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Investigation of the extent of surface coating via mechanofusion with varying additive levels and the influences on bulk powder flow properties

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ABSTRACT

The objective of this study was to investigate if the coating extent created by a mechanofusion process corresponded with observed changes in bulk powder properties. A fine lactose powder (approximate median diameter 20 μm) was dry coated with magnesium stearate using from 0.1 to 5% (w/w) content. An ultra-thin coating layer of magnesium stearate was anticipated, but previous attempts to determine such thin layers on these fine particles have had limited success, with poor resolution. In this study, the surface coating was examined using the state-of-the-art XPS and ToF-SIMS systems. The powder flow was characterized by Carr index and shear cell testing. XPS was successfully applied to demonstrate variations in surface coverage, as a function of additive levels, and indicated near complete coating coverage at additive levels of 1% (w/w) and above. ToF-SIMS results supported such coating coverage assessment, and indicated coating uniformly across the fine particle surfaces. The flow metrics employed could then be related to the coating coverage metrics. The mechanofusion process also modified the apparent surface roughness observed by SEM and BET. It was suggested that the changes in the surface chemical composition exerted a more evident and direct impact on the powder cohesion and flow characteristics than the changes in the surface morphological properties after the mechanofusion in this study.

1. Introduction

A powder's bulk behaviours such as flow, entrainment, fluidization and aerosolization are highly influential and often critical with particulate handling, processing and formulation functions (Igwe, 1991). Fine cohesive powders are commonplace in a pharmaceutical context. Handling such cohesive powders is a generic industrial problem because such powders are prone to poor flowability and restricted dispersion due to the strong inter-particle interactions associated with small particle sizes (Valverde et al., 2000).

Since the powder flowability is associated with surface properties (Orband and Geldart, 1997), surface modification appears a logical approach to improve the flow of fine cohesive powders. In our earlier studies, we have demonstrated substantially enhanced powder flow, as a result of surface coating by a mechanofusion process, of a series of fine cohesive lactose monohydrate milled powders (median particle size ranging approximately from 4 to 20 μm), with magnesium stearate (MgSt) as the coating material (Zhou et al., 2010a). Much better powder flow was obtained compared to similar compositions that were blended using a conventional tumbling mixer, indicating that the nature and intensity of the process were critical factors, which were proposed to lead to a more effective coating. Furthermore, the improvements in flow characteristics obtained using MgSt were superior to those obtained using an equivalent quantity of colloidal silica, which is otherwise the "gold standard" flow aid additive (Zhou et al., 2010b).

However, it was recognized from this previous work that there is a need to establish the nature of coatings, and for a detailed study of the relationship between the extent and nature of the coating and the inter-particle interactions as well as bulk powder characteristics. In part, this has been difficult to achieve because of the technological challenge of characterizing such thin coating layers on the surface of particles that are 20 μm and smaller. Recent advances in surface characterization technologies have helped facilitate this. Recent enhancements in time-of-flight secondary ion mass spectrometry (ToF-SIMS) have yielded a highly sensitive analytical technique that provides chemical information regarding elemental, isotopic and molecular structure from the first 1–2 monolayers of small particles (Adriaens et al., 1999; Van Vaeck et al., 1999). X-ray photoelectron spectroscopy (XPS) can also provide specific chemical information regarding coating quality of small particle samples. With XPS, the chemical information is obtained

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from the top layer of the material surface being analyzed and it has been widely used to characterize thin coating films (Davies et al., 1989; Lamb et al., 1988; Viornery et al., 2002). In a study, recently submitted for publication, we have shown that ToF-SIMS and XPS can be employed as appropriate tools for characterizing coating quality of thin MgSt layer on such fine lactose powders, and correlated to surface energy measurements.

Consequently, in this study, we report a further advance in this study by investigating the mechanical dry coating of a model fine lactose powder with a range of concentrations of magnesium stearate from 0.1 to 5% (w/w), and using various surface analysis techniques to quantify the surface coating. The relationship between this coating extent and the bulk powder flow and cohesion characteristics has then been explored by employing both traditional methods based on bulk density measurements and a powder shear testing approach.

2. Materials and methods

2.1. Materials

An α-lactose monohydrate sample, Pharmatose® 450M (P450, median particle size approximately 20 μm), was donated by DMV International, Veghel, The Netherlands. Magnesium stearate NF (MgSt) was supplied by Mallinckrodt Chemicals, Phillipsburg, USA. All samples were used as received.

2.2. Methods

2.2.1. Mechanical dry coating

The lactose sample was mechanically dry coated with MgSt in a Nobilta mechanofusion system (AMS-Mini, Hosokawa Micron Corporation, Osaka, Japan). Prior to mechanofusion treatment, lactose samples (approximately 15 g) were manually premixed with 0.1, 0.5, 1, 2 or 5% (w/w) MgSt. Each mixture was poured into the process vessel (process volume ~ 80 ml). The mechanofusion processing was performed for 10 min at processor rotation speeds of 4000 rpm. These conditions have been previously shown to be optimal from our previous studies (Zhou et al., 2011a). Several different and effective mechanofusion systems have been previously described, and the "Nobilta" processor was selected here as it gave promising results from previous studies (Zhou et al., 2010c), and given its simplicity of action is argued in principle to be scalable for coating fine powders. Cold water was circulated through the incorporated water jacket to prevent vessel temperatures exceeding 25 °C.

2.2.2. Scanning electron microscopy

The morphology of the lactose samples was examined using a scanning electron microscope (Phenom™, FEI Company, Hillsboro, Oregon, USA). Each sample was poured onto double-sided carbon black tape which was mounted on a sample holder, and excess powder then gently removed by shaking. Samples were then 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 the in-built image capture software.

2.2.3. Surface area

Specific surface area of the lactose carriers was determined by the BET gas adsorption method using nitrogen as adsorbent gas (Tristar 3000, Micromeritics Instrument Corporation, Norcross, GA, USA). Five different relative pressures in the range of 0.05–0.2 p/p^0 were used to calculate the specific surface area value. Each lactose sample (approximately 2 g) was weighed and poured into a sample cell and degassed under vacuum for 24 h at 40 °C prior to each measurement. Measurements for each batch were carried out in triplicate and the results averaged.

2.2.4. ToF-SIMS

ToF-SIMS experiments were performed using a PHI TRIFT V nanoTOF instrument (Physical Electronics Inc., Chanhassen, MN, USA) equipped with a pulsed liquid metal $^{79+}$Au primary ion gun (LMIG), operating at 30 kV energy. Dual charge neutralization was provided by an electron flood gun and 10 eV Ar^+ ions. Surface analyses were performed using "unbunched" Au_1 instrument settings to optimize spatial resolution. Raw data was collected in positive SIMS mode at a number of locations typically using a 100 μm × 100 μm raster area, with 2 min acquisitions. For purposes of statistical interrogation, 25 particles of interest were imaged per sample to collect a representative data set.

Region-of-interest analyses were performed on the collected raw image data using WincadenceN software (Physical Electronics Inc., Chanhassen, MN, USA). This involved the extraction of mass spectra specifically from within the boundaries of the particles of interest. This allowed the surface chemistry of the particle to be extracted from the background signals. Signals of Mg (m/z 24) and one ring of intact molecular of lactose ($C_6H_{11}O_5$, m/z 163) were collected as indication of MgSt and lactose, respectively. The reference spectra of Mg and $C_6H_{11}O_5$ were chosen from earlier reported literature to acquire the appropriate intensity of the signals for mapping purpose as measured on the samples involved in this study (Belu et al., 2000).

Integrated peak values of the selected ions were normalized to the total secondary ion intensities. The resulting data were then compared qualitatively by preparing plots of average normalized counts (with 95% confidence intervals) for each species of interest.

2.2.5. XPS

XPS analysis was performed with an AXIS HSi Spectrometer (Kratos Analytical Ltd., Manchester, UK), equipped with a monochromated Al Kα source at a power of 144 W (12 mA, 12 kV). A small quantity of each sample was filled into shallow wells of custom-made powder sample holders. Charging of the samples during irradiation was compensated for by an electron flood gun in combination with a magnetic immersion lens. A reference binding energy of 285.0 eV for the aliphatic hydrocarbon C1s component was used to correct for any remaining offsets due to charge neutralization of specimens under irradiation (Beamson and Briggs, 1992). The pressure in the main vacuum chamber during analysis was typically 5×10^{-6} Pa. Spectra were recorded with the nominal photoelectron detection normal to the sample surface. Note, however, that in the case of irregular powder particles, the microscopic emission angle is inherently ill-defined. As a consequence the sampling depth might vary between 0 nm and 5–10 nm depending on the kinetic energy of the measured photoelectrons.

The elemental composition of the samples was obtained from survey spectra (320 eV pass energy) using sensitivity factors supplied by the manufacturer. High resolution spectra of individual peaks were recorded at 40 eV pass energy which results in a peak width (full width at half maximum) of typically 1.0–1.1 eV.

2.2.6. Powder bulk densities and Carr index

The poured density (ρ_p) was measured by a previously validated approach (Carr, 1965; Zhou et al., 2010b). Samples were slowly poured into a 10 ml measuring cylinder via a funnel at a fixed height. The tapped density (ρ_t) was determined after 1250 taps of an automatic tapper (AUTOTAP™, Quantachrome Instruments, Boynton Beach, USA), where 1250 taps had been shown to be a satisfactory consolidation end point. The tapper operated with a 3.18 mm vertically travel at a tapping speed of 260 tap/min. Four replicates were carried out for each measurement.

Carr index (CI) was calculated from the poured density and tapped density using the following equations (Carr, 1965):

$$\mathrm{CI} = \frac{\rho_t - \rho_p}{\rho_t} \tag{1}$$

2.2.7. Shear testing

Powder flow behaviours and inter-particle cohesive interactions represented by their shear properties, were characterized using the small-scale shear test module of the FT4 powder rheometer system (Freeman Technology, Worcestershire, UK). In the shear test, a shear head was attached to the powder rheometer and shear stress was measured with respect to the normal stress for a given consolidating stress (Freeman, 2007). A fuller description of the principles of shear cell testing was described by (Schwedes, 2001). 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 as curves to represent the maximum shear stress the sample can support under a certain normal stress. The inter-particulate cohesion forces of each sample were calculated by extrapolating the yield loci to zero normal stress. From the yield loci, standard Mohrs circle constructions provide the unconfined yield strength (σ_c) and major principle stress (σ_1). The flow function (ff_c) is defined as the ratio of major principle stress to the unconfined yield strength and used as an indicator of powder flowability (Schulze, 2008).

2.2.8. Statistical analysis

The statistical analysis of data derived from different batches of lactose samples 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

3.1. SEM

Selected representative SEM micrographs of the lactose samples are shown in Fig. 1. Irregularly angular, sharp edged, ridged and elongated shapes can be observed for the untreated lactose particles (Fig. 1a). The surface of these untreated lactose particles were substantially flat with sharp edges, but cracks, ridges and apertures were obvious on the particle surfaces. In contrast, the particles of the 1% mechanofused lactose sample possessed mainly rounded edges and undulating surfaces (Fig. 1b), whose texture was noticeably different to the flat but flawed surfaces for the untreated lactose particles. These rounded edges could be attributed to attrition and/or plastic deformation during the high shear coating process. However, unlike the smooth undulating surface for the 1% sample, the lactose particle surfaces of the 5% MgSt mechanofused sample were shown to be different again, being apparently rougher, with small holes and what may be gaps between applied MgSt coating layers. It is suggested from this, that the 1% of MgSt may provide sufficient material for a uniform thin-film coating. However, where the MgSt is present in excess of this, for example at 5%, excess MgSt may form overlapping and flaking layers. Thus, the surfaces appeared more uneven as a result of gaps between different and potentially mobile MgSt flakes.

3.2. Surface area

The specific surface area of the lactose powder was reduced significantly from 1.079 ± 0.007 $\mathrm{m^2/g}$ for the untreated sample to 0.770 ± 0.012 $\mathrm{m^2/g}$ for the 1% MgSt mechanofused sample ($p < 0.001$) (Table 1). Previous studies indicated that the particle size distributions of such fine lactose powders were not substantially altered after mechanofusion (Zhou et al., 2010b, 2011a), and

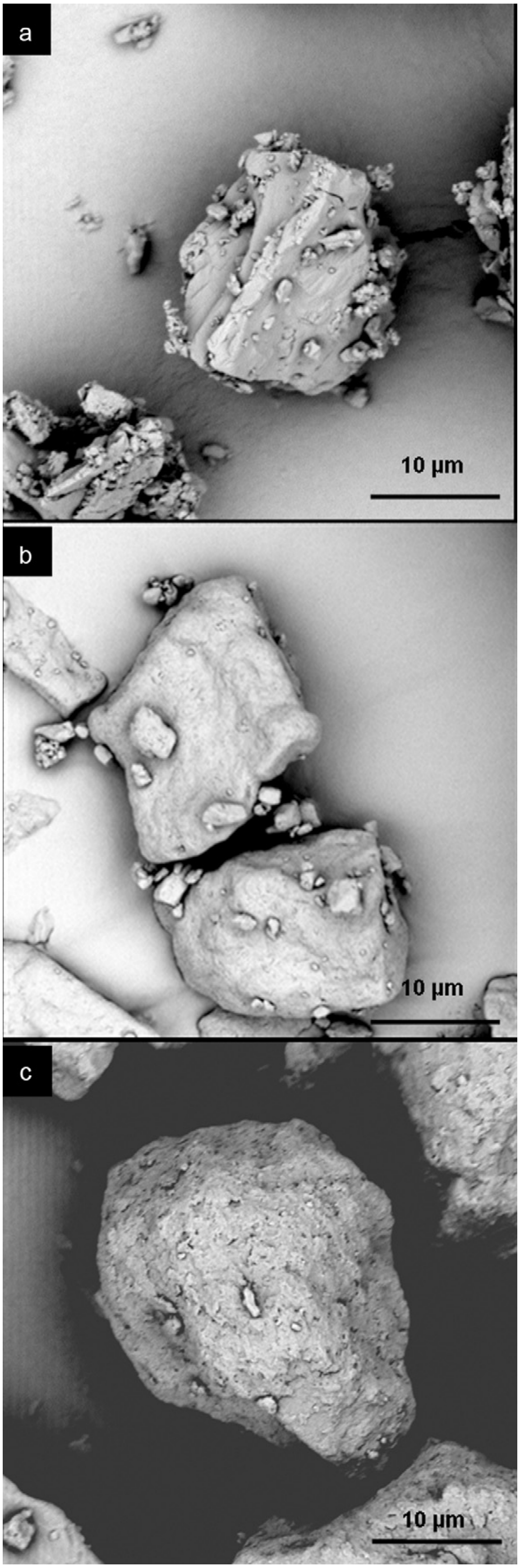

Fig. 1. SEM micrographs of lactose samples: (a) untreated; (b) mechanofused with 1% MgSt; (c) mechanofused with 5% MgSt.

Table 1
Surface area of lactose samples measured by BET adsorption (mean ± SD, $n = 3$).

	BET surface area (m^2/g)
Untreated	1.079 ± 0.007
0.5%	0.826 ± 0.005
1%	0.770 ± 0.012
5%	0.913 ± 0.075

hence that reduction in surface area would not be attributable to an increase in particle size. This reduction in measured surface area was therefore suggested to be due to the decrease in surface irregularities proposed to occur by filling MgSt into such surface flaws and a relative smoothing of the lactose particle surface due to plastic deformation and/or a surface polishing effect with the MgSt coating layer, which was apparent from the SEM images, and has been previously suggested (Roblottreupel and Puisieux, 1986). However, when MgSt content was further increased from 1% to 5%, the specific surface area increased to 0.913 ± 0.075 m^2/g. This is consistent with the suggestion proposed from the SEM images that the surfaces of the coated lactose particles effectively become rougher when MgSt is present in an excess to that required to form an optimal thin layer coating.

3.3. ToF-SIMS

The ToF-SIMS mapping of different signals on the various powder samples are shown in Figs. 2 and 3. For the untreated lactose sample, the signal mapping of $C_6H_{11}O_5$ was clearly observed (Fig. 2a). In contrast, there was no detected Mg signal for the untreated lactose sample (Fig. 3a), which indicated that any Mg signal detected for the mechanofused sample, would come from any MgSt coating present. For the mechanofused lactose sample with 0.1% MgSt, the $C_6H_{11}O_5$ signals could be clearly observed (Fig. 2b) and with only a low Mg signal noted (Fig. 3b). When the MgSt content was increased to 0.5%, the density of the $C_6H_{11}O_5$ signals observed were relatively reduced while the density of the Mg signals increased markedly (Figs. 2c and 3c). After coating with 1% or higher MgSt content, virtually no $C_6H_{11}O_5$ signal was observed on the particles, consistent with a coherent coverage of MgSt on the lactose particles (Figs. 2d, e, 3d and e).

The normalized counts detected for the Mg and $C_6H_{11}O_5$ signals for the selected samples are given in Table 2, and although subject to a high degree of variation, these were consistent in a qualitative sense with the visual observations from Figs. 2 and 3. The percentage normalized counts do not give a measure of absolute coverage, because the specific signals identified here were percentages over the total ion signals of all species, but appear useful for examination of relative changes. For the untreated lactose sample, there was no Mg signal detected on the particle surfaces. After mechanofusion with 0.1% MgSt, the Mg signal normalized counts increased to a relatively low value of 0.12%. When MgSt content was increased further to 0.5%, the normalized counts increased substantially to 4.34%. The normalized counts of Mg achieved the greatest value when the lactose sample was mechanofused with 1% MgSt. Accordingly, the $C_6H_{11}O_5$ signal normalized counts substantially decreased from 0.84% for the untreated sample to 0.03% for the 1% MgSt mechanofused sample, and the data were consistent with formation of a substantial covering layer of MgSt coated onto the lactose particle surfaces during the mechanofusion process when MgSt content was higher than 0.1% (w/w).

Table 2
Normalized counts of Mg (m/z 24) and $C_6H_{11}O_5$ (m/z 163) signals over the total ion signals of lactose samples measured using ToF-SIMS at scan area of 200 μm × 200 μm (mean ± SD, $n = 25$).

Sample	Normalized counts (%)	
	Mg	$C_6H_{11}O_5$
Untreated	–	0.84 ± 0.21
0.1%	0.12 ± 0.04	0.78 ± 0.12
0.5%	4.34 ± 0.82	0.07 ± 0.03
1%	5.92 ± 0.77	0.03 ± 0.02
5%	5.39 ± 1.02	0.02 ± 0.02

Table 3
Element compositions calculated as relative atomic ratio to carbon for lactose samples measured by XPS (mean ± SD, $n = 3$).

Sample	Atomic ratio	
	O	Mg
Untreated	0.781 ± 0.013	–
0.1%	0.749 ± 0.005	–
0.5%	0.334 ± 0.003	0.018 ± 0.003
1%	0.262 ± 0.001	0.019 ± 0.001
5%	0.253 ± 0.002	0.024 ± 0.001

3.4. XPS

The elemental composition relative ratios over carbon for each sample measured by XPS are listed in Table 3. There was no detection of Mg on the untreated lactose surface indicating that any Mg detected on the surface of the mechanofused sample should only result from the MgSt applied as a coating layer. Mg could not be detected from XPS for the mechanofused sample with 0.1%. But Mg ratios increased with an increase of MgSt content from 0.5% to 5%. A ratio of Mg to carbon at 0.024 for the mechanofused lactose with 5% MgSt was close to the value of 0.028 measured for the pure MgSt, indicating Mg was dominating the signal, and that a high level of MgSt coverage was present on the lactose particle surfaces, even if only 5% (w/w) is added. It is considered unlikely that the signal even for a complete coating would reach 0.028, as the depth of a MgSt layer in the current proportions used is likely to be only a few nanometres thick (Green et al., 2009), and given the depth probed by the XPS beam would allow some other signals to form part of the ratio. Furthermore, a precise coating quantification of coverage and depth will be hindered by the inherent variation in angles encountered by the probe beam as these irregular particles lie in random orientations. A progressive coating formation was also supported by the carbon composition results shown in Table 4. The proportions of "C–C" (which should only be present in MgSt) increased from 0.063 for the untreated sample to 0.698 for the mechanofused sample with 5% MgSt, while the proportions of "C–O" (characteristic only for lactose) decreased substantially from 0.731 for the untreated sample to 0.257 for the mechanofused sample with 5% MgSt.

Given the relative small amount of Mg on the particle surface and thus low intensity of the signal, surface component proportions (lactose or MgSt) for the mechanofused samples were then calculated from calculating C1s curve fits using model spectra obtained by analyzing reference compounds (Beamson and Briggs, 1992). From this analysis, the effective estimated coverage of the MgSt coating layer increased to approximately 75% (Table 5).

These results may have two possible implications regarding the coating coverage. If the coating coverage is 75% as indicated by C1s curve fits calculation, it is suggested that a coherent coating film of MgSt may not be required for the substantial improvement in powder flow. A significant coverage of 75% may be sufficient for the substantial improvement in powder flow for this fine lactose powder. However, the uncertainties noted above with regard to coating thickness and probe beam depth as well as incidence angle, mean this value does not necessarily mean that 25% of the surface remains exposed lactose, because the percentage estimated

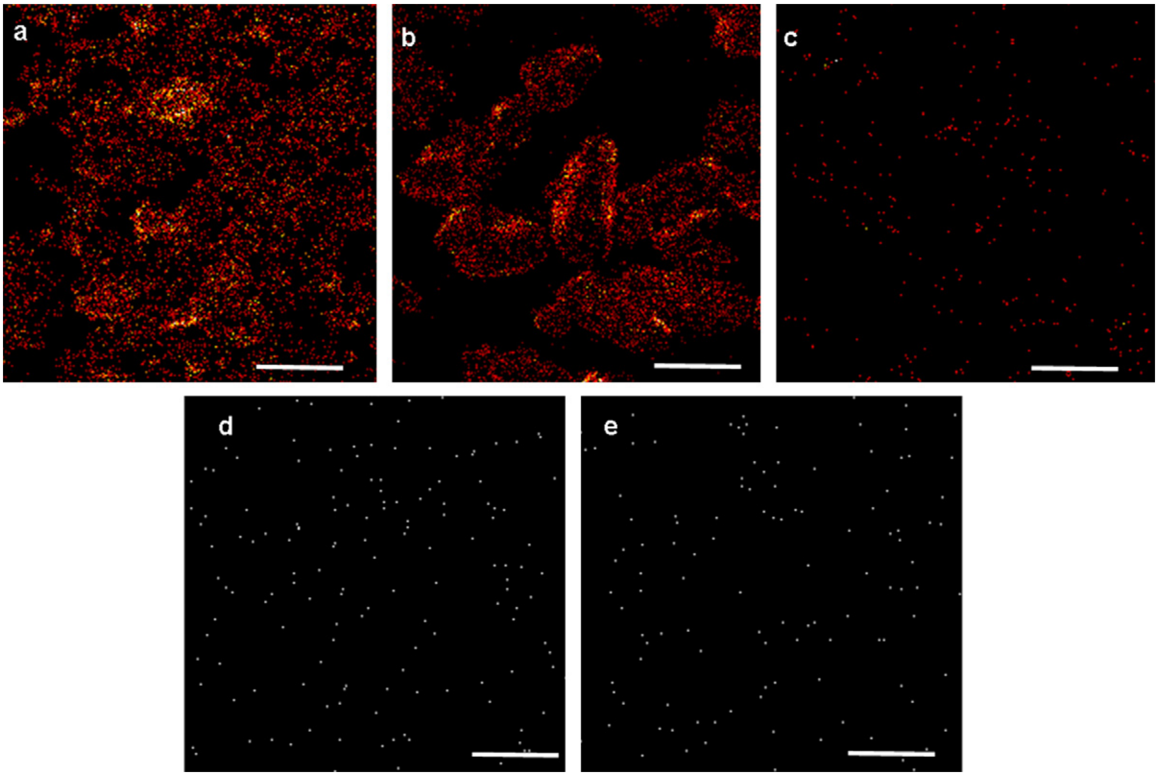

Fig. 2. TOF-SIMS micrographs at scanning area of 200 μm × 200 μm as indicated as functional group $C_6H_{11}O_5$ (m/z 163) signals for the samples of (a) untreated lactose; (b) mechanofused lactose 0.1%; (c) mechanofused lactose 0.5%; (d) mechanofused lactose 1%; (e) mechanofused lactose 5% (scale bars represent 50 μm).

also includes the composition down to a relative depth of the probe beam. Therefore, a near- or fully coherent coverage may have formed, but may be thinner in depth than that of probe beam-hence fully coverage would not be indicated (Zhou et al., 2011b). The estimated coverage values of 75% were then consistent in the range close of MgSt content between 1 and 5%. Further investigation on this issue may improve the discrimination of surface coverage.

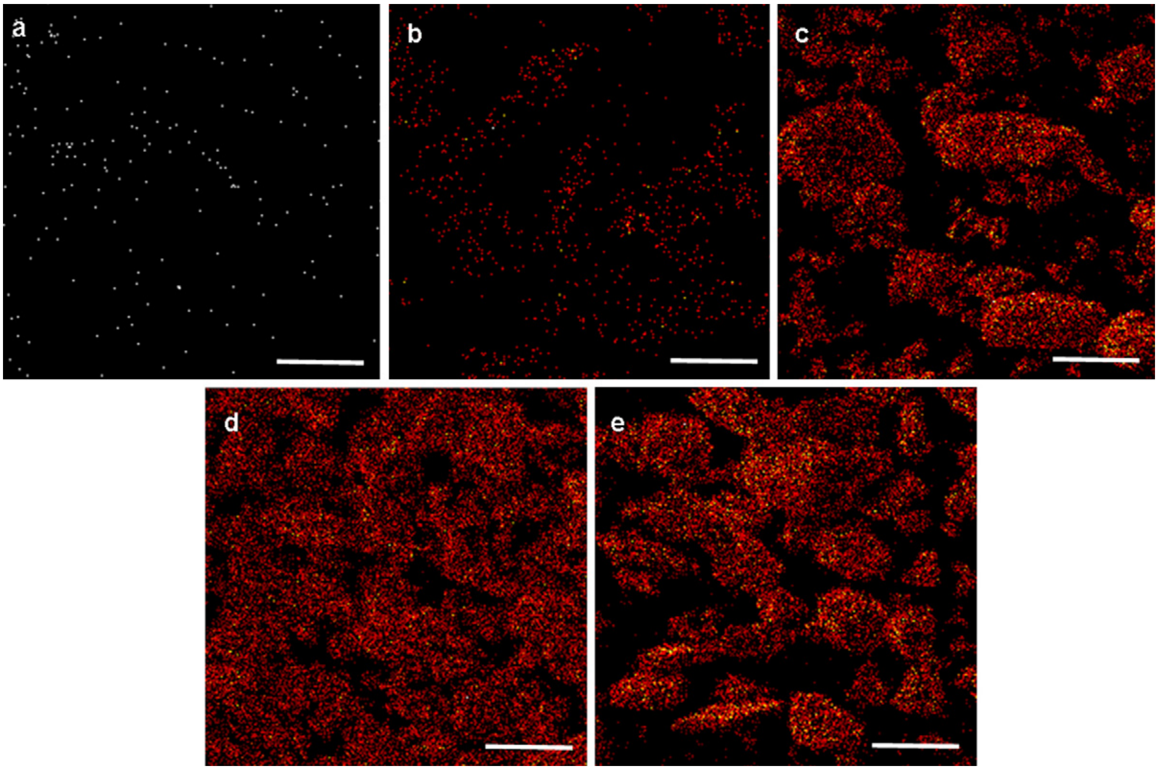

Fig. 3. TOF-SIMS micrographs at scanning area of 200 μm × 200 μm as indicated as Mg (m/z 24) signals for the samples of (a) untreated lactose; (b) mechanofused lactose 0.1%; (c) mechanofused lactose 0.5%; (d) mechanofused lactose 1%; (e) mechanofused lactose 5% (scale bars represent 50 μm).

Table 4
Carbon compositions for lactose samples measured by XPS (mean ± SD, $n = 3$).

Sample	Atomic ratio			
	C–C	C–O	O–C–O, C=O	O–C=O
Untreated	0.063 ± 0.008	0.731 ± 0.006	0.188 ± 0.004	0.017 ± 0.002
0.1%	0.129 ± 0.004	0.663 ± 0.009	0.191 ± 0.004	0.017 ± 0.001
0.5%	0.603 ± 0.015	0.306 ± 0.014	0.072 ± 0.001	0.018 ± 0.001
1%	0.687 ± 0.001	0.238 ± 0.004	0.060 ± 0.002	0.015 ± 0.005
5%	0.698 ± 0.003	0.227 ± 0.002	0.056 ± 0.001	0.019 ± 0.001

Table 5
Coverage of MgSt coating on the lactose surface after mechanofusion calculated by curve-fitting C1s using pure components as reference spectra to fit components for the mechanofused lactose samples measured by XPS (mean ± SD, $n = 3$).

Sample	Coverage of MgSt on lactose surface
0.1%	8.5 ± 0.2
0.5%	64.5 ± 0.8
1%	75.0 ± 0.3
2%	72.5 ± 0.2
5%	75.1 ± 0.1

Table 6
Bulk densities and Carr index results for lactose samples (mean ± SD, $n = 4$).

Sample	Poured density (g/ml)	Tapped density (g/ml)	Carr index
Untreated	0.390 ± 0.008	0.772 ± 0.019	0.495 ± 0.006
0.1%	0.462 ± 0.006	0.751 ± 0.006	0.384 ± 0.007
0.5%	0.566 ± 0.007	0.794 ± 0.007	0.288 ± 0.009
1%	0.696 ± 0.013	0.946 ± 0.013	0.264 ± 0.012
2%	0.640 ± 0.009	0.960 ± 0.036	0.303 ± 0.021
5%	0.743 ± 0.020	1.031 ± 0.007	0.279 ± 0.022

3.5. Powder bulk densities and Carr index

Bulk density metrics and derived indices have previously been shown to substantially change on mechanofusion of similar cohesive fine powders (Zhou et al., 2010a,b). Table 6 showed in the current study that the poured and tapped density of samples increased in a general pattern from the untreated sample, with an increase in MgSt content. There were no significant differences in tapped density between the untreated batch and the 0.1% batch, or between the 1% batch and the 2% ($p > 0.05$). The Carr index values for P450 decreased from the highest value of 0.495 ± 0.006 for the untreated batch to the lowest value of 0.264 ± 0.012 for the 1% batch (Table 6). There was no significant difference in Carr index value between the mechanofused batches of 1% and 5% ($p > 0.05$).

3.6. Shear testing

The results from shear testing are provided in Fig. 4 and Table 7, and appear generally consistent in relating to Carr index results. The cohesion values of P450 samples reduced by 77%, from 1.59 ± 0.16 kPa for the untreated sample to 0.36 ± 0.06 kPa for the 1% batch. There was no significant difference in cohesion value between the batches of 1%, 2% and 5% ($p > 0.05$). Furthermore, the ff_c values of the starting material and 0.1% MgSt powder, being below 4 indicate a material that is “cohesive” (Schulze, 2008). Although the mean ff_c values for the 1% batch was calculated as the highest, there was no significant difference in ff_c values between the batches of 1%, 2% and 5% ($p > 0.05$), and all would rate as “free flowing”. The shear stress results demonstrated that the untreated sample exhibited the highest shear stress at each normal stress (Fig. 4). The shear stress of the 1% mechanofused batch at each normal stress was shown as the lowest.

Table 7
Shear results for lactose samples (mean ± SD, $n = 3$).

Sample	Cohesion (kPa)	ff_c
Untreated	1.59 ± 0.16	2.90 ± 0.21
0.1%	1.22 ± 0.03	3.66 ± 0.04
0.5%	0.56 ± 0.12	7.76 ± 1.41
1%	0.36 ± 0.06	11.73 ± 1.99
2%	0.42 ± 0.05	10.32 ± 1.15
5%	0.41 ± 0.04	10.73 ± 1.08

4. Discussion

In the current study, state-of-the-art surface analytical systems of XPS and ToF-SIMS were employed in order to explore capabilities these techniques provided in qualitatively and quantitatively assessing the extent of the surface coating formed from mechanofusion of varying contents of MgSt onto a fine cohesive lactose powder. In this study, the ToF-SIMS results were consistent with the formation of a relatively uniform and substantial coverage MgSt coating layer on the fine lactose particle surfaces. XPS also supported such a high degree of coverage by the MgSt. The results were consistent with a relative surface coverage that increased with the increase of MgSt content added from 0 to 1%. Further increase in MgSt content appeared to only provide a marginal increase in surface coverage indicating that mechanofusion with of the order of 1% (w/w) MgSt on such fine lactose particles with a median diameter of approximately 20 μm successfully achieved an effective and approximately complete coating.

As it has previously been shown that the particle size distribution of such a fine lactose powder was not observed to be altered substantially after mechanofusion (Zhou et al., 2010b, 2011a), hence the changes in powder flow behaviour should not be attributed to any size enlargement or granulation of the fine particles. The effects of the surface coverage with MgSt on the powder bulk cohesion and flow properties of the coated powders are shown in Fig. 5a and b: an estimation of surface layer content

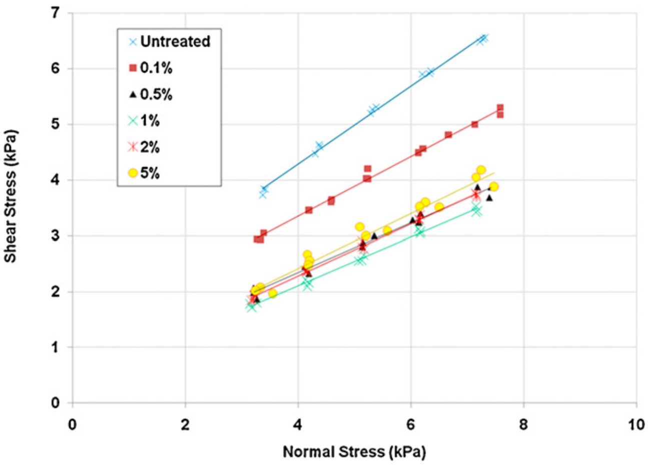

Fig. 4. Shear stress results for lactose samples measured by the shear module of FT4 powder rheometer.

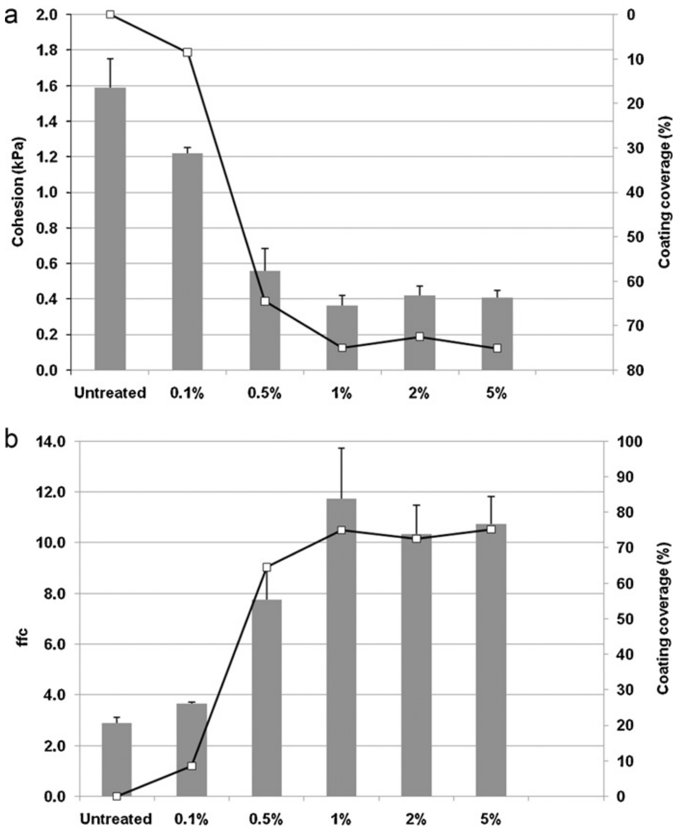

Fig. 5. Effect of surface coating coverage measured by XPS on the (a) cohesion and (b) flow function of the lactose samples.

of Mg, derived from the XPS data, has been added to these figures. Fig. 5a shows that the cohesion values of the lactose powders measured by shear testing are substantially reduced corresponding with the increase of MgSt in the powder, and of the estimated surface layer content, up to a level of 1% MgSt. Similarly, the flow function data derived from shear testing (shown in Fig. 5b) shows an increase within this range of increasing MgSt. Consequently, the results indicate that the powder inter-particle interactions and bulk flow behaviours are dependant on their surface chemical composition. In a previous study, the surface energy results measured using IGC at finite dilution indicated substantial reductions in the derived dispersive energy for the majority of the lactose surfaces after mechanofusion (Zhou et al., 2011b). Given that a coating of MgSt should reduce long-range Van der waals (Gold et al., 1968) as well as capillary forces (Zimon, 1982) between the particle surfaces, this study supports our hypothesis that it is the level of MgSt coverage that primarily dictates the bulk powder properties.

This study provided evidence from both SEM images and BET surface area results, that the surfaces of lactose particles were made relatively smoother after mechanofusion with specific levels of MgSt, namely in this case around 1%. This can be explained as resulting from the mechanical action of the mechanofusion process by filling MgSt into the surface irregularities on the lactose particle surfaces, surface polishing effects due to plastic deformation and MgSt lubrication. Further increase in MgSt content from 1% to 5% was believed to result in excessive MgSt multi-lamellar layers and increased surface roughness but the bulk characteristics for the 5% MgSt batch remained free-flowing. These results are proposed here to indicate that the improvements of the flow characteristics of the fine lactose powder studied here, which has undergone the mechanofusion processing, were primarily dependent on the surface chemical changes from the coating rather than their surface morphological properties in this study. Further ongoing study is required to clarify these relative effects.

5. Conclusions

This study indicated that the improvement in flow behaviours for a cohesive fine milled lactose monohydrate powder with median diameter around 20 μm was dependent on the MgSt surface coating quality that has been created by the intensive mechanical dry coating process of mechanofusion. Evidence was produced from innovative employment of a range of surface chemical probe techniques that a near complete coverage was achieved after mechanofusion with approximately 1% (w/w) MgSt. The techniques used show promise in future to be used to optimize such coating parameters. The changes in surface chemical properties were suggested to exert a more substantial impact on powder flow and cohesion characteristics than the changes in surface morphological properties for the fine lactose powders studied here after surface coating. The capability to substantially change these bulk characteristics of fine cohesive particles may have utility in future pharmaceutical dosage forms, including powders used in meeting very varying demands for example, from inhalation powders (Morton, 2006) to oral drug delivery forms (Morton, 2010).

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