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Improving aerosolization of drug powders by reducing powder intrinsic cohesion via a mechanical dry coating approach

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ABSTRACT

The aim of this study was to investigate the effect of coating on the aerosolization of three model micronized powders. Three model powder materials (salbutamol sulphate, salmeterol xinafoate, triamcinolone acetonide) were chosen not only for their different chemical properties but also for their different physical properties such as shape and size distribution. Each powder was coated with 5% (w/w) magnesium stearate using two different dry mechanofusion approaches. After mechanofusion, both poured and tapped densities for all three model drug powders significantly increased. There were significant improvements in aerosolization behavior from an inhaler device for all model powders after mechanofusion. Such improvements in aerosolization were attributed to the reduction in agglomerate strength caused by decreasing powder intrinsic cohesion via surface modification. The work also indicated that the effect of the coating was dependant on the initial particle properties.

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1. Introduction

Only drug-containing aerosol particles with aerodynamic diameter below about 5 μm can be efficiently transported through the upper airways to reach the target sites in lungs (Timsina et al., 1994). However, as dry powders in isolation, such fine particles will generally exhibit poor flowability and poor aerosolization behaviors, given the inherent strong cohesive forces as a result of their small particle size and high relative surface area (Chan and Chew, 2003). Thus, in practice, dry powder inhaler (DPI) formulations are frequently developed as ordered mixtures which include a coarse lactose carrier to improve the flowability and ensure consistency of aerosolization of the formulations (Smyth and Hickey, 2005).

However, there are some disadvantages of carrier-based DPI formulations which may limit the use of such a lactose carrier. Undesired chemical reactions may occur between the lactose and certain drugs, for example some peptides or proteins (Patton and Platz, 1992). Moreover, lactose intolerance restricts its use, and protein contaminants of lactose may restrict use in the formulation for those patients who are allergic to such substances (Kretchme and Faber, 1972). Furthermore, for those medications requiring high-dose drug treatment, the use of carriers will, in practice, substantially limit the drug load of the formulation to a maximum in the order of a few milligrams or often much less. In the absence of a carrier, drug pelletization may be used to overcome flow issues; however, the control of agglomerate strength is critical since it needs a favorable balance in agglomerate strength between the formation and de-agglomeration of loose agglomerates (Smyth and Hickey, 2005). The precise control of the agglomerate strength during the pelletization process is a challenge. Alternatively, new technologies can be used to generate highly porous low density particles with large physical size but small aerodynamic size (Edwards et al., 1997). This concept provides an elegant solution, but such particles are generally complex and challenging to produce and handle in practice, and such low density can require an impractically large volume of powder. Moreover, the delivery of such physically large particles to the lungs may experience difficulty given that the peripheral airway of the lungs is relatively small (Smyth and Hickey, 2005). Therefore, there is a motivation to develop simple and practical technologies that could lead to carrier-free high-dose DPI formulations with suitable flow, fluidization and de-agglomeration behaviors.

A general aim has long been recognized to reduce the intrinsic cohesion of a fine powder. This concept was recognized as far back as the 1850s, when active substances were attached to the pollen of the lycopodium forming a low cohesion vehicle for powder inhalation (Collins and Collins, 1851). Several recent studies have explored various strategies to develop appropriate formulations by modifying particle surface properties. Increasing the corrugation of the drug particle surfaces through spray drying has been demonstrated to result in better aerosolization behavior of bovine serum albumin (BSA) (Chew and Chan, 2001). Such improvements were attributed to the reduced cohesive forces between fine drug particles caused by decreasing their contact area (Adi et al., 2008).

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Coating tobramycin-containing powder with lipids via a spray drying approach also was shown to improve the aerosolization (Pilcer et al., 2006). Similarly, modifying the surface of drug particles with amino acids such as leucine, using spray drying or a physical vapor deposition approach, has also been shown to improve the drug delivery efficiency of dry powder inhaler formulations (Ganderton et al., 2000; Najafabadi et al., 2004; Rabbani and Seville, 2005; Raula et al., 2008). This improved efficiency was attributed to an enrichment of leucine at the surface of the drug particles, reducing the inter-particle cohesive forces (Chew et al., 2005). However, using the spray drying route in developing DPI formulations, particularly for those containing small organic molecules, may bring general concerns over forming meta-stable amorphous structures that are generally characteristic of the spray drying approach (Chow et al., 2007).

Recently, mechanical dry coating techniques have attracted interest. These techniques appear well suited to modifying inter-particulate interactions of dry powders by changing their surface characteristics. A single-step mechanical dry coating method that is solvent-free should be simpler, cheaper, safer, easier to scale up and more environment-friendly than liquid-based alternatives (Bose and Bogner, 2007). "Mechanofusion" is a generic term used for several types of mechanical dry coating approaches for particle and powder modification (Pfeffer et al., 2001). A number of different mechanofusion systems and mechanisms are available, but in general they consist of a cylindrical chamber and a process head which rotate relative to each other at high speed to create intense shear and compression of the core (host) and coating (guest) particles both via impaction with the face of the process head and via compression as the particles are pushed between the edge of the head and the chamber wall. The process head motion will break-up agglomerates of the cohesive host particles to expose their surfaces as it rotates at high speed. A considerable amount of thermo-mechanical energy is generated which coats the guest material onto the exposed surfaces of the host particles (Alonso et al., 1989). However, unlike more conventional milling and co-milling processes, the energy input in mechanofusion is more tightly controlled because the process head geometry, speed and gap from the wall are fixed and the process can be tuned to encourage coating but not size reduction, thus, excess heat or damage kept to a minimum (Morton, 2006). Several reports have demonstrated that the powder flowability can be improved by coating host particles with the traditional glidant fumed silica (Ramlakhan et al., 2000; Yang et al., 2005). The reduction in inter-particulate attractive forces after dry coating with silica is believed to occur by the increasing the distance of closest approach of the host particles or by reducing the contact area between two or more host particles. In previous studies, we have demonstrated that the flowability of a range of fine lactose powders can be improved substantially via mechanofusion with the lubricant magnesium stearate (and to a greater extent than that observed with fumed silica) (Zhou et al., 2010). Given that the improvements in powder flowability have been demonstrated to be attributed to the reduction in intrinsic powder cohesion after coating (Zhou et al., 2009), mechanofusion appears a potential technology to improve aerosol performance of high-dose DPI formulations by modifying drug particles. There are very few published studies that have applied the dry coating approach in carrier-free DPI formulation development, although it has been used to engineer the much larger lactose carrier particles (Kumon et al., 2006), but these powders already have good flow properties in their original state. Kawashima et al. (1998) reported the co-processing of micronized pranlukast hydrate particles with anhydrous silicic acid, but there are concerns about the safety issues of inhaling nanoparticles of silicic acid (Rogueda and Traini, 2007).

An earlier study reported a preliminary investigation on improving dispersibility of drug powders using mechanofusion (Begat et al., 2009). However, the relationship between powder aerosolization behaviors and their intrinsic cohesion has not been explored. In this work, a detailed study was undertaken using a more diverse range of drug powders, with a selected variation in particle properties. Three micronized drug powders (salbutamol sulphate, salmeterol xinafoate, triamcinolone acetonide) were selected based not only on the differences in their chemical properties but also in their physical properties such as particle shape and particle size. Salbutamol sulphate exhibits hydrophilic nature (Brodka-Pfeiffer et al., 2003) while salmeterol xinafoate and triamcinolone acetonide are hydrophobic (Murnane et al., 2008; Williams et al., 1999). Furthermore, these micronized drug powders were believed to possess different particle shapes. In the preliminary part of this study, examination of the shapes and size distributions of each respective material is reported, and confirms a number of such differences. It should also be noted that although each of these drug materials are well known for their use in inhaled therapy, their use here was solely as model materials and no attempt was made to formulate them to specific realistic dose levels or into a final optimized formulation: in contrast, they were selected as three different models to assess how efficiently a hypothetical high-mass of powder (i.e. $\geq$10 mg) could be aerosolized from a simple device. The powder cohesion was modified by mechanofusing drug particle surfaces with a pharmaceutical lubricant, magnesium stearate. The intrinsic cohesion was characterized using a well established shear cell method. The relationship between the aerosolization behavior of model powders from a simple inhaler device and their intrinsic cohesion was therefore investigated.

2. Materials and methods

2.1. Materials

Micronized triamcinolone acetonide (TA) was supplied by (Farmabios S.p.A., Gropello Cairoli, Italy). Micronized salmeterol xinafoate (SX) was donated by GlaxoSmithKline, Middlesex, UK. Micronized salbutamol sulphate (SS) was supplied by Cambrex Profarmaco, Milan, Italy. Magnesium stearate (MgSt) was supplied by Mallinckrodt Baker Inc., Phillipsburg, NJ. Cyclohexane and methanol were supplied by Scharlau Chemie S.A., Barcelona, Spain. All samples were used as received.

2.2. Methods

2.2.1. Intensive mechanical dry coating

Dry coating of drug powders with MgSt was carried out in an AMS-Mini mechanofusion system with either the Nobilta or Nanocular process module (Hosokawa Micron Corporation, Osaka, Japan). The two processors have different geometries in design (Fig. 1) and the effect of processor geometry on the coating was evaluated in this study. Fig. 1 illustrates the contrasting blade geometries. The Nanocular system comprises a solid circular blade with two semi-circular rounded protrusions or "press heads" that are configured largely to compress powders against the internal vessel wall. The Nobilta system in contrast is configured as a series of "propeller" blades that will cause more impact collisions with powder particles as the blades rotate, as well as compression as powders are thrown outwards and interact between the edge of the blades and the internal vessel walls. No previous studies were found that compared these two blade configurations for the coating of micronized powders.

Each drug sample (approximate 10 g) was combined with 5% (w/w) of MgSt and then was transferred to the process vessel. The minimum quantities of the coating material required for a success-

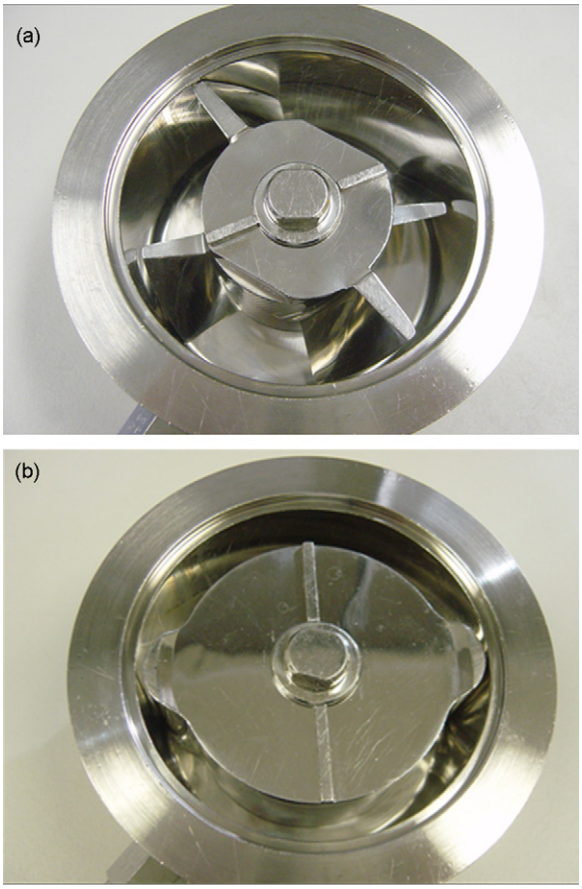

Fig. 1. Diagram of the mechanofusion units with (a) Nobilta or (b) Nanocular processor.

ful coating are dependent on the surface area of the host particles (Zhou et al., 2009). Previous literatures indicated that 5% (w/w) of MgSt were enough for successful coating for micronized particles (Morton, 2006), thus, 5% (w/w) of MgSt were used for all three samples for the ease of comparison. The mechanofusion processing was performed for 10 min at 5000 rpm to coat the MgSt onto the host drug particles. Cold water was circulated through the incorporated water jacket to prevent vessel temperatures exceeding 25 °C.

The mechanofusion process has been reported previously and its reproducibility illustrated (Morton, 2006; Begat et al., 2009; Zhou et al., 2009), but as a validation exercise, three batches of the mechanofused salbutamol sulphate powders were produced under identical circumstances, with 5% (w/w) MgSt using the Nobilta processor. The consistency in powder properties demonstrates its reproducibility for the resulting powders (Table 1).

2.2.2. Scanning electron microscopy

Morphology of drug samples was investigated using a scanning electron microscope (Phenom™, FEI Company, Hillsboro, OR). Each sample was slowly poured onto double-side carbon black tape mounted on a sample holder, and excess powder not adhered to the tape was gently removed. Samples were sputter coated with gold using an electrical potential of 2.0 kV at 25 mA (SCD005, BAL-TEC AG, Balzers, Germany). SEM micrographs were taken using in-built image capture software.

Table 1
Summary of powder property data of mechanofused salbutamol sulphate from three different batches to demonstrate process reproducibility (mean ± SD, $n = 4$).

	Batch 1	Batch 2	Batch 3
FPF (%)	68.6 ± 1.6	66.4 ± 2.7	67.5 ± 2.1
ED (%)	68.0 ± 1.2	69.2 ± 1.0	67.4 ± 0.7
D_{50} (μm)	2.67 ± 0.08	2.61 ± 0.06	2.59 ± 0.03
Poured density (g/ml)	0.28 ± 0.01	0.29 ± 0.02	0.29 ± 0.01
Tapped density (g/ml)	0.58 ± 0.02	0.56 ± 0.01	0.56 ± 0.02

2.2.3. Powder bulk densities

The poured density (ρ_p) was measured by pouring samples slowly into a 10 ml calibrated measuring cylinder through a funnel at a fixed height above the cylinder. The tapped density (ρ_t) was determined after 1250 taps of an automatic tapper (AUTOTAP™, Quantachrome Instruments, Boynton Beach, FL). The tapper operated with a 3.18 mm vertical travel at a tapping speed of 260 tap/min. Four replicates were carried out for each measurement.

2.2.4. Particle size analysis

Particle size distributions of both original and processed powder samples were measured by laser diffraction (Mastersizer® S, Malvern Instruments, Worcestershire, UK) using the 300 RF lens equipped with a small volume sample presentation unit (capacity 150 ml). The dispersant liquid was a drug-saturated solution of 0.5% (w/v) Span 80 in cyclohexane (see method of Murnane et al., 2009). The volume median diameter (D_{50}), D_{10} (diameter at 10% undersize), D_{90} (diameter at 90% undersize) were calculated for each sample.

2.2.5. Particulate interactions by shear test

Particulate interactions in each powder sample were characterized using the Freeman FT4 system in its shear module configuration (Freeman Technology, Worcestershire, UK). Briefly, a shear head was attached to the module drive and shear stress was measured with respect to a given consolidating normal stress. A fuller description of the principles of shear cell testing was described by Schwedes (2003). For this application, a consolidating stress of 9 kPa was applied to the powder bed prior to each test. Shear tests were then carried out at normal stresses of 7, 6, 5, 4 and 3 kPa. The shear stress at each normal stress was recorded and yield loci were derived. The cohesion of each sample was evaluated as the shear stress at zero normal stress by extrapolating the yield loci. A higher cohesion value corresponds to higher cohesive inter-particle forces and hence a more cohesive powder.

2.2.6. Powder de-agglomeration by laser diffraction

Powder de-agglomeration behavior was evaluated by aerosolising the powders into a real-time laser diffraction particle sizer (SprayTec, Malvern Instruments, Worcestershire, UK) equipped with an inhalation cell attachment. This approach to characterize aerosol behavior was made possible due to the lack of any carrier or other components being present. Approximate 10 mg of each powder was loaded into size 3 HPMC capsules (Capsugel, Peapack, NJ, USA). Each capsule was aerosolized using a Monodose inhaler device (Miat S.p.A., Milan, Italy) at air flow rate of 60 l/min calibrated using a TSI 4000 series flow meter (TSI, Shoreview, MN, USA). All measurements were made on four replicates at room temperature and humidity (20 ± 2 °C, 50 ± 5% relative humidity). Before aerosolization, a stainless steel pin punched each end of the capsule allowing powders to be released from the capsule by providing two holes with diameters of about 1 mm. Each measurement was performed over 4 s. The size distributions of the aerosolized powders were analyzed using in-built software. The proportion of particles with volumetric diameters smaller than 6.3 μm over the total aerosolized powder was calculated based on the SprayTec laser diffraction output.

2.2.7. In vitro aerosol performance

The *in vitro* aerosol dispersion performance of the powder formulations was determined using a twin-stage impinger (TSI, Apparatus A, British Pharmacopoeia, 2008). Purified water was used as the collecting liquid for SS and methanol (HPLC grade) for SX and TA. The airflow was drawn through the TSI using a vacuum pump (HCP5, Copley, Nottingham, UK) and the airflow rate was adjusted to 60 l/min at the mouthpiece prior to each measurement calibrated using a TSI 4000 series flow meter (TSI, Shoreview, MN, USA). Drug powder (approximate 10 mg) was loaded into HPMC capsules (size 3, Capsugel, Peapack, NJ, USA). A single capsule was actuated from a Monodose inhaler device (Miat S.p.A., Milan, Italy) for 4 s for each measurement ($n = 4$). All deposition studies were conducted in an air-conditioned laboratory ($20 \pm 2\,^{\circ}C$, $50 \pm 5\%$ relative humidity). The concentrations of each drug were determined by validated UV spectroscopy methods. An ultra-violet spectrophotometric analysis method was selected in preference to an HPLC approach as the high levels of each drug being used permitted appropriate validation and sufficient sensitivity, and its simplicity in use. The fine particle fraction (FPF %) was defined as the amount of drug deposited in the lower stage (stage two) of the TSI as a percentage of the emitted mass. The emitted dose (ED %) was calculated as the dose of drug recovered from all stages of the TSI (excluding inhaler) as a percentage of total recovered doses.

2.2.8. UV analysis of drug content

Validated UV spectroscopy methods (Cary 3 Bio, Varian Instruments, Australia) were used for the analysis of the drug content recovered from TSI studies at wavelength of 276 nm for SS, 280 nm for SX and 239 nm for TA (Tay et al., 2010). Linear regression analysis over the drug concentration range of 5–200 μg/ml using five concentrations and three replicates was performed using Microsoft Excel (Microsoft Corporation, Redmond, Washington, USA). The regression coefficient (r^2) values were greater than 0.9998 showing good linearity, and there was no significant deviation from the zero intercept ($p > 0.05$) for all drugs. The accuracy ranged from 98.9 to 101.3% and the coefficient of variation (CV) for precision ranged from 1.3 to 2.2% for representative low, medium and high concentrations along the calibration plot. The limit of detection (LOD) and the limit of quantification are calculated as (3.3 × standard deviation of response)/slope and (10 × standard deviation of response)/slope, respectively. The calculated LOD and LOQ values were less than 0.003 and 0.007, respectively, which both were far smaller than the minimum absorbance measured in the TSI tests.

2.2.9. Statistical analysis

Statistical analyses of data was carried out using analysis of variance (ANOVA) with Tukey's post hoc analysis at a p-value of 0.05 (SPSS, Version 15.0.0, SPSS Inc., Chicago, USA).

3. Results and discussions

3.1. SEM

From the SEM micrographs, SS particles can be seen to exist as short needles or elongated prisms, with poly-disperse distributions including some particles larger than 5 μm in one-dimension (Fig. 2a). SX particles exhibited tabular flake forms with apparently smooth dominant primary particle faces, upon which some ultra-fine particles could be seen; again the size distribution was poly-disperse with the major dimension of the flakes often several microns (Fig. 3a). TA particles appeared as much smaller primary particles than the SS or SX particles, and, at the resolution used, appeared as rounded but irregular lumps, although due to the smaller size and state of agglomeration, primary particle shapes were difficult to observe (Fig. 4a).

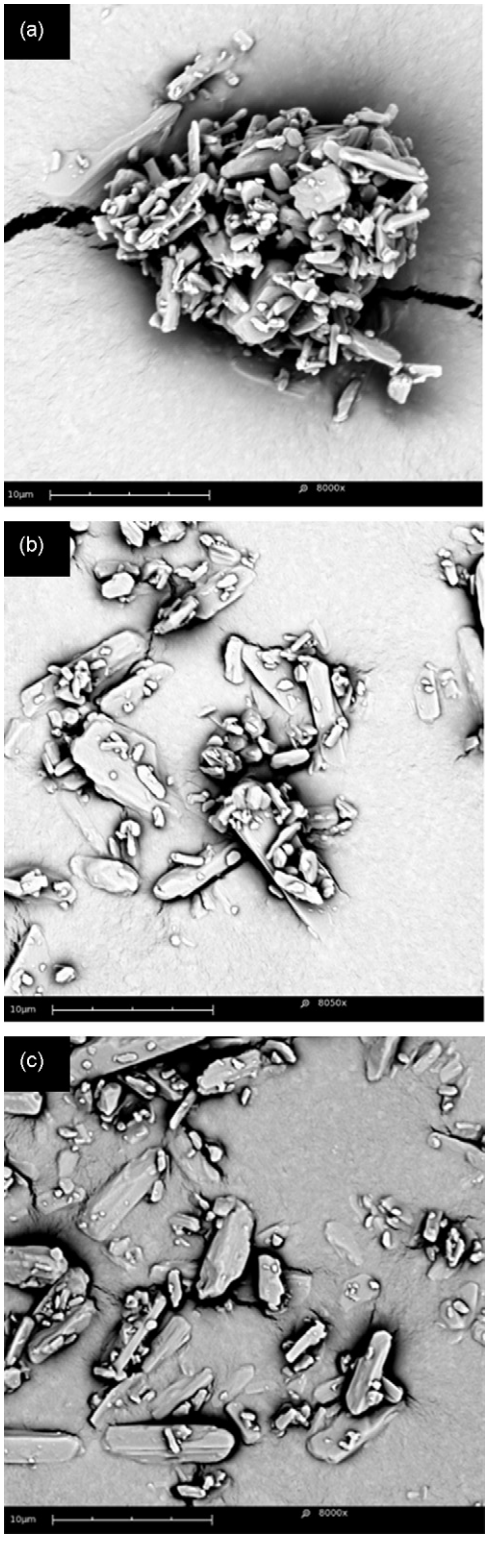

Fig. 2. SEM micrographs of SS samples: (a) untreated; (b) mechanofused with Nobilta module; (c) mechanofused with Nanocular module.

It can be observed that untreated batches of all three model drug powders existed as substantially agglomerated powders, whose agglomerates sizes were of the order of tens of microns and above. The agglomerates were subjectively different in form, with particle packing affected by the respective acicular, tabular and rounded

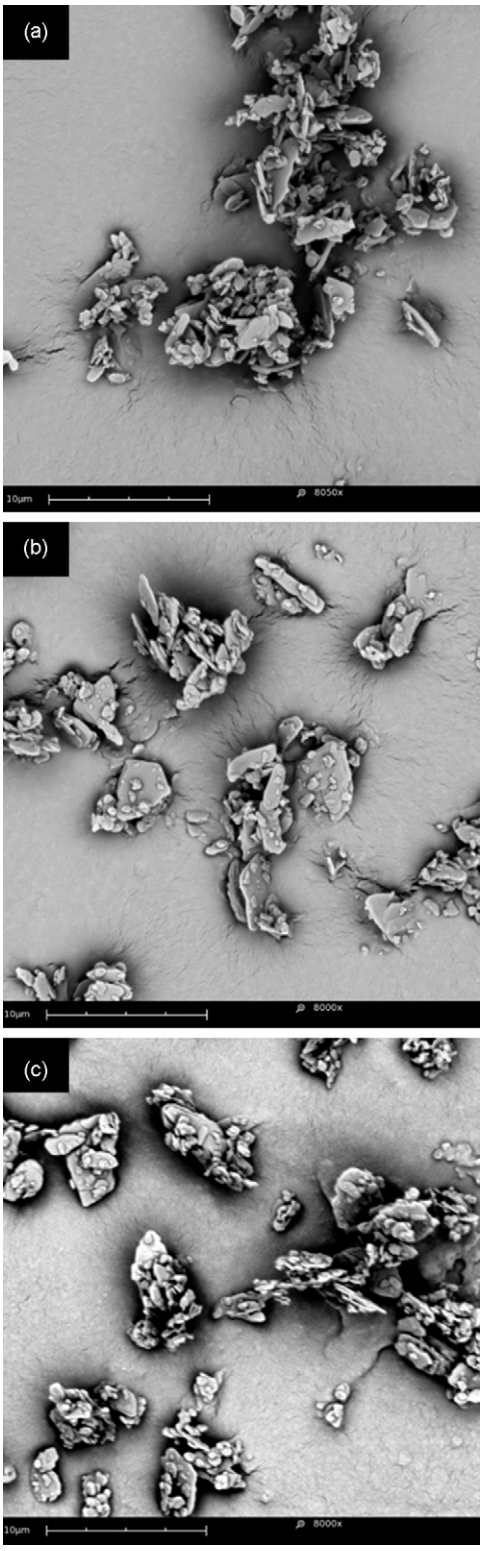

Fig. 3. SEM micrographs of SX samples: (a) untreated; (b) mechanofused with Nobilta module; (c) mechanofused with Nanocular module.

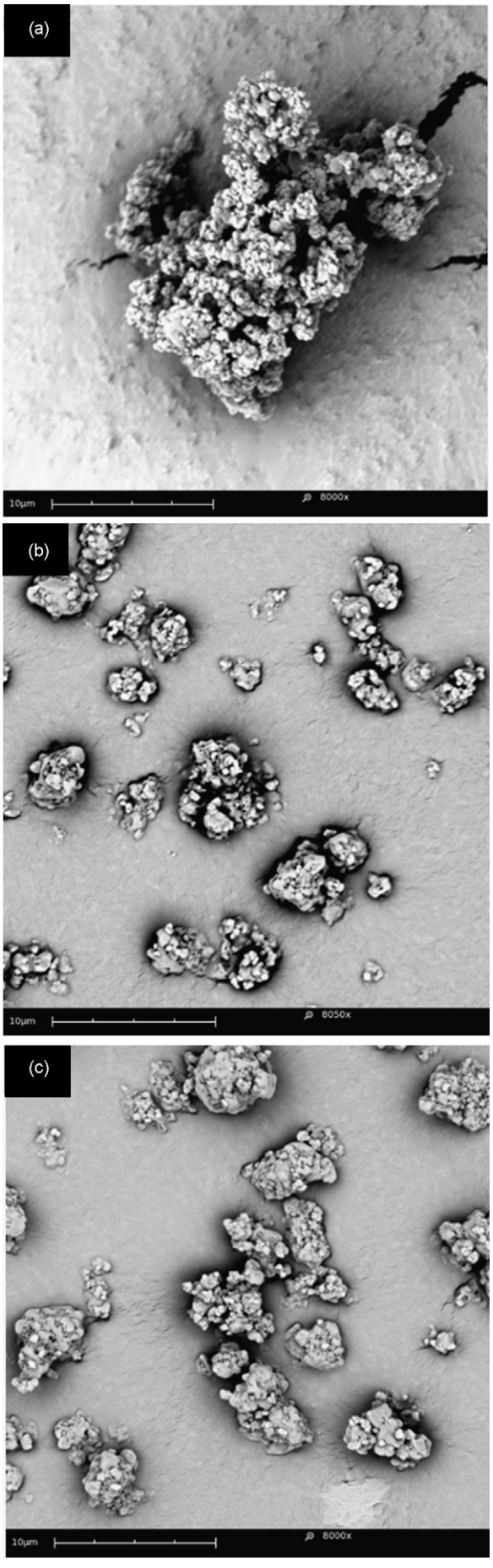

Fig. 4. SEM micrographs of TA samples: (a) untreated; (b) mechanofused with Nobilta module; (c) mechanofused with Nanocular module.

Table 2
Bulk properties of drug powder samples (mean ± SD, $n = 4$).

		Poured density (g/ml)	Tapped density (g/ml)	CI	Particle size distribution		
					D_{10} (μm)	D_{50} (μm)	D_{90} (μm)
SS	Untreated	0.15 ± 0.00	0.28 ± 0.01	0.46 ± 0.01	0.68 ± 0.05	3.64 ± 0.12	9.50 ± 0.50
	Nobilta	0.28 ± 0.01	0.58 ± 0.02	0.51 ± 0.01	0.72 ± 0.03	2.67 ± 0.08	7.41 ± 0.30
	Nanocular	0.29 ± 0.04	0.55 ± 0.01	0.48 ± 0.06	0.76 ± 0.04	2.75 ± 0.06	7.53 ± 0.11
SX	Untreated	0.10 ± 0.01	0.15 ± 0.00	0.34 ± 0.05	0.35 ± 0.01	1.05 ± 0.02	3.99 ± 0.01
	Nobilta	0.14 ± 0.01	0.20 ± 0.02	0.43 ± 0.04	0.36 ± 0.01	1.08 ± 0.07	4.08 ± 0.25
	Nanocular	0.13 ± 0.01	0.22 ± 0.00	0.42 ± 0.01	0.36 ± 0.01	1.15 ± 0.02	4.29 ± 0.03
TA	Untreated	0.14 ± 0.01	0.27 ± 0.01	0.50 ± 0.02	0.54 ± 0.02	1.90 ± 0.05	4.69 ± 0.04
	Nobilta	0.27 ± 0.02	0.51 ± 0.01	0.47 ± 0.03	0.56 ± 0.01	1.96 ± 0.04	5.08 ± 0.07
	Nanocular	0.26 ± 0.01	0.49 ± 0.01	0.47 ± 0.02	0.56 ± 0.01	1.97 ± 0.06	5.04 ± 0.08

forms. After mechanofusion treatment, the samples observed for all three drug powder were shown to be much less agglomerated. In short, the images suggested that after mechanofusion they tended to disperse as separated particles rather than relatively large agglomerates during the SEM sample preparation. After mechanofusion with either blade configuration, there were no clear changes in particle shape observed from SEM images for any of the three model drugs (Figs. 2b and c, 3b and c, 4b and c). Thus, it is indicated that any changes in their powder and aerosol properties should not be due to the substantial modification of their respective particle shapes. That said, the SEM resolution would not indicate surface roughness changes at a nanometer level or coating efficiency and relative coverage, and it is noted that work in this area is ongoing as a separate study.

3.2. Particle size distributions

The particle size distributions of untreated and processed drug samples measured using the Mastersizer S are listed in Table 2. D_{50} values of the untreated batches of all three model drug samples were all less than 4 μm, which confirmed that all model drug samples were suitably micronized prior to any processing. D_{50} values were consistent with SEM observations that the SS particles were larger than the SX and SS. After mechanofusion with either the Nobilta or Nanocular processors, there were no observed differences in particle size distributions for SX and TA. A measured, but relatively minor, reduction in particle size (dropping by approximately 1 μm) was observed for SS after mechanofusion processing with both Nobilta and Nanocular processors. These changes might be due to slight attrition during the processing of primary particles and/or slight plastic deformation, but these were not observed from SEM images and it is proposed to be more likely due to breaking of stronger bridges between primary particles (that was not achieved during dispersion), occurring during the high shear processing of the mechanofusion (Zhou et al., 2010). It was clear from these results that no large changes occurred in particle size distributions following mechanofusion, and that these results proved that any changes in powder bulk properties could not be attributed to a granulation or substantial particle enlargement in primary particle size of the model drug samples.

3.3. Powder bulk densities

Powder poured and tapped bulk densities are listed in Table 2. Both the poured and tapped densities of the mechanofused samples were significantly greater than those of their corresponding untreated samples for all three model drug samples ($p < 0.05$). However, such differences in bulk densities were more substantial for SS and TA, with increases approaching 100% for both poured and tapped densities for the mechanofused batches compared to their untreated batches ($p < 0.001$). For SX, the increases were less than 50%. There were no significant differences in both density values between the batches mechanofused with the Nobilta processor and those mechanofused with the Nanocular processor for any of the three drug samples ($p > 0.05$).

For the untreated micronized drug powders, very low poured densities indicated that the powders existed as large open cohesive agglomerates where loose powder structures formed with large volumes of interstitial air. This was consistent with the SEM micrographs. It is also consistent with the cohesive structures described by Kendall and Stainton (2001) that are indicative of strong cohesive forces. Low tapped densities suggested that even after compression during the tapping, the agglomerates did not totally collapse and could not be tightly packed due to their relative high agglomerate strength. However, after mechanofusion treatment, the drug particles were more easily consolidated in the powder bed during handling and formed more densely packed powder structures. This was attributed to a reduction in interparticle cohesive forces. It is also worth noting that such increased powder bulk densities would permit a greater drug dose to be delivered from a fixed volume, for example from a capsule.

3.4. Shear test

The FT4 shear test results are shown in Figs. 5 and 6. The untreated materials demonstrated the highest shear stress value at each normal stress for all drug samples ($p < 0.05$). The batches mechanofused with the Nobilta processor were shown to posses shear patterns similar to the corresponding Nanocular batches for each drug. The greatest differences in shear patterns between the untreated batches and the mechanofused batches were found for SS and the least differences for SX. This observation was consistent with the pattern observed for density changes. Shape related powder packing properties may be the main explanation here. When a powder contains anisometric particles such as platelets, a high void fraction of powder packing may occur when the orientations of the particles are random (Dullien, 1997). Also during the mechanofusion, such a high void fraction of powder packing may introduce less contact of particle surfaces with the processor or MgSt, resulting in different coating effects between drug particles with different shapes.

The cohesion values for the mechanofused batches were substantially lower than the corresponding untreated batches for all drug samples ($p < 0.05$). The greatest reduction of 67% in cohesion was observed for SS after mechanofusion with the Nobilta processor. The cohesion values for the mechanofused batches with the Nobilta processor were slightly lower than their corresponding batches processed with Nanocular processor, which may reflect the contrasting influence of either impaction or compression during processing.

In the absence of substantial particle size enlargement, these shear testing results provided evidence that after dry coating

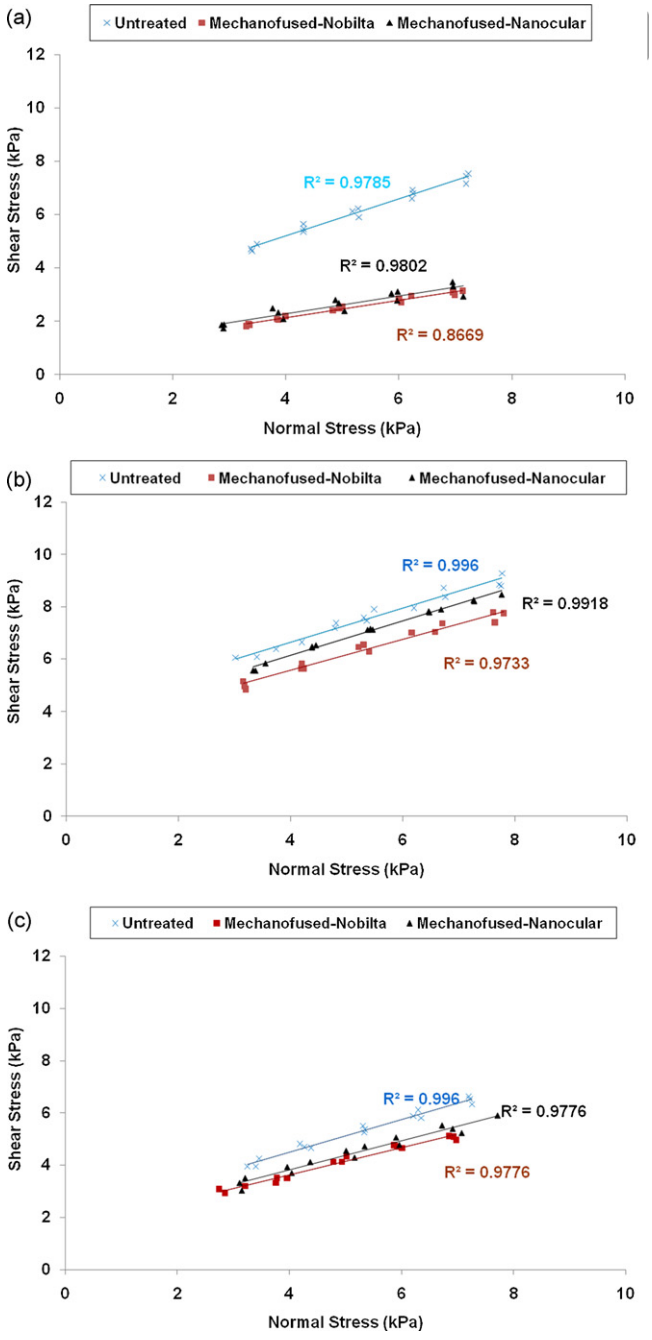

Fig. 5. Shear results measured by FT4 for the drug powder samples of (a) SS; (b) SX; (c) TA.

with magnesium stearate, the inter-particle interactive forces had been substantially reduced. This was consistent with bulk density results. Such reductions in inter-particle forces can be attributed to a high degree of surface modification and coating of the drug particles. A previous report of study with equivalent process conditions

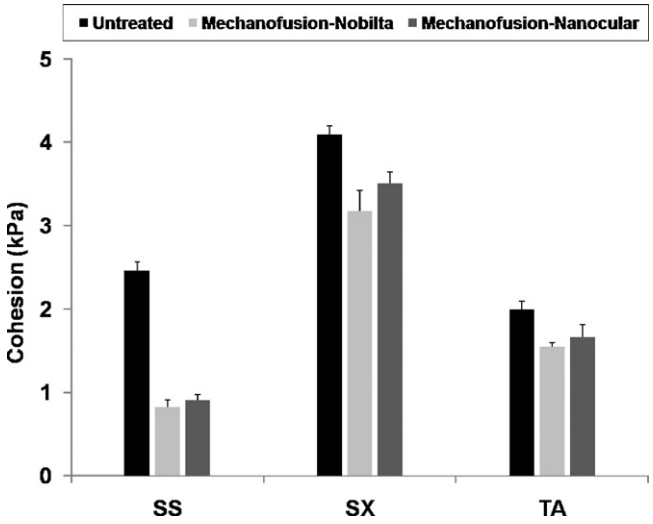

Fig. 6. Cohesion results of model drug powders measured by FT4 (error bars represent standard deviations).

has shown that such mechanfusion processes produced measurable nano-scale magnesium stearate coating layers on micronized particles (Green et al., 2009).

3.5. De-agglomeration behaviors

The de-agglomeration performance of the model powder samples were represented by the particle (or agglomerate) size distributions measured by SprayTec during the aerosolization test (Figs. 7 and 8 and Table 3). The cumulative particle size distributions of the two mechanofused batches (Nobilta and Nanocular) for each drug were almost identical. However, the size distributions of their corresponding untreated batches were much larger over the whole size range. This was confirmed by D_{50} results of the aerosol size distributions. D_{50} values of the mechanofused batches were significantly lower than those of their corresponding untreated batches for all three drug samples ($p < 0.001$), indicating that the coated powder was better de-agglomerated during the aerosolization process. Fig. 8 also shows that more agglomerates were broken into respirable particles during the aersolization after mechanofusion treatment as reflected by greater proportions of particles smaller than 6.3 μm. This suggested that efficient coating of drug powders with MgSt could substantially improve drug delivery efficiency of high-dose DPI formulations.

These results demonstrated that the untreated powders exhibit relatively poor de-agglomeration performance, which was consistent with their possessing strong inter-particle cohesive forces. During the aerosolization, the shear and energy provided by the air flow was insufficient to break the strong agglomerates into smaller agglomerates or fine primary particles efficiently. By reducing the cohesive forces via dry coating, the agglomerate strength can be significantly reduced and such weaker agglomerates can be broken into smaller agglomerates or primary particles.

Table 3
Particle size distributions of the drug aerosols measured by SprayTec at flow rate of 60 l/min (mean ± SD, $n = 4$).

	SS			SX			TA		
	Untreated	Nobilta	Nanocular	Untreated	Nobilta	Nanocular	Untreated	Nobilta	Nanocular
D_{10} (μm)	2.19 ± 0.05	1.57 ± 0.09	1.35 ± 0.04	2.18 ± 0.12	1.56 ± 0.06	1.71 ± 0.06	4.52 ± 0.15	2.07 ± 0.05	2.11 ± 0.06
D_{50} (μm)	8.08 ± 0.41	5.01 ± 0.51	4.50 ± 0.20	7.65 ± 0.82	4.51 ± 0.21	5.66 ± 0.40	11.00 ± 0.50	5.62 ± 0.05	5.85 ± 0.18
D_{90} (μm)	128.31 ± 5.50	16.45 ± 2.32	27.05 ± 3.97	71.10 ± 11.70	29.14 ± 2.87	29.82 ± 2.07	29.22 ± 2.31	17.11 ± 0.19	20.42 ± 1.16

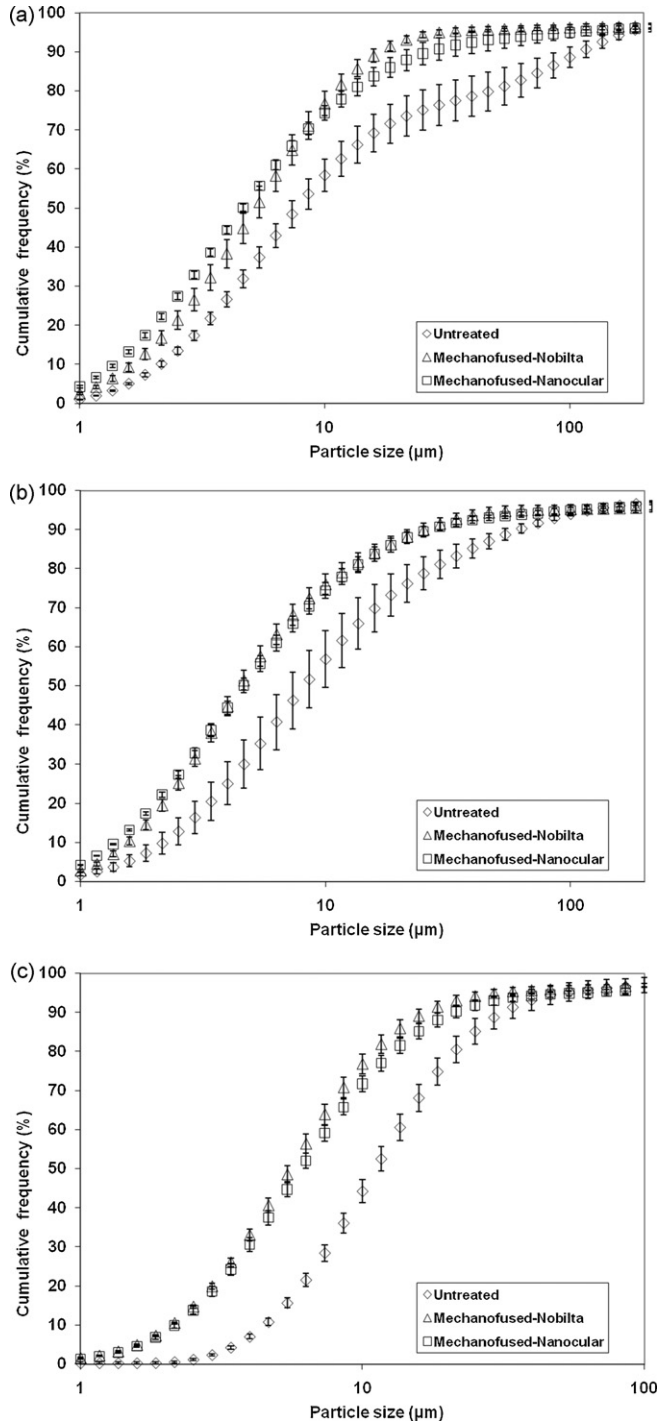

Fig. 7. Particle size distributions of the drug powder samples during the aerosolization at the flow rate of 60 l/min measured by SprayTec: (a) SS; (b) SX; (c) TA (error bars represent standard deviations).

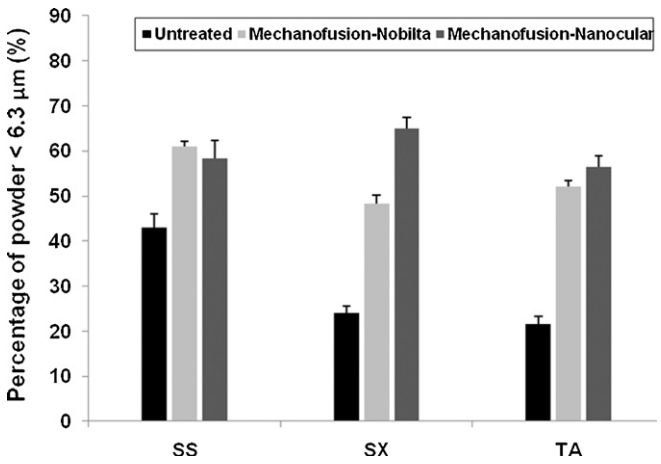

Fig. 8. De-agglomeration behavior of drug powder samples measured by SprayTec during the aerosolization at the flow rate of 60 l/min (error bars represent standard deviations).

3.6. *In vitro* performance

The *in vitro* performance of the model drug powders is represented by their FPF and ED values as listed in Table 4. For SS, there was a minor decrease in ED after mechanofusion. However, the FPF values increased substantially from 51.4 ± 0.3% (the untreated batch) to 68.6 ± 1.6% or 68.5 ± 1.1% after mechanofusion either with Nobilta or Nanocular processors, respectively ($p < 0.001$). There was no significant difference between batches mechanofused with different processors ($p > 0.05$). For SX, the ED of the batch mechanofused with the Nanocular processor was significantly lower than the untreated batch ($p < 0.05$). The FPF values for both mechanofused batches (73.1 ± 0.8% for Nobilta and 69.3 ± 1.1% for Nanocular) were significantly greater than the FPF of the untreated batch of SX (59.9 ± 2.2%, $p < 0.001$). For TA, there were no significant differences in ED values between the untreated and the mechanofused batches ($p > 0.05$). The FPF value for the untreated TA was as low as 26.4 ± 1.8%. After mechanofusion treatment, the FPF value was substantially increased to 51.6 ± 1.5% for Nobilta processor and to 48.3 ± 1.1% for Nanocular processor ($p < 0.001$).

These results demonstrate that agglomerate break-up into fine inhalable particles (or fine inhalable agglomerates) is much more efficient after the mechanofusion treatment with a relatively small amount of magnesium stearate for all three drugs. These aerosolization results are also in agreement with the de-agglomeration results measured using the SprayTec, and provided further evidence that the agglomerate strength of the drug powders was substantially reduced after mechanofusion.

The relationship between agglomerate strength and cohesion has previously been described by Kendall and Stainton (2001) as:

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

where σ is the tensile strength of the agglomerate, Φ is the packing fraction (volume of particles/volume of aggregate), W is the work

Table 4
In vitro aerosol performance of drug powders measured by TSI at flow rate of 60 l/min (mean ± SD, $n = 3$).

	SS			SX			TA		
	Untreated	Nobilta	Nanocular	Untreated	Nobilta	Nanocular	Untreated	Nobilta	Nanocular
ED (%)	71.5 ± 1.8	68.0 ± 1.2	71.5 ± 1.4	73.5 ± 2.4	73.9 ± 1.8	68.5 ± 0.6	76.8 ± 0.4	71.4 ± 1.6	72.8 ± 3.5
FPF (%)	51.4 ± 0.3	68.6 ± 1.6	68.5 ± 1.1	59.9 ± 2.2	73.1 ± 0.8	69.3 ± 1.1	26.4 ± 1.8	51.6 ± 1.5	48.3 ± 1.1

of adhesion/cohesion and d is the particle diameter. In this study, the shear results confirmed that intrinsic inter-particle cohesion of the drug powders could be substantially reduced, as a result of the surface modification. It is also interesting to note that despite apparent decreases in agglomerate tensile strength (as indicated by the improved de-agglomeration), the packing fraction of each of these powders increased, as shown by the density increases following mechanofusion. Indeed the approximate doubling of the bulk density as seen for the salbutamol and triamcinalone materials, could then be related on this basis to an estimated 16-fold increase in the agglomerate strength. Thus, such reductions in powder intrinsic cohesion must substantially more than compensate for the increase in packing fraction, therefore, resulting in significant decreases in the tensile strength of the agglomerates. Such results prompt further interest in the understanding at a single particle and molecular contact level of the fundamental changes and mechanisms of cohesion. As noted above, the authors are consequently investigating the surface changes at a molecular level, on both a physical and a chemical basis in further studies.

Given the minor reduction in ED observed for some of these tests after mechanofusion it is suggested that this can be attributed to the reduction of inter-particle interactions in the powder. With the strong cohesion of the micronized drug powders, such powders appear to exist as relatively strong agglomerates rather than free flowing individual particles. As the cohesive forces between drug particles appear much weaker after successful mechanofusion, drug particles may detach from the weaker agglomerate structures and hence have a greater tendency to stick on the inhaler surfaces during the aerosolization. These may result in a minor decrease in ED compared with the untreated drug powders, as a dusting of the inhaler surface occurs.

It should also be noted that the coating material used here, magnesium stearate, is highly hydrophobic. The coating of a thin layer of such a hydrophobic material onto micronized drug particles may result in the modification of their dissolution profile. One previous study showed no measurable influence in dissolution of a hydrophilic drug after mechanofusion with magnesium stearate (Tilley, 2008). However, in another study, mechanofusion treatment of a low water solubility drug, budesonide, with MgSt has demonstrated a retarded drug release profile during the dissolution test (Poole and Green, 2009). Since the dissolution is influenced by both surface coating and agglomeration state considerations causing both dissolution inhibition and enhancement (Allahham and Stewart, 2007), thus, the effect of coating on the dissolution profile is very complex and this aspect also deserves further investigation.

3.7. Effects of coating parameters

This study demonstrated that only small differences, if any, could be observed in the bulk and de-agglomeration properties of drug powders mechanofused using the two different process heads (Nobilta and Nanocular). Both of the mechanofusion processors gave improvements in powder bulk behaviors as well as in their aerosolization behaviors.

Although the mechanofusion process successfully modified the particle interactions for all three drug powders, this work suggests that the efficiency of such powder modification was dependent on the constituent particle properties. It can be observed that the increases in FPF after mechanofusion for SX were less than those for SS and TA. This was consistent with the smaller increase in poured and tapped densities for SX after the mechanofusion treatment. The shear test results were also consistent with this, in that the changes in powder intrinsic cohesion were less for SX than for the other two drugs.

In our previous report, it was shown that host particle size has a significant effect on the coating and therefore the resulting powder properties following dry coating (Zhou et al., 2009). SS particles, with elongated prismatic shapes, have the largest particle size distributions in this study. It is not surprising that SS particles could exhibit better improvements in powder cohesion compared to the smaller and flake-shape SX particles. It is considered that tabular forms such as SX are more difficult to mechanically coat to a consistent level than other shapes when such platelets are randomly packed and less particle surface is in contact with processors or coating materials. The relative movement between plates under compression may well be different compared to more rounded shape particles. It is also proposed that it is not surprising that the TA particles with a relatively smaller particle size have shown lower FPF compared with those for the relatively larger SS particles. Recent work has suggested that particles size changes for particles smaller that about 10 μm, can be highly influential in increasing cohesion, due to the relative competition between the influence of gravitational forces and the cohesive forces (Louey et al., 2004). It is likely therefore that while de-agglomeration is substantially improved, controlling the flow and fluidization of such micronized powders (required for good consistent ED at all flow rates) may not be possible via coating alone. In this case, the controlled pelletization or use of some carrier material may be required for optimum formulation design.

In addition, it is interesting to note that previous studies have demonstrated that the micronized particle with elongated and plate shapes are easier to be aerosolized than the spherical particles (Hassan and Lau, 2009; Zeng et al., 2000). These observations show that the effect of particle properties such as shape and size on the coating effectiveness are complex and should be considered when dry coating is used to modify powder bulk properties, and further work on the effect of particle shape on coating and bulk properties is also warranted, and may also consider the material hardness if plastic deformation is considered an important factor.

4. Conclusions

Three micronized drug powders were dry coated with relatively low levels (5%, w/w) of magnesium stearate to successfully alter the cohesion and aerosolization properties. After mechanofusion, there was no substantial granulation or size enlargement occurring for all three drug powders. However, both the poured and tapped densities of all three drug powders were substantially increased after mechanofusion demonstrating significant changes in powder structure. The aerosol performance of all three drug powders was significantly improved after mechanofusion as represented by much higher FPF values measured by TSI testing and smaller agglomerate sizes measured by SprayTec. Such improvements in the aerosol performance were attributed to the reduction in agglomerate strength caused by decreasing powder intrinsic cohesion after surface modification, which was confirmed by cohesion measurement from shear testing. Demonstration of this relationship between shear measurement and aerosolization indicates the shear test approach may have further value in development of inhaled powder formulations. Two different processors with different geometries gave successful and consistent powder improvements for the micronized particles. The work has also indicated that the nature or effect of the coating is dependent on the initial particle properties such as shape and size distribution.

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