The Influence of Force Control Agents on the Cohesive-Adhesive Balance in Dry Powder Inhaler Formulations†

P. Begat and R. Price
Pharmaceutical Technology Research Group
Department of Pharmacy & Pharmacology
University of Bath

H. Harris, D.A.V. Morton and J.N. Staniforth
Vectura Ltd.

Abstract

The aim of the study was to investigate the specific influence of force control agents (FCAs) (leucine, lecithin and magnesium stearate) on the interfacial properties of a salbutamol sulphate-lactose dry powder inhaler formulation. The influence of FCAs on the cohesive and adhesive force balance was directly assessed via an atomic force microscopy (AFM) colloid probe technique, with a recently developed cohesive-adhesive balance (CAB) graphical analysis procedure. Co-processing of constituent particles was conducted by a novel dry mechanical fusion method (Mechanofusion). The in vitro deposition profile of the model salbutamol sulphate formulations was investigated using a Monohaler® DPI device with a next generation impactor (NGI) apparatus. The CAB-graph analysis of a salbutamol sulphate-lactose binary system suggested a predisposition for an interactive mixture. However, the reduced intermixing coefficient \( \frac{F_{\text{drug/lactose}}}{F_{\text{drug/drug}}} \) suggested that a significant amount of energy would be required to overcome the strong adhesive interaction for efficient dispersion of the drug from a lactose surface. The processing of lactose with leucine, lecithin or magnesium stearate, prior to formulating with the drug, significantly reduced the adhesive interactions of the salbutamol with modified lactose samples. The CAB analyses indicated that the reduced intermixing coefficients shifted to such an extent that cohesive drug interactions dominated. These dramatic shifts in the balance of forces were shown to lead to poor blend homogeneity and potential for significant segregation between drug and carrier particles. Conversely, the conditioning of salbutamol sulphate with leucine, lecithin and magnesium stearate, which modified both the adhesive and cohesive interactions, formed homogenous interactive blends with advantageously weaker drug-lactose interactions. Formulations with pre-conditioned drug, in contrast to conditioned lactose, offered the best drug delivery performances. The use of the colloid AFM technique in combination with the cohesive-adhesive balance (CAB) approach provided a very accurate means of predicting dry powder formulation behaviour and the specific influence of particulate interactions on aerosol performance.

Key words: Inter-particulate, AFM, Magnesium stearate, DPI, Inhalation, Aerosols, Mechanofusion, Nanotechnology

INTRODUCTION

Dry powder inhalers (DPIs) represent a significant advance in pulmonary drug delivery, mainly by overcoming patient related issues of co-ordination with conventional pressurised metered dose inhaler systems. The fluidisation, de-aggregation and dispersion of a dry powder formulation are achieved via the patient's inspiratory action. Arguably more so than...
other drug delivery platforms, the characteristic properties of the dry powder formulation are critically important to the effective performance of a DPI system\(^1,2\).

The formulation should exhibit good flow properties to aid metering, fluidisation and avoid excessive device retention. Meanwhile, the fluidised powder must disperse into a fine aerosol (\(\Omega \sim 5\mu m\)) for efficient drug delivery\(^3,4\). This leads to the well-known paradox that respirable sized particles tend to be highly cohesive, which causes entrainment problems due to their poor flowability and limits the dispersibility into an aerosol cloud\(^5,6\). In addition, strong cohesion forces hinder the handling of the powder during manufacture.

To overcome the highly cohesive nature of respirable powders, the drug is commonly co-processed (blended) with larger carrier particles of an inert excipient to aid flowability and drug re-dispersion. This carrier based formulation approach is limited by the restrictive availability of excipient materials. The only widely approved excipients for use as carriers are lactose and glucose. Thus, the development of a dry powder formulation is a highly specialised, complex and unpredictable operation. A formulation is typically required to go through several iterative and optimisation steps before a product specification can be achieved, and even then variability over time and between batches is common.

By blending a micronised drug with a carrier, the shear forces generated may be sufficient to overcome the cohesive (drug-drug) interactions in forming an interactive mixture. Drug particles need to be sufficiently attracted to the carrier during mixing to support blend homogeneity, device filling and formulation stability. Yet the active ingredient must be readily detached from the carrier upon activation to form a fine particle cloud. Thus, the balance of inter-particulate forces within the carrier-based formulation is critically important.

Numerous techniques have been applied to modify particulate interactions in dry powder formulations. The majority have targeted the physical properties of the carrier. These include modifying the shape\(^7\), size\(^8\), or surface features such as rugosity\(^9-12\) of the excipient. Other methods involve the manufacture of more uniform respirable drug particulates by particle engineering technologies such as spray drying\(^13\) or supercritical fluid precipitation\(^14\). One of the most simple and popular advances is via the addition of a ternary agent, such as fine particles of lactose. For these complex blends, it is proposed that the ternary agent occupies high energy sites on the carrier particles, such as clefts and areas of increased molecular disorder\(^15,16\). As a consequence, only low energy sites remain available for drug-carrier adhesive interaction. The possibility of a marked reduction in particle adhesion would facilitate more effective drug detachment upon device actuation. Extensive work on the use of fines in dry powder formulations and their influence on delivery performances have been reported\(^17-19\).

In addition to passifying active sites, researchers have shown that the addition of fine ternary particles may lead to the formation of fine particle multiplets or metastable agglomerates\(^20\). The critical formation of agglomerate particles, which remain adhered to the coarse carrier lactose during processing and handling, may dramatically reduce the inspirational energy requirements in elutriating and de-aggregating drug particles upon aerosolisation.

The co-processing of carrier particles with low surface free energy materials has also been reported as a possible means of increasing the aerosolisation efficiencies of dry powder inhaler formulations\(^19,21,22\). The primary role of these materials is to modify the interfacial properties of the excipient particles to decrease drug-excipient adhesion. These force control agents (FCAs) preferably exhibit anti-adherent and/or anti-friction properties. Typical FCAs include amino acids such as leucine, phospholipids such as lecithin or fatty acid derivatives such as magnesium stearate (MgST)\(^23\).

To optimise the efficiency of a carrier based formulation, the force control agent must be specifically introduced into the dry powder formulation to selectively target the particle interactions to be modified. In this study, the FCA was mechanically fused via a highly intensive co-processing system termed “Mechanofusion” to ensure a nanometre thick coating of the specific components of the formulation\(^24\). This approach was recently developed by Staniforth and Morton for inhalation powders\(^25\). In contrast to other low energetic mixing or intensive mixing, this dry coating process is designed to provide a relatively complete ultra thin coating onto the host particles via the application of high shear forces (Fig. 1). Succinctly, a Mechanofusion mixer is composed of a large rotor with rounded blades revolving in a steel vessel at very high speed (typically of the order of 5000rpm). The gap size between the rotor blades and the vessel wall can be adjusted in order to vary the mixing energy delivered to the powder blend. As a result, the particles experience very high shear
forces as they are compressed between the inner drum wall and the rotor.

The aim of this study was to investigate the specific influence of force control agents (leucine, lecithin and magnesium stearate) on the interfacial properties of a salbutamol sulphate-lactose dry powder inhaler formulation. The influence of the FCAs on the cohesive and adhesive force balance was directly assessed via an AFM colloid probe technique, with a recently developed CAB-graph analysis procedure. This novel procedure allows quantification of cohesive-adhesive balances (CAB) in a dry powder formulation, and, thus, can be directly utilised to highlight their specific affect on formulation behaviour and delivery characteristics. The in vitro deposition profile of the model salbutamol sulphate formulations was investigated to elucidate any correlation between the cohesive and adhesive nature of the modified formulations with their aerosol delivery performance.

**MATERIALS AND METHODS**

**Materials**

Micronised salbutamol sulphate, donated by Vectura Ltd., and Sorbalac 400 lactose (M eggie, Wasserburg, Germany) were used as supplied. The use of Sorbalac 400 lactose particles (<10µm) with respect to more conventional carrier sizes (63-90µm) was dictated by the need to minimise the potential influence of larger carrier particles over fluidisation and de-aggregation processes of particle agglomerates. L-Leucine was supplied from Ajinomoto Co. (batch number 601FK72, Tokyo, Japan), lecithin from Lipoid GmbH (batch number 25661113-1/14, Ludwigshafen, Germany) and magnesium stearate from Avocado (batch number H1028A, Heysham, UK). All materials were used as supplied. Ultra pure water was produced by reverse osmosis (MilliQ, Millipore, Molsheim, France).

**Preparation of powder formulations**

Powder mixing was achieved in two successive steps involving different energetic processes. Pre-blends of salbutamol sulphate and FCA (5% w/w) or lactose and FCA (5% w/w) were prepared using a Mechanofusion system. (Hosokawa-Alpine, Augsburg, Germany). Powders to be processed were sealed into the Mechanofusion system core. Cold-water circulation was applied using an incorporated water jacket to dissipate localised heating. Samples were mixed at 5000rpm for 10 minutes to achieve the required process intensity and mechanically fuse the FCA to the host particles.

The formulations were subsequently prepared by geometrically mixing 1g of pre-blend and 1g of either lactose or drug depending on the nature of the pre-blend in 100mg increments via a Whirlimixer (Fisons Scientific Apparatus, Loughborough, UK). The resulting mixture was further mixed in a Turbula (Glen Creston Ltd., Middlesex, UK) at 46rpm for 30 minutes. This blend design was not intended to reflect any commercial available or relevant DPI powder formulation. This formulation was selected solely to suit the objectives of the study of the cohesive-adhesive balance between drug and lactose components.

**Preparation of compressed powder substrates**

Model surfaces of the powder formulations were prepared by high-pressure compression (TA HDI Texture analyser, Stable Micro Systems, Surrey, UK). Approximately 250mg of material was weighed into a 10mm stainless steel die and compacted over 3min, with a load of 500kg.

**Scanning electron microscopy**

The morphology of the various powder formulations was investigated using a scanning electron microscope (SEM) (Jeol 6310, Jeol, Tokyo, Japan). Samples were gold-coated (Edwards Sputter Coater, Crawley, UK) prior to imaging.

**Force measurements by atomic force microscopy (AFM)**

Prior to force measurements, salbutamol sulphate, lactose and the corresponding conditioned particles (n=3 for each material) were fixed onto standard V-shaped tipless cantilevers (DNP-020, Digital Instruments, CA, USA) using an epoxy resin glue (Araldite, UK). The spring constant (k) of the cantilevers was determined by the thermal noise method (k=0.282 ± 0.039 N/m). The AFM was housed in an environmental chamber.
to maintain constant temperature of \(25^\circ\text{C} \pm 0.2^\circ\text{C}\) and relative humidity of \(35\%\text{RH} \pm 3\%\). The partial water vapour pressure was controlled via a custom-built perfusion unit coupled to a highly sensitive humidity sensor (Rotronic AG, CH). The interaction forces were measured by recording the deflection of the AFM cantilever as a function of the substrate displacement \((z)\) by applying Hooke’s law \((F = -kz)\). Individual force curves \((n=4096)\) were conducted over a \(10\mu\text{m} \times 10\mu\text{m}\) at a scan rate of 4Hz and a compressive loading of \(10\text{nN}\). These parameters were kept constant throughout the study.

### Cohesive-adhesive balance (CAB) graphs

The wealth of information from AFM measurements of the interparticulate forces were analysed using a recently developed cohesive-adhesive balance procedure. Detailed information regarding the CAB graphical analysis is described elsewhere\(^{26}\). Briefly, the construction of a CAB-graph requires a set of probes \((n \cdot 3)\) and well-defined substrates of each respective material to investigate all possible interactions (drug-drug, drug-excipient and excipient-excipient).

The adhesive force measurements between drug and excipient are plotted on the X-axis; the related cohesive forces of the respective materials are plotted on the Y-axis. The relative position of the aligned plots with respect to the bisector indicates an affinity for the probe material to develop adhesive interactions (below the bisector) or a dominancy of cohesive properties (above the bisector).

To express the affinity of the drug (material 1) to interact with the carrier (material 2), the reduced intermixing coefficient \((\Lambda_{12})\) was introduced. The \(\Lambda_{12}\) corresponds to the ratio of the adhesive interactions \((F_{12})\) and cohesive interactions \((F_{11})\) of two interacting materials and can be directly calculated from the slope:

\[
\Lambda_{12} = \frac{F_{ad}}{F_{co}} = \frac{1}{k_{12}} \quad (1)
\]

The position of \(\Lambda_{12}\) with respect to unity is a direct indication of the predisposition \((\Lambda_{12}>1)\) or the reluctance \((\Lambda_{12}<1)\) for the drug particles to blend with another material.

For direct visualisation of the influence of the addition of the FCA on the interfacial behaviour of drug and excipient interactions, the CAB graphs for the virgin and treated surfaces have been superimposed. The graph in the foreground corresponds to the interparticulate forces observed between the micronised drug (\(\bullet\)) and lactose (\(\triangle\)) probes and the virgin substrate surfaces of the drug and excipient (Fig. 1). The background graph corresponds to the interaction measurements when a ternary agent was processed either with the drug (\(\bigcirc\)) or the lactose (\(\bigtriangledown\)).

#### Content uniformity measurements

The content uniformity of the salbutamol sulphate-lactose blends was measured by analysing the quantity of active in \(10\text{mg} \pm 0.5\text{mg}\) samples \((\times 10)\). Relative standard deviation between samples was calculated to assess the homogeneity of the different blends. Drug content was analysed by UV-spectrometry (CECIL instruments, CE 7200, Cambridge, UK). Salbutamol sulphate was analysed using a 0.06M NaOH solvent and a UV detection wavelength set at 295nm.

#### In vitro aerosol deposition studies

Approximately \(10\text{mg}\) of the carrier formulations was accurately weighed into a gelatine capsule to be loaded into a Monohaler® device (Miat SpA, Milan, Italy). In vitro deposition investigations were performed using a next generation impactor (NGI) (Copley Scientific, Nottingham, UK). The loaded device was connected to the throat of the NGI via a moulded mouthpiece. In vitro analysis was performed upon each actuation of the device \((n=3)\). Testing was performed at \(60\text{L.min}^{-1}\) flow rate with a 5 second exposure. Each NGI plate was rinsed with solvent and the subsequent solution was collected in a 50ml volumetric flask. Statistical analysis of the data was performed using one-way ANOVA. The levels of significance are indicated in the legend of the respective graphs.

#### RESULTS & DISCUSSIONS

Previous studies have emphasized the relative strength of the adhesive salbutamol sulphate-lactose adhesive forces with respect to salbutamol sulphate cohesive forces\(^{26}\). The initial part of this study was to investigate possible variations in formulation behaviour upon modifying the cohesive and adhesive bonds, quantified by AFM measurements, via the introduction of a force control agent. This was achieved by first conditioning the lactose with various force control agents using a Mechanical fusion system, prior to mixing with the drug.

The CAB-graph obtained for a salbutamol sulphate-lactose binary system, without the presence of a FCA, is shown in Fig. 2. The relative position of the data below the bisecting line indicated a stronger affinity...
between salbutamol sulphate and lactose than their cohesive forces. This suggested a predisposition for an ordered blend. However, the quantitative measurement of the relative strength of the cohesive-adhesive ratio indicated that the adhesive salbutamol sulphate-lactose interaction was approximately six times greater (Λ12=6.25) than the cohesive salbutamol sulphate bond. It should be stressed that previous assessments performed with model crystal substrates revealed a salbutamol sulphate-lactose reduced intermixing coefficient of 16.88. This disparity may be explained by the inevitable increase in surface roughness by using compressed powder substrates in contrast to smooth crystalline substrates. This would have a considerable effect on both van der Waals forces and capillary forces. Nevertheless, both studies revealed a consequent adhesively led system, suggesting that a significant amount of energy would be required to overcome the adhesive interaction for efficient dispersion of the drug from a lactose surface.

Thus, the introduction of a FCA was intended to advantageously lower the adhesive interactions between drug and excipient to facilitate the detachment of the drug particles from the carrier upon aerosolisation provided that an adhesive-led system is maintained.

1. Carrier-based formulations with conditioned lactose

The CAB-graphs obtained for the interaction of salbutamol sulphate probes and conditioned lactose probes with leucine, lecithin and MgST are shown in Fig. 3A, 3B and 3C, respectively. As expected,
the addition of FCAs significantly modified the salbutamol-lactose interactions. In all cases, the introduction of the ternary agent significantly reduced the adhesive interactions of the salbutamol probe with the various modified lactose substrates. However, particle adhesion decreased to such an extent that the reduced intermixing coefficient \( (F_{\text{drug-lactose}}/F_{\text{drug-drug}}) \), calculated from the gradient of the CAB plots, was below 1 (Table 1). This shift moved the CAB system to one synonymous of a cohesive-led system. The conditioning of lactose with MgST resulted in the lowest intermixing coefficient value \( (\Lambda_{12} = 0.61) \) while the addition of leucine and lecithin reduced the intermixing coefficient to 0.96 and 0.88, respectively. Thus, the pre-conditioning of lactose particles with leucine, lecithin or MgST transformed a system which was dominated by the adhesive drug-lactose forces into a cohesive system. Such lowering of the interactions between drug and excipient via the introduction of the FCAs may possibly lead to an unstable formulation, subjected to undesirable segregation.

Consequently, to highlight the influence of the modifications of the intermixing coefficient on the blending characteristics via the introduction of FCAs, scanning electron microscopy and drug content uniformity analyses of the blends were investigated. Representative SEM images of formulations of salbutamol sulphate mixed with lactose-leucine, lactose-lecithin and lactose-MgST conditioned particles are shown in Fig. 4A, 4B and 4C, respectively. As anticipated from the intermixing coefficient measurements, scanning electron micrographs highlighted a high degree of drug segregation resulting from introduction of the FCAs. A very limited adhesive interaction was apparent between agglomerated salbutamol sulphate particles and conditioned lactose-leucine (Fig. 4A). However, large quantities of drug particles were present as loose agglomerates. This segregation was even more pronounced for lecithin (Fig. 4B) and MgST (Fig. 4C) conditioned lactose particles. Virtu-
ally no interaction was observed between drug and the conditioned lactose surfaces, which resulted in the formation of large drug agglomerates. Interestingly, the mechanofused Sorbalac 400 lactose particles appeared to be smoother after pre-conditioning with leucine, lecithin or magnesium stearate, compared to the as supplied Sorbalac27). This suggested a smooth continuous coating of the FCAs over the surface of the lactose particles.

As anticipated, dose content uniformity measurements revealed an increase in the relative standard deviation of salbutamol sulphate of each blend. The RSD of 4.2% for micronised salbutamol sulphate mixed with lactose increased to 8.92% with the conditioning of lactose with leucine, 9.31% for lactose-lecithin and 15.51% for lactose-MgST. These observations suggested a good correlation between the reduction of the intermixing coefficients, which were all significantly below 1, and the content uniformity measurements of salbutamol sulphate in the corresponding carrier-based formulations.

The de-agglomeration and dispersion behaviour of the salbutamol sulphate particles from the model carrier based formulations are shown in Fig. 5. The emitted dose of the salbutamol sulphate-lactose formulation via the low resistance Monohaler® device was quite high (76.57%). However, a significant percentage of the drug was recovered in the throat and the first stage of the NGI apparatus. These results were in accordance with a previous in vitro study conducted with a Rotahaler® and Turbuhaler® DPI devices21). This study suggested that the observed deposition pattern was due to the limited detachment of the drug from the carrier upon actuation caused by the highly adhesive salbutamol sulphate-lactose interactions.

The mechanical fusion of leucine with lactose resulted in a similar drug emission efficiency to the conventional blend. However, the amount of salbutamol sulphate recovered in the first stage of the NGI significantly increased with respect to the non coated lactose blend. The coating of lactose with either lecithin or MgST slightly reduced the device retention of the active ingredient from 23.43% to 18.73% and 18.99% respectively. Although the interaction between drug and coated lactose surfaces were significantly decreased, a large amount of drug was still recovered on the upper stage of the in vitro apparatus.

These results were consistent with the assessment from the CAB-graphs. The CAB analysis indicated that the energy of interaction between the drug and coated lactose would reduce to such an extent that the adhesively led salbutamol sulphate-lactose formulation would shift to an unfavourable cohesive system. The aerosolisation performances of the modified lactose carrier-based formulations may have not improved since the dramatic shift in the force balance was shown to lead to poor blend homogeneity and the

![Fig. 5](image-url)
potential for significant segregation between drug and carrier particles.

2. Carrier-based formulations with conditioned drug

The conditioning of excipient particles with a FCA modified the adhesive interaction between drug-carrier and excipient-excipient interactions. In contrast, the processing of the micronised drug particles with the FCA would alter both the cohesive (drug-drug) and adhesive (drug-lactose) interactions. To further investigate the possibility of selectively modifying both these interactions within a carrier based formulation, the drug was mechanoconfused with the FCAs.

The CAB-graphs obtained for the interaction between conditioned salbutamol sulphate with leucine, lecithin or MgST and lactose are shown in Fig. 6A, 6B and 6C, respectively. The balance remained adhesive for all three systems, although the drug-lactose forces decreased by more than a half of its original value. The conditioning of salbutamol sulphate with leucine, lecithin and MgST led to an intermixing coefficient of 1.89, 2.13 and 1.52, respectively. These mixtures would therefore be expected to form homogeneous interactive blends with advantageously weak drug-lactose interactions. As expected, the lactose force balance transformed from an adhesive to a cohesive system. Nevertheless, it can be speculated that this shift should not greatly affect the formulation properties as this change of behaviour is predominantly due to a decrease of the adhesive (drug-lactose) forces and not in an increase of the lactose cohesive bonds.

Representative scanning electron micrographs of the lactose particles blended with conditioned salbutamol sulphate-leucine, salbutamol sulphate-lecithin, and salbutamol sulphate-MgST are shown in Fig. 7A, 7B and 7C, respectively. In contrast to the ternary mixture of drug and conditioned lactose shown in Fig. 4, the conditioned drug particles strongly interacted with the lactose particles for all three FCAs. This suggested an effective adhesive disposition, in agreement with the CAB data analyses. The corresponding content uniformity measurements of the ternary mixtures reflected an adhesive led system with low relative standard deviations for lactose mixed with salbutamol sulphate-leucine (2.92%), salbutamol sulphate-lecithin (3.00%) and salbutamol sulphate-MgST (3.62%) conditioned particles.

These observations suggested good correlation between the reduced intermixing coefficients and the characteristics of the respective carrier-based formul-
lations. Such formulations would be expected to be stable during handling and storage, and may lead to a greater de-agglomeration and dispersion efficiency of the respirable particles.

The in vitro deposition profile of conditioned salbutamol sulphate carrier-based formulations are shown in Fig. 8. The mechanism of the force control agents to the salbutamol sulphate particles resulted in a significant decrease in device retention from 23.42% for the FCA free formulation to 12.51% with leucine, 14.52% with lecithin and 8.23% with MgST. These results suggested a lubrication effect of the FCA and subsequent reduction in interaction between the powder bed and the capsule, while the formulation preserved its metastability as suggested by the CAB analyses. More dramatic was the significant decrease of the percentage of drug deposited on the first stage (cut off diameter·8.06·m) of the NGI apparatus. Stage 1 deposition decreased from 22.89% to 6.16% for the conditioning of salbutamol sulphate with leucine, 9.20% for salbutamol sulphate-lecithin and 7.99% for salbutamol sulphate-MgST. This indicated a greater de-agglomeration efficiency of the coated salbutamol sulphate particles in the carrier based formulations. This was further highlighted by the increase deposition of the active ingredient in the lower stages of the in vitro apparatus. These data clearly indicated that the characteristic properties of carrier based formulations can be controllably

![Fig. 7](image_url)

*Fig. 7* Representative scanning electron micrographs of ternary mixtures of lactose and salbutamol sulphate pre-conditioned with leucine (A), lecithin (B) or magnesium stearate (C).

![Fig. 8](image_url)

*Fig. 8* In vitro deposition of salbutamol sulphate carrier-based formulations with conditioned drug (mean±S.D., n=3).

* p<0.05, ** p<0.01, *** p<0.001: significant difference compared to without force control agent by ANOVA one-way.
enhanced by judicious selection of the interparticulate interactions to be modified by the introduction of the FCAs.

A summary of the device retention, fine particle fraction (% respirable particle of the emitted dose) and total fine particle fraction (% respirable particle from total recovered dose) of the salbutamol sulphate carrier-based formulations is shown in Fig. 9. A clear pattern of formulation performance was observed depending on whether the force control agent was fused either with the drug or the lactose. Formulations with pre-conditioned drug, in contrast to conditioned lactose, offered the best drug delivery performances. It is suggested that the conservation of an adhesive system for the pre-conditioned drug particles directly led to the increased de-aggregation performance. Meanwhile, the selective decrease of the drug-lactose interfacial interaction for conditioned lactose particles led to a dominant cohesive (drug-drug) system, which resulted in poor blend homogeneity and poor fluidisation. The highest %FPF of the emitted dose was obtained for formulations with leucine and lecithin coated salbutamol sulphate particles (73.72% and 71.87% respectively). The low drug retention of salbutamol sulphate-MgST conditioned particles (8.23% device retention) contributed to deliver an equivalent total fine particle dose as for leucine and lecithin (64.43% for leucine, 61.41% for lecithin and 63.79% for MgST).

CONCLUSIONS

The influence of force control agents on the properties and performances of model salbutamol sulphate carrier based formulations was investigated. The cohesive and adhesive dependencies were controlled by conditioning either the drug or the carrier before mixing in order to create selective modifications of the inter-particulate interactions within a dry powder formulation. The conditioning of these fine inhalation powders was conducted via a Mechanofusion system. This new technique was intended to enable effective particle covering with a nano-scale coating, a process which is difficult to achieve via conventional approaches.

The colloid probe AFM technique together with the novel cohesive-adhesive balance (CAB) analysis procedure was utilised to measure the variations in interparticulate forces of binary and ternary blends. The CAB-graph method successfully predicted substantial modifications in the behaviour of the formulations, dependant on whether the FCAs were conditioned with the drug or the lactose. This novel approach of applying FCA to the drug is in contrast to previous work in this area where force control agents have traditionally been applied to carrier particles.

This work emphasized that the CAB analysis method can be utilised for pre-formulation studies and in the design of new formulation systems for dry powder inhalers. The work also confirmed the poten-
REFERENCES

1) D. Ganderton and N. M. Kassem. Advances in Pharmaceutical sciences, Academic Press, London, 1992.
2) A. R. Clark. Medical Aerosol Inhalers — Past, Present, and Future. Aerosol Science and Technology 22: 374-391 (1995).
3) D. Ganderton and T. Jones. Drug Delivery to the Respiratory Tract, Camelot Press, Southampton, 1987.
4) W. C. Hinds. Aerosol technology: Properties, Behaviour and measurements of airborne particles, Wiley, New York, 1999.
5) J. C. Feeley, P. York, B. S. Sumby, and H. Dicks. Determination of surface properties and flow characteristics of salbutamol sulphate, before and after micronisation. International Journal of Pharmaceutics 172: 89-96 (1998).
6) X. M. Zeng, G. P. Martin, and C. Marriott. Particulate Interactions in Dry Powder Formulations for Inhalation. Taylor & Francis, London, 2001.
7) X. M. Zeng, G. P. Martin, C. M arriott, and J. Pritchard. The influence of crystallization conditions on the morphology of lactose intended for use as a carrier for dry powder aerosols. Journal of Pharmacy and Pharmacology 52: 633-643 (2000).
8) X. M. Zeng, G. P. Martin, S. K. Tee, A. Abu Ghoush, and C. Marriott. Effects of particle size and adding sequence of fine lactose on the deposition of salbutamol sulphate from a dry powder formulation. International Journal of Pharmaceutics 182: 133-144 (1999).
9) R. Price, P. M. Young, S. Edge, and J. N. Staniforth. The influence of relative humidity on particulate interactions in carrier-based dry powder inhaler formulations. International Journal of Pharmaceutics 246: 47-59 (2002).
10) M. D. Louey and P. J. Stewart. Particle interactions involved in aerosol dispersion of ternary interactive mixtures. Pharmaceutical Research 19: 1524-1531 (2002).
11) M. D. Louey, P. Mulvaney, and P. J. Stewart. Characterisation of adhesional properties of lactose carriers using atomic force microscopy. Journal of Pharmaceutical and Biomedical Analysis 25: 559-567 (2001).
12) Y. Kawashima, T. Serigano, T. Hino, H. Yamamoto, and H. Takeuchi. Effect of surface morphology of carrier lactose on dry powder inhalation property of pranlukast hydrate. International Journal of Pharmaceutics 172: 179-188 (1998).
13) L. Yu. Amorphous pharmaceutical solids: preparation, characterization and stabilization. Advanced Drug Delivery Reviews 48: 27-42 (2001).
14) P. York. Strategies for particle design using supercritical fluid technology. Pharmaceutical Science and Technology Today 2: 430-440 (1999).
15) X. M. Zeng, K. H. Pandith, and G. P. Martin. The influence of lactose carrier on the content homogeneity and dispersibility of beclomethasone dipropionate from dry powder aerosols. International Journal of Pharmaceutics 197: 41-52 (2000).
16) N. Islam, P. J. Stewart, I. Larson, and P. G. Hartley. Lactose surface modification by decantation: Are drug-fine lactose ratios the key to better dispersion of salmeterol xinofate from lactose interactive mixtures? Pharmaceutical Research 21: 492-499 (2004).
17) S. K. Tee, C. Marriott, X. M. Zeng, and G. P. Martin. The use of different sugars as fine and coarse carriers for aerolised salbutamol sulphate. International Journal of Pharmaceutics 208: 111-123 (2000).
18) S. K. Tee, G. P. Martin, A. R. Leeds, C. Walker, A. Kicman, D. A. Cowan, and C. Marriott. The influence of a tertiary component on the in vivo disposition of salbutamol isomers aerolised from a dry powder inhaler formulation. Thorax 56: PS1 (2001).
19) X. M. Zeng, G. P. Martin, S. K. Tee, C. M arriott. The role of fine particle lactose on the dispersion and deaggregation of salbutamol sulphate in an air stream in vitro. International Journal of Pharmaceutics 176: 99-110 (1998).
20) P. Lucas, K. Anderson, and J. N. Staniforth. Protein deposition from dry powder inhalers: Fine particle multiplets as performance modifiers. Pharmaceutical Research 182: 562-569 (1998).
21) M. J. Clarke, M. J. Tobyn, and J. N. Staniforth. The formulation of powder inhalation systems containing a high mass of nedocromil sodium trihydrate. Journal of Pharmaceutical Sciences 90: 213-223 (2001).
22) J. N. Staniforth. Improvement in drug powder inhaler performance: surface passivation effects. Proceedings of Drug Delivery to the Lungs VII 86-89 (1996).
23) P. Begat, M. Green, D. A. V. Morton, A. Whittcock, and J. N. Staniforth. PowderHale: A Novel High Performance Dry Powder Inhaler Formulation Technology for Targeted and Systemic Drug Delivery, Drug Delivery to the Lung XII 119 (2001).
24) R. Pfeffer, R. N. Dave, D. G. Wei, and M. Ramlakhan. Synthesis of engineered particulates with tailored properties using dry particle coating. Powder Technology 117: 40-67 (2001).
25) J. N. Staniforth and D. A. V. Morton. Powder Technology Research Leading to Improvements in Inhaler Products. Powder Science and Engineering 34: 60-64 (2002).
26) P. Begat, D. A. V. Morton, J. N. Staniforth, and R. Price. The cohesive-adhesive balances in dry powder inhaler formulations I: Direct quantification by atomic force microscopy. Pharmaceutical Research 21: 1591-1597 (2004).
27) P. Begat, D. A. V. Morton, J. N. Staniforth, and R. Price. The cohesive-adhesive balances in dry powder inhaler formulations II: Influence on fine particle delivery characteristics. Pharmaceutical Research 21: 1826-1833 (2004).
28) J. L. Hutter and J. Bechhoefer. Calibration of Atomic-
Force Microscope Tips. Review of Scientific Instruments 64:1868-1873 (1993).

29) T. J. Senden and W. A. Ducker. Experimental-Determination of Spring Constants in Atomic-Force Microscopy. Langmuir 10:1003-1004 (1994).

30) R. Price, M. Tobyn, and J. N. Staniforth. Variation in Particle Adhesion Due to Capillary and Electrostatic Forces. Respiratory Drug Delivery VII (2000).

31) J. C. Hooton, C. S. German, S. Allen, M. C. Davies, C. J. Roberts, S. J. B. Tendler, and P. M. Williams. An atomic force microscopy study of the effect of nanoscale contact geometry and surface chemistry on the adhesion of pharmaceutical particles. Pharmaceutical Research 21:953-961 (2004).

Author’s short biography

Philippe Begat
Dr. Philippe Begat is currently an Inhalation Project leader at Pfizer Inc. Philippe has an MSc in Chemistry. He joined Vectura Ltd in 2001, working on the optimization of PowderHale™ technology. In 2002, he joined the pharmaceutical surface science research group at the University of Bath, as an Experimental Officer, to develop novel methods for characterizing and improving dry powder formulations. He was awarded his PhD in 2005. Philippe has since joined Pfizer Inc. to manage the development of new drug products for their dry powder inhaler programmes.

Robert Price
Dr. Robert Price is a senior lecturer at the Department of Pharmacy and Pharmacology at the University of Bath. He gained a BSc in Physics and a PhD in Physical Chemistry from Cardiff University. He leads the pharmaceutical surface science research group, investigating physico-chemical properties governing inter-particle interactions, surface stability issues of processes particles and the general area of particle engineering and crystal growth. He has published a series of original research articles in the areas of surface electrochemistry, crystal growth, atomic force microscopy and pharmaceutical technology.

Haggis Harris
Haggis is currently a postgraduate student at Bath University in the Department of Pharmacy and Pharmacology investigating inter-particle interactions in dry powder inhaler formulations. Prior to studying at Bath University, Haggis was employed at Vectura for four years where his primary focus was research and development of high intensity blending techniques to be used in dry powder inhaler formulation.

David A.V. Morton
Dr. David Morton is currently Head of Intellectual Property and Technology at Vectura Group plc. He gained a PhD from Bristol University in Structural Chemistry. In 1997, David joined the Centre for Drug Formulation Studies at the University of Bath to manage their dry powder inhaler product development programmes. In 1999, this group spun out into the drug delivery company Vectura, and David was appointed Head of Pulmonary Research, where he co-developed the emerging PowderHale™ technology. He is also known in the inhalation field for his lead role in organising the Aerosol Society ‘Drug Delivery to the Lung’ conference series.
Author’s short biography

John N. Staniforth

Professor John Staniforth is Chief Scientific Officer and a Founder of Vectura Group plc. He has a BSc in Pharmacy and a PhD in Pharmaceutical Technology. He became Professor of Pharmaceutical Technology and Head of Pharmaceutics at the University of Bath, Department of Pharmacy. In 1999, he led the spin-out of two groups based at the University to establish Vectura. John is a registered Pharmacist and a Chartered Chemist. He has been elected a Fellow of a number of international scientific societies, including the American Association of Pharmaceutical Scientists and is a Member of the Royal Pharmaceutical Society of Great Britain.