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Influence of fines on the surface energy heterogeneity of lactose for pulmonary drug delivery

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ABSTRACT

The effects of the blending of lactose fines to the overall adhesion property of coarse α-lactose monohydrate carrier particles were investigated. Five samples, three of them commercial samples from DOMO (Lactohale® LH100, LH210, and LH250) whilst the other two are blends of LH210 and LH250, were studied. Characterisation included particle sizing, SEM, PXRD and IGC. Dispersive surface energy γ_{SV}^{d} was determined using a finite concentration IGC method to obtain a distribution profile. The γ_{SV}^{d} distribution of lactose crystals was found to vary from 40 to 48 mJ/m^2. The unmilled coarse crystalline lactose sample (LH100) γ_{SV}^{d} was lowest and showed less heterogeneity than the milled sample (LH250). Fines (LH210) were found to have the highest γ_{SV}^{d} value. The samples with loaded LH210 were found to have a higher energy than LH100. The amount of LH210 in Blend 1 was not able to decrease surface energy heterogeneity, whereas sample Blend 2 showed adequate loading of fines to obtain a relatively homogeneous surface. Addition of fines resulted in an increase in γ_{SV}^{d}, suggesting that coarse lactose surfaces were replaced by surfaces of the fines. Increasing the loading of fines may result in a more homogeneous surface energy of lactose particles.

1. Introduction

Pulmonary drug delivery is an attractive way of introducing medication for lung diseases like asthma and COPD. Besides, pulmonary delivery is increasingly used for delivery of drugs in medications that cannot be swallowed like proteins and peptides (Del Valle et al., 2009). The lungs are very attractive for the uptake of medications due to their large surface area (70–100 m^2 for an adult) and their easily permeable membrane. In order to reach the active area of the lungs, drug particles need to be in the aerodynamic particle size range of 1–5 μm. These small particles tend to form strong agglomerates caused by cohesive forces and these forces need to be overcome to produce an aerosol with particles that are able to reach the lungs. In dry powder inhalers, a coarse carrier, most commonly lactose monohydrate, is blended with the micronised drug particles. Current literature reports that upon inhalation, an aerosol is produced where the fine drug particles are detached from the coarse carrier particles.

The performance of carrier-based dry powder inhalation (DPI) formulation is determined, to a significant degree, by the preparation of the formulation, as well as the design of aerosolisation device, the inhalation mode and the respiratory-tract anatomy and physiology of the patient (Timsina et al., 1994). One of the methods, that have been extensively researched, to optimise drug delivery of the active ingredient is the use of a ternary formulation where a small amount of fine excipient particles or *fines* is added to the coarse carrier and the drug blend (Podczeck, 1998; Louey and Stewart, 2002; Shur et al., 2008). Despite the evidence that the use of such methods show an improved fine particle dose (FPD) or fine particle fraction (FPF) of the active drug, the mechanism by which the fine particles alters the performance of the formulation has remained elusive (Jones and Price, 2006).

One such hypothetical mechanism that has been proposed is the passivation of strong binding sites or high energy sites by fine excipient particles (Jones and Price, 2006). The fines are thought to preferentially adhere to the surface regions of the coarse carrier with the highest surface energy, therefore forcing drug particles to bind to surfaces with lower surface energy. When the formulation is kinetically activated through the respiratory-tract, the drug particles are more easily separated from the surface of the carrier, thus increasing the inhaled dose in the lower airways (Fig. 1). Zeng et al. (1999) observed an increase of ~120% in FPF of the drug when fine lactose particles were blended to the coarse lactose carrier before the addition of drug to the formulation, thus providing the fines with the first opportunity to adhere to the high energy sites. Other

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Nomenclature

a_m	molecular cross-sectional area of adsorbates
A	chromatogram area
F	carrier gas exit flow rate
ΔG^0	standard energy of adsorption
ΔG^0_{AB}	standard polar (acid–base) adsorption energy
h	chromatogram peak height
j	James–Martin correction factor
m	sample mass
n	amount adsorbed
n_m	monolayer coverage
N_A	Avogadro's number
P	pressure
P_0	saturation pressure
P_{inj}	partial pressure of probe at injection loop
R	universal gas constant
SSA_{BET}	specific surface area from nitrogen adsorption isotherm
t_R	retention time
t_0	dead time
T	temperature
T_{Loop}	injection loop temperature
V_{Loop}	injection loop volume
V_N	net retention volume
W_A	work of adhesion
γ^d_{LV}	liquid–vapour dispersive surface energy component
γ^p_{LV}	liquid–vapour polar surface energy component
γ^d_{SV}	solid–vapour dispersive surface energy component
γ^p_{SV}	solid–vapour polar surface energy component
θ	surface coverage

blending order was found to yield a smaller increase in FPF compared to the control, *i.e.* the binary mixture of coarse carrier and drug. However, it was also noted that the blending order had no significant impact on the formulation performance when the blending

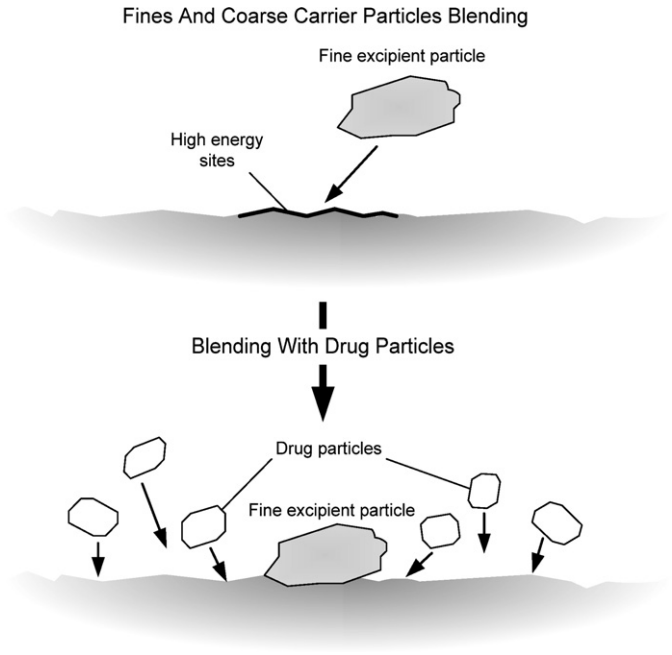

Fig. 1. Passivation of high energy sites: fines are first blended with coarse carrier particles before blending with the particles of the active drug.

time was increased, speculatively due to the redistribution of particles between binding sites for prolonged blending time (Zeng et al., 2000).

It is clear that with the current state of knowledge, the influence of fine particles to improve DPI formulation will require a more fundamental understanding of the interparticulate interactions of the components in the mixture, in order to clarify the mechanism by which the fines work (Jones and Price, 2006). In an attempt to understand the change in the overall adhesion property when lactose fines are added to the coarse carrier, this study seeks to determine the surface energetic distribution of different processed coarse lactose and the subsequent changes to the surface energy distributions by the blending of fine lactose particles. Such a study will confirm (or otherwise) the commonly and widely accepted view that addition of fines leads to a reduction in surface energy. This study was conducted via a recently developed methodology using inverse gas chromatography (IGC) at finite concentrations.

1.1. Inverse gas chromatograhy (IGC)

The inverse gas chromatography technique has been widely used in the characterisation of solids, fibres, films including pharmaceutical solids (Heng et al., 2006). By measuring the time a probe molecule takes to elute through a packed column of sample materials, the thermodynamic properties of the solid phase can be determined. The net retention volume, V_N which is a fundamental surface thermodynamic property of the solid–vapour interaction process, is given by:

$$V_N = \frac{j}{m} \cdot F \cdot (t_R - t_0) \cdot \frac{T}{273.15} \quad (1)$$

where T is the column temperature in Kelvin (K), F is the carrier gas exit flow rate at 1 atm and 273.15 K, t_R is the retention time for adsorbing probe and t_0 is the mobile phase hold-up time (dead time), m is the sample mass in the packed column and j is the James–Martin correction, which corrects the retention time for the pressure drop along the column bed. V_N can be related to the free energy of adsorption, ΔG^0, and the work of adhesion of vapour adsorbates to the surface, W_A, by:

$$-\Delta G^0 = RT \ \ln V_N + K = N_A \cdot a_m \cdot W_A \quad (2)$$

where R is the universal gas constant, K is a constant, N_A is the Avogadro's number, a_m is the cross-sectional area of the adsorbate.

According to Owens and Wendt (1969), the work of adhesion between a solid and liquid is the summation of geometric mean terms of dispersive and polar surface energy components as shown in Eq. (3):

$$W_A = 2\sqrt{\gamma^d_{LV} \cdot \gamma^d_{SV}} + 2\sqrt{\gamma^p_{LV} \cdot \gamma^p_{SV}} \quad (3)$$

Hence, the injection of a series of infinite concentration of non-polar ($\gamma^p = 0$) probes into the sample column will result in a linear regression on a plot of $RT \ln V_N$ *versus* $a_m(\gamma^d_{LV})^{1/2}$, and γ^d_{SV} can be calculated from the slope (Schultz et al., 1987) (Fig. 2). The polar component of surface energy can also be determined by applying a polar adsorbate ($\gamma^p_{LV} \neq 0$) and as such, the V_N measured is summation of a dispersive and polar component. Knowing γ^d_{LV} of the polar probe allows the polar (also cited in literature as acid–base) energy of adsorption, ΔG^0_{AB}, to be obtained.

IGC has been used to access the performance of dry powder inhalation formulations (Cline and Dalby, 2002; Tong et al., 2006). Tong et al. (2006) investigated the relative influence of drug–drug cohesion and drug–carrier adhesion on the *in vitro* performance of salmeterol xinafoate (drug) with lactose (carrier) by measuring surface energies and solubility parameters of the components by IGC at infinite dilution (zero surface coverage). The inhaler performance

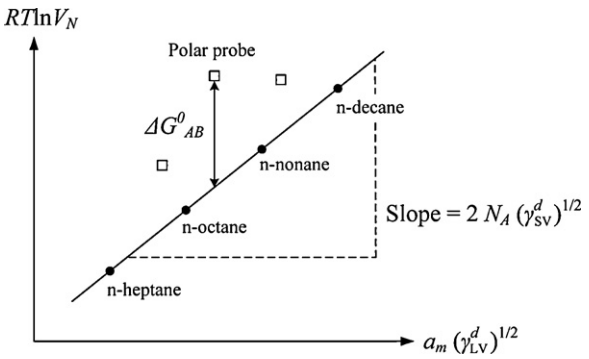

Fig. 2. Determination of γ_{SV}^{d} and ΔG_{AB}^{0} from a plot of net retention volume *versus* vapour surface property.

of salmeterol xinafoate was found to improve significantly if the drug–carrier adhesion was stronger than drug–drug cohesion. Cline and Dalby (2002) similarly observed that increasing surface energy interaction between drug and carrier resulted in an improved FPF of the drug.

1.2. Surface free energy distribution

A recently developed method (Thielmann et al., 2007) using inverse gas chromatography at finite concentration has been shown to be able to distinguish surfaces energetics of pharmaceutical solids exhibiting markedly different surface properties, *i.e.* heterogeneity and homogeneity (Ho et al., in press), as well as small variation in surface energy distributions resulting from small changes in crystal habits (Ho et al., 2009). In this study, the methodology was utilised to characterise surface energetic profiles of different inhalation grade lactose, and the effects to the surface energetics when they are mixed in a two component blend were also investigated.

The measurement of dispersive and polar surface energy distribution relies on a series of finite concentration IGC experiments using a series of n-alkanes and at least one polar solvent. In the current study, the determination of γ_{SV}^{d} and ΔG_{AB}^{0} distribution profiles consists of three main steps which are displayed in Fig. 3. First, the adsorption isotherms for four n-alkane probes (C6-C10) and ethanol are measured using the IGC. Employing the peak maximum methodology (Thielmann et al., 2007), the retention volume and equilibrium partial pressure, *P*, are calculated for each single injection of increasing solute concentration via Eqs. (1) and (4):

$$P = \frac{h}{F \cdot A} \cdot V_{Loop} \cdot \frac{273.15}{T_{Loop}} \cdot P_{inj} \tag{4}$$

where *h* is the chromatogram peak height, *A* is the chromatogram peak area, V_{Loop} is the injection loop volume, T_{Loop} is the injection loop temperature and P_{inj} is the partial pressure of the probe at the injection loop. The adsorbed amount, *n*, and therefore the adsorption isotherm for each probe vapour can then be obtained by integration of V_N *versus P*. If the Brunauer–Emmett–Teller (BET) specific surface area, SSA_{BET}, of the sample is known, the monolayer

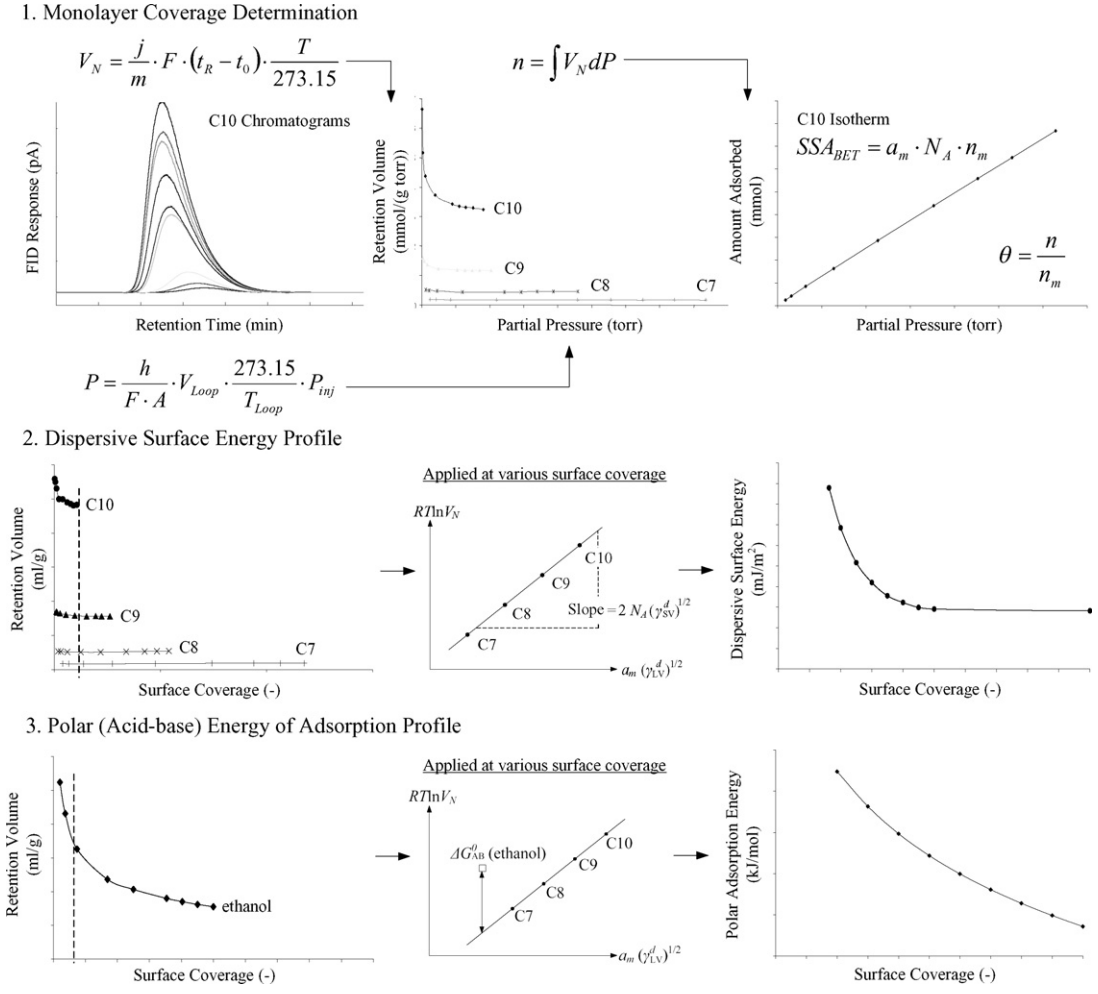

Fig. 3. Surface energy heterogeneity determination.

capacity, n_m, for each probe vapour can be calculated from:

$$SSA_{BET} = a_m \cdot N_A \cdot n_m \quad (5)$$

From the monolayer capacity, the corresponding surface coverage, n/n_m or θ, at each injection concentration can then be measured from the amount adsorbed n. Since the retention volumes of each probe are now expressed as a function of sample surface coverage, both γ_{SV}^d and ΔG_{AB}^0 can now be calculated at a particular surface coverage in the same way as described previously in Fig. 2 using the Schultz approach (1987). The calculations of γ_{SV}^d and ΔG_{AB}^0 across a range of surface coverages, therefore, result in a distribution of dispersive and polar surface energies. Further details of the methodology can be found elsewhere (Thielmann et al., 2007; Yla-Maihaniemi et al., 2008).

2. Materials and methods

2.1. Materials

Details of the five lactose samples are tabulated in Table 1. Three of them are commercial samples from DOMO (Lactohale® LH100, LH210, and LH250), the other two are blends of LH210 and LH250. LH100 are coarse lactose crystals that were sieved through a 310 μm sieve, LH210 and LH250 are milled and classified grades of lactoses, with LH210 being a fine fraction and LH250 being a coarse fraction.

Blend 1 and Blend 2 were prepared by weighing the appropriate amounts of LH210 and LH250 in a bottle and turning and rotating the closed bottles for >1 min. Blending ratios are for Blend 1: 82 g of LH250 and 18 g of LH210, and for Blend 2: 70 g of LH250 and 30 g of LH210.

2.2. Particle size measurement

Particle size distributions were measured with a Sympatec HELOS laser diffractometer (Sympatec GmbH, Clausthal-Zellerfeld, Germany). All powders were dispersed in air at a pressure of 1.5 bar through the detection zone of the diffractometer. The diffracted laser light was focussed with an R5 lens with a measuring range of 0.5/4.5–875 μm.

2.3. Finite concentration inverse gas chromatography

Lactose powder (2.5–2.8 g) samples were packed by gentle vibration into separate pre-silanised glass columns (300 mm × 4 mm ID) with silanised glass wool packing at each end to prevent powder movement. The experiments were conducted using an SMS-iGC 2000 (Surface Measurement Systems, London, UK) system. Prior to measurements, samples were pre-treated at 303 K and 0% RH for 2 h under flowing helium to remove any residual moisture or solvent adsorbed on the powder surface. Following pre-treatment, pulse injections using a 0.25 ml gas loop at 303 K were performed. Purely dispersive n-alkane vapour probes (decane, nonane, octane and heptane) and polar probe (ethanol) were injected at 0.03, 0.05, 0.10, 0.20, 0.35, 0.55, 0.70, 0.80, 0.95 P_{inj}/P_0 and V_N was determined using a peak maximum analysis. Methane gas was used as a non-interacting probe giving t_0 for the column, with concentrations of 0.10 P_{inj}/P_0. Helium was used as the carrier gas at a flow rate of 10.0 standard cubic centimetres per minute for all injections. The γ_{SV}^d and ΔG_{AB}^0 were calculated according to the Schultz method (1987).

2.4. Specific surface area

The BET specific surface area for all five lactose samples was obtained based on N_2 adsorption isotherm measured using a gas adsorption analyser (Tristar 3000, Micromeritics, Norcross, GA). Approximately 4 g of each sample was degassed with helium flow at 50 °C for at least 5 h before BET measurement. Surface area was determined using the BET model in the P/P_0 range from 0.05 to 0.30. Each sample was measured in duplicate.

2.5. SEM images

SEM images were acquired with a tabletop microscope system TM-1000 (Hitachi, Tokyo, Japan) in the charge-up reduction mode.

2.6. Polymorph identification

X-ray powder diffraction spectra were obtained for the lactose samples using a X'Pert Pro diffractometer (PANalytical B.V., Almelo, The Netherlands) over the range of 7–40° 2θ with a Cu Kα X-ray source at 40 kV and 40 mA.

3. Results and discussion

Particle size and BET specific surface area of LH100, LH210, LH250, Blend 1 and Blend 2 are displayed in Table 2, whereas the SEM images are shown in Fig. 4. From Table 2, the fine lactose (LH210) has the smallest median-averaged equivalent spherical diameter (18 μm) amongst the three unblended lactose samples. The unmilled sample LH100 has the largest median-averaged diameter, whereas the gently milled and classified LH250 possesses a smaller median-averaged diameter than LH100 due to the size reduction procedure. The particle sizes of Blend 1 and Blend 2 are both between the median-averaged diameter of LH250 and LH210, and are also consistent with the blending ratio of LH250 to LH210. As can be seen from Fig. 4, LH100 exhibits the normal tomahawk crystal shape expected for α-lactose monohydrate crystals (Raghavan et al., 2001). On the other hand, the crystal shape of the gently milled LH250, was found to be more irregular and it seems that the difference in crystal shapes (habit) between LH100 and LH250 could be due to the cleavage of weakly attached facets upon milling. The particle size of Blend 1, which was blended with 18% fine lactose, is approximately 20% bigger than Blend 2 which contains the same batch of LH250 blended with 30% fines. Post-blending operations, the fines can be seen to adhere onto particular surface regions of both Blend 1 and Blend 2. However, some portions of fine particles also seem to form into clusters or aggregates which are adhered to the coarse crystal surfaces of Blend 1 and Blend 2. The amount of fines, which is defined here as the fraction of particles below 15 μm, follow the same trend as the median particle size: the smaller the median size, the larger the percentage of fine particles (Table 2). The coarse LH100 and LH250 only have about 3% of fine particles, whereas the fine LH210 has over 40% of fines. The two blends can also be seen to have quantities of fines that are there in between LH210 and LH250. The trend in BET specific surface areas, which are also displayed in Table 2, is in good agreement with the median-averaged particle size of the samples. Comparisons of γ_{SV}^d and ΔG_{AB}^0 distributions for the five lactose samples are shown in Figs. 5 and 6, respectively. All unblended lactose, LH210, LH250 and LH100 show a small degree of dispersive surface energy heterogeneity within the range of surface coverage, θ, examined (Fig. 5), although very different γ_{SV}^d values. As the fines content of the unblended samples increases, the range of γ_{SV}^d shifts to higher values. This means that the finer lactose crystals, in particular the LH210 fines, possess a greater degree of long-ranged van der Waals surface forces compared to the coarse lactose LH100 and LH250.

β-Lactose can be present in milled materials, attributed to the recrystallisation of amorphous lactose during storage (Haque and Roos, 2005). In order to understand the variation in γ_{SV}^d for these

Table 1
Details of the lactose samples used in the current investigation.

Sample	Code	Description
Lactohale® LH100	LH100	Unmilled, crystalline
Lactohale® LH210	LH210	Milled, fine fraction
Lactohale® LH250	LH250	Crystalline, gently milled with fines removed
Lactohale® LH250 with Lactohale® LH210	Blend 1	LH250 and LH210 in 82:18 ratio
Lactohale® LH250 with Lactohale® LH210	Blend 2	LH250 and LH210 in 70:30 ratio

Table 2
Particle size and BET specific surface area of the lactose samples.

Sample	Particle size (based on an equivalent sphere)				BET specific surface area (m^2/g)
	d_{10} (μm)	d_{50} (μm)	d_{90} (μm)	% <15 μm	
LH100	59.0	149.1	228.5	2.65	0.1164 ± 0.0016
LH210	3.2	18.0	48.0	42.2	0.8120 ± 0.0036
LH250	36.6	80.7	138.2	3.2	0.1893 ± 0.0016
Blend 1	10.6	65.2	131.3	13.0	0.2785 ± 0.0020
Blend 2	7.2	53.9	124.2	18.2	0.3510 ± 0.0023

three lactose samples, polymorphic identification was conducted by PXRD. The PXRD patterns of both coarse lactose (LH100 and LH210), the fines (LH210), including both blends 1 and 2, are comparable to the peaks of pure α-lactose monohydrate. As such, the higher γ_{SV}^{d} measured for LH210 cannot be explained by β-lactose content.

Figs. 5 and 6 show the γ_{SV}^{d} and ΔG_{AB}^{0} distributions as a function of n/n_m, respectively. The γ_{SV}^{d} for zero surface cov-

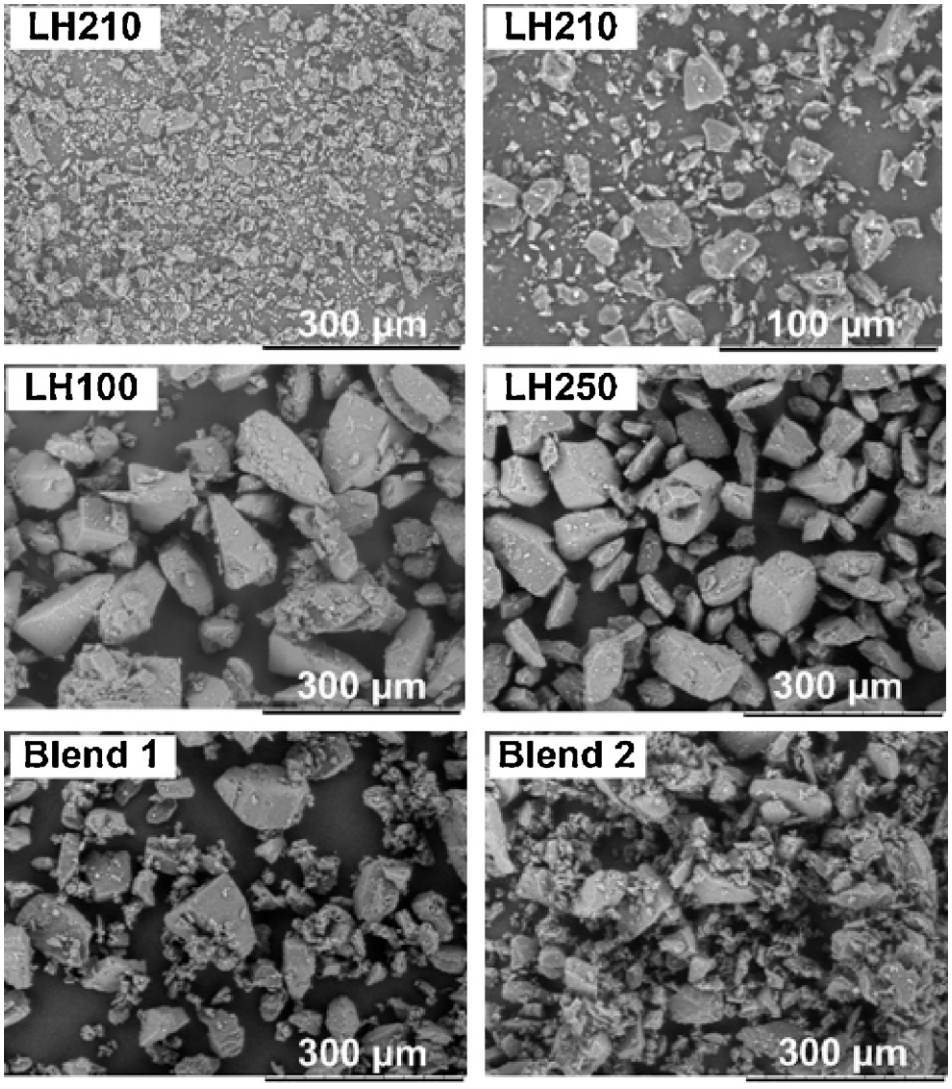

Fig. 4. SEM images of lactose crystals and blends of fine and coarse lactose.

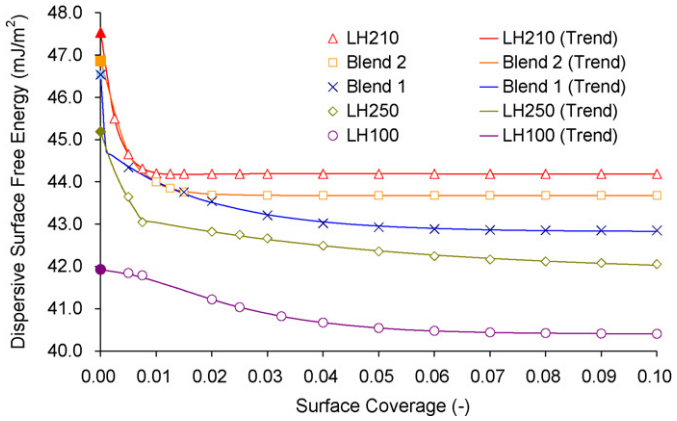

Fig. 5. Dispersive surface energy distributions (*versus* surface coverage) for all lactose samples used in the study.

erage (Fig. 5) is calculated based on infinite dilution IGC, whereby injection size of alkane probes is held constant at $P/P_0 = 0.03$. We obtain values: LH210 = 47.53 mJ/m^2, Blend 2 = 46.86 mJ/m^2, Blend 1 = 46.54 mJ/m^2, LH250 = 45.18 mJ/m^2 and LH100 = 41.93 mJ/m^2.

When the fines (LH210) were blended with coarse lactose (LH250) as in Blend 1 and Blend 2, it is expected that the surface energy of the system would increase with increasing fines content because the fines posses both higher γ_{SV}^{d} and ΔG_{AB}^{0}. This is exactly the case for Blend 1 and Blend 2 as shown in Figs. 5 and 6. In the case of Blend 1, the introduction of fines shifted the γ_{SV}^{d} profile of LH250 from approximately 42 mJ/m^2 to about 43 mJ/m^2, an increase of ~2.5%, at $n/n_m = 0.10$, whereas the Blend 2 sample was shifted to ~44 mJ/m^2 (~5% increase), resulting in a surface energy value close to that of LH210. This indicates that surfaces of the coarse lactose (LH250) were replaced by surfaces of the fines (LH210), with greater propensity for Blend 2 than Blend 1, due to the higher loading of fine particles. It is interesting to note from the surface energy profiles that the blending of fines did not decrease the overall surface energy of the coarse lactose, but actually increased the overall adhesion property of the blend due to the fact that the fines possess much higher surface energy. As the high energy fines were blended with low energy coarse carrier, the fines seem to have adhered together to form clusters of fines as well as adhering to the specific regions of the coarse lactose (Fig. 4), suggesting that surfaces with high energy or binding characteristics do seem to adhere together. The blending of fines to LH250 resulting in an increase in ΔG_{AB}^{0} values, resulting in the blends possessing characteristics of LH210.

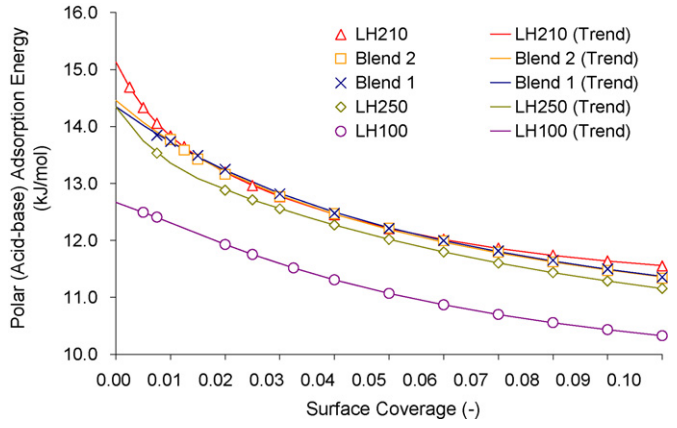

Fig. 6. ΔG_{AB}^{0} (ethanol) distributions (*versus* surface coverage) for all lactose samples used in the study.

The current results provide the first evidence that the surface energetics of both fine and coarse lactose is an important parameter in ternary inhalation formulation. The inclusion of higher energy fines to coarse carrier will increase the drug–carrier adhesion interactions, because surfaces are replaced by those having stronger adhesion characteristics. Fines would passivate high energy surfaces only if the fines possess smaller surface energy compared to the coarse carrier. However, the increase of drug–carrier adhesion was reported to increase inhalation performance of drug (Cline and Dalby, 2002; Tong et al., 2006), and it seems that more study is required in order to understand the relative influence of drug–carrier adhesion and drug–drug cohesion of the drug in the performance of inhalation formulations.

4. Conclusions

The surface properties of lactose crystals were found to be heterogeneous and the surface energy varies from 40 to 48 mJ/m^2. The unmilled coarse crystalline lactose sample (LH100) showed less heterogeneity than the milled sample (LH250). The loaded fines (LH210) have a higher energy than the coarse lactose. The amount of fines in Blend 1 was not able to alter the surface energy heterogeneity, whereas sample Blend 2 showed adequate loading of fines to obtain a relatively homogeneous surface. The current surface energy distribution methodology was able to distinguish the differences between these lactose samples. Surfaces of the coarse lactose were shown to be replaced by surfaces of the fines. We conclude that the effects of fines result in an overall increase in surface energy.

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