compliant with the British Pharmacopoeia standard as not more than one sample lay outside the limits of 85–115% of the average content.

2.9. In vitro aerosol performance analysis

The influence of polystyrene carrier size on the aerosolisation efficiency of salbutamol sulphate was studied using a multi-stage liquid impinger with USP specification inlet port (MSLI; Copley scientific, Nottingham, UK). Since the driving force behind the efficient separation of drug from carrier is due to the air flow-rate (and thus the energy imparted into the system) the performance was evaluated as a function of flow rate (at 40, 60, 80 and 100 l min^{-1}). Prior to testing, 20 ml of water was accurately added to stages 1–4 and the flow rate through the MSLI set at the required value using a GAST Rotary vein pump (Erweka GmbH, Heusenstomm, Germany) and a calibrated flow meter (TSI 3063, TSI instruments Ltd., Buckinghamshire, UK). 50 mg of chosen formulation was placed into the sample compartment of a Rotahaler™ DPI device (GlaxoSmithKline, Uxbridge, UK), which was then placed into the mouthpiece adaptor of the USP inlet port. The MSLI was operated so that 4 L of air was drawn through the device before the MSLI and all stages were washed into suitable volumetrics for HPLC analysis. All blends were analysed at 40, 60, 80 and 100 l min^{-1} in triplicate. Mass recoveries from each stage were inputted into a custom spreadsheet that used log-normal regression to calculate the mass of particles with an aerodynamic diameter less than 5 μm; based on the cut-off diameters given in Table 1. Environmental conditions in the laboratory were 45% RH and 25 °C throughout the study and samples were randomised for both carrier diameter and flow rate.

2.10. High performance liquid chromatography

High performance liquid chromatography (HPLC) was used to determine the content uniformity of salbutamol sulphate in each blend and on mass on each stage of the MSLI. The HPLC system consisted of a CBM-20A controller, LC-20AT pump, SPD-20A UV–VIS detector at 276 nm, and SIL-20A HT Autosampler with LCSolution software (all Shimadzu Corporation, Japan). The mobile phase consisted of 60:40% v/v methanol:water with 0.1% w/v sodium dodecyl sulphate. A 4 μm C18 column (3.9 mm × 150 mm) was used for separation at a flow rate of 1 ml min^{-1} (Waters NovaPak, Waters, MA, USA). The injection volume was 100 μl and linearity was observed between 0.05 and 10 μg ml^{-1} with a retention time of approximately 5 min.

Table 1
Calculated cut-off diameters[a] for MSLI stages at different flow rates.

Flow rate	Calculated cut-off diameter (μm)			
	100 l min^{-1}	80 l min^{-1}	60 l min^{-1}	40 l min^{-1}
Stage 1	10.07	11.26	13.00	15.92
Stage 2	5.27	5.89	6.80	8.33
Stage 3	2.40	2.68	3.10	3.80
Stage 4	1.32	1.47	1.70	2.08
Filter	<1.32	<1.47	<1.70	< 2.08

[a] Cut-off points calculated as defined in the British Pharmacopoeia (2009).

2.11. Statistical analysis

Data subjected to statistical analysis using the SPSS Statistics 18.0 software package (SPSS Inc., Chicago, IL, USA). ANOVA one-way analysis (with Tukeys' post hoc analysis) was utilised to test for significance. Difference was considered significant when $p < 0.05$.

3. Results

3.1. Particle size analysis

Particle size distributions of the micronized salbutamol sulphate and three polystyrene samples are shown in Fig. 1. Analysis of the salbutamol size distribution data suggested it to be of suitable size as a model drug ($d_{0.5}$ = 4.2 μm) for inhalation, while the three polystyrene samples had discrete (non-overlapping) size ranges. Specifically $d_{0.1}$, $d_{0.5}$ and $d_{0.9}$ values of 60.8 μm, 82.8 μm and 112.6 μm for TS-80, 169.5 μm, 277.5 μm and 300.8 μm for TS-230 and 427.2 μm, 582.9 μm and 801.2 μm for TS-500, respectively.

3.2. Scanning electron microscopy

Representative SEM images of the polystyrene beads are shown in Fig. 2A, B and C for TS-80, TS-230 and TS-500, respectively. In addition, SEM images for the polystyrene-salbutamol sulphate blends are shown in Fig. 2D, E and F for TS-80, TS-230 and TS-500, respectively. From the SEM images, the polystyrene samples were

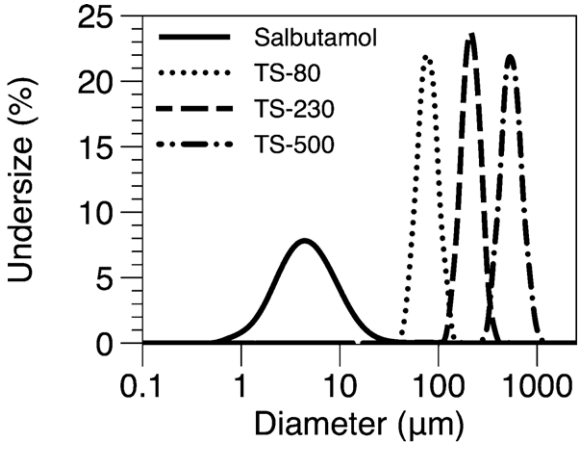

Fig. 1. Mean particle size distribution of the salbutamol sulphate and three polystyrene samples.

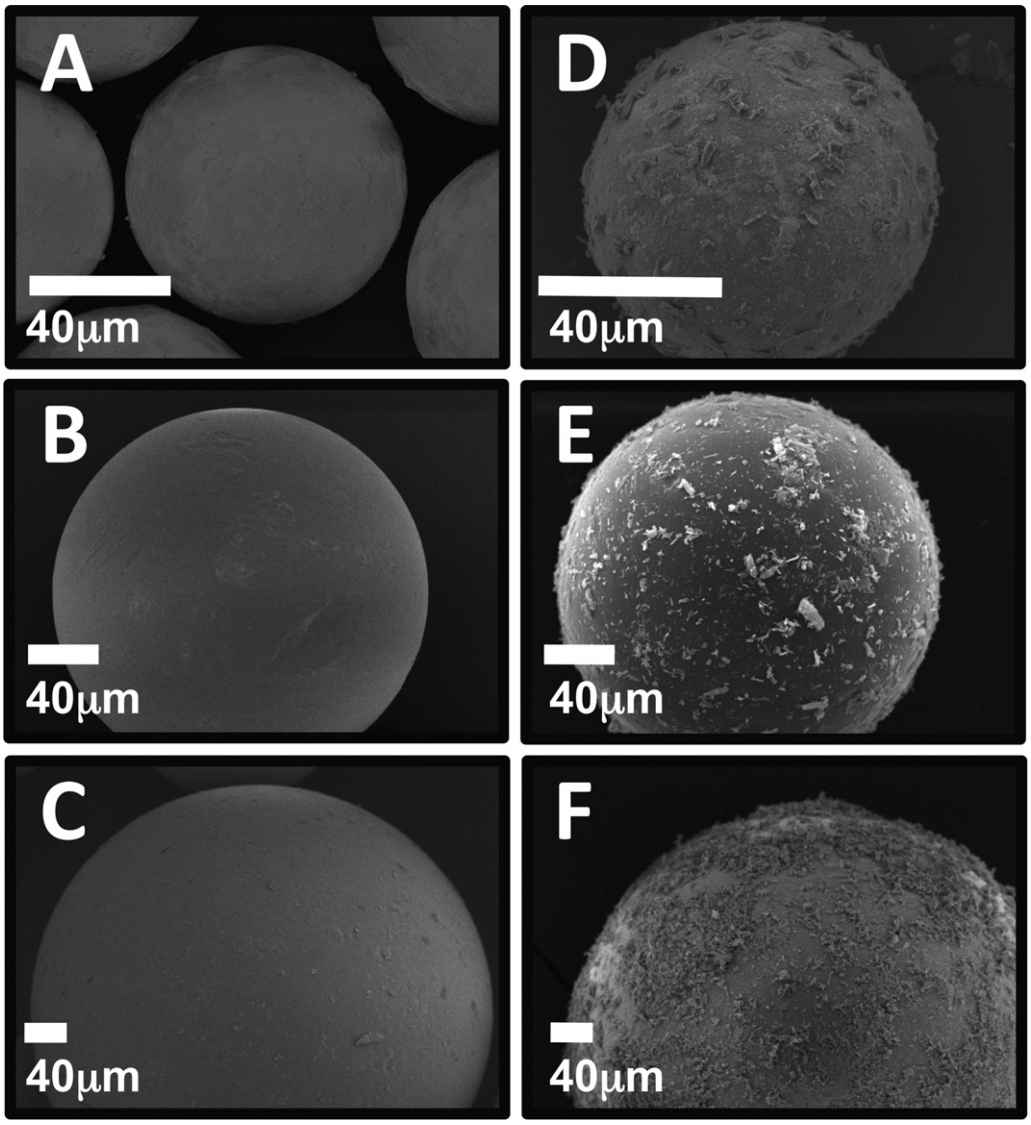

Fig. 2. Scanning electron microscopy images of: (A) TS-80, (B) TS-230, (C) TS-500, (D) TS-80, (E) TS-230, and (D) TS-500 blends with salbutamol sulphate.

spherical in nature and within the size range described by the particle size analysis. Furthermore, all the samples appeared to have a smooth surface. As expected, analysis of the blends suggested that as the particle size of the polystyrene carrier increased the number of salbutamol sulphate particles per carrier increased (due to a reduction in carrier particle number and associated surface area as size is increased while drug:carrier blend ratio remains constant). It is important to note that, for this particular drug:carrier mass ratio, all formulations appeared to be ordered mixes (Hersey, 1975) with drug adhered to the carrier rather than being inter-dispersed throughout the carrier 'powder bed'.

3.3. True density

The density of TS-80, TS-230 and TS-500 was reported as $1.04 \pm 0.01\,g\,cm^{-3}$, $1.05 \pm 0.01\,g\,cm^{-3}$ and $1.03 \pm 0.01\,g\,cm^{-3}$, respectively.

3.4. Dynamic vapour sorption

The moisture sorption isotherms for the three polystyrene carriers are shown in Fig. 3. In general all isotherms were reversible and repeatable (over two cycles) and for the polystyrene samples, an increase in particle diameter resulted in a decrease in the mass percentage moisture absorbed (for example the % adsorbed at 40% RH was 0.04, 0.03 and 0.02 for TS-80, TS-230 and TS-500, samples, respectively). Such observations are expected since the surface area to mass ratio increases as diameter decreases. Analysis of the micronized salbutamol sulphate data suggested that the moisture

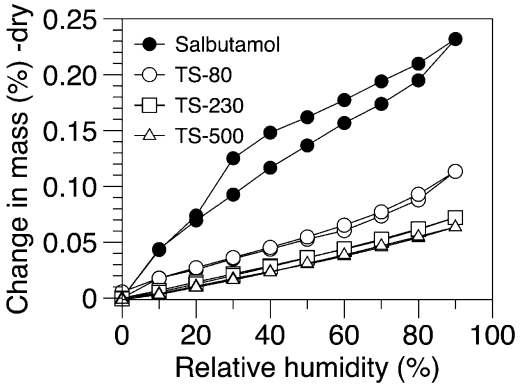

Fig. 3. Representative dynamic vapour sorption isotherm (cycle 1) of micronized salbutamol sulphate and the three polystyrene carriers; TS-80, TS-230 and TS-500.

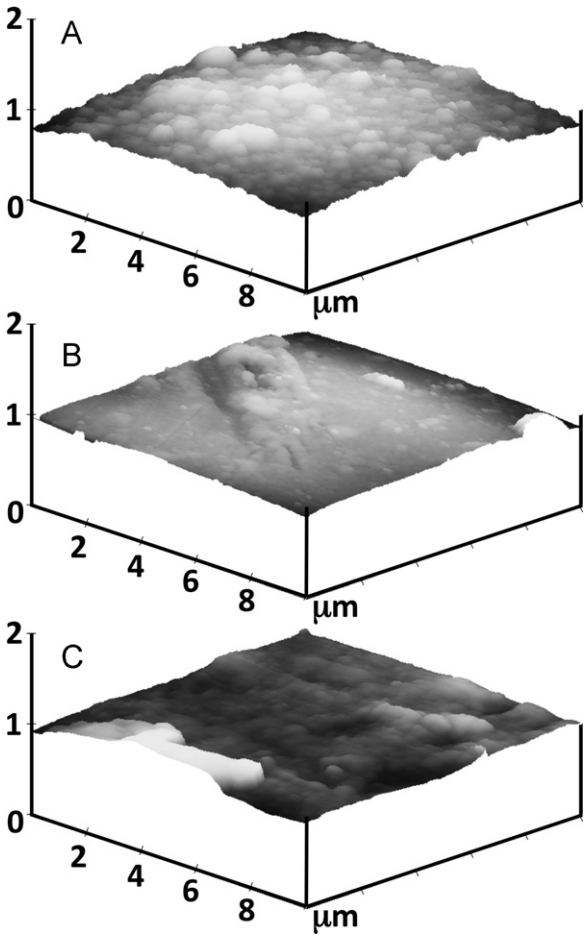

Fig. 4. AFM topography images of TS-80, TS-230 and TS-500 polystyrene sphere surfaces.

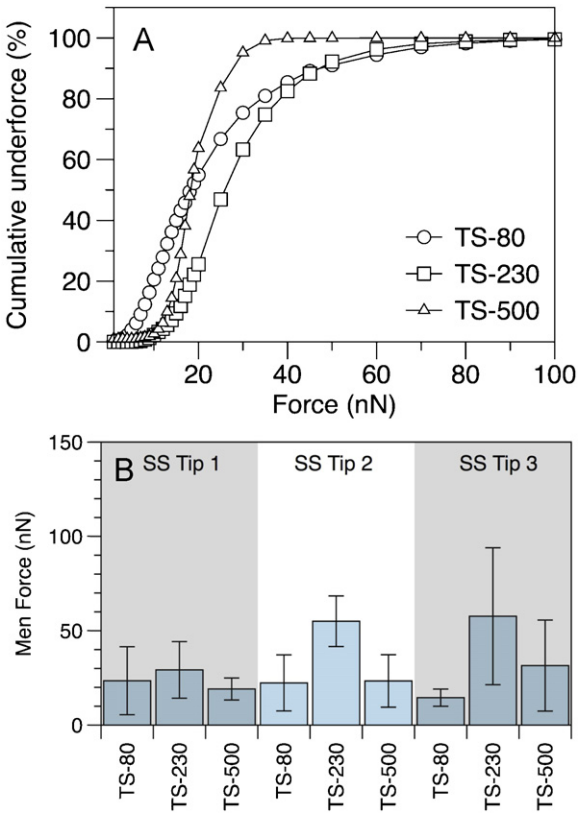

Fig. 5. A Typical force of adhesion distributions for salbutamol sulphate drug probe 1 on each carrier ($n = 4096$ force curves over 10 μm × 10 μm areas). (B) Mean force of adhesion for each salbutamol sulphate probe and carrier type ($n = 4096$ measurements per sample ± standard deviation).

sorption was greater (e.g. 0.12% at 40% RH) than for the polystyrene with a hysteresis between the adsorption and desorption cycles. The higher moisture sorption for salbutamol sulphate when compared to the polystyrene carriers is likely to be due to two factors; firstly the median diameter is approximately two-orders of magnitude less than the carrier and secondly, salbutamol sulphate is a hydrophilic and soluble drug molecule while polystyrene is insoluble and inherently hydrophobic (Dann, 1970). In addition, analysis of the salbutamol sulphate mass & humidity time plots suggested there was no characteristic mass loss during the sorption cycle; that is usually indicative of a amorphous to crystalline transformation (Columbano et al., 2002; Young and Price, 2004). Thus it can be assumed that the drug sample was predominately crystalline.

3.5. Atomic force microscopy

Five particles for each polystyrene batch were imaged (10 μm × 10 μm areas) using AFM in tapping mode. A representative image of each particle system is shown in Fig. 4. Post imaging, the topographical data were flattened using a quadratic background subtraction algorithm and the root mean square roughness (R_{RMS}) calculated. The R_{RMS} for TS-80, TS-230 and TS-500 were 112.0 ± 9.6 nm, 49.0 ± 3.0 nm and 109.67 ± 6.4 nm, respectively. Analysis of the data suggested significant differences in roughness between samples, with post hoc tests indicating that TS-230 was smoother than the other two samples (no difference in roughness was observed between TS-80 and TS-500). It is important to note that, all samples may be considered to have microscopically smooth surface morphologies of equivalent roughness to those observed on crystalline lactose samples (Adi et al., 2006; Traini et al., 2006; Young et al., 2002, 2009). Importantly, the coefficients of variation for all samples were low (≤9%) suggesting that the carrier morphology was homogeneous in nature rather than heterogeneous (as observed in commercial lactose carrier systems). While the roughness of TS-230 was less than that of the other two carriers it may be considered that this difference will have little on the contact geometry between the irregularly shaped micronized drug particles and each carrier surface. Indeed, a previous report by Young et al. (2002), suggested that the adhesion between micronized beclomethasone dipropionate drug particles and a lactose carrier changed little when the surface roughness of lactose was reduced from 108 nm to 27 nm; with no observable change in aerosol performance of the respective blends. Interestingly, previous studies have shown significant increases in adhesion occur when carrier roughness approaches atomic smoothness (i.e. <1 nm) (Traini et al., 2006); although orders of magnitude less than studied here. However, the differences observed in this study should be considered as a potential variable when evaluating the aerosol performance.

3.6. Colloid probe microscopy

Three salbutamol sulphate drug probes were used to evaluate the adhesion on the surface of each polymer carrier. Approximately 4096 force-curve measurements were conducted over 10 μm × 10 μm areas and the data processed to produce adhesion histograms. A representative adhesion histogram for drug probe 'number one' on each of the polymers is shown in Fig. 5A. Analysis of the data suggested a normal adhesion distribution on each of the polymers (likely due to the homogeneous smooth morphology) and thus mean adhesion and standard deviations were used

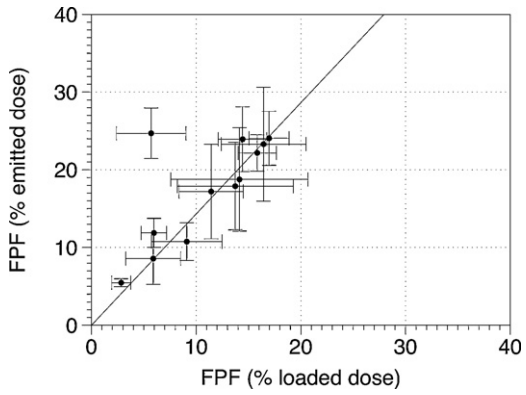

Fig. 6. Relationship between FPF_{ED} and FPF_{LD} for salbutamol sulphate aerosolised from different sized polystyrene carriers. Data represent all carriers and all flow rates (error bars represent standard deviation for each data set; $n = 3$).

to describe the profiles. Mean adhesion force values for each drug probe on each of the carrier surfaces are shown in Fig. 5B. Statistical analysis of the data set suggested no significant difference between adhesion values for each specific probe on the three carriers, suggesting the adhesion force was similar for salbutamol sulphate on all carriers.

3.7. In vitro aerosol performance analysis

In vitro deposition data were analysed and the total dose, emitted dose, fine particle dose (aerodynamic diameter $\leq 5\,\mu m$) and fine particle fraction (where the percentage of particles with an aerodynamic diameter $\leq 5\,\mu m$) were calculated based on both the emitted (FPF_{ED}) and loaded (FPF_{LD}) dose. Comparison of the FPF_{ED} with the FPF_{LD} was plotted on opposing axis (Fig. 6) to evaluate the variation in device removal efficiency with respect to carrier size and flow rate. Linear regression of the entire data set suggested a poor correlation ($y = 1.4863x$; $R^2 = 0.3856$). The lack of a positive correlation may be due the poor emitted dose from the TS-80 carrier at the lowest flow rate ($71.8 \pm 16.7\%$ salbutamol sulphate remains in the device for the TS-80 carrier at $40\,l\,min^{-1}$), resulting in an outlier. The poor emitted dose for this particular sample maybe due to an insufficient flow for the efficient fluidisation of the powder bed. Indeed, if this outlier is removed from the data set a linear correlation is observed between FPF_{ED} and FPF_{LD} ($y = 1.4318x$; regression line in Fig. 6 where $R^2 = 0.91882$) suggesting that the removal efficiency of the carrier–drug formulation as a whole remains constant. This is not to say that the removal efficiency of the drug from the carrier surface remains constant since a range of FPF values and standard deviations were observed indicating differences in performance and variability.

A plot of the FPF_{LD} and FPF_{ED} as a function of flow rate is shown in Fig. 7A and B, respectively. Analysis of the data suggests that as flow rate increased over the range 40–100 l min^{-1} a concurrent increase in FPF_{LD} was observed. For the TS-90 and TS-230 samples a maximum performance was observed at 80 l min^{-1} after which, no further change was observed. In comparison, for the larger TS-500 samples the mean FPF_{LD} increased linearly across the whole flow range, however, significant differences were only observed between non-adjacent samples (i.e. 40, 80; 40, 100 and 60, 100). As expected, similar results were observed or the FPF_{ED} when excluding the TS-80 sample at the lowest flow rate.

Further analysis of the data present in Fig. 7 suggested that carrier size had an impact on drug liberation of salbutamol sulphate; however, this appeared to be dependent on the flow rate. At the highest flow rate (100 l min^{-1}) the performance between different carriers were similar. To further study this, the FPF_{LD} and FPF_{ED}

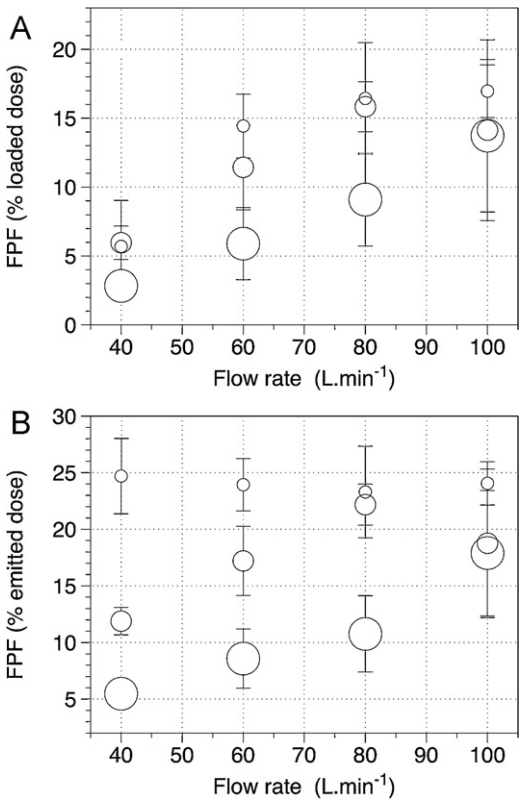

Fig. 7. Relationship between (A) FPF_{ED} or (B) FPF_{LD} and flow rate for salbutamol sulphate from each carrier system. Increasing symbol size represents increasing carrier size (i.e. T-80, T-230 and T-500, respectively) ($n = 3$).

were plotted as a function of carrier size and are shown in Fig. 8A and B, respectively. Analysis of the FPF_{LD} as a function of carrier diameter suggested that significant differences in aerosol performance were observed at flow rates of 40, 60 and 80 l min^{-1}. Post hoc analysis for the 40 and 80 l min^{-1} flow rates reported significance difference between the TS-80, TS-500 carrier-pairs but not between TS-80 and TS-230 suggesting that the two smaller carriers resulted in similar drug aerosol performance at these flow rates. At 60 l min^{-1} post hoc analysis reported significant difference with respect to all carrier diameters. As with the analysis of the influence of flow rate the FPF_{ED} showed similar results to the FPF_{LD} when studying carrier size as a variable if TS-80 measurements at 40 l min^{-1} are excluded.

4. Discussion

This study was designed to evaluate the performance of carrier based dry powder inhalation formulations with respect to both flow rate and carrier diameter. In order to study these factors it is important to eliminate all other variables, which may interfere with the observations. Subsequently, a spherical based carrier system was used, where carrier density, shape, roughness and surface chemistry were similar. Concurrently, other factors including the drug, device and environmental conditions were kept constant. Prior to discussion, it is important to highlight that the use of polystyrene spheres as a carrier and identify key differences with respect to α-lactose monohydrate. While this does not affect the validity of this experiment, the authors feel it is useful as it allows direct comparison with previous lactose-based studies.

For example, the T-80 polystyrene carrier roughness reported here was 112 nm. Previous studies by the group, using sieve fractioned α-lactose monohydrate of similar size ($d_{0.5}$ 67–118 μm) to

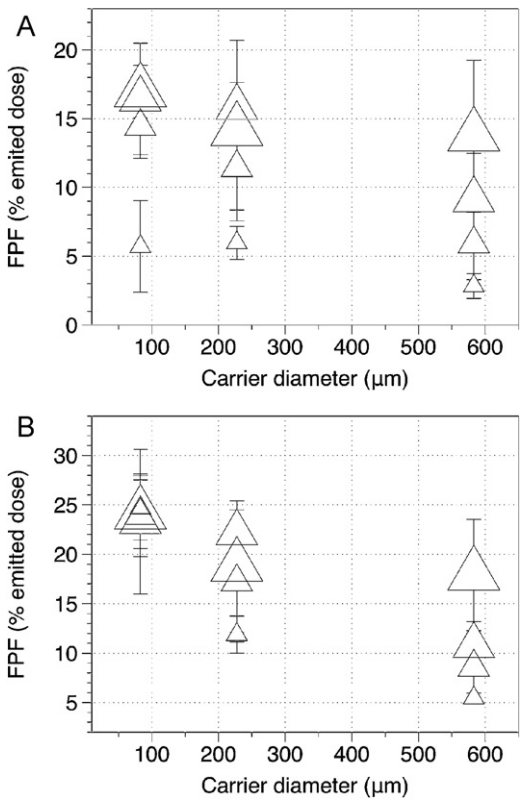

Fig. 8. Relationship between (A) FPF_{ED} or (B) FPF_{LD} of salbutamol sulphate as a function of carrier diameter. Increasing symbol size represents increasing flow rate (i.e. 40, 60, 80, and 100 l min^{-1}, respectively) ($n = 3$).

that of TS 80 (83 μm) reported roughness values that fell within the range of the polystyrene spheres measured here (90–145 nm) (Young et al., 2002, 2009; Traini et al., 2006). Furthermore, previous adhesion force measurements between salbutamol sulphate drug particles and sieve fraction carriers have reported similar values. For example work by Traini et al. (2006) reported median adhesion forces of ~50 nN while the study here reported values ranging from 15 to 57 nN. While it is impossible to make direct comparisons, similarity between these two carrier systems does exist.

In terms of the polystyrene carrier system studied here, analysis of the data suggested that both flow rate and carrier size influence drug liberation from the carrier surface. It is clear that in general, as the carrier size increases the aerosol performance of drug decreases; indicating that more drug particles remained attached to the larger carrier based system. With respect to flow rate, increased air velocity resulted in increased drug liberation from the carrier surface with the optimum airflow being reached at 80 l min^{-1} for the TS-80 and TS-230 carriers and 100 l min^{-1} for the TS-500 carrier. Such observations suggest that increased flow results in a higher energy input into the system resulting in a higher probability of drug–carrier separation. However, it is unclear what this mechanism may be. In order to evaluate the data obtained here, one must consider the influence carrier size and flow have on the formulation components. The basic differences in the formulations with respect to carrier size are highlighted in Fig. 9 along with their potential affects on blending and aerosolisation mechanisms.

As carrier size is increased the relative surface area decreases. For a given formulation mass, with a fixed formulation ratio, there will be more drug particles per carrier in the large carrier system. In addition as the carrier size is increased its mass will become larger, resulting in greater momentum during powder movement.

During the blending process the greater momentum of the large carrier may result in increased press-on forces making it more difficult to remove the drug during aerosolisation. Conversely, the increased mass of the larger carrier will result in higher particle–particle and particle–device impaction forces. This higher impact force is likely to result in a greater momentum transfer (a potential detachment force) between the carrier and drug, and thus, improved FPF. In addition, the larger carrier particle will encounter a greater drag force in the turbulent airstream providing a greater potential detachment force. Since the larger carrier performed poorly when compared to the small carriers (until high flow rates were utilised) it may be assumed that impact forces, momentum transfer and drag forces on the carrier surface do not play a dominant role in drug liberation however blending forces should be considered further.

It may be assumed that the momentum, and thus force, in a low shear blender would be less than that in a DPI; since the maximum velocity of a given particle will be less than in a DPI airflow (for example the average impact velocity at the grid section of a Aerosolizer® device, at 60 l min^{-1} is ~18 m s^{-1} (Coates et al., 2005)). However, it should also be important to consider the duration of low shear mixing and the total formulation mass. To assess the potential for increased press-on force affects on aerosol performance, a simple salbutamol sulphate carrier blend was prepared, as previously described, using glass beads of a similar size to the TS-80 polystyrene. Glass beads of 66.0 μm diameter were used with a density of 2.45 g cm^{-3} (2.4 times that of the polystyrene with a ~23% increase in mass). A formulation was prepared and tested at 100 l min^{-1} using the same protocol to that of the polystyrene study. Analysis of the data suggested no significant differences between the polystyrene and glass carrier (13.8 ± 3.4% FPF for the glass system compared to 16.9% FPF for the polystyrene). While such observations are suggestive that press on forces did not influence performance in this study, it is important to note that the glass carrier will have a very different surface chemistry and Young's modulus to the polystyrene, making it difficult to ascertain a true relationship under these compounding variables. Future studies should focus on the relationship between low shear blending, press on forces and aerosol performance. Indeed, a recent study by Marek et al. reported processing pressures of up to 15 kPa did not influence the aerosol performance of conventional inhalation grade lactose carrier blend formulations.

In addition to considering mass related momentum and momentum transfer processes encountered during blending and aerosolisation, it is also important to consider the number of carrier particles and their relative surface area. When the formulation mass and drug to carrier ratios are kept constant (as occurred in this study), the following factors occur when the variable carrier size is decreased:

(1) increased number of carrier particles,
(2) increased surface area,
(3) decreased number of drug particles per carrier,
(4) increased inter-carrier adhesion, and
(5) increased number of collisions in the powder bed during aerosolisation.

These changes in the powder formulation may be the contributing factors to the relative differences in performance. A higher number of particles result in a greater number of collisions. Since direct momentum transfer from carrier to drug does not appear to be a driving force for drug liberation, it is envisaged that frictional and rotational forces induce particle detachment in the turbulent airstream. Subsequently a greater number of collisions (i.e. as observed in the small carrier system) would result in improved particle aerosolisation over the force of the collisions (as observed in

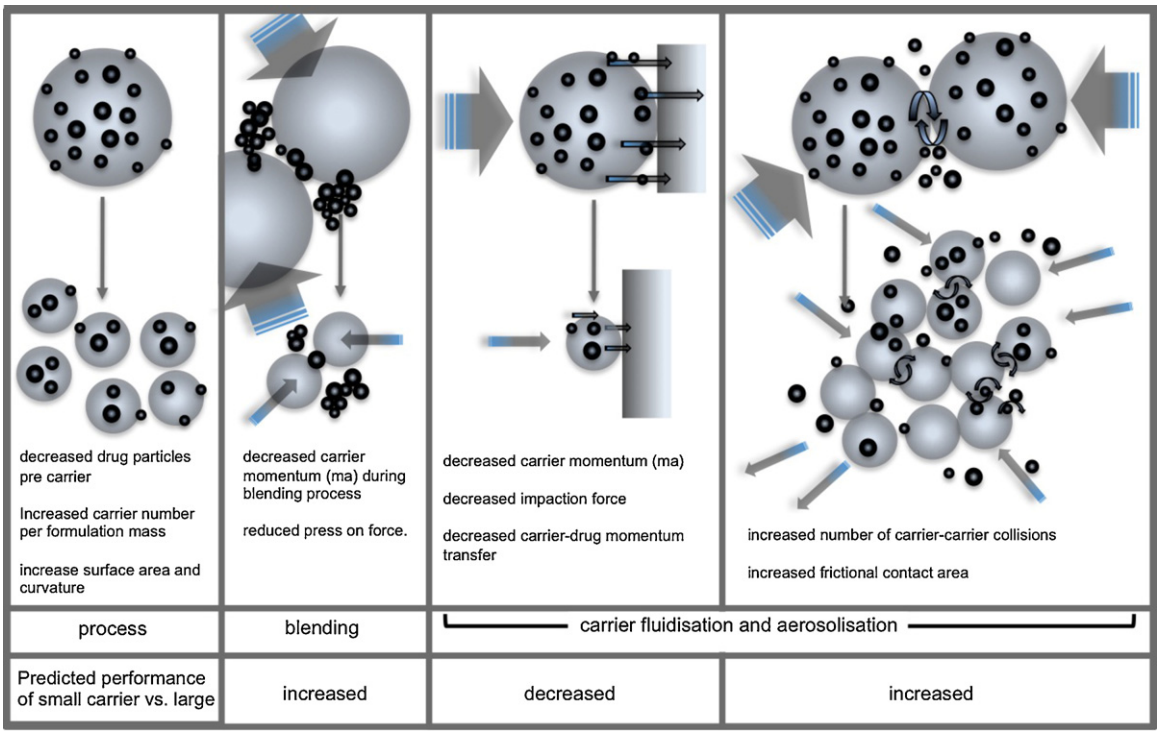

Fig. 9. Schematic highlighting the difference between carrier size and the impact those differences may have during blending and aerosolisation process with respect to drug removal.

the large carrier system). Furthermore, if frictional and rotational forces drove such a system, it stands to reason that a higher surface area would result in a greater probability of detachment, as observed in the TS-80 system.

5. Conclusions

This study has attempted to ascertain the mechanism for drug–carrier detachment in relatively dilute (67.5:1) carrier:drug formulation; with a specific focus on carrier size. In order to study this, as many compounding variables as possible (i.e. carrier shape, morphology, drug–carrier adhesion) were removed choosing a model spherical polystyrene carrier. Blends were tested with a range of carrier sizes over a range of flow rates. Clear differences in aerosol performance were observed with respect to flow rate and carrier size. As flow rate increased so did the degree of drug liberation from the carrier surface. As carrier size decreased there was a concurrent increase in aerosol performance. These observations suggest that: (a) higher energy processes result in improved drug aerosolisation, and (b) drug liberation appears to be primarily driven by the number of frictional and rotational collisions rather that the conventional momentum transfer. This study focused on a series of formulations that contained a constant drug:carrier ratio (i.e. the number of drug particles per carrier changed with respect to size) that were prepared in an identical manner.

Future studies should consider the influence of carrier ratio, with respect to carrier size, on aerosolisation performance. Furthermore, this fundamental approach can be used to study other parameters such as blending dynamics and the influence of carrier surface chemistry, via functionalisation of the polystyrene surface.

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