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Processing effects on the surface properties of α-lactose monohydrate assessed by inverse gas chromatography (IGC)

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As mechanically induced processing effects on powdered materials are primarily manifested in small regions on the particle surface, they frequently remain undetected by routine chemical and physical measurement techniques. Inverse gas chromatography was employed in this study to characterize the surface properties of α-lactose monohydrate and determine any changes induced by milling and blending. Results highlighted the potential of this technique to detect and quantify surface energy differences induced by milling and blending and demonstrated how a second unit operation often achieves its effects by means of disrupting flaws caused during the first process. Studies of the flow properties revealed how the bulk behavior of powdered materials can change depending upon processing history, further emphasizing the importance of surface characterization in understanding the behavior of powdered materials.

1. Introduction

The downstream behavior of powdered materials can vary depending upon their processing history. Mechanical processes, such as milling, often lead to disruption or activation of the crystalline structure [1], resulting in a reduction in the degree of crystallinity. If this disorder is more extensive than inherent crystallographic molecular defects and dislocations, it can be viewed as an amorphous region at the surface or near-surface of a particle. The presence of even small amounts (as little as 1% of total weight) of amorphous regions have a significant impact on the physicochemical nature of the powdered material [2].

Blending has also been shown to lead to activation [1]. It exposes powdered materials to translational, rotational, gravitational and/or centrifugal forces that cause relative movements of individual and groups of particles. The subsequent collisions lead to friction between the particles resulting in the build up of electrostatic charges at the particle surfaces and fragmentation of brittle powdered materials.

It is therefore imperative to understand and characterize fully the extent of activation/disorder in powders before and after manufacturing processes in order to maximize stability of the system and to improve the quality of final products.

Several recent publications have explored new approaches to study the changes in various powder properties induced by alternative pretreatment operations. Alternative milling processes had been found to alter contact angles of samples of the same material [3] and the enthalpy of water vapor sorption was found to vary for samples of a drug milled by different individual or sequential milling processes [4]. From these studies, it is hypothesized that the milling process changes the orientation of molecules on the surface of the powder particles, and thus alters surface energetics [5]. However, it is only recently that techniques have emerged which are capable of probing such phenomena and are sufficiently sensitive to test this hypothesis.

In dry powder inhalers (DPIs), large inert carrier particles (30–90 μm) of α-lactose monohydrate are often incorporated with micronised drug powder to improve the flow properties of the blend. This, in turn, improves handling of the formulation during manufacturing processes and helps overcome the challenges of dose metering and dose uniformity [6].

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The blended micronised drug:carrier mixture formed can be described as an ordered or adhesive mixture [7], in which the fine drug particles adhere to the surface of the carrier particles. Obtaining a balance between the adhesion forces necessary for such formulations to resist segregation, while allowing sufficient drug to be released during inspiration remains a considerable formulation challenge. The adhesive forces between drug and carrier particles are therefore the most critical determinants of the redispersion of micronised drug particles in the inspired air [8] and as a result, the availability of the medicament to the lungs.

The thermodynamic work of adhesion which has to be expended to bring two surfaces into adhering contact depends on the surface free energies of the two surfaces and the energy of the contact interface [9]. It is known that the chemical structure of substances dictates their adhesion properties. Kebin *et al.* [10] pointed out that adhesion depends on the crystallographic orientation at the surface, which finds its expression in the surface free energy. Therefore, the higher the surface free energy the larger the adhesion force.

Appropriate manipulation of the physico-chemical characteristics of the inert carrier powder component can yield performance improvements which potentially help patient therapy. A starting point for these manipulations is to retain a base particle size range, such as that known to provide good downstream processing in conjunction with excellent entrainment characteristics, whilst selecting an appropriate size distribution (which may be multi-modal) such that the base carrier diameter is accompanied by other, principally finer particles [11]. Use of a multi-modal carrier particle size distribution relies on the existence of active and passive adhesion sites on particle surfaces [7] which lead to a variable pattern of particle-particle adhesion forces (iso-energetic adhesion sites) at different surface sites. This manipulation utilizes the finest particles to occupy the highest energy sites on the coarser carrier size fraction. This leaves only the lower energy sites available for adhesion of drug particles, which would be expected to be detached more efficiently and completely under any given inspiratory effort and drug-lactose combination [11].

Drug particle adhesion to carrier lactose surfaces can also be modified by alteration of particle shape and texture. Wong *et al.* [12] showed that irregular particles tended to adhere more strongly than equivalent more regular particles. Furthermore, Kassem [13] showed that carrier particles with low surface roughness facilitated a more effective re-dispersion of drug particles in an inhaled air-stream. The effect of such shape/textural changes may result, at least in part, from modification of the iso-energy profile of a given lactose crystal surface [11]. For example, Staniforth *et al.* [14] showed that rougher surfaces (associated with deeper energy traps) produce higher adhesion profiles than for the same adherent particle component blended with smooth carrier particles.

Once surfaces are in contact, the magnitude of the adhesion force will also depend on competing factors such as micromeritic and environmental effects. Increasing relative humidity is known to decrease adhesion characteristics due to increased adsorbed moisture [15]. Reducing relative humidity will reverse the process but is likely to promote increased electrostatics, which influence drug particle capture as well as adhesion [16]. Electrostatic attractive forces will enhance both the number and strength of active adhesion sites, whereas electrostatic repulsion is likely to weaken adhesive contact. For this reason, although this variable has not been examined in this study, measurements of electrostatic force contributions are of critical importance in providing information about interactions likely to influence DPI formulations.

Staniforth [11] has recently achieved a reduction in bond strength of carrier particles by utilizing a single step process called 'corrasion'. In this process, aerosol grade lactose plus 1% of a non-toxic, naturally-occurring ternary formulation agent are processed to provide beneficial iso-energy profiles. The corrasion process is designed to ensure that the bond strength of the drug particles to the carrier is sufficient to allow efficient downstream processing, but rapid and easy detachment from the carrier substance during the inhalation process.

However the effects of formulation variables, such as the surface properties of the carrier particles in relation to the respiratory deposition of the inhaled drug:carrier mixture, are not yet precisely known. A continuing scientific challenge is that the analytical techniques used to date to identify any changes in powder properties after various processing stages have not revealed property changes even though differences in performance have been noted for final products [17]. The reason may be that studies have examined the bulk or particulate properties of powders, whereas variations in the surface properties of materials although more subtle and difficult to detect could be as, if not more, influential.

The most widely used technique to determine surface properties of powdered materials is contact angle measurement. However, the technique for particulate systems is constrained as the particles are often compressed to form a flat surface. Compression causes changes in surface properties and the rough micro-surface produced often leads to contact hysteresis, reducing the accuracy of results [18]. Inverse gas chromatography (IGC) does not require sample pre-treatment and as such assesses the surface energetics of samples in particulate form.

IGC is an extension of conventional gas chromatography (GC) in which a non-volatile material to be investigated is immobilized within a GC column. This stationary phase is then characterized by monitoring the passage of volatile probe molecules of known properties as they are carried through the column via an inert gas [19]. Although only a small number of studies have reported the use of IGC for particulate solids, data indicate that this technique is suitable for surface analysis of pharmaceutical powdered materials. Applications to date include a study on water adsorption by cyclosporin [20] and studies of organic vapors onto different microcrystalline celluloses [21], xanthine bronchodilators [22], salbutamol sulphate [18, 23] and propranolol hydrochloride [24].

In this study, IGC was employed to characterize the surface properties of α-lactose monohydrate and to determine any changes induced by milling and blending.

2. Experimental

One batch of α-lactose monohydrate (batch 19398, Borculo, Chester, UK) was examined by IGC before processing (raw material, R1) after milling (milled/preblended, M1) and after blending (postblender, B1) to study the effects of milling and blending processes used to produce inhalation grade α-lactose monohydrate. The milling process was performed using a MikroPul ACM (Air Classifier Mill) (Hosokawa Micron Limited, Runcorn, UK) and blending was carried out in a Vrieco-Nauta Conical Mixer.

The particle size distribution of the samples was measured using the Aerosizer Particle Size Analyzer (Amherst Process Instruments, Amherst, MA, USA). A pulse jet disperser, the Aerodisperser (Amherst Process Instruments, Amherst, MA, USA) was employed to introduce the material to the Aerosizer as primary particles. Samples were analysed for 300 seconds employing high deagglomeration conditions, high feed rate (10000 particles per second) and medium shear (1.5 psi) with experiments carried out in triplicate. A calibration check was carried out using 1 μm and 10 μm standards (Sigma Pharmaceuticals, Poole, UK).

The specific surface area of the samples was measured using a Micromeritics Flowsorb Model 2300 (Micromeritics Instrument Corporation, Norcross, USA). Prior to measurement, samples were accurately weighed into sample tubes and degassed under a flow of 30 : 70, nitrogen:helium for 16 hours at 40°C, in order to achieve a stable surface. Samples were then equilibrated at various partial pressures of nitrogen between 5 and 30% nitrogen in a balance of helium, and the volume of nitrogen desorbed following adsorption of nitrogen at −196°C was recorded. Calibration checks for the apparatus were carried out using an alumina standard obtained from the Government Science Laboratories (Reference M11.05, surface area 2.09 m^2/g ± 0.15 m^2/g).

The moisture content of the samples was measured using Karl-Fischer Titration Analysis on a Metrohm 701KF Titrino (Herisau, Switzerland). The apparatus was calibrated using 30 μl samples of water. A known weight of sample was then introduced into the chamber of the apparatus and titrated against Karl-Fischer Reagent. Titration was repeated five times and the mean water content of each sample was calculated.

Inverse gas chromatography was undertaken on a Hewlett Packard 5880A GC (Hewlett Packard, Penna, USA). Data were obtained by flowing nitrogen gas at 10 $cm^3 min^{-1}$ through a silanised glass column packed with a known weight of material and injecting small amounts of a range of liquid probes with differing polarities. The retention times of the probes were measured at infinite dilution or near zero surface coverage (equivalent to 10^{-4}–10^{-7} μl of liquid) where retention is independent of the quantity of probe injected. For each sample three columns were prepared and each individual column was analysed twice.

The non-polar probes utilized in this study were hexane (BDH Laboratory Supplies, Poole, UK), heptane (Sigma-Aldrich, Gillingham, UK), octane (Aldrich Chemical Company, WI, USA) and nonane (Aldrich Chemical Company, WI, USA). Owing to their structure, n-alkanes have no dipole moment and no functional groups which undergo specific interaction, hence they are referred to as non-polar and interact by induced dipole forces. The polar probes employed comprise of a diverse range of volatile liquids which exhibit a large number of specific interactions. The polar probes used cover specific interactions from acidic e.g. chloroform (Sigma-Aldrich, Gillingham, UK), through amphoteric e.g. acetone (Sigma-Aldrich, Gillingham, UK), to basic e.g. ethylacetate (Sigma-Aldrich, Gillingham, UK) and tetrahydrofuran (Rathburn Chemicals Ltd., Scotland, UK) and are well characterized in the literature [25].

The Aeroflow powder avalanching analyzer (Amherst Process Instruments, API, Amherst, USA) was used to analyze the dynamic avalanching behavior of the samples. 60 ml of the material under test was added to partially fill a drum, and the drum rotated at 70 rpm for 1000 seconds. As the drum rotated the powder bed was carried up to an unstable state when an avalanche occurred. The time between successive avalanches was recorded by the projection of a light beam through the drum onto a photocell array [26]. The flowability of all samples was assessed in triplicate under controlled temperature and humidity.

3. Results and discussion

Dispersive and specific interactions are considered to contribute independently to the adsorption of probe molecules and represent the non-polar and polar properties, respectively, of a material's surface. Adsorption of non-polar probes results from dispersive interactions only, whereas polar probes are capable of both dispersive and specific acid-base interactions with the surface. From the IGC method of Schultz *et al.* [27] who derived the equation:

$$RT \ln V_n = a\left(\gamma_l^d\right)^{1/2} \cdot 2N \cdot \left(\gamma_s^d\right)^{1/2} + C \qquad (1)$$

where V_n is the primary experimental parameter measured in IGC known as the net retention volume, a is the surface area of the probes, γ_l^d is the dispersive component of surface free energy of the relevant probe and γ_s^d is the dispersive component of surface free energy of the solid sample, γ_s^d is calculated from the gradient of the straight line produced by the non-polar, usually alkane, probes. The specific component of surface free energy ($-\Delta G_A^{SP}$) can then be determined from the vertical distance of the polar probes above this line (see Fig. 1).

The values of γ_s^d and $-\Delta G_A^{SP}$ in Table I show equivalent dispersive components of surface free energy (γ_s^d) for all three samples, indicating that there is no change in the dispersive or inductive interactions at the surface of these particles after they have undergone either milling alone or milling followed by blending. In contrast, the specific component of surface free

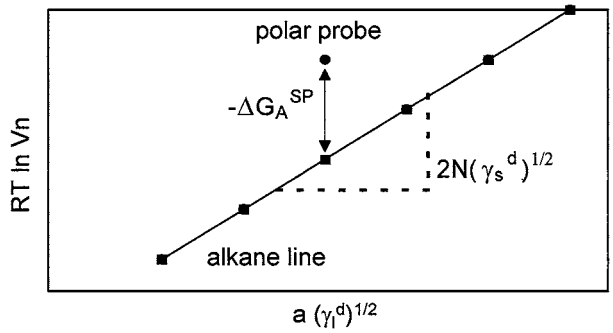

Figure 1 Plot to show γ_s^d and $-\Delta G_A^{SP}$ are calculated.

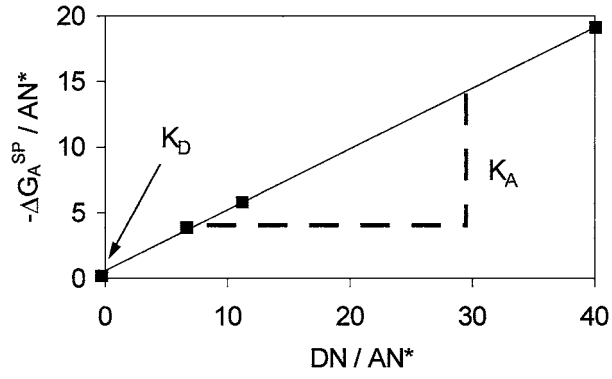

Figure 2 Plot to show how K_A and K_D are calculated.

energy ($-\Delta G_A^{SP}$) for three of the polar probes indicates stronger specific interactions for the milled/pre-blended and post-blender samples whereas for the acidic polar probe (chloroform) $-\Delta G_A^{SP}$ has decreased.

From the theories developed by Drago *et al*. [28] and Gutmann [29] the specific interactions derived from IGC are essentially Lewis acid-base interactions or electron acceptor-donor interactions, which enables an estimate of the acid-base surface properties of the material to be determined. The donor number (DN) defines the basicity or electron-donor ability of a probe whilst the acceptor number (AN) defines the acidity or electron-acceptor ability. Recently Fowkes [30] created a more suitable acceptor number (AN*) correcting for a dispersive component contribution to AN.

From the mean $-\Delta G_A^{SP}$ values determined by IGC, in combination with Gutmann's donor number (DN) and Fowkes' acceptor number (AN*) the acid (K_A) and base (K_D) parameters of the powder surface can be calculated according to the equation:

$$-\Delta G_A^{SP} = K_A \cdot DN + K_D \cdot AN^* \qquad (2)$$

Plotting $-\Delta G_A^{SP}$/AN* against DN/AN* (see Fig. 2) produces a straight line with K_A and K_D evaluated from the gradient and the intercept, respectively, enabling a quantitative assessment of the acidity and basicity of the surface to be made. The values of K_A and K_D for the three lactose samples are shown in Table I.

The three probes which demonstrated an increase in $-\Delta G_A^{SP}$ were either electron donating (ethylacetate and tetrahydrofuran) or amphoteric (acetone) in nature and will interact with electron accepting groups. Hydroxyl groups, which are the predominant functional group of α-lactose monohydrate, are generally acidic or electron accepting in nature. Therefore, an increase in the interaction of the basic and amphoteric polar probes suggests an increased interaction with hydroxyl groups which is supported by the observed increase in K_A and decrease in K_D.

Although a certain amount of variability is present in the $-\Delta G_A^{SP}$ values listed in Table I, statistical analysis (see Table II) showed the differences between M1 and

TABLE I γ_s^d, $-\Delta G_A^{SP}$, K_A and K_D values for R1, M1, and B1[a]

Sample	γ_s^d (mNm^{-1})	$-\Delta G_A^{SP}$ (KJmol^{-1})				K_A	K_D
		Chloroform	Acetone	Ethylacetate	Tetrahydrofuran		
R1	41.70	1.98	7.34	7.18	6.06	0.28	0.90
	(0.66)	(0.18)	(0.10)	(0.15)	(0.06)	(0.00)	(0.01)
M1	41.50	1.44	8.38	8.06	6.95	0.33	0.86
	(0.77)	(0.11)	(0.11)	(0.18)	(0.15)	(0.01)	(0.02)
B1	41.60	0.99	8.79	8.44	7.57	0.36	0.83
	(0.73)	(0.13)	(0.12)	(0.06)	(0.20)	(0.01)	(0.01)

[a]Standard deviation figures in brackets.

TABLE II Statistical significance of the IGC data obtained for M1 and B1

Grouping	nM1	Mean M1	Std. dev. M1	nB1	Mean B1	Std. dev. B1	*s*	*t*	Probability	Significant
$-\Delta G_A^{SP}$ (Chloroform)	6	1.44	0.11	6	0.99	0.13	0.120	6.473	$p < 0.001$	Yes
$-\Delta G_A^{SP}$ (Acetone)	6	8.38	0.11	6	8.79	0.12	0.115	−6.169	$p < 0.001$	Yes
$-\Delta G_A^{SP}$ (Ethylacetate)	6	8.06	0.18	6	8.44	0.06	0.134	−4.906	$p < 0.001$	Yes
$-\Delta G_A^{SP}$ (Tetrahydrofuran)	6	6.95	0.15	6	7.57	0.2	0.177	−6.075	$p < 0.001$	Yes
K_A	6	0.33	0.01	6	0.36	0.01	0.010	−5.196	$p < 0.001$	Yes
K_D	6	0.86	0.02	6	0.83	0.01	0.016	3.286	$p < 0.001$	Yes

s is the pooled standard deviation for the two groups, M1 and B1, that are being compared. The calculation assumes that the standard deviations of both groups were the same, but were "unknown". Unknown means that the sample size is too small to make a firm estimate of the value and is therefore appropriate to use in this case.

t is the parameter that determines the probability that the two groups, M1 and B1, are the same (as in *t*-test). t is a measure of the overlap of the two groups. The larger the value of *t*, the less the two groups overlap. The less the two groups overlap, the less likely that they are actually the same.

TABLE III Particle size, specific surface area, water content and mean avalanche times and irregularity of flow values for R1, M1 and B1[a]

Sample	Aerodynamic diameter (μm)	Specific surface area (m^2/g)	Water content (%w/w)	Mean avalanche times (secs)	Irregularity of flow (secs)
R1	71.42 (4.12)	0.30 (0.01)	5.18 (0.04)	2.87 (0.20)	1.30 (0.15)
M1	35.36 (3.16)	0.37 (0.01)	5.26 (0.02)	4.98 (0.18)	2.44 (0.12)
B1	34.60 (3.84)	0.37 (0.02)	5.27 (0.03)	6.13 (0.19)	2.76 (0.11)

[a]Standard deviation figures in brackets.

B1 to be significant. The K_A and K_D values calculated from the $-\Delta G_A^{SP}$ results were also shown to be significantly different, although the K_A values evaluated from the gradient appear to be more reliable than the K_D values taken from the y-axis intercept.

From these observations, it is proposed that breakage during milling has produced surfaces rich in hydroxyl groups, producing more acidic surfaces. Furthermore, the milled and blended sample, B1, appears to be an even stronger electron acceptor and even weaker electron donor than the milled alone sample, M1. This suggests that blending takes the crystallographic disordering process one step further, increasing the disruption of the lattice already produced by milling. Any remaining particles which are damaged but not completely fractured during the milling process are then broken up during the blending process resulting in surfaces richer in hydroxyl sites. However, it should be noted that particle breakage during blending is minor since, although a reduction in the particle size is observed, no change is detectable in the surface area of the milled/pre-blended and post-blender samples (Table III).

This observation is consistent with that reported by Buckton *et al*. [4] who showed that if two consecutive mechanical processes are used it is probable that the second process achieves its effect by means of disrupting flaws caused during the first process. Therefore, there is a case for utilizing the first process to which a material is subjected as a means of obtaining the most desirable surface properties.

The water contents measured by Karl-Fischer Titration (Table III) all lie within the expected range of 4.5–5.5% w/w water [31]. However, the milled/pre-blended and post-blender samples have larger water contents compared with the raw material. This is attributed to increased amounts of adventitious water on the surface of the particles. The mechanical stresses applied to the milled/pre-blended and post-blender particles will most likely have increased the amorphous content. As this domain is thought to be the primary adsorbing region for adventitious water, the processed samples will adsorb more surface water than the raw material.

Dynamic powder flow assessment of the three lactose samples was performed with the Aeroflow powder avalanching analyzer. The interval times between avalanches were plotted as discrete phase maps known as strange attractor plots [32] (see Fig. 3). Clear differences can be observed in the strange attractor plots of the three samples. The raw material, R1, demonstrates the best flow properties but this is a reflection

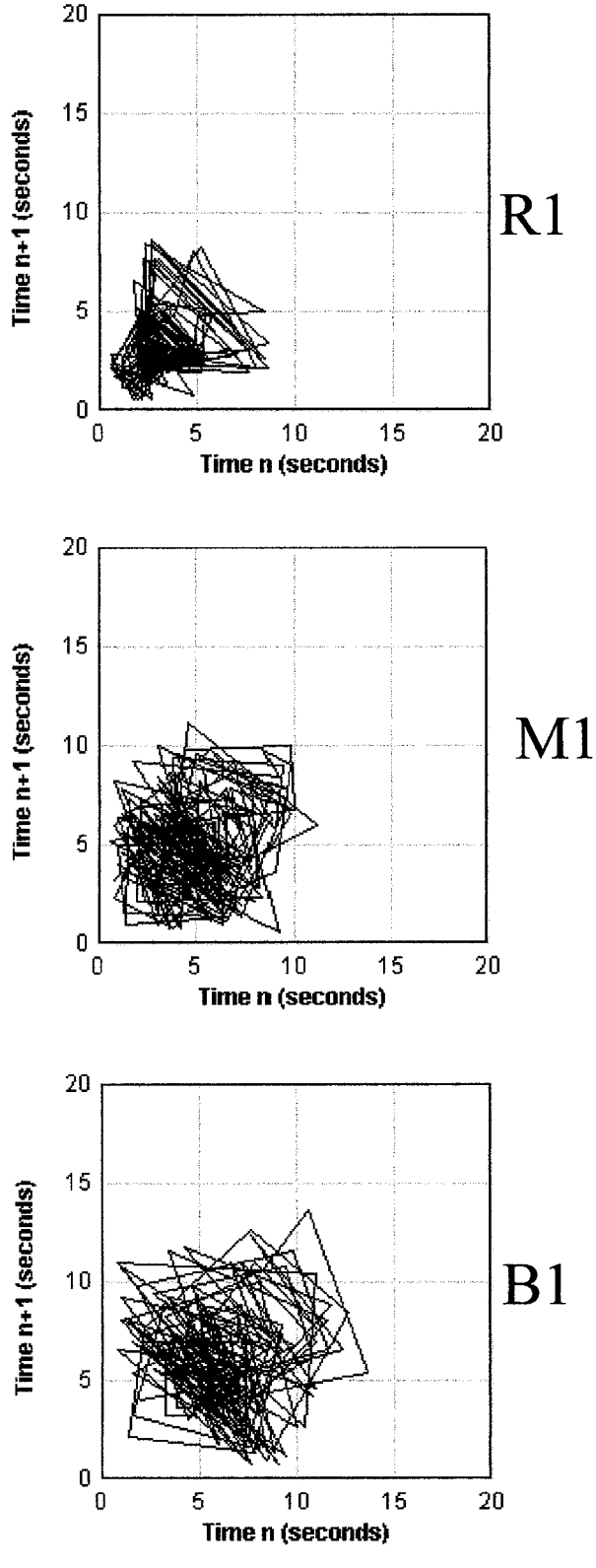

Figure 3 Strange attractor plots for R1, M1 and B1.

of its larger particle size (see Table III). Although the milled/pre-blended and post-blender samples have very similar size distributions, specific surface areas and water contents (see Table III), the blended sample, B1, clearly has poorer flow properties than the milled/pre-blended sample, M1, with more rogue avalanches reaching into the ten to fifteen second domains.

The mean and range of avalanche times shown in Table III confirm this observation. The blended sample, B1, has a higher mean avalanche time and irregularity of flow value than the milled/pre-blended sample, M1. Therefore, the blended material (with the more energetic surfaces) has the poorest flow properties.

This finding can be considered as particularly disadvantageous for dry powder inhalation processing, given the fact that one of the main reasons for inclusion of a carrier material, such as inhalation grade α-lactose monohydrate, is to improve processing conditions by making inhalation formulations freer flowing and thus easier to handle during manufacture. More importantly, in the action of dry powder inhalers, the α-lactose monohydrate carries adhered drug particles from the inhaler device into the upper respiratory tract, where the components should separate, ensuring delivery of the inhaled drug and preventing inhalation of the larger carrier particles. However, if the adhesion force between drug and carrier surfaces is too strong, potentially as a result of the increase in surface free energy or acid/electron accepting interactions, drug particle: carrier assemblies may not break apart. If the particles do not separate there is a high probability of the carrier: drug particles depositing in the throat on account of their large size, impairing the passage of the fine drug particles towards the lung.

Thus, the success or failure of these powder blend formulations can depend upon the nature of the surfaces of the materials used, and as such, measurement of surface energetics is of paramount importance.

4. Conclusion

Results demonstrate the potential of IGC and the Aeroflow powder avalanching analyzer to detect and quantify changes in a powdered material, before and after processing by milling and blending. These observed differences in surface energetic properties and flow characteristics, which frequently remain undetected, emphasize the importance of surface characterization in understanding the processing behavior of particulate material.

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