Research Paper

The Role of Fines in the Modification of the Fluidization and Dispersion Mechanism Within Dry Powder Inhaler Formulations

Jagdeep Shur,[1] Haggis Harris,[1] Matthew D. Jones,[1,2] J. Sebastian Kaerger,[3] and Robert Price[1,4]

Purpose. To investigate the role of *in situ* generated fine excipient particles on the fluidization and aerosolization properties of dry powder inhaler (DPI) formulations.

Materials and Methods. Carrier based DPI formulations were prepared under low and high shear blending. Powder rheometry was utilized to measure bulk powder properties in a consolidated and aerated state. Powder fluidization and aerosolization characteristics were related to bulk powder properties using high speed imaging and inertial impaction measurements.

Results. High shear blending of formulations resulted in the *in situ* generation of excipient fines, which corresponded to an increase in aerosolization efficiency. The generation of fines were shown to increase the tensile strength and free volume of the carrier, which resulted in a characteristic change in the fluidization properties, as observed by high speed imaging. The increase in minimum fluidization velocity and aerodynamic drag forces required to aerate the powder may provide the source of energy for the increase in fine particle re-suspension.

Conclusions. The *in situ* generation of excipient fines affect bulk powder properties of DPI formulations, which directly affects fluidization and aerosolization behaviour of DPI formulations. The study suggests an alternative mode of action by which fines increase DPI formulation performance.

KEY WORDS: dry powder inhaler; fluidization; particle re-suspension; powder flow; ternary agents.

INTRODUCTION

Dry powder inhaler (DPI) formulations are usually prepared as homogenous interactive mixtures (1), comprising of micronized drug particles and a coarse carrier (2). The coarse carrier, traditionally α-lactose monohydrate (3), are employed within DPI formulations to improve flow properties and metering of the highly cohesive drug particles (4). The entrainment and subsequent aerosolization of the formulation is achieved using the patient's inspiratory force (5), which is required to elutriate the micronized active pharmaceutical ingredient from the surface of the carrier particle for delivery to the lower airways of the respiratory tract (6). A common approach utilized to increase the deaggregation efficiency and, thus, the therapeutic efficacy of a DPI formulation is *via* the addition of ternary agents (7,8). For such preparations, a small quantity of fine excipient particles (of similar geometric size to the active ingredient) are either co-processed with the active and coarse carrier

particles or are generated during the processing of the excipient (8). Extensive research into the role of fine excipient particles suggests that their inclusion results in increased liberation of drug particulates, for which a number of mechanisms have been proposed (1,9,10). The dramatic influence of the presence or the addition of fine excipient particles on the aerosolization performance of ternary formulations have been related to mechanisms such as corrasion (i.e. the filling of active sites) (1) and the formation of drug/fines agglomerates (9).

A critical step in generating a therapeutic aerosol *via* a DPI device is the fluidization and entrainment behaviour of the bulk powder (11). Powder fluidization is the process by which a powder mass is disturbed by a stream of airflow resulting in the powder bed exhibiting 'fluid-like' properties (12). Following fluidization, the powder removed from the fluidized column is said to be entrained into the airflow (13). The process of powder fluidization is primarily governed by the packing properties of the powders, which can be related to the physicochemical properties of the particles and their interfacial interactions (14).

In the context of passive DPI systems, the process of fluidization involves the transition of the powder bed located within the device from a static to a suspended state using the airflow generated by the patient's inspiratory action (5,11). During this process, air is passed over the powder mass generating a pressure differential across the bed (15). A schematic representation of this response to an increasing

[1] Pharmaceutical Surface Science Group, Department of Pharmacy and Pharmacology, University of Bath, Claverton Down, Bath, BA2 7AY, UK.

[2] Department of Pharmaceutics, The School of Pharmacy, University of London, 29/39 Brunswick Square, London, WC1N 1AX, UK.

[3] Novartis Pharma AG, Basel, Switzerland.

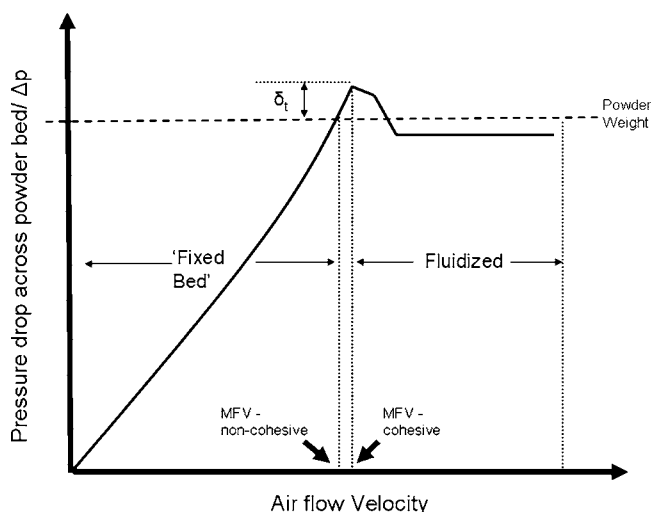[4] To whom correspondence should be addressed. (e-mail: r.price@bath.ac.uk)

Fig. 1. Typical relationship between airflow velocity and pressure gradient across a powder bed. The pressure drop increases linearly with airflow velocity whilst the powder bed remains static. The point at which the pressure drop is equal to the weight of the powder is identified as the minimum fluidization velocity (*MFV*). The MFV-cohesive determines the beginning of fluidization of a cohesive powder for which the tensile strength (δ_t) of the powder bed must be overcome.

airflow velocity during fluidization is illustrated in Fig. 1. During the initial airflow acceleration phase of a forced inspirational breath, the powder bed remains initially unperturbed as the pressure drop increases across the powder bed. This behaviour is described by Carman's law and the response is highly dependant on the packing behaviour of the powder bed (16). With increasing airflow velocity, the pressure drop across the powder bed reaches a threshold, referred to as the point of incipient fluidization or minimum fluidization velocity (MFV), as shown in Fig. 1 (13). The MFV is the point at which the pressure drop across the static powder bed is equivalent to the weight of the powder and is the point of fluidization for powders which exhibit no particle-particle interaction (12). Since all powders experience some degree of interparticulate forces, the pressure drop continues to increase until the interactive forces are overcome by the airflow velocity. The shift in the MFV is characterized by a sudden decrease in the pressure drop across the powder bed (17). The increase in the pressure drop generated in overcoming the interparticulate forces will directly influence the entrainment and aerosolization efficiency of the drug formulation within a DPI device. It is at this breaking point that the pressure drop and differential velocity (between the airflow and the static powder bed) is at its maximum, giving rise to the largest aerodynamic drag force that can be exerted upon the powder within a DPI device (17). The increase in pressure drop beyond the weight of the powder is related to the resistance of the powder and this difference is determined as the tensile strength (σ_t) of the powder, which is directly related to the interparticle forces and the free volume within the powder bed (17).

The fluidization of a DPI formulation is primarily a function of the relationship between the pressure differential generated between the airflow and the powder bed and the corresponding tensile strength of the DPI formulation. Hence,

processes which may influence the tensile strength of a powder blend may play a critical role in determining the fluidization and subsequent aerosolization behaviour of a DPI formulation. In addition to interparticulate forces, the tensile strength of a processed formulation is influenced by consolidation stresses and packing properties (e.g. free volume) of the powder bed (18). The inter-relationship between these components is complex. However, previous studies have shown that the tensile strength of a powder increases with increasing consolidation stress and free volume (18).

Upon entrainment, agglomerates and individual particles may de-aggregate from the carrier particles either *via* the aerodynamic drag force generated by the pressure differential in response to the MFV or *via* particle–particle or particle–wall collisions within the device (12,19). The detachment forces encompass aerodynamic, centrifugal, inertial, shear and frictional forces which attempt to overcome the interparticulate forces between components within the formulation (20). The process of fluidization, entrainment and dispersion can be further modified by the engineering of devices in increasing the Reynolds number and the number of impaction events within a particular device (11). These features may include forming tortuous airflow paths through the device, use of impactor grids and/or increasing airflow resistance within a device (21).

The bulk physicochemical properties (e.g. particle shape and size) of binary and ternary DPI formulations are critical in determining the fluidization and entrainment behaviour of DPI formulations (22). Indeed, powder flow properties of DPI formulations are an important consideration and have been shown to be a key component in predicting *in vitro* and *in vivo* performance of passive DPI systems (23). Previous studies have shown that the flow properties of carrier based DPI formulations are related to device emptying (24). A correlation between powder packing efficiencies and flowability has been previously reported, where it has been suggested that powders that pack uniformly also exhibit good flow properties (18). As particle shape will affect material packing properties it is therefore, likely to effect powder flow. However, for materials consisting of particles of similar shape, this relationship is primarily governed by the tensile strength and the cohesive/adhesive nature of materials, where powders with good flow and packing properties have low tensile strengths (17). The specific relationship between powder flow properties, tensile strength, powder fluidization and DPI performance is an area which has generally been overlooked.

Despite much work, there is a paucity of data on the influence of formulation blending processes, on the physicochemical properties of the bulk powder formulation or indeed the resultant effect on powder fluidization and DPI performance. During blending, the type of blender and mixing principle will determine the magnitude of the shear, inertial and frictional press-on forces during the blending process, which may have considerable effects on the bulk powder properties of the formulation, in terms of particle size and powder flow. Changes to the bulk powder properties of the formulation may, therefore, also affect the fluidization and entrainment behaviour of the formulation and thereby the performance of the DPI system.

The aim of this study was to investigate the effect of different blending techniques and the specific role of fine

excipient material generated during processing on the fluidization and entrainment properties of DPI formulations. A novel powder re-suspension technique is described, which was utilized to determine the mechanism of powder fluidization and entrainment, and the manner in which fine particle delivery may be modified by the physical properties of the carrier particles within a DPI formulation.

MATERIALS AND METHODS

Materials

Micronised budesonide was supplied from Sicor (Santhia, Italy), Pharmatose P200M α-lactose monohydrate was donated by DMV International (Veghel, Netherlands). HPLC grade acetonitrile and laboratory grade hexane were supplied by Fisher Chemicals (Loughborough, UK). Silicone oil was supplied by Acros Chemicals (Loughborough, UK). Water was purified by reverse osmosis using an Elix-S system (Millipore, Molsheim, France).

Methods

Sieving

Lactose was dry sieved through appropriately sized sieves (Endecotts Ltd, London, UK) using an Analysette 3 Pro vibratory sieve shaker (Fritsch, Idar-Oberstein, Germany) to obtain a 63–90 μm particle size fraction.

Particle Size Analysis

Particle size analysis was carried out in the dry state using a Sympatec HELOS (Sympatec GmbH, Clausthal-Zellerfeld, Germany) laser diffraction system. Approximately, 33 mg of powder was loaded into a measuring vial, which was dispensed using the ASPIROS (Sympatec GmbH, Clausthal-Zellerfeld, Germany) micro-dosing unit. The powder was then dispersed into the HELOS system using the RODOS (Sympatec GmbH, Clausthal-Zellerfeld, Germany) dry disperser preset at 2.0 bar. Particle size analysis was performed using WINDOX 4.0 software (Sympatec GmbH, Clausthal-Zellerfeld, Germany). Particle size distributions were performed in triplicate and determined using Fraünhofer theory.

Preparation of Blends

The influence of formulation blending processes on drug aerosolization efficiency was evaluated using three batches of binary formulations containing 0.61% w/w budesonide, which were prepared using three different blending methods. Each binary formulation contained 0.61 g budesonide and 9.939 g lactose, and was prepared by geometric mixing. Following this, one batch was further blended in a stoppered test tube in a Whirlimixer (Fisons WM/250/SC/P, Loughborough, UK) for 1 min. Another blend was subsequently prepared using a Turbula T2F (Willy A Bachofen AG, Basel, Switzerland) at 46 rpm for 40 min. A third blend was mixed in a high shear mixer (Braun KSM2, Kronberg, Germany) for 1 minute. The KSM2 consists of two opposed flat knife-like blades rotating at approximately 500 rpm in a bowl. In addition, 10 g batches containing lactose alone were also produced under the same conditions.

High Performance Liquid Chromatography (HPLC) and Content Uniformity Analysis of Budesonide

HPLC was used to determine drug content. The HPLC consisted of a pump (Jasco PU-980, Jasco Corp., Japan) coupled to a UV detector (Jasco UV-975) set at 248 nm. The mobile phase was 60:40 water/acetonitrile by volume. The pump flow rate was set to $1.5 \, \text{ml min}^{-1}$ through a 5 μm Hypersil MOS C8 column (Jones Chromatography Ltd, Hengoed, UK).

Following blending, the drug content uniformity of all the formulations was assessed. From each formulation, ten random samples of 33 ± 1 mg were taken from random positions of the powder bed and dissolved in 100 ml of mobile phase. The proportion of drug in each sample was calculated and the content uniformity expressed by percentage relative standard deviation.

Inertial Impaction Testing of Prepared Blends

Following content uniformity testing, 33 ± 1 mg of each blend was loaded into size 3 hydroxypropylmethyl cellulose capsules (HPMC, Shionogi Qualicaps SA, Basingstoke, UK). The capsules were stored at 44% RH for 24 h prior to in vitro performance testing. Testing was performed using a Next Generation Impactor (NGI) with pre-separator, which was connected to a vacuum pump (GE Motors). Prior to testing, the pre-separator was filled with 15 ml of mobile phase and the cups of the NGI cups were coated with 1% v/v silicone oil in hexane to eliminate particle bounce. For each experiment, ten individual capsules of the same formulation were discharged into the NGI at $60 \, \text{l min}^{-1}$ for 4 s via a Monohaler® (Miat SpA, Milan, Italy) DPI device. Following aerosolization, the NGI apparatus was dismantled and the inhaler, capsules and each part of the NGI was washed down into known volumes of HPLC mobile phase. The mass of drug deposited on each part of the NGI was determined by HPLC. This protocol was repeated three times for each blend, following which, the mass median aerodynamic diameter (MMAD), geometric standard deviation (GSD), fine particle dose (FPD) and fine particle fraction of the emitted dose (FPF$_{ED}$) were determined. The FPD represented the mass of drug that was collected on stages 3–8 of the NGI.

Scanning Electron Microscopy

The morphology of all formulations was investigated using scanning electron microscopy (SEM, Jeol 6310, Tokyo, Japan) at 10 or 15 keV. Samples were mounted on carbon sticky tabs and gold-coated (20 nm thickness) before imaging (Edwards Sputter Coater, Crawley, UK).

Surface Area Analysis

The specific surface areas of the sieved lactose 63–90 μm particle size fraction and processed lactose samples produced using the different blending methods were measured using a Gemini 2360 surface area analyser (Micromeritics Instrument Corporation, Norcross, USA). A five-point BET nitrogen

adsorption analysis was carried out after degassing the samples for 24 hours in a FlowPrep 060 degasser (Micromeritics Instrument Corporation, Norcross, USA).

High Speed Imaging Analysis

High speed images of the mechanics of fluidization and entrainment of the lactose samples processed using whirlimixer, turbula and high shear mixing were captured following fluidization via a powder reservoir holder of a Sympatec ASPIROS using a monochrome high speed imaging system (Redlake MotionPro X-4, Lake Image Systems Ltd, Tring, UK). Images were captured at a rate of 5145 frames per second. The images produced were used in the qualitative analysis of the influence of blending processes on the fluidization behaviour of the prepared formulations.

Dynamic Powder Flow Analysis

A FT4 Powder Rheometer (Freeman Technology, Welland, UK) was used to measure the flow properties of batches of lactose (without drug) that were processed using the whirlimixer, turbula and high shear blender, respectively. In each case, 10 ml of sample powder was analysed in a 25 mm bore borosilicate glass cylinder. The samples were conditioned using a 23.5 mm blade which was moved down a helical path with a helix angle of $5°$ at a velocity of 20 mm s^{-1}. This provides a gentle displacement of the powder, which removes the packing history of the powder and any operator influence and, thus, generating a homogenised or uniform low packing stress in the powder. Furthermore, as the mass, volume, height and applied force experienced by the powder bed was recorded, the bulk density of the respective powders was also determined (25).

Powder permeability studies were conducted at a constant airflow velocity of 2 mm s^{-1}, which was passed through the powder bed, with varying normal stress between 1 and 20 kPa being applied on to the sample. The pressure drop across the powder bed was measured as a function of the applied normal stress. This provides information regarding the resistance of the powder bed to air permeation and, thus, relating to fluidization behaviour of a powder. In all cases measurements were performed in triplicate.

Statistical Analysis

Linear regression analysis was used for the assessment of HPLC calibration. Statistical analysis between different populations carried out using one-way analysis of variance. Comparison of the mean values was performed by Tukey's multiple comparison. All statistical analyses were performed using GraphPad Prism software (GraphPad Software Inc, California, USA). Error bars in graphical representations of data show ±1 standard deviation in all cases.

RESULTS AND DISCUSSION

Characterisation of Micronized Budesonide and α-Lactose Monohydrate

Particle size analysis of micronized budesonide determined a median equivalent volume diameter of $1.62 \pm$

0.03 μm, with 90% of particles under 5.0 μm. Hence, the active was suitable for pulmonary delivery. The particle size distribution of the 63–90 μm sieve fractioned lactose monohydrate, shown in Fig. 2, had a broad distribution with a d_{10} and d_{90} value of 5.6 and 117.70 μm, respectively. The proportion of fine excipient particles less than 5 μm was approximated to be 9.3% *v/v*. The specific surface area of the sieved lactose was 0.324 ± 0.004 m^2 g^{-1} (Fig. 3).

Influence of Varying the Blending Process on the Bulk Powder Properties of α-Lactose Monohydrate

To investigate the influence of blending processes on the bulk powder properties of DPI formulations, batches of lactose (without drug) were processed using a whirlimixer, a turbula blender and under high-shear.

In comparison to the pre-sieved lactose, processing of lactose via either the whirlimixer or turbula had no significant effect upon the particle size distribution and the percentage of fine excipient, as shown in Fig. 2. This is further supported by scanning electron micrographs of the sieved, whirlimixer and turbula processed lactose, shown in Fig. 4A,B and C, respectively. These data suggest that low to moderate shear processing had little effect upon the percentage of intrinsic fines and the particle size distribution of the carrier. However, surface area measurements of the whirlimixer processed lactose suggested a slight decrease in the surface area, as indicated in Fig. 3. This small but significant ($p<0.05$) decrease in the specific surface area of lactose processed using the whirlimixer (0.300 ± 0.004 m^2 g^{-1}) may either be attributed to aggregate formation of fine lactose material and/or loss of the fines to the walls of the glass container during processing.

In contrast, high shear blending of the sieved lactose resulted in a decrease in the median particle size (Fig. 2) and a concomitant increase in the specific surface area (0.903 ± 0.008 m^2 g^{-1}), as shown in Fig. 3. The d_{10} and d_{90} percentiles of the high shear processed lactose were 1.6 and 75.5 μm, respectively, with approximately 22% *v/v* less than 5 μm. These data indicated that high shear processing of lactose reduced particle size and generated a significant increase in
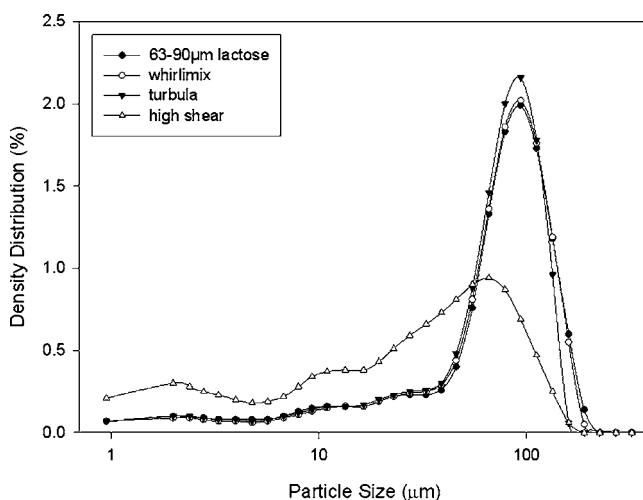

Fig. 2. Particle size distribution of the sieved 63–90 μm α-lactose monohydrate before and after, whirlimixer, turbula and high shear processing.
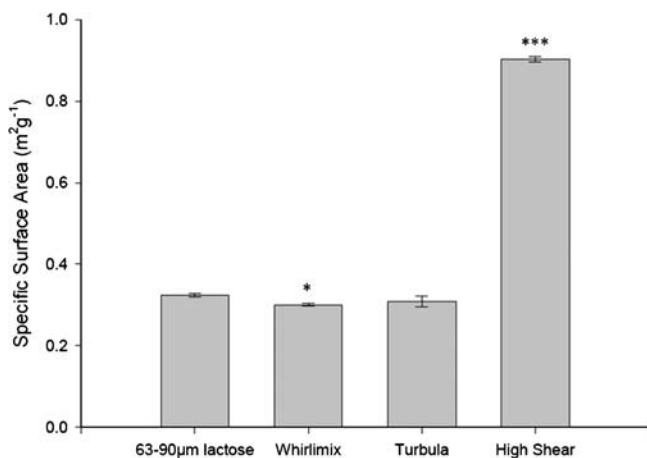
Fig. 3. The specific surface area of the sieved 63–90 μm α-lactose monohydrate before and after, whirlimixer, turbula and high shear processing (*$p<0.05$, **$p<0.001$ with reference to the sieved lactose).

the amount of intrinsic fine lactose material. This is further supported by scanning electron micrograph in Fig. 4D. These data suggest that particle–particle iteration processes and the shear forces exhibited during high shear blending of lactose, have led to a reduction in the particle size of the source material with a corresponding increase in fine lactose material. Such behaviour was not characteristic of the other blending processes.

In Vitro Aerosol Deposition of Budesonide

The relative standard deviation of the drug content uniformity within the formulations were all less than 3%. These data suggested that the active ingredient was uniformly distributed and confirmed that the blending process did not affect drug homogeneity.

Stage by stage deposition data of the formulations of budesonide and α-lactose monohydrate mixed using whirli-mixing, turbula and high-shear blending are shown in Fig. 5. In addition, the calculated MMAD and GSD of the drug particles along with the emitted dose and fine particle fraction of the emitted dose (FPF$_{ED}$; <5 μm), are tabulated in Fig. 5.

The emitted dose and FPF$_{ED}$ of the formulation blended using the whirlimixer was determined as 132.2 ± 7.6 μg and $31.5\pm1.1\%$, respectively (Fig. 5). The aerosol delivery performance of the formulation processed using the turbula was significantly ($p<0.01$) lower than the whirlimixer blend, with a FPF$_{ED}$ of $27.7\pm0.8\%$. In contrast, high shear blending led to an increase in the overall performance of the formulation with a significant increase ($p<0.001$) in the emitted dose (161.9 ± 1.6 μg) and the fine particle fraction ($39.2\pm0.4\%$, $p<0.01$). These data support the stage-by-stage deposition data shown in Fig. 5, which indicated that high shear processing significantly ($p<0.05$) increased the amount of drug deposited on the lower stages of the impactor. It is further evident that the high shear processed formulation presented significantly
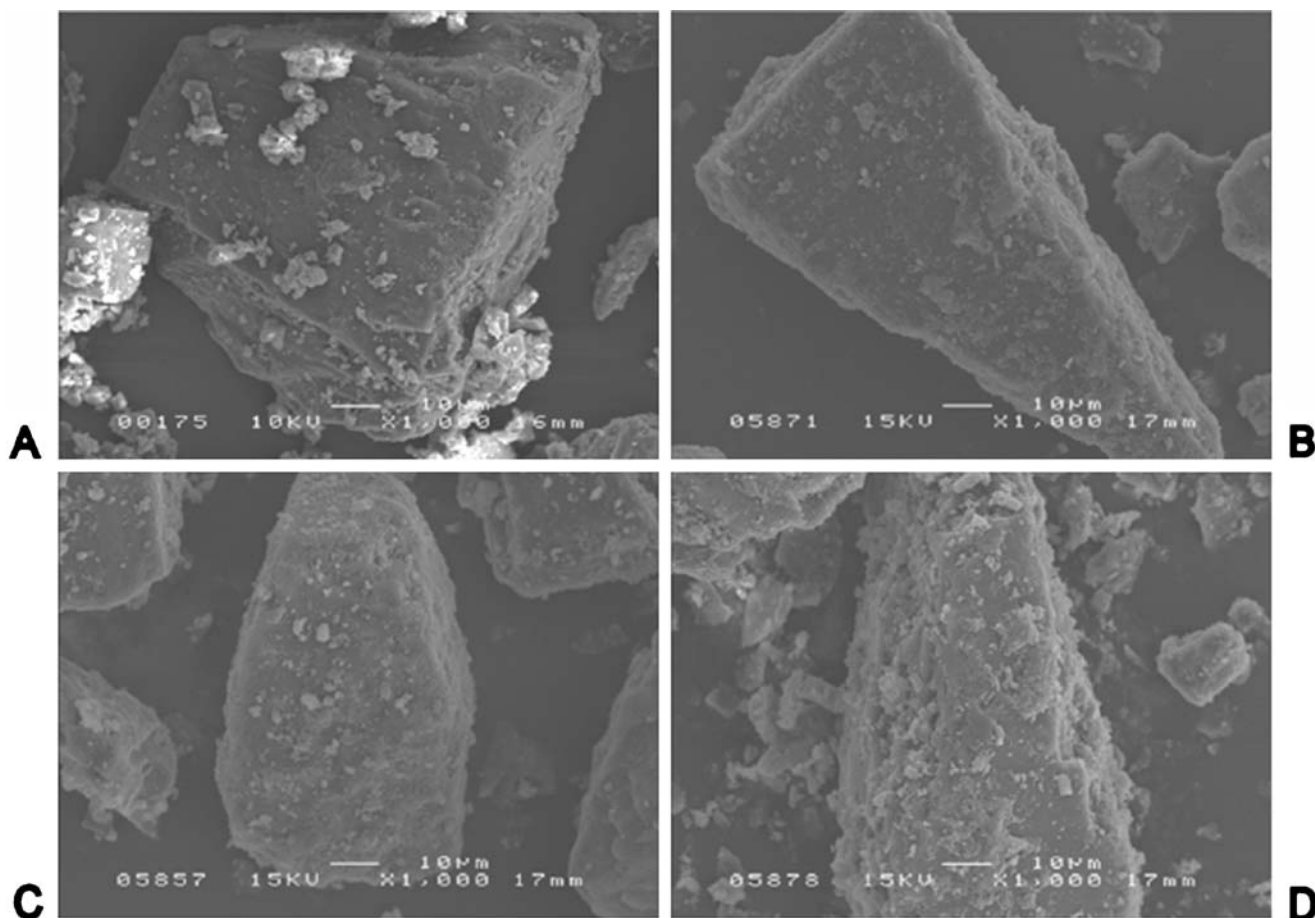

Fig. 4. Scanning electron micrographs of **A** sieved 63–90 μm lactose, **B** whirlimixer processed lactose, **C** turbula processed lactose and **D** high shear processed lactose at ×1,000 magnification.
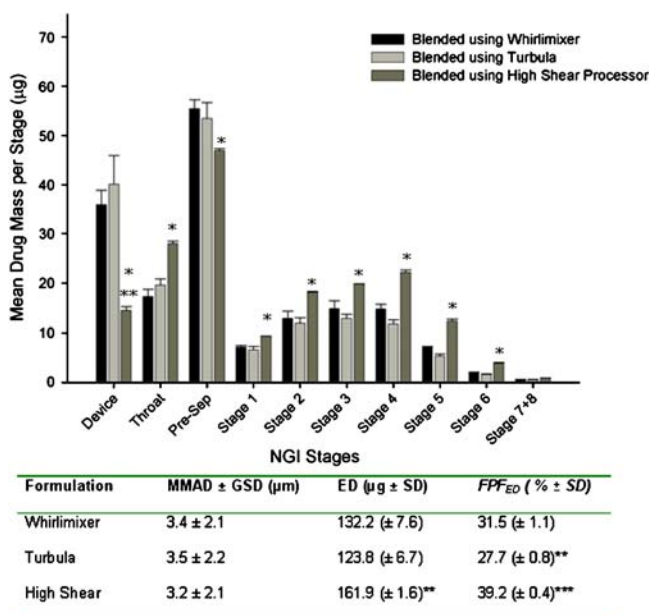
Fig. 5. Stage-by-stage deposition profile of the whirlimixer, turbula and high shear blended formulation on aerosolization into a NGI at 60 l min^{-1}. (*$p<0.05$, **$p<0.01$, ***$p<0.001$).

($p<0.001$) lower levels of drug retention in the device than formulations blended by the other mixing processes.

The different blending systems employed to process the carrier based DPI formulations have been shown to affect the respective performance of the formulations. The increase in the performance of the DPI formulation blended *via* high shear mixing can be directly associated with process induced changes to the excipient resulting in the size reduction of the lactose and the *in situ* generation of intrinsic fine excipient material. Although high shear processing of lactose did result in a decrease in the median particle size of the carrier, a number of studies have demonstrated that it is the presence of fine excipient particles and not carrier particle size that directly affects DPI performance (10,26).

Numerous studies have shown that carrier materials containing intrinsic or extrinsic fine excipient material increases the performance of DPI formulations (8,10). The mechanisms by which fines improve DPI formulation performance remain speculative, although as mentioned previously both the "active site" and "drug/fines agglomerate" theories have been proposed.

The active site theory suggests that the fine lactose material bind to high energy or active sites present on the carrier particle, thereby leaving passive (low adhesion) sites for drug-carrier adhesion (1). The corresponding reduction in adhesion allows the drug to be dispersed more freely and thereby increases fine drug particle delivery (8,27). Previous studies investigating the effect of blending order of drug, coarse carrier and fine excipient material on formulation performance have found contradicting evidence to support the active-site theory (21,28). One particular study found that for formulations where the coarse carrier was blended with fine excipient material prior to the addition of the active resulted in greater fine particle delivery than those formulations that were produced by pre-blending the coarse carrier and drug prior to the addition of the excipient fines (29).

However, similar studies have found that the performance of ternary DPI formulations produced greater fine particle delivery regardless of blending order (30,31). Such investigations have brought into question the validity of the active site theory as a mechanism of action of fines in DPI systems. In contrast, the agglomerate theory suggests that during blending processes, there is redistribution of the drug between the carrier surface and fine excipient particles in producing mixed agglomerates of drug and fine excipient that can be more easily detached from the carrier surface and dispersed (9,32,33).

While a combination of these theories have been utilised to explain the mechanism by which fines improve performance, there remains limited evidence on the role of fines on powder fluidization and the elutriation behaviour of the active ingredient.

Powder Fluidization and Entrainment

The *ex situ* addition or the *in situ* generation of excipient fines within carrier based DPI formulations will have a significant influence on the bulk characteristics of the formulation (i.e. powder flowability, packing properties and tensile strength), which may have a dramatic effect on powder fluidization and hence drug product performance. An understanding of the possible influence of fines on the flow properties, compressibility and free volume of the formulation on powder fluidization is therefore critical.

In order to determine the influence of blending processes on the bulk powder properties and fluidization behaviour of the respective formulations, powder compressibility and permeability tests were conducted in conjunction with high speed imaging to visualize the fluidization behaviour of the processed powders.

The compressibility of the powders was measured as a function of an applied normal stress using a FT4 powder rheometer. The helical blade of the rheometer was replaced with a porous piston that was pressed on to the powder bed. In this way, the change in the free volume of the powder as a function of applied normal stress was measured. The behaviour of powders under compression can be used as a generic criterion for powder flowability and fluidization. Generally, less cohesive powders exhibit ordered packing and good flowability and are not very compressible under consolidation (18). In contrast, cohesive powders pack in open structures and compress easily, and demonstrate poorer flowability than less cohesive materials (18). In terms of powder fluidization, cohesive powders are generally more difficult to fluidize than less cohesive materials (34).

The bulk powder characteristics and powder flow properties of the processed lactose samples suggested significant differences between lactose batches processed under the different blending regimens. The bulk tap density of lactose processed with a whirlimixer, turbula and high shear blender were measured as 0.67 ± 0.02 g cm^{-3}, 0.66 ± 0.05 g cm^{-3} and 0.47 ± 0.01 g cm^{-3}, respectively. The lower bulk tap density of the high shear processed lactose is indicative of the higher fines content associated with the material. Furthermore, the free volume of a powder mass can be defined as $\varepsilon=(1-\rho/\rho_\mathrm{p})$, where ρ is the bulk density of the powder and ρ_p is the particle density of lactose (1.54 g cm^{-3}; 35). The ε values of
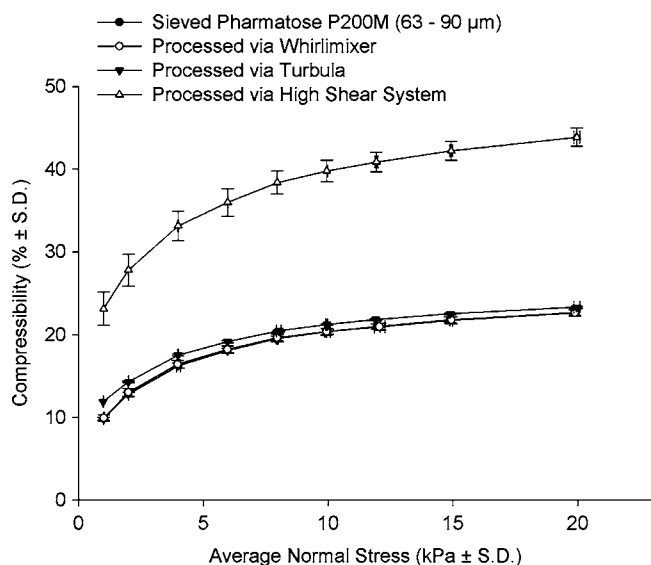
Fig. 6. The %compressibility of the sieved lactose before and after, whirlimixer, turbula and high shear processing with increasing normal stress.

the whirlimixer and turbula processed lactose were 0.56 and 0.57, respectively, whereas the ε value of the high shear processed lactose was determined as 0.69. The higher ε value of the high shear processed lactose demonstrated that the material had a greater free volume than the other batches. These data suggest that the lactose powder processed *via* high shear blending exhibited poor packing. For the high shear processed lactose, the *in situ* formation of excipient fines may increase the cohesivity of the powder thereby increasing the free volume of the powder bed.

The degree of compressibility (%compressibility) of the processed lactose samples as a function of applied load is shown in Fig. 6. The %compressibility describes the percentage increase in bulk density (decrease in free volume) of the powder on application of a normal stress. It is evident from Fig. 6, that between applied loads of 1–20 kPa the % compressibility of the sieved and whirlimixer processed lactose increased from 9.9 ± 0.4 to $22.6\pm0.4\%$, whereas the %compressibility of the turbula processed lactose increased from 11.9 ± 0.3 to $23.3\pm0.1\%$. There were no statistically significant differences between the %compressibility of whirlimixer and turbula processed lactose. In contrast, the %compressibility of high shear processed lactose significantly ($p<0.05$) increased from 23.1 ± 2.0 to $43.9\pm1.1\%$ with increasing load.

The greater compressibility of the high shear processed lactose supports the bulk density measurements of the material in comparison to lactose powder processed *via* the whirlimixer and turbula. These data suggest that the presence of fines increases the cohesive interparticulate forces within the powder bed and thereby affect the tensile strength of the material under stress. Previous studies have shown that under increasing consolidation stresses the tensile strength of a cohesive material will increase (17,18,36). Thus, consolidation stresses imposed on the material during processing, device filling and handling may directly affect the tensile strength of the bulk powder, which may influence the fluidization and hence the overall performance of a DPI formulation.

To understand the effects of the bulk powder properties on the fluidization properties of the respective processed materials, powder permeability tests were also conducted. For these investigations, a constant airflow rate of 2 mm s^{-1} was permeated through the powder bed under varying applied load, whilst the pressure drop across the powder bed required to maintain the constant airflow velocity was determined. The average pressure drop across powder beds of sieved, whirlimixer, turbula, and high shear processed lactose as a function of the stress applied to the powder bed is shown in Fig. 7. There were no statistically significant differences between the pressure drop created across the sieved, whirlimixer and turbula processed lactose, with pressure drop values ranging from 0.27 ± 0.01 to 0.46 ± 0.01 kPa as the applied load was increased from 1–20 kPa. These measurements suggested that sieved, whirlimixer and turbula processed lactose powders were highly permeable and exhibited low cohesivity and tensile strength. These powders should exhibit, therefore, a low MFV during fluidization and may not create a significant pressure differential in increasing the aerodynamic drag forces across the static powder bed. Such powders have previously been observed to fluidize homogenously owing to their lower tensile strength (14).

In contrast, the pressure drop generated across the high shear processed lactose were significantly ($p<0.05$) greater, with values ranging from 0.49 ± 0.08 to 1.54 ± 0.01 as the normal applied stress was increased from 1–20 kPa (Fig. 7). Such behaviour is indicative of a cohesive powder, which has low permeability to the flow of air through the powder bed (37). These data suggest that the presence of greater fine excipient content in the high shear processed lactose powder, may contribute to an increase in the cohesive interparticulate forces within the powder bed, thereby increasing the tensile strength of the powder bed. Jackson previously reported that the presence of cohesive interparticulate forces generates a greater tensile strength within the powder bed, which
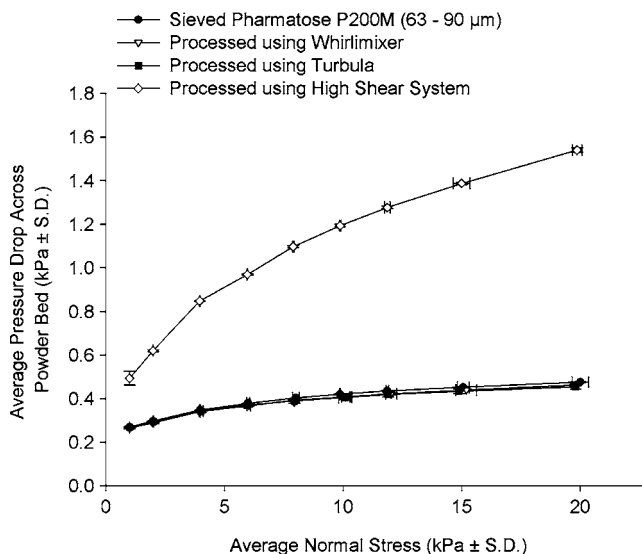

Fig. 7. The average pressure drop across powder beds of sieved 63–90 μm α-lactose monohydrate before and after, whirlimixer, turbula and high shear processing at a constant airflow velocity of 2 mm s^{-1} under increasing normal stress.
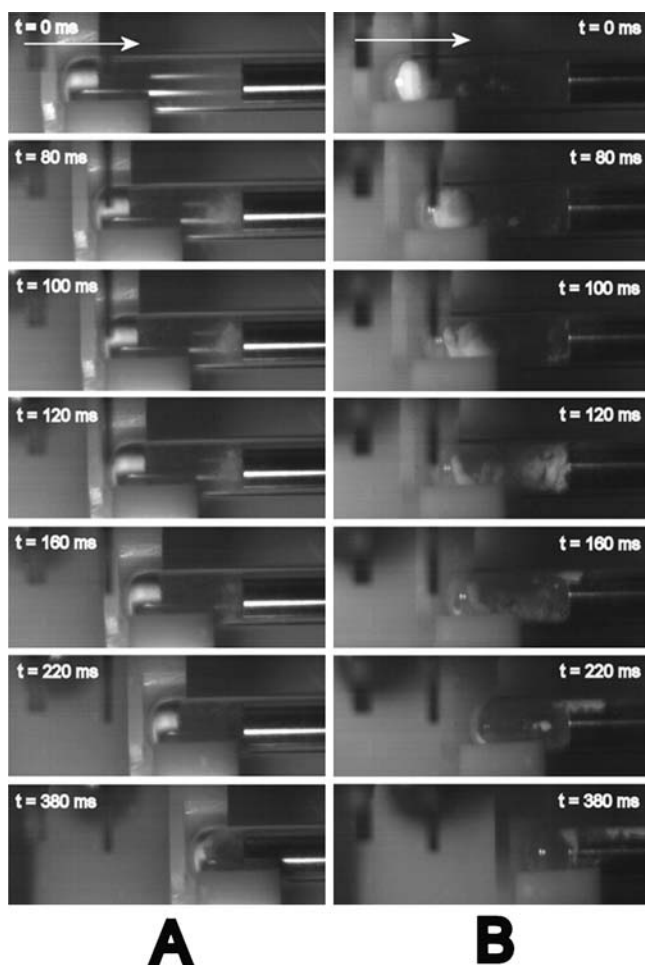
Fig. 8. High speed images of the fluidization and dispersion properties of **A** turbula and **B** high shear processed lactose as determined in the modified re-suspension rig. Arrows indicate the direction of airflow. The time shown in milliseconds, determined from the onset of activation.

stabilizes it to disturbances *via* an airflow (38). As a result, air is not free to permeate through the powder bed, and therefore, the airflow permeates through channels formed within the powder bed and will result in the powder being lifted as a plug in relation to the fracturing of the powder bed. It is conceivable therefore that the increase in airflow resistance due to the greater tensile strength of the powder would shift the MFV, resulting in the generation of higher aerodynamic drag forces within a DPI device. Thus, the fluidization and entrainment properties of the formulations processed using these different mixing methods may be directly related to differences in their bulk powder properties.

These data suggest that the *in situ* formation or the *ex situ* addition of fine excipient material may affect the bulk powder properties of a DPI formulation, which in turn may directly affect the fluidization and aerosolization behaviour of the material. It is therefore suggested that the presence of excipient fines act to increase the cohesivity and the corresponding tensile strength of the powder, which will directly influence the MFV and increase the aerodynamic drag forces generated within the DPI device.

Cohesive powders are known to be difficult to fluidize and have been shown to lift as plugs or fracture in comparison

to less cohesive powders, which fluidize more homogenously *via* an erosion mechanism (39). To investigate the fluidization and entrainment mode of the low and high shear processed lactose, a modified powder re-suspension rig was employed. The rig utilised a Sympatec ASPIROS powder dispersion unit, in which small concentric vials (inner diameter equivalent to a size III capsule) were loaded with approximately 33 mg of powder. A high-speed camera (Redlake MotionPro X-4, Lake Image Systems Ltd, Tring, UK) was positioned into the ASPIROS unit to visualise the fluidization and entrainment of the lactose samples processed using whirlimixer, turbula and high shear mixing. The images produced were used for qualitative analysis of the influence of processing on the fluidization behaviour of the prepared formulations and their relationship to the bulk powder measurements and formulation performance.

The re-suspension behaviour of the processed powders are shown at well-defined time intervals in Fig. 8. Two distinct mechanisms of powder fluidization were evident. The fluidization of the turbula processed lactose was found to follow an erosion mechanism. Particles were continually entrained from the surface of the powder bed into the airflow as small pockets of powder from the surface of the powder bed. This is indicated in frames 1–5 in Fig. 8A, which show the progressive erosion of material from the surface of the powder bed, which was maintained at a steady rate resulting in a continuous stream of particles being entrained into the airflow. A similar trend was observed for the sieved and whirlimixer processed lactose (data not shown). This process is similar to the 'dispersive' fluidization mode suggested by Zeng *et al.* (19) and is primarily exhibited by non cohesive powders (13,36,39).

In contrast, high speed images of the fluidization behaviour of the high shear processed lactose indicated a completely different mode of fluidization. As shown by the difference in response of the powder after 80 and 100 ms, and shown more clearly in Fig. 9, the images indicate that the powder bed fractures towards the bottom of the bed. It is interesting to note, that the powder does not fracture at the point of contact between the powder and the tube interface. Valverde *et al.* (17) have previously concluded that conditions for the tensile
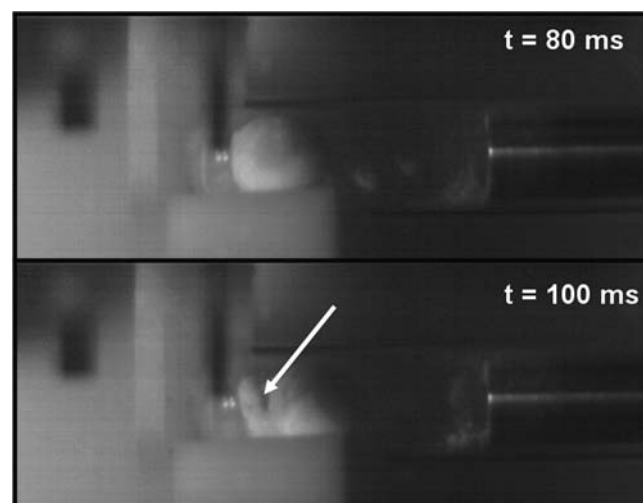

Fig. 9. High-speed photographs of the fracturing behaviour of the high shear processed lactose bed. *Arrow* indicates the point of fracture in the bed.

yield strength are always met towards the bottom of the bed but not specifically at the interface with the support. It is thought that the "fracture" process is driven by the dynamic equilibrium between interparticle attractive forces and flow shear, which supports the particle weight under gravity (12).

Upon fracture the powder bed is shown to entrain as a plug. Eventually the powder plug yields to produce a dense cloud of particles and agglomerates, which exhibit chaotic behaviour with a high frequency of particle–particle and particle–wall collisions (Fig. 8B). This type of fluidization of cohesive powders such as the high shear processed lactose has been previously observed by Valverde *et al.* (14) and Shrimpton (39).

The differences observed in the fluidization and entrainment properties of lactose processed using the turbula and high shear blending, may account for the different formulation performances of the respective formulations. For the proposed mechanisms of powder fluidization and entrainment, the high shear processed formulation, which follows the "fracture" mechanism had greater fine particle delivery and lower drug retention in the device than the whirlixmixer and turbula processed formulations, which exhibited a surface erosion mechanism.

The greater fine particle delivery of the high shear processed formulation is primarily due to the formation of the intrinsic fines. However, whilst mechanisms by which fines increase fine particle delivery have concentrated on active site and agglomerate theory, an alternative mode of action of fines may be directly related to their effect on bulk powder properties and, thereby, fluidization and entrainment behaviour of the powder bed. The presence of excipient fines have been shown to increase the cohesivity of lactose and thereby the tensile strength of the powder bed. The greater tensile strength of formulations containing fines will lead to a significant shift in the MFV, which will result in the drug particulates experiencing greater aerodynamic drag force within the device.

The formation of high-density aerosol clouds *via* the fracture mechanism may also result in greater particle–particle and particle–surfaces collisions, which may enhance the removal of drug fines from the carrier lactose surface. This has been previously investigated by John *et al.* who showed that impacting airborne particles are more effective in causing particle re-suspension, because the momentum of airborne particles, owing to their density, are three orders of magnitude higher than that of the equivalent volume of air (40). Theerachaisupakij *et al.* (41) have also suggested that the re-entrainment of particles larger than several micrometers is controlled by aerosol collision. The implication of impacting airborne particles, as observed for the high shear processed lactose, provides sufficient detachment force to overcome the particle–particle interactions between the fine drug particles and large carrier lactose. In overcoming these interactive forces, a greater proportion of fine particles are liberated leading to an increase in fine particle delivery of the drug in the respiratory tract.

CONCLUSION

Different blending regimens used to produce carrier based DPI formulations of budesonide and lactose monohydrate were found to have a significant influence on bulk powder, fluidization and aerosolization characteristics. High shear blending of the excipient was shown to increase the percentage of fine excipient material, which resulted in a significant increase in the FPF of the formulation. The *in situ* generation of fine excipient material was shown to increase the %compressibility and decrease the air permeability of the powder bed. High speed photography suggested fluidization properties of low and high shear processed lactose were different. The increase in the cohesive properties within the bulk powder with the generation of fines resulted in the fracturing of the powder bed at a critical point. The powder bed was lifted as a plug, which subsequently collapsed forming a high density aerosol cloud. As a result, the likelihood of interparticle collision and particle–wall collision with any de-aggregating mechanism in the device is high compared to the other processes which showed a steady and continual entrainment from the surface of the powder bed.

The effect of fine excipient particles on powder fluidization and, hence, DPI performance may be related to an increase in the tensile strength of the powder bulk, which significantly shifts the MFV and thereby increasing the aerodynamic drag forces exerted to fluidize the powder bed. The potential for increasing the aerodynamic drag force experienced by the powder and an increase in the frequency of particle–particle and particle–wall collisions may improve the likelihood of drug particles attached to the carrier particles surfaces being de-aggregated and thus improving aerosol performance.

This study highlights that controlling and understanding the effect of blending regimes on the bulk powder characteristics and fluidization properties is critical to producing robust and effective DPI formulations. Furthermore, the use of the modified re-suspension rig, in conjunction with bulk powder characterisation tools may assist in understanding the dynamic link between processing, bulk powder properties and formulation performance.

REFERENCES

1. J. A. Hersey. Ordered mixing: A new concept in powder mixing practise. *Powder Technol.* **11**:41–44 (1975).
2. R. J. Malcolmson, and J. K. Embleton. Dry powder formulations for pulmonary delivery. *Pharm. Sci. Technol. Today* **1**:394–398 (1998).
3. S. Edge, A. Kibbe, and K. D. Kussendrager. Lactose monohydrate. In R. C. Rowe, P. J. Sheskey, and S. C. Owen (eds.), *Handbook of Pharmaceutical Excipients*, Pharmaceutical Press, London, UK, 2005, pp. 389–395.
4. H. W. Frijlink, and A. H. de Boer. Dry powder inhalers for pulmonary drug delivery. *Expert Opin. Drug. Del.* **1**:67–86 (2004).

5. T. Srichana, G. P. Martin, and C. Marriott. Dry powder inhalers: The influence of device resistance and powder formulation on drug and lactose deposition *in vitro*. *Eur J. Pharm. Sci.* **7**:73–80 (1998).

6. M. D. Louey, M. van Oort, and A. J. Hickey. Standardised entrainment tubes for the evaluation of pharmaceutical dry powder dispersion. *J. Aerosol. Sci.* **37**:1520–1531 (2006).

7. M. D. Louey, and P. J. Stewart. Particle interactions involved in aerosol dispersion of ternary interactive mixtures. *Pharm. Res.* **19**:1524–1531 (2002).

8. S. K. Tee, C. Marriott, X. M. Zeng, and G. P. Martin. The use of different sugars as fine and coarse carriers for aerosolised sulbutamol sulphate. *Int. J. Pharm.* **208**:111–123 (2000).

9. P. Lucas, K. Anderson, and J. N. Staniforth. Protein deposition from dry powder inhalers: Fine particle multiplets as performance modifiers. *Pharm. Res.* **15**:562–569 (1998).

10. N. Islam, P. Stewart, I. Larson, and P. Hartley. Lactose surface modification by decantation: Are drug-fine lactose ratios the key to better dispersion of salmeterol xinafoate from lactose-interactive mixtures? *Pharm. Res.* **21**:492–499 (2004).

11. M. Telko, and A. J. Hickey. Dry powder inhaler formulations. *Respir. Care* **50**:1209–1227 (2005).

12. A. Castellanos, J. M. Valverde, A. T. Perez, A. Ramos, and P. K. Watson. Flow regimes in fine cohesive powders. *Phys. Rev. Lett.* **82**:1156–1159 (1999).

13. A. Castellanos. The relationship between attractive interparticle forces and bulk behaviour in dry and uncharged fine powders. *Adv. Phys.* **54**:263–376 (2005).

14. J. M. Valverde, N. Rasenack, A. Castellanos, and P. K. Watson. The tensile strength of cohesive powders and its relationship to consolidation, free volume and cohesivity. *Powder Technol.* **97**:237–245 (1998).

15. J. R. Howard. *Fluidized Bed Technology: Principles & Application*, Adam Hilger, Bristol, UK, 1989, pp. 25–32.

16. P. C. Carman. Fluid flow through granular beds. *Trans. Inst. Chem. Eng.* **15**:150 (1937).

17. J. M. Valverde, A. Ramos, A. Castellanos, and P. K. Watson. The tensile strength of cohesive powders and its relationship to consolidation, free volume and cohesivity. *Powder Technol.* **97**:237–245 (1998).

18. P. K. Watson, J. M. Valverde, and A. Castellanos. The tensile strength and free volume of cohesive powders compressed by gas flow. *Powder Technol.* **115**:45–50 (2001).

19. X. M. Zeng, G. P. Martin, and C. Marriott. *Particulate Interaction in Dry Powder Formulations for Inhalation*, Taylor & Francis, London, UK, 2001, pp. 104–114.

20. A. H. de Boer, P. Hagedoorn, D. Gjaltema, J. Goede, and H. W. Frijlink. Air classifier technology (ACT) in dry powder inhalation: Part 1. Introduction of a novel force distribution concept (FDC) explaining the performance of a basic air classifier on adhesive mixtures. *Int. J. Pharm.* **260**:187–200 (2003).

21. D. Ganderton. General factors influencing drug delivery to the lung. *Respir. Med.* **91**:13–16 (1997).

22. P. L. Stephenson, and W. J. Thiel. The mechanical stability of ordered mixtures when fluidised and their pharmaceutical application. *Powder Technol.* **26**:225–227 (1980).

23. N. M. Concessio, M. van Oort, M. R. Knowles, and A. J. Hickey. Pharmaceutical dry aerosols: Correlation of powder properties with dose delivery and implications for pharmacodynamic effect. *Pharm. Res.* **16**:828–834 (1999).

24. T. Crowder, and A. J. Hickey. Powder specific active dispersion for generation of pharmaceutical aerosols. *Int. J. Pharm.* **327**:65–72 (2006).

25. R. Freeman. Measuring the flow properties of consolidated, conditioned and aerated powders—A comparative study using a powder rheometer and a rotational shear cell. *Powder Technol.* **174**:25–33 (2007).

26. P. M. Young, H. K. Chan, H. Chiou, S. Edge, T. H. S. Tee, and D. Traini. The influence of mechanical processing of dry powder inhaler carriers on drug aerosolization performance. *J. Pharm. Sci.* **96**:1331–1341 (2007).

27. P. M. Young, S. Edge, D. Traini, M. D. Jones, R. Price, D. El-Sabawi, C. Urry, and C. Smith. The influence of dose on the performance of dry powder inhalation systems. *Int. J. Pharm.* **296**:26–33 (2005).

28. X. M. Zeng, S. K. Tee, G. P. Martin, and C. Marriott. *Effects of Mixing Procedure and Particle Size Distribution of Carrier Particles on the Deposition of Salbutamol Sulphate from Dry Powder Inhaler Formulations, Proceedings of Drug Delivery to the Lungs 7*, The Aerosol Society, London, UK, 1996, pp. 40–43.

29. X. M. Zeng, G. P. Martin, S. K. Tee, A. A. Ghoush, and C. Marriot. Effects of particle size and adding sequence of fine lactose on the deposition of salbutamol sulphate from dry powder formulations. *Int. J. Pharm.* **182**:133–144 (1999).

30. X. M. Zeng, K. H. Pandhal, and G. P. Martin. The influence of lactose carrier on the content homogeneity and dispersibility of beclomethasone dipropionate from dry powder aerosols. *Int. J. Pharm.* **197**:41–52 (2000).

31. T. Hartmann, and H. Steckel. *Influence of Mixer Type and Mixing Conditions on Delivery Efficiency from Flowcaps, a Capsule-Based Dry Powder Inhaler, Proceedings of Drug Delivery to the Lungs 15*, The Aerosol Society, London, UK, 2004, pp. 178–181.

32. N. Islam, P. Stewart, I. Larson, and P. Hartley. Surface roughness contribution to the adhesion force distribution of salmeterol xinafoate on lactose carriers by atomic force microscopy. *J. Pharm. Sci.* **94**:1500–1511 (2005).

33. H. Adi, P. J. Stewart, and I. Larson. *Influence of Different Sugars on the Dispersion of Salmeterol Xinafoate in Ddry Powder Inhalation Formulations, Proceedings of Fformula IV: Frontiers in Formulation Science*, Royal Society of Chemistry, London, UK, 2005, pp. 25–28.

34. J. M. Valverde, and A. Castellanos. Types of gas fluidization of cohesive granular materials. *Phys. Rev. E.* **75**:1–6 (2007).

35. M. D. Jones *An Investigation into the Dispersion Mechanisms of Ternary Dry Powder Inhaler Formulations by the Quantification of Interparticulate Forces*, PhD Thesis, University of Bath, Bath, UK, 2006, pp. 110–111.

36. J. M. Valverde, and A. Castellanos. Compaction of fine powders: From fluidized agglomerates to primary particles. *Granul. Matter* **9**:19–24 (2007).

37. A. Castellanos, J. M. Valverde, and M. A. S. Quintanilla. Fine cohesive powders in rotating drums: Transition from rigid-plastic flow to gas-fluidized regime. Phys. Rev. E. 65: Art. No. 061301 (2002).

38. R. Jackson. *The Dynamics of Fluidized Particles*, Cambridge University Press, Cambridge, UK, 2000, pp. 117–124.

39. J. Shrimpton. *The challenge of predicting particle dynamics in dry powder inhalers, Proceedings of Drug Delivery to the Lungs 16*, The Aerosol Society, London, UK, 2005, pp. 84–88.

40. W. John, D. N. Fritter, and W. Winklmayr. Re-suspension induced by impacting particles. *J. Aerosol. Sci.* **22**:723–736 (1991).

41. W. Theerachaisupakij, S. Matsusaka, Y. Akashi, and H. Masuda. Re-entrainment of deposited particles by drag and aerosol collision. *J. Aerosol. Sci.* **34**:261–274 (2003).