The Cohesive-Adhesive Balances in Dry Powder Inhaler Formulations II: Influence on Fine Particle Delivery Characteristics

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Purpose. To investigate the influence of the cohesive-adhesive balances on dry powder formulation aerosolization and delivery characteristics.

Methods. De-agglomeration properties of pharmaceutical powders were investigated using an Aerosizer at various shear forces. Aerosol drug deposition properties of drug-only formulations and carrier-based formulations were investigated using a low-resistance device (Rotahaler) and a high-resistance device (Turbuhaler) via a twin-stage impinger.

Results. A paradoxical relationship between particle cohesive strength and de-agglomeration efficiencies of drug-only formulations was observed, where an increase in cohesive strength led to a higher fine particle fraction. A possible explanation for the variation in the fluidization and aerosolization properties between low and high cohesive particles was modeled on the relationship between cohesion, metastable agglomerate size, and the resulting aerodynamic drag force acting on the fluidized agglomerates. The addition of a fine particle lactose carrier influenced the drug deposition patterns in different ways depending on the relative cohesive and adhesive force balances within the formulation.

Conclusions. The use of the colloid Atomic Force Microscrope (AFM) technique in combination with the cohesive-adhesive balance (CAB) system provides a novel preformulation tool for investigating the likely behavior of a dry powder formulation and a possible means of interpreting the possible de-aggregation and dispersion mechanisms of carrier-based formulations.

KEY WORDS: adhesion; cohesion; Atomic Force Microscope (AFM); DPI; drag force; particle.

INTRODUCTION

Dry powder inhaler (DPI) formulations are commonly prepared as a binary blend of a coarse carrier, typically α-lactose monohydrate, and micronized drug (1). The homogeneity of the blend and the de-aggregation and dispersion properties of the respirable particles upon activation (driven by the patients inspirational energy) are, on a microscopic scale, governed by the resulting cohesive (drug-drug) and adhesive (drug-excipient) interaction forces within the formulation. Excessive adhesive forces may prevent elutriation of the respirable particles from the carrier surfaces, leading to upper airway deposition. Similarly, strong cohesive forces may enhance segregation and agglomerate formation, which could directly affect the fluidization and dispersion characteristics of the formulation (2,3). Numerous studies have investigated the *in vitro* deposition characteristics of respirable drug particles from carrier-based DPI formulations (4–6). Many of these studies have indicated that the choice of inhaler device and inspiration flow rate is of crucially important in the fluidization and aerosol characteristics of a formulation (7–9). This suggests that the aerodynamic forces, generated within the device, play a crucial role in powder aerosolization by overcoming the force balances within the formulation.

In an attempt to modify and optimise particulate interactions within a DPI formulation, the majority of research and development has been focused on modifying the physical properties of the carrier, such as particle shape (10), size (1,11), rugosity, or surface passivation of high surface free energy sites by the addition of ternary agents (12,13). Although these alterations have been shown to directly influence the de-aggregation and dispersion of active particles, their specific influences on drug-carrier and drug-drug interaction forces have not yet been fully quantified.

Recently, a novel Atomic Force Microscope (AFM)-based approach has been developed to evaluate the various interaction forces within a model carrier-based DPI formulation (14). This study has shown that upon maintaining a stable environment (temperature and relative humidity) and uniform contact area of interaction, direct quantification of the cohesive-adhesive balances within a dry powder formulation is achievable. A predictive cohesive-adhesive balance (CAB) graph of binary and complex formulation systems can readily be generated. This process may subsequently be utilised as a rapid preformulation tool to ascertain the relative strength of the various interaction forces and possibly to predict the behavior of DPI formulations.

The aim of this study was to investigate the specific role of the cohesive and adhesive force balances via the AFM colloid probe technique on the de-agglomeration efficiencies and deposition characteristics of drug only and model drug-lactose formulations.

MATERIALS AND METHODS

Materials

Micronized budesonide was supplied from Sicor (batch no.6157/MI, Santhia, Italy), micronized salbutamol sulfate from Becpharm Ltd (batch no. 940077, London, UK), and Sorbalac 400 lactose from Meggle (Wasserburg, Germany). All materials were used as supplied. Methanol and acetonitrile were HPLC grade (Fisher Chemicals, Loughborough, UK). AnalaR grade ethanol and acetic glacial were supplied by BDH (Poole, UK). Water was produced by reverse osmosis (milliQ/milliRo; Millipore, Molsheim, France).

Preparation of Powder Formulations

Drug-lactose blends were prepared by geometrically mixing 1g of drug and 1 g of Lactochem lactose in 100-mg increments via a Whirlimixer (Fisons Scientific Apparatus, UK). The resulting blend was further mixed in a Turbula

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(Glen Creston Ltd, Middlesex, Longhborough, UK) at 46 rpm for 30 min.

Scanning Electron Microscopy

The morphology of the different powders was investigated using scanning electron microscopy (SEM; Jeol 6310, Jeol, Japan) at 10 keV. Samples were gold-coated prior to imaging (Edwards Sputter Coater, Crawley, UK).

Particle Size Analysis

The particle size distribution of the as supplied budesonide, salbutamol sulfate, and lactose samples were determined by laser light scattering (Mastersizer X, Malvern, UK), using a 30-0mm lens. Samples were dispersed in cyclohexane and sonicated for 5 min prior to analysis (Ultrasonic Bath FS300b, Decon, Hove, UK).

The aerodynamic diameter of budesonide, salbutamol sulfate, and lactose samples were determined using an Aerosizer in conjunction with an Aerodisperser (Amherst Process Instruments, Inc., Hadley, MA, USA). Approximately 5 mg of powder was introduced into the sample cup of the Aerodisperser. Experiments were carried out at a medium feed rate, with a run time of 180 s at both low shear (1 psi ≈ 6.895 kPa) and high shear forces (5 psi ≈ 34.474 kPa), by varying the pressure drop across the annular gap between the disperser pin and the pin bowl of the Aerodisperser.

HPLC Analysis of Salbutamol Sulfate and Budesonide

The HPLC system consisted of a pump (Jasco PU-980, JASCO Corp., Tokyo, Japan), a multiple UV detector (Jasco UV-975), a Sperisorb 5 μm ODS1 column (Waters, Milford, MA, USA) for salbutamol sulfate, and a 5 μm Hypersil column (Hypersil MOS C8, Jones Chromatography Ltd, Hengoed, UK) for budesonide. Salbutamol sulfate was analyzed using a mobile phase consisting of methanol and water in a 60:40 ratio (%v/v) with 0.1% (%v/v) of acetic acid. The HPLC pump was operated at 1.25 ml·min^{-1} and the UV detection wavelength set at 276 nm. Budesonide was analyzed by HPLC using a mobile phase consisting of 60% of water and 40% of acetonitrile (%v/v). The HPLC pump was operated at 1.5 ml · min^{-1} and the UV detection wavelength set at 248 nm.

Content Uniformity Measurements

The content uniformity of the salbutamol sulfate-lactose and budesonide-lactose blends was measured by analyzing the quantity of active in 10 mg ± 0.5 mg samples. Drug content was analyzed by HPLC, as described above. Relative standard deviation between samples was calculated to assess the homogeneity of the different blends.

In Vitro Aerosol Deposition Studies

To determine the influence of the aerodynamic drag forces on the fluidisation and aerosol characteristics of the cohesive and adhesive formulations, a low and high resistance device were chosen. Various measurements of the internal resistance of dry powder inhaler devices as a function of flow rate have been previously studied (7). A Turbuhaler (Astra Draco AB, Lund, Sweden) was used as a high-resistance device and a Rotahaler (Glaxo Wellcome, Ware UK) as a low-resistance device. Approximately 1.5 mg of the drug only and carrier formulations was accurately weighed into the metering chamber of the Turbuhaler and 2.5 mg into a gelatine capsule to be loaded into the Rotahaler device.

In vitro deposition investigations were performed using a twin-stage liquid impinger (TSI) (Copley, Nottingham, UK). The first and second stages were filled with 7 ml and 30 ml of mobile phase, respectively. The loaded device was connected to the glass throat of the TSI via a moulded mouthpiece. *In vitro* analysis was performed after each actuation of the device. Each experiment (n = 3) was performed at 60 L · min^{-1} flow rate with a 5 s exposure. The cutoff aerodynamic diameter of the first stage was 6.4 μm.

RESULTS AND DISCUSSION

General Physical Characterization

Representative scanning electron micrographs of the as supplied lactose, salbutamol sulphate, and budesonide are shown in Figs. 1A, 1B, and 1C, respectively. Each powder sample exhibited variations in particle size, shape, and morphology. Electron micrographs suggested that lactose (Sorbalac 400) particles were significantly larger than the active ingredients. Variations in the degree of agglomeration of the particles were also evident. The salbutamol sulfate particles were assembled as loose agglomerates, whereas the budesonide particles formed highly dense agglomerates.

The particle size measurements of ultrasonically dispersed lactose, salbutamol sulfate and budesonide samples measured by laser scattering are shown in Table I. As each distribution followed a lognormal fit, the diameter was thus expressed as the median (d_{50}). In addition, the dispersion of the distribution was characterised by the 16th and 84th percentiles. Both salbutamol sulfate and budesonide exhibited a median diameter below the respirable size of 5 μm (15). The median particle diameter of the lactose samples was ca. 10 μm, in accordance with the SEM and suppliers data.

Influence of Particle Cohesiveness on Powder Behavior

Given the differences in cohesiveness between salbutamol sulfate and budesonide, an investigation of the deaggregation properties and *in vitro* performances of these materials was undertaken to examine the relationship between cohesive forces and powder behavior.

The aerodynamic particle size distributions of aerosol clouds generated from micronized lactose, salbutamol sulfate, and budesonide at low and high shear forces are summarized in Table II. At high shear forces, the data exhibited relatively narrow lognormal distributions. The median aerodynamic diameter of micronised salbutamol sulfate and budesonide particles was 2.91 μm and 2.63 μm, respectively. As expected, the median aerodynamic diameter of lactose was significantly larger at 10.54 μm. Correlating these data with ultrasonically dispersed laser scattering measurements suggested complete de-agglomeration of the powder at high shear forces.

At low shear forces, a significant shift in the particle distribution of the time of flight data was observed for both lactose and budesonide (Table II). However, only a very small shift was observed for micronized salbutamol sulfate. The increase in the median aerodynamic diameter and dispersion of the particle size data for lactose and budesonide suggested that the applied low shear force was insufficient to overcome the cohesive bonds within the bulk powders. How-

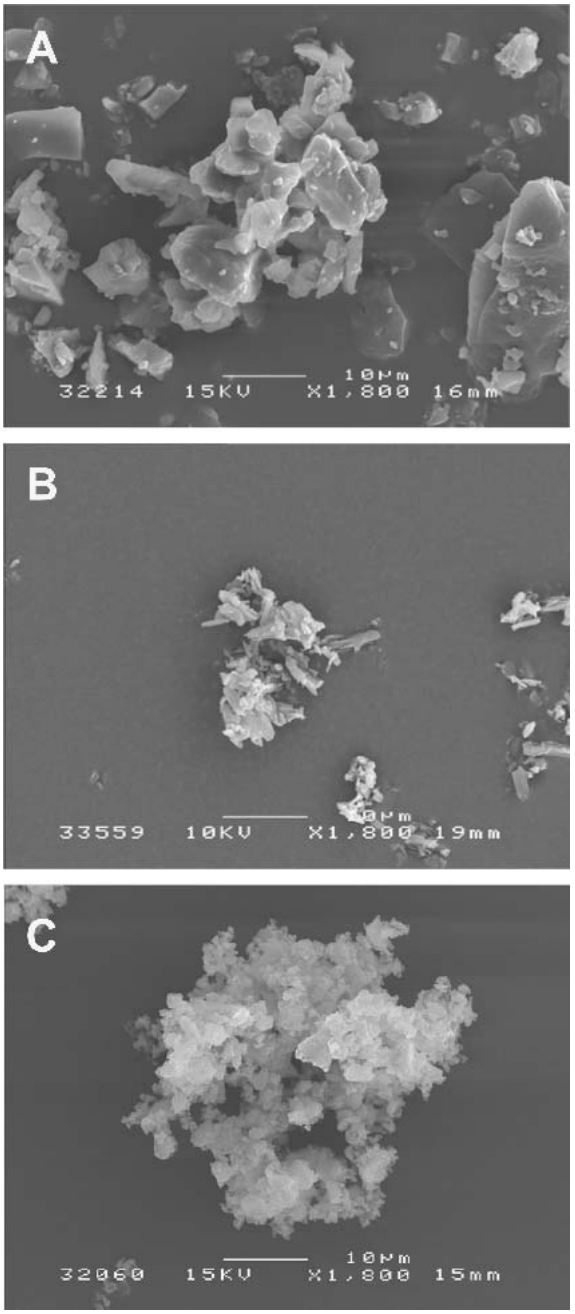

Fig. 1. Representative SEM images of as supplied lactose Sorbalac 400 (A), salbutamol sulfate (B), and budesonide (C).

ever, the similarity of the aerodynamic diameter measurements of salbutamol sulfate at low and high shear forces suggested salbutamol sulfate particles can readily be de-agglomerated under these conditions of shear. Similar changes to particle size distributions of powder samples as a function of shear force have been reported previously (16).

Further information regarding the possible role of powder cohesiveness on variations in aerodynamic size measurements with shear can be obtained from the difference in the apparent aerodynamic volume. By assuming that the aerodynamic diameters observed for a particular powder at high and low shear are the median particle diameter of the de-agglomerated powder and median diameter of the agglomerated particles, respectively, the agglomerate volume can be expressed as:

$$V_{agglomerate} = n \cdot V_{particle} + \delta_v \quad (1)$$

where n is the number of particles in the agglomerate and δ_v is the interstitial volume between particles.

Figure 2 shows a corresponding plot of the apparent aerodynamic volume ratio (on a logarithmic scale) vs. the corresponding cohesive balance dependencies of the powders. The cohesive dependencies of the particles were obtained from the quantitative colloidal AFM measurements undertaken in the first part of this study into the cohesive and adhesive balance in dry powder formulations (14). A fit of the data indicated that the degree of de-agglomeration decreased exponentially as a function of agglomerate cohesive strength. Thus, the efficiency of de-agglomeration has been dramatically affected by the relative internal cohesive strength of agglomerated particulates and shear force applied. This, in turn, may directly influence the aerosol characteristics and deposition behavior of an agglomerated system.

The *in vitro* deposition behavior of a drug only formulation of micronized salbutamol sulfate delivered via low (Rotahaler) and high (Turbulaher) internal resistance DPI devices are shown in Fig. 3A. The emitted dose percentage of the two devices were very high (>80%). This indicated that the pressure drop variations between the two devices, at 60 $L \cdot min^{-1}$, had no significant affect on the fluidization of the micronized salbutamol sulfate particles. However, significant differences between the devices were observed in the amount of the active material collected in the first and the second stages of the TSI ($p < 0.05$). The high resistance device increased the fine particle fraction by 2-fold. Nevertheless, a considerable amount of drug was recovered for both devices in the first stage of the TSI. This large percentage suggested that micronized salbutamol sulfate did not fully de-aggregate upon aerolization. These results were rather surprising considering the relatively low cohesive strength of salbutamol sulfate and the high de-agglomeration efficiency of the particles upon exposure to low shear forces of the Aerodisperser.

The deposition pattern of a drug only formulation containing micronised budesonide from both a Rotahaler and Turbuhaler DPI are shown in Fig. 3B. Although a small increase in the percentage of emitted dose was observed for the Turbuhaler device, a very high percentage of the budesonide remained within the devices upon activation. More significantly, however, was the variation in the aerosol characteristics between the two devices. The high-resistance device led to a 4-fold increase in the de-agglomeration efficiency of budesonide with respect to the low-resistance inhaler device.

This significant increase in the de-agglomeration efficiency of budesonide with increasing airflow resistance may

Table I. Particle Size Distribution Characteristics of Lactose Sorbalac 400, Micronized Salbutamol Sulfate, and Micronized Budesonide by Laser Scattering (mean ± SD, n = 5)

	Lactose	Salbutamol sulfate	Budesonide
d_{16} (µm)	3.00 ± 0.19	2.17 ± 0.03	2.06 ± 0.02
d_{50} (µm)	9.29 ± 1.07	4.77 ± 0.13	3.75 ± 0.05
d_{84} (µm)	20.26 ± 2.36	11.58 ± 1.09	6.81 ± 0.2

Table II. Particle Size Distribution Characteristics of Lactose Sorbalac 400, Micronized Salbutamol Sulfate, and Micronized Budesonide by Time of Flight Measurements at High (5 psi) and Low (1 psi) Shear Forces (mean ± SD, n = 5)

	Lactose		Salbutamol sulfate		Budesonide	
	High shear force	Low shear force	High shear force	Low shear force	High shear force	Low shear force
d_{16} (μm)	5.59 ± 0.37	18.35 ± 3.53	1.89 ± 0.08	2.04 ± 0.40	1.63 ± 0.20	20.65 ± 2.34
d_{50} (μm)	10.54 ± 0.70	29.70 ± 4.58	2.91 ± 0.30	3.58 ± 0.88	2.63 ± 0.28	35.96 ± 3.12
d_{84} (μm)	14.47 ± 1.29	41.39 ± 6.1	4.32 ± 0.86	5.33 ± 1.35	3.92 ± 0.40	49.18 ± 3.1

relate to a crucial energy requirement of the device in overcoming the highly cohesive nature of budesonide particles.

It should be stressed that *in vitro* aerosol behavior of pure micronized salbutamol sulfate and budesonide particles were unexpected, and highlighted the highly complex nature of de-agglomeration and aerosol dispersion mechanisms even in the most basic of formulations.

To understand further this apparent paradoxical behavior, the stability of agglomerated particles entrained in an air flow was modeled relative to the aerodynamic drag force generated through the device (17). Assuming a physical system of an object (agglomerate) in an airborne flow, the drag force generated by the displacement of air molecules with respect to the moving object can be expressed as:

$$F_{drag} = C_d \frac{\pi}{8} \rho_{air} \Phi_{agg}^2 v_{flow}^2 \quad (2)$$

where C_d is the drag coefficient, which is dependant on the ratio of inertial and frictional forces of the agglomerated particles in the airflow, ρ_{air} is the density of the air, Φ_{agg} is the effective diameter of the agglomerate, and v_{flow} is the airflow velocity. The corresponding initial kinetic energy of the moving object may be expressed as:

$$E_c^{t0} = \frac{\pi}{12} \rho_{agg} (\Phi_{agg}^{t0})^3 v_{flow}^2 \quad (3)$$

where ρ_{agg} is the density of the agglomerate. Equations 2 and 3 indicate that the aerodynamic drag force acting on an object and the kinetic energy of a moving object are directly proportional to the square and the cube of its diameter, respectively. As a result, the aerodynamic drag force and kinetic energy differences between a 5 μm and 50 μm object at a constant settling velocity would be 10^2 and 10^3, respectively. Consequently, these relationships would play a significant role in the de-aggregation and dispersion of agglomerated particles.

Thus, despite the significant increase in the cohesive strength of budesonide particles, with respect to salbutamol sulfate, the drag force experienced by airborne budesonide aggregates may lead to a higher efficiency in the de-agglomeration and dispersion of respirable particles than for smaller agglomerates with a lower cohesive strength. Furthermore, the substantial increase in kinetic energy of large agglomerates may increase de-aggregation efficiency within the device via impaction (assuming an inelastic collision and no subsequent energy loss).

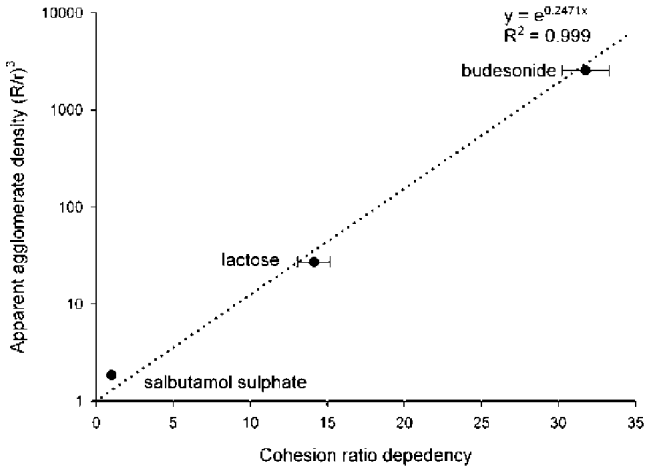

Fig. 2. Apparent agglomerate volume vs. cohesion ratio dependency of salbutamol sulfate, budesonide, and lactose (mean ± SD, n = 3).

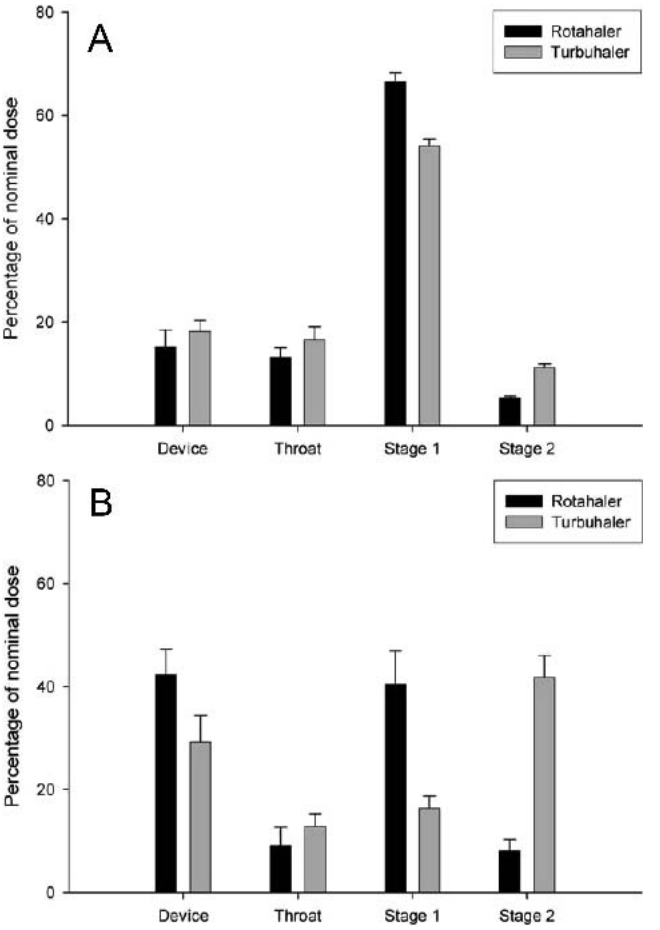

Fig. 3. *In vitro* deposition of salbutamol sulfate (A) and budesonide (B) from a Rotahaler and a Turbuhaler DPI (mean ± SD, n = 3).

Hence, it is proposed that during the de-aggregation and dispersion process, a state can be reached where the internal binding forces of the agglomerate and the drag forces generated within the device reach an equilibrium ($F_{coh} = F_{drag}$). This would subsequently lead to a critical agglomerate size at which suspension of the elutriation process occurs. The characteristic properties of the metastable aggregate would be directly dependent on the airflow characteristics via an inhaler device and the cohesive properties of the particles within the agglomerate.

A schematic representation of the possible aerosol dispersion mechanisms of salbutamol sulfate and budesonide agglomerated particles are illustrated in Fig. 4. The low cohesive strength of salbutamol sulfate particles, which readily allows aerosolization and entrainment of relatively small agglomerates, will quickly attain their aerodynamic metastable state, thereby decreasing the degree of respirable particle dispersion. As indicated by *in vitro* measurements, this may lead to high emission yet poor fine particle delivery performances. In contrast, highly cohesive budesonide particles require a significantly higher amount of energy to fluidize the aggregated powder, and may lead to the entrainment of larger agglomerates. However, these agglomerates will exhibit greater inertial properties and experience significantly greater aerodynamic drag forces than smaller agglomerates and may experience more collisions within the device. These effects on powder de-agglomeration will subsequently lead to higher dispersion efficiency and greater percentage of fine respirable particles, as indicated by *in vitro* measurements.

Influence of Drug-Excipient Interactions on Formulation Behavior

Rowe *et al.* have significantly advanced the efficiency of wet granulation preparation of powders for oral solid dosage forms by judiciously selecting binding agents on the basis of their spreading coefficient (λ_{12}) (18,19). The reduced spreading coefficient is defined as the ratio between the work of adhesion of the substrate and the binder and the work of cohesion of the binder (20). A similar approach for blending characteristics of carrier-based formulation systems has been applied in this study. The term reduced intermixing coefficient (Λ_{12}), derived from the reduced spreading coefficient, can be described by the following relationship:

$$\Lambda_{12} = \frac{F_{12}^{ad}}{F_{11}^{co}} \tag{4}$$

where Λ_{12}, a dimensionless parameter, corresponds to the force ratio between adhesive interactions (F_{12}) and cohesive interactions (F_{11}) of two interacting materials. For carrier based systems, a reduced intermixing coefficient reflects the affinity of the drug (material 1) to interact with the carrier (material 2). Hence, the position of Λ_{12} with respect to unity is a direct indication of the alacrity ($\Lambda_{12} > 1$) or the reluctance ($\Lambda_{12} < 1$) of the active particles to form an interactive mixture with the carrier particles. The reduced intermixing coefficients between salbutamol sulfate, budesonide, and α-lactose monohydrate were consequently calculated from the quantitative cohesive-adhesive balance (CAB) dependencies obtained from the related AFM study (14) and are summarized in Table III. A clear distinction between salbutamol sulfate and budesonide (materials 1) was observable with α-lactose monohydrate (material 2). The disparity in the reduced intermixing coefficients of salbutamol sulfate ($\Lambda_{12} = 16.88$) and budesonide ($\Lambda_{12} = 0.22$) strongly suggests that agglomerated salbutamol sulfate particles can be easily displaced to form an interactive mixture within a carrier based formulation, whereas budesonide would require an intensive mixing process to form a metastable carrier-based formulation.

To highlight the influence of the intermixing coefficient on the blending characteristics of salbutamol sulfate and budesonide carrier-based formulation, scanning electron microscopy and drug content uniformity analyses of the blends were investigated. Scanning electron micrographs of salbutamol sulfate-lactose and budesonide-lactose are shown in Figs. 5A and 5B, respectively. The electron micrographs suggested a uniform distribution of highly dispersed salbutamol sulfate particles over the lactose surface. In contrast, budesonide particles appeared to remain agglomerated and unevenly spread over the lactose carrier. Predictably, dose content uniformity analysis revealed a relative standard deviation of 4.2% for salbutamol sulfate and 28.1% for budesonide. These observations suggested good correlation between the reduced intermixing coefficient and the characteristics of the respective

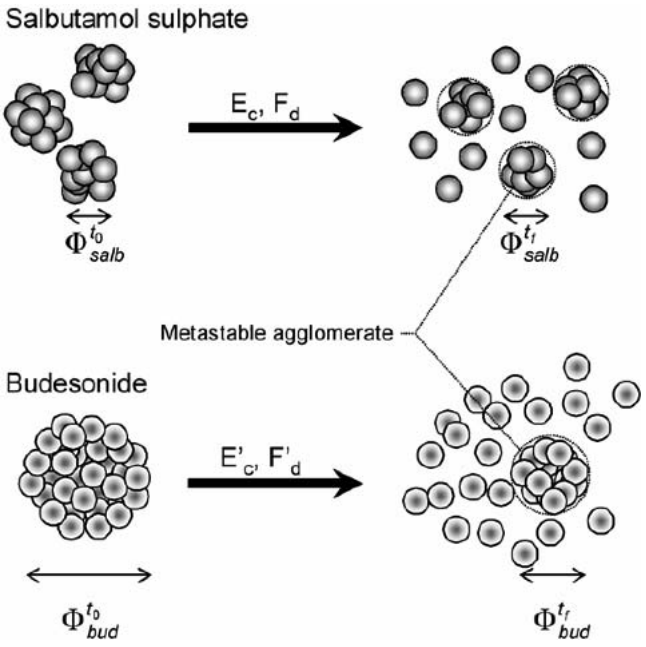

Fig. 4. Schematic representation of the possible de-aggregation and dispersion mechanisms of weakly cohesive (salbutamol sulfate) and highly cohesive (budesonide) particles.

Table III. Reduced Intermixing Coefficient of Salbutamol Sulfate, Budesonide, and Lactose (mean ± SD, n = 3)

Sample	Reduced intermixing coefficient (Λ_{12})		
	Salbutamol sulfate[b]	Lactose[b]	Budesonide[b]
Salbutamol sulfate[a]	—	16.88 ± 0.91	6.59 ± 0.21
Lactose[a]	1.19 ± 0.42	—	0.5 ± 0.31
Budesonide[a]	0.21 ± 0.13	0.22 ± 0.21	—

[a] Material 1.
[b] Material 2.

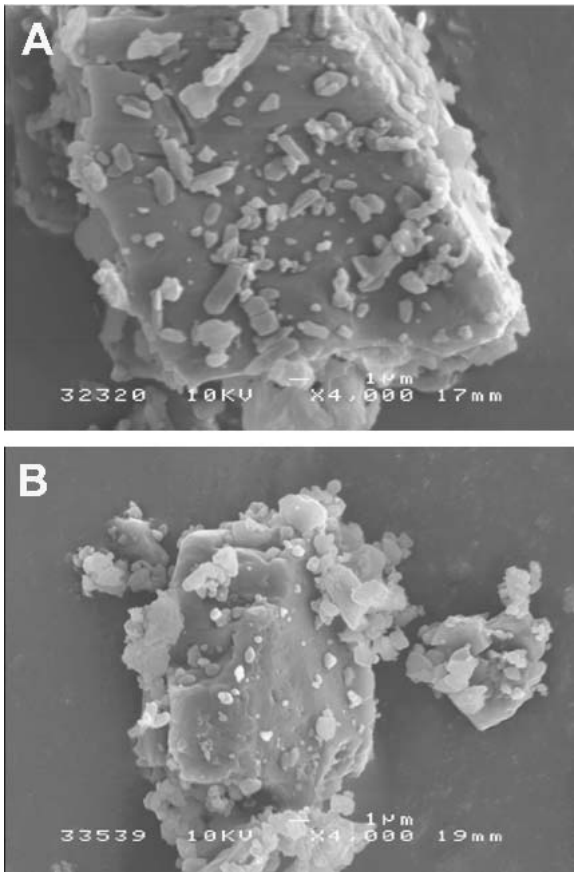

Fig. 5. Representative SEM micrographs of blends of salbutamol sulfate-lactose (A) and budesonide-lactose (B).

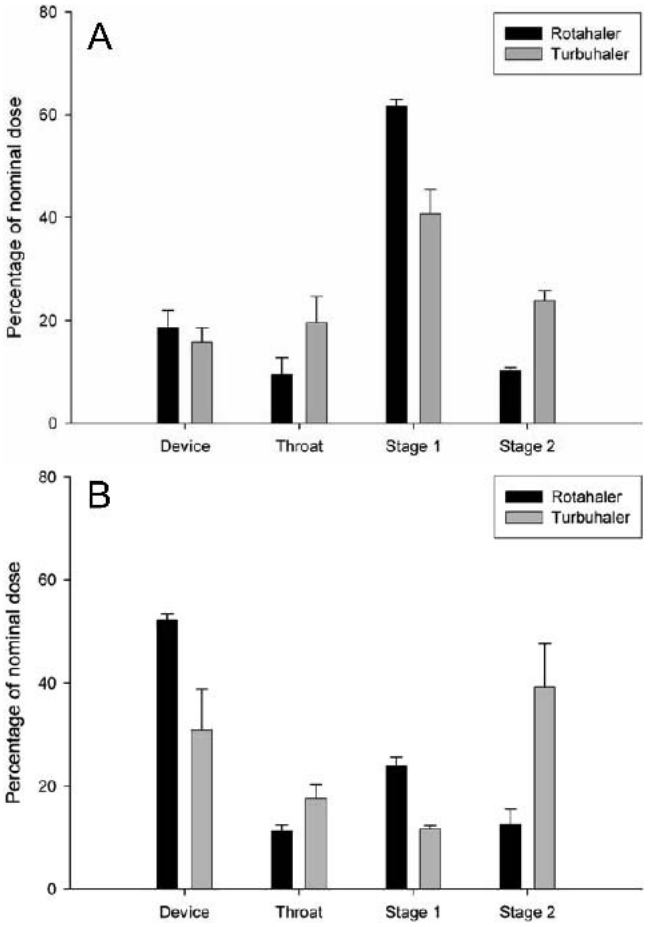

Fig. 6. *In vitro* deposition of salbutamol sulfate-lactose (A) and budesonide-lactose (B) carrier-based formulation from a Rotahaler and a Turbuhaler DPI (mean ± SD, n = 3).

carrier based formulations. In addition to providing pertinent information regarding the blending characteristics of carrier formulations, the reduced intermixing coefficient may also provide an insight into the stability and aerosol characteristics of such systems.

The aerosol delivery properties of salbutamol sulfate and budesonide carrier-based formulations from both a Rotahaler and Turbuhaler DPI are shown in Figs. 6A and 6B, respectively. The use of smaller lactose particles (<10 μm) with respect to more conventional carrier sizes (63–90 μm) was dictated by the desire to minimize the potential influence of larger carrier particles over fluidisation and de-aggregation processes of particle agglomerates.

The emission efficiency of salbutamol sulfate-lactose formulations (81.9% ± 3.3%) was very similar to the drug only formulation (84.9% ± 3.4%), with no significant differences between the two devices. Significant changes in the fine particle delivery behavior were, however, measured between the two systems. The significant decrease in stage 1 deposition ($p < 0.05$) for a carrier-based formulation led to an increase in stage 2 deposition ($p < 0.05$), resulting in a net increase in fine particle fraction delivery.

The co-processing of budesonide with α-lactose monohydrate resulted in a significant decrease in stage 1 deposition and an associated improvement in fine particle delivery performance via a Rotahaler device ($p < 0.05$) with respect to micronized budesonide studies. No significant variations between drug only and carrier-based formulations were measured with a high resistance Turbuhaler inhaler. A summary table of the deposition percentages of the drug only and carrier-based formulations are shown in Table IV.

The high reduced intermixing coefficient between salbutamol sulfate and lactose suggested that salbutamol sulfate particles would interactively mix with α-lactose monohydrate. Thus, the de-aggregation and dispersion behavior of the salbutamol sulfate particles should be dominated by the drug-excipient interactions. *In vitro* measurements indicated, however, that the performance of the carrier-based formulation was analogous to the drug-only formulation. This may be attributed to the excessive adhesive forces leading to an incomplete detachment of the salbutamol sulfate from the carrier, as indicated by the related atomic force microscopy studies (14). This may subsequently lead to a substantial amount of active material deposition in the throat and stage 1. The high emission efficiency of the carrier-based formulation was possibly a result of the high affinity of salbutamol to the carrier reducing the potential for segregation during storage and handling. Meanwhile, the increase in the fine particle performance of the carrier-based formulation may relate to the higher aerodynamic drag force experienced by the particulates adhering to the excipient particle surface. This behavior was corroborated by the improvement in drug detachment at higher shear forces. These measurements further supported

Table IV. Fine Particle Fraction and Emission Efficiency of Salbutamol Sulfate and Budesonide Carrier-Based Formulations from a Rotahaler and Turbuhaler DPI (Mean ± SD, n = 3)

Formulation	Rotahaler[a]		Turbuhaler[b]	
	FPF (%)	Emission (%)	FPF (%)	Emission (%)
Salbutamol sulfate	6.2 ± 0.6	84.9 ± 3.4	13.7 ± 0.5	81.9 ± 2.1
Salbutamol + lactose	12.6 ± 1.2	81.3 ± 3.3	28.4 ± 1.5	84.2 ± 2.7
Budesonide	14.4 ± 4.9	57.7 ± 5.0	63.4 ± 3.4	64.8 ± 4.6
Budesonide + lactose	26.3 ± 6.2	47.7 ± 1.2	58.9 ± 7.1	66.3 ± 8.0

[a] Rotahaler, 0.68 kPa pressure drop at 60 L · min^{-1}.
[b] Turbuhaler, 8.5 kPa pressure drop at 60 L · min^{-1}.

the requirement for the formation of stable agglomerate of crucial dimensions to induce a significant aerodynamic drag force within the device to disperse the respirable particles. The dimensions and aerodynamic properties of the fine carrier particles may, therefore, have a significant affect on the dispersion energy of the adhering drug particles, as it will directly influence the aerodynamic drag force experienced by the adhered drug.

The colloidal AFM measurements also indicate that modifying the adhesive-cohesive force balance may enhance the efficiency of dispersion. For a salbutamol sulfate formulation, this may be achieved by lowering the interfacial energy of interaction between drug and excipient, leading to adhesive forces which nonetheless remain stronger than the drug cohesive forces. The advantage for the adhesive forces to be slightly stronger than the drug cohesive forces is to reduce the potential for segregation of the active ingredient during manufacturing and handling.

The reduced intermixing coefficient between budesonide and lactose suggested that budesonide particles would not interactively mix with α-lactose monohydrate. These findings were supported by electron micrographs and content uniformity measurements. The instability of budesonide particles in a carrier-based formulation was corroborated by similar low emission efficiency and reduction in fine particle fraction delivery of carrier-based budesonide formulations under high shear with respect to pure budesonide. This suggested that an increase in the aerodynamic drag coefficient resulted in the rapid separation of the cohesive budesonide agglomerates from the lactose surface, introducing a similar dispersion mechanism as for the drug only formulation. It would therefore appear that the drug-drug interaction forces are the predominant factor in the delivery characteristics of highly cohesive drug systems. Optimisation of such dry powder formulations would require passivation of the excessive cohesive bonds through controlled modifications of the interfacial energetics.

CONCLUSIONS

The influence of the cohesive and adhesive dependencies of salbutamol sulfate and budesonide particles in model dry powder formulations was investigated. A surprising relationship between particle cohesive strength and de-agglomeration efficiencies of drug only formulations was observed. A possible explanation for the dramatic variation in the fluidization and aerosolization properties between low and high cohesive particles was modeled on the relationship between cohesion, metastable agglomerate size, and the resulting aerodynamic drag force acting on the fluidized agglomerates. The addition of a fine particle lactose carrier influenced the drug deposition patterns in different ways. This was proposed to be dependant on the relative cohesive and adhesive force balance within the formulation. The use of the colloid AFM technique together with the novel development of CAB-graph system provides a novel preformulation tool for investigating the likely behavior of a dry powder formulation and a possible means of interpreting the possible de-aggregation and dispersion mechanisms of carrier-based formulations.

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