Adhesion of Powders for Inhalation: An Evaluation of Drug Detachment from Surfaces following Deposition from Aerosol Streams

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Purpose. To evaluate micronized powder retention and detachment from inhaler surfaces following reproducible deposition by impaction, coupled with centrifugal particle detachment (CPD).

Methods. Micronized albuterol sulfate (AS) and beclomethasone dipropionate (BDP) were aerosolized as dry powders and deposited by cascade impaction onto different contact surfaces. Drug detachment from the surfaces was characterized using CPD, coupled with HPLC assay and scanning electron microscopy.

Results. Drugs which accumulated as aggregates on model surfaces detached with distinctive profiles for % remaining vs. applied centrifugal force; each profile showed reproducible values for the minimum force required to initiate drug detachment, F_{yield}. While differences occurred in the observed detachment profiles for different drugs and contact surfaces (polyacetal vs. aluminum), the deposited drug particle size had the most significant effect on these profiles, e.g., F_{yield} for AS (2.1–3.3 μm) was 383 ± 12.7 μN compared with 18 ± 13.8 μN for AS (4.7–5.8 μm).

Conclusions. A technique was developed which enabled the experimental review, and subsequent data analysis, of the adhesive properties between different DPI construction materials and drug substances deposited from aerosol clouds. The technique appears to be of greater relevance to inhaler design decisions than earlier studies in the literature claiming to show differences in the adhesion of single drug particles to surfaces.

KEY WORDS: centrifugal particle detachment; adhesion; autohesion; powder aerosols; impaction; inhalers.

INTRODUCTION

Optimization and control of particle–particle and particle–inhaler interactions is of critical importance in the development of efficient dry powder inhaler (DPI) systems. DPI development scientists are confronted regularly with the need to ensure that their systems meter and aerosolize micronized (usually <5 μm) powders reproducibly (1). Unfortunately, the autohesive (cohesive) and adhesive properties of these powders create a variety of regulatory problems. In the event that powder buildup occurs in an inhaler or on an inhaler component, its subsequent detachment can cause failure of delivered dose uniformity specifications and influence the emitted particle size distribution. Ironically, replacing critical inhaler components during development, with those made from less "adhesive" materials, to overcome potential drug retention problems, can require that major clinical trials be repeated to ensure safety and efficacy of each "new" inhaler system.

While particle-particle and particle-container interactions are important in every aspect of micronized powder handling, drug adhesion to equipment, carrier particle, and inhaler surfaces occurs following two major types of contact. During powder processing, powder filling and inhaler emptying, bulk drug or drug-blend particles are most typically moved over surfaces with which they are in frictional contact. Typical shear forces acting on particles in this scenario exceed gravitational forces and are imposed by mixers, filling equipment and the impellers and airjets used as powder deaggregating mechanisms in inhalers. Contact of an aerosolized powder with an inhaler mouthpiece, or other component in the flowing aerosol stream is the other major type of powder–surface interaction in inhalers. When it results in deposition and adhesion, clumps or multi-particle assemblies form, due primarily to new particles impacting on and around those that are already attached. This is illustrated in Fig. 1 although the phenomenon occurs to different extents in all DPIs.

For adhesion in inhalers to be a significant pharmaceutical problem, random detachment must occur in quantities likely to affect the magnitude of the dose seen by the patient (say, >5% of the fine particle dose). Thus, detachment studies designed to assess the adhesive interaction between a surface and a single micronized particle (single powder particles ≤5 μm in diameter have masses <100 pg while inhaled fine particle doses are 10^5–10^6 times larger) may not be relevant.

It is likely, furthermore, that the way in which an adhered powder clump is formed, relates to the force necessary to detach it and thus, the likelihood of it causing a problem in an inhaler. Perhaps because of the extreme variability seen with the adhesion of bulk micronized drug to some surfaces (2), and the difficulty of studying different surfaces when impact detachment techniques are employed (3), most previous work has concentrated on the adhesion and subsequent detachment of individual particles on different surfaces using centrifugal particle detachment (CPD) (4–11) and atomic force microscopy (AFM) (12–14). Because of the ease with which the centrifugal technique may be manipulated to change the materials used as particle attachment surfaces, this paper specifically focuses on the use of CPD as a means of characterizing drug material / surface interactions relevant to DPI systems. However, in contrast to previous work we have developed a means of reproducibly depositing aerosolized powder clumps on different surfaces, and then assessing the overall forces necessary to detach powder masses capable of affecting DPI reproducibility.

MATERIALS AND METHODS

Albuterol sulfate (AS; Batch 970118) and beclomethasone dipropionate (BDP; Batch J009141-1) were donated by Dura Pharmaceuticals, San Diego, California and micronized using a jet mill (Model 00 Jet-O-Mizer, Fluid Energy Processing Equipment Co., Hatfield, Pennsylvania). Each powder was stored at 55% Relative Humidity at 24 ± 1°C prior to use.

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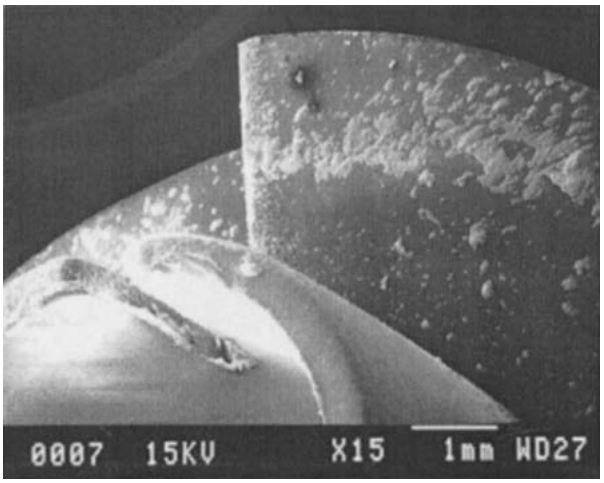

Fig. 1. Multilayer deposition of cromolyn sodium aggregates on the propeller of the Spinhaler™ DPI device, following aerosolization of two Intal Spincaps by the USP delivered dose uniformity method (18).

The particle size distributions of the micronized drug materials were characterized using the Aerosizer with Aero-Disperser (API, Hadley, Massachusetts), using experimental conditions recommended by Hindle and Byron (15). The volume median aerodynamic diameters of AS and BDP were 1.4 ± 0.2 and 1.8 ± 0.2 μm with 90% of the particles having an aerodynamic diameter <2.2 ± 0.1 and 3.0 ± 0.2 μm, respectively (mean ± SD of 5 determinations). Delrin (polyacetal) and aluminum contact surfaces were obtained from MSC Industrial Supply Co. (Melville, New York) and machined into circular disks of 16 mm diameter and 1.5 mm height.

Deposition of Micronized Drug Particles onto Contact Surfaces

A prototype Spiros device, donated by Dura Pharmaceuticals, San Diego, California, was used to aerosolize the pure micronized drug powders into a 28.3 L/min vacuum-induced airstream flowing through an Andersen Cascade Impactor (ACI; Mark II, Graseby Andersen, Smyrna, Georgia). Use of Spiros (previously Dryhaler; which contains a flow–activated impeller to mechanically disperse powders placed in its aerosol chamber) for this purpose has been described previously (16). Particles were separated from the aerosol stream and deposited by impaction onto polyacetal or aluminum disks positioned on stages 2 and 4 of the ACI, to retain aerosol particles with aerodynamic diameters in the 4.7–5.8 μm and 2.1–3.3 μm size ranges, respectively (17–20). All disks were washed with solvent and air-dried prior to handling with clean metal forceps before use. Nineteen disks (randomized with respect to material) were placed on each of the inverted collection plates for stages 2 and 4 (inversion is recommended in the ACI Manual to hold the jet to impaction surface distance effectively unchanged) as shown in Fig. 2a. The ACI was assembled according to USP recommendations and the preseparator and stage 1 coated with Silicone Release Spray (Dow Corning, Michigan) to minimize particle reentrainment (21). Five mg of micronized drug was weighed accurately and introduced into the Spiros aerosol chamber immediately prior to connection to, and actuation into the

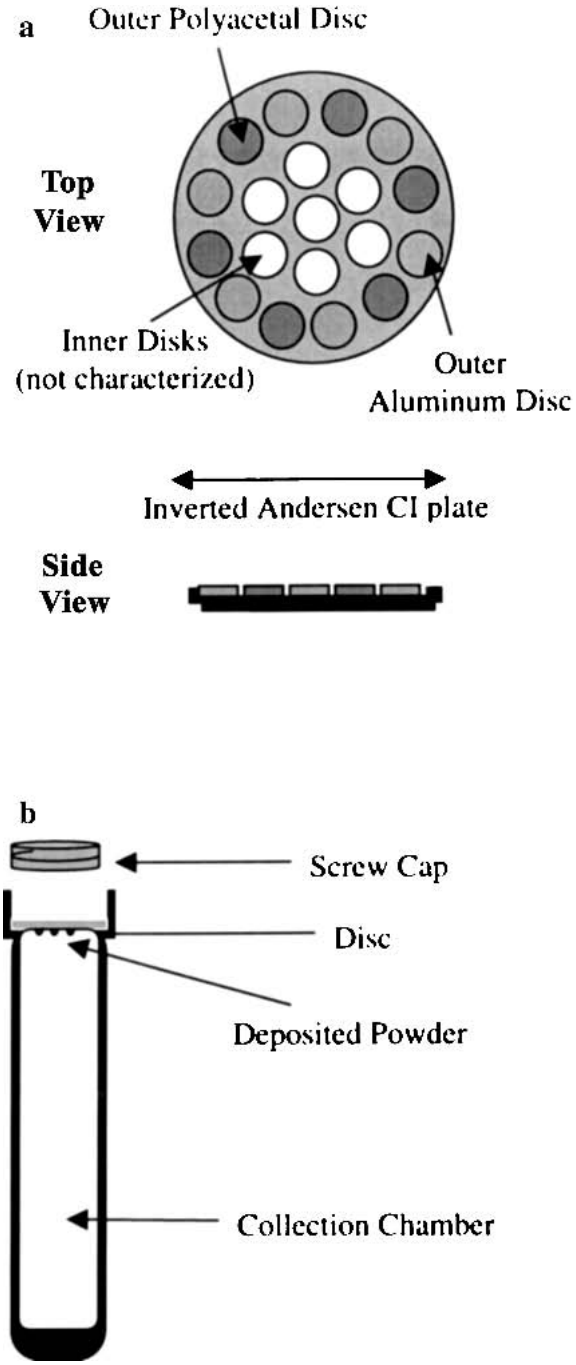

Fig. 2. Schematic diagram of (a) polyacetal and aluminum disks positioned on the collection plate of the Andersen cascade impactor and (b) centrifugal cell assembly.

ACI for 8 s (18). Following actuation, the ACI was dissembled and the 12 outer disks from stages 2 and 4 positioned, with drug surfaces facing downward, in the centrifugal cell assemblies shown in Fig. 2b.

Characterization of Adhesion and Autohesion

Adhesion measurements were performed using a Beckman Coulter ultracentrifuge (L8-60M, Fullerton, California) equipped with a SW 41 Ti swinging basket rotor, which al-

lowed 6 centrifuge cell assemblies to be spun simultaneously, with drug-loaded disks normal to the axis of rotation, at speeds up to 41,000 rpm. The distance between the drug contact surface and the axis of rotation was 67.4 mm. Particle detachment was investigated by drug specific assay following acceleration to, and maintenance for 5 min of, rotor speeds of 5000, 10,000, 15,000, 20,000, 25,000, 30,000, 35,000, and 40,000 rpm; relative centrifugal forces (RCF) ranging 1887–121,000 *g*. Following centrifugation, each cell assembly was dismantled and the sample holder/disk and collection chamber rinsed separately with solvent and assayed for drug by HPLC. Six disks were studied at each centrifuge speed in 2 separate lots of 3 disks each. Additional experiments were also performed to better define detachment profiles in regions of interest. Experiments were randomized with respect to the order in which centrifuge speeds were assigned during the study. All testing and powder handling was performed at ambient temperature and humidity (24 ± 1°C and 46 ± 10% RH). In a small number of satellite experiments, the appearance of drug retained on the contact surfaces before and after centrifugation was characterized by scanning electron microscopy (Joel JSM-820, Jeol, Peabody, Massachusetts).

Drug Analysis

HPLC analysis of AS and BDP employed a C-18 Spherisorb ODS-2 5μm column (Alltech Associates Inc., Deerfield, Illinois). The mobile phases were 0.1% ammonium acetate solution: methanol (30:70% v/v) for AS and acetonitrile: water (60:40% v/v) for BDP. The mobile phases were pumped at 0.8 and 1.0 ml/min for AS and BDP respectively. Fluorescence detection (Shimadzu RF 551 Fluorescence Detector,) was employed for AS (excitation and emission at 276nm and 609nm, respectively) while UV detection at 238nm (Shimadzu SPD-6A UV Spectrophotometric Detector, Shimadzu Corporation, Japan) was used for BDP. Calibration curves of peak area vs. concentration for AS and BDP were linear ($r^2 > 0.999$) over the range employed during the experiments. The within day precision (RSD, n = 6) for AS was 4.6% and between day precision (RSD, n = 12) was 4.3%. The within day precision for BDP was 0.47% and between day precision was 0.49%. The accuracy (% DFN, n = 6) for the determination of AS in 0.1% ammonium acetate solution: methanol (30:70% v/v) was 2.0% at an AS concentration of 700 ng/ml. The accuracy for the determination of BDP in acetonitrile: water (60:40% v/v) was 1.0% at a BDP concentration of 1000 ng/ml. The values for limit of detection (LOD) for AS and BDP were 54 ng/ml and 85 ng/ml, respectively.

RESULTS AND DISCUSSION

Deposition of Albuterol Sulfate Particles onto Contact Surfaces

Stage 2 and 4 of the ACI collect particles with aerodynamic diameters in the 4.7–5.8 μm and 2.1–3.3μm size ranges most effectively (18). In practice, a range of aerodynamic sizes on these stages may result because the stage cutoffs in this, and other impactors, are not absolute (17,19,20,22) e.g., calculated 50% collection efficiency cutpoints have been reported to range 4.59–4.81 (stage 2) and 2.01–2.18 μm (stage 4), respectively (20). These stages were chosen for this study because they effectively represented the small and large size fractions of the complete spectrum of respirable particles (23). Determining how each of these size categories detach from surfaces should therefore provide insight into how efficiently inhalation pathway components in DPIs can be expected to grasp impacted powder deposits. Note however, that omission of different stages from the cascade impactor readily enables reproducible collection of material with different aerodynamic diameter ranges. Also, because both aerodynamic diameter and crystal packing efficiency are affected by shape and density, geometric dimensions of particles adhering to surfaces after impaction may or may not correspond to these size ranges (see, for example, Fig. 3).

Clearly, powder deposition onto contact surfaces in this study is brought about differently to that in other reports (2–4,8,9). In essence, retention of powder in DPI inhalation pathways can only occur after impaction from the air stream, as dictated by the relative velocities of aerosolized particles and the inhaler components. Thus, aerosol impaction is expected to occur in DPIs on rapidly moving impellers (Fig. 1), at points where directional changes occur in the air stream and in areas of high turbulence, such as the spiral channels in Turbuhaler mouthpiece (24).

Highly variable adhesion results from the interaction of bulk micronized drug even with standardized surfaces, a fact which made comparison of results for different surfaces and conditions almost impossible to study (RSDs up to 46%, (2)). In contrast, Table I shows that deposition of AS and BDP onto polyacetal and aluminum surfaces from powder aerosol streams was reproducible (RSD < 20%) and quite simply achieved by impaction in 1.1 through 1.5 ug powder heaps. SEM (Fig. 4) showed that drug powders were deposited in discrete heaps (stage 2, heap diameter ~0.8mm, ~10 heaps per disk; stage 4, heap diameter ~1.0mm, ~10 heaps per disk) with significant mass differences per heap between size fractions (mass of small AS < mass of large AS; $P < 0.05$) but no significant difference between surfaces (ANOVA and Fish-

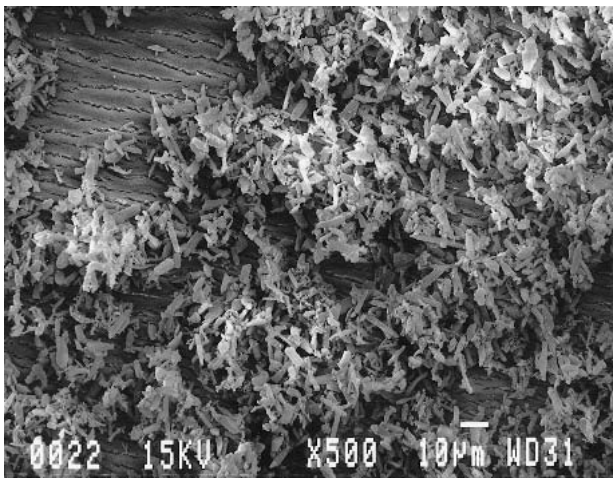

Fig. 3. Scanning electron micrograph of AS 4.7 – 5.8 μm deposited onto polyacetal following CPD at RCF = 7550 g. Image shown represents 40% drug detachment. *The aerodynamic diameter of these particles is probably influenced mainly by their cross sectional area, not needle length. Thus particles can possess similar aerodynamic properties despite large differences in mass (27).

Table I. Summary of the Mass Deposition of Albuterol Sulfate (2.1–3.3 μm and 4.7–5.8 μm) and BDP (2.1–3.3 μm) onto Polyacetal and Aluminum

Deposited material	Size fraction	Contact surface	[a]Mass (ng) per deposit mean (SD)	[b]n
Albuterol Sulfate	2.1 to 3.3	Aluminum	1122 (128)	50
Albuterol Sulfate	2.1 to 3.3	Polyacetal	1198 (166)	56
Albuterol Sulfate	4.7 to 5.8	Polyacetal	1543 (302)	60
BDP	2.1 to 3.3	Polyacetal	1058 (142)	48

[a] Calculated by dividing the total mass of drug recovered from each disk by the total number of deposits for that particular disk, [b] number of disks.

er's pairwise comparisons; Minitab, Minitab Inc., Pennsylvania). In some studies, where the mass per heap following 1 and 2 Spiros actuations was compared, the average mass / heap *per actuation* differed insignificantly ($P < 0.05$, *t*-test), indicating that stage overload and particle re-entrainment within the ACI during each single actuation experiment was not apparent (21). In the case of BDP (2.1–3.3 μm), 2 actuations were necessary to deposit a mass (~1.1 μg) which was comparable to that following a single actuation of AS, on each contact surface.

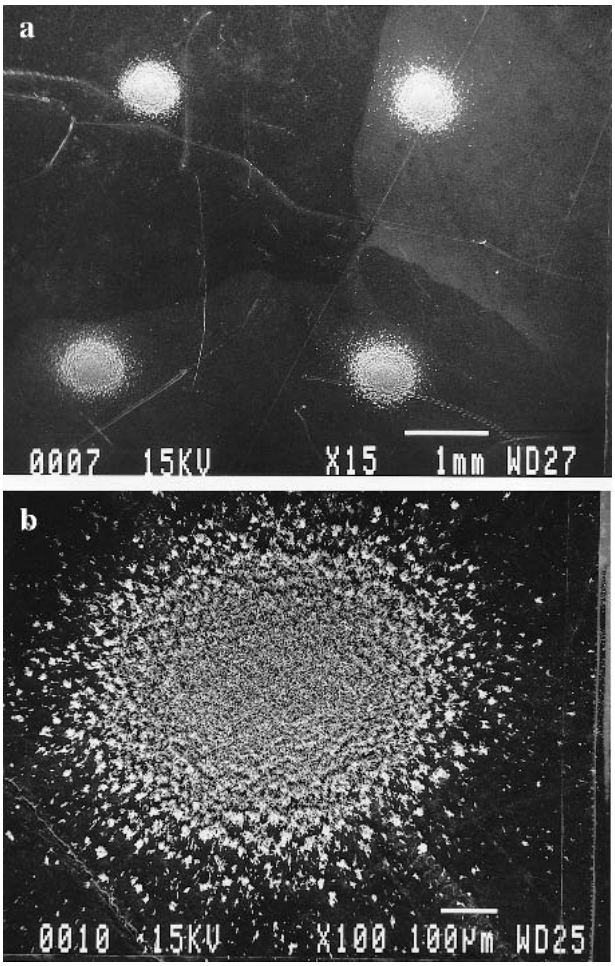

Fig. 4. Scanning electron micrograph of discrete powder deposits containing AS particles (2.1 to 3.3 μm)(aluminum contact surface)(a) low magnification and (b) high magnification.

Thus, while not replicating exact airflow conditions within DPI devices, this proved to be a reproducible technique to deposit drug particles by impaction from an aerosol cloud, as powder heaps/aggregates. The method appeared to be more relevant than currently used techniques to distribute micronized drug particles onto inhaler surfaces. Moreover, the detachment of powder heaps from DPI surfaces is more likely to significantly affect the results for delivered doses and fine particle doses than the detachment of single particles.

Characterization of Adhesion and Autohesion

Figure 5 shows the data for percent detachment of AS from polyacetal and aluminum contact surfaces and BDP from polyacetal surfaces. Plots of percent retention, R, vs. force acting on each deposit, F, were generated after first calculating force as the product of the average mass per deposit (total drug recovered from disc and collection chamber / number of deposits per disc) and RCF. The solid curves in Fig. 5 are best fits using least mean square nonlinear regression analysis of the unweighted data (Scientist, Micromath Scientific Software, Salt Lake City, Utah). Data for R vs. F was fitted to equation 1

$$\text{For } F < F_{yield},\ R = R_0$$

$$\text{For } F \geq F_{yield},\ R = (R_0 - R_{inf})e^{-a(F - Fyield)} + R_{inf} \quad (1)$$

where F_{yield} is the minimum force required to cause drug detachment, a is a system dependent constant with units of μN^{-1} and dimensions equivalent to reciprocal force, and R_o and R_{inf} refer to the value of R at zero and infinite force, respectively [Numerous functions were reviewed for the purpose of fitting this data, however, most of these had too many parameters to provide unambiguous best estimates of the critical variables. Equation 1 was selected from a number of possibilities to enable best statistical estimates to be obtained by nonlinear regression analysis for the terms F_{yield}, R_{inf} and a]. During data fitting, values for R_{inf}, a and F_{yield} were allowed to float while R_o was fixed at 100%. The results of data fitting are presented in Table II. Values for $r^2 \geq 0.897$ in all cases indicated that the model was appropriate.

Drug Detachment from Aluminum and Polyacetal Disks

Figures 5a and 5b showed that for detachment of AS to occur, the centrifugal force must be increased to exceed a certain yield point, after which, a small increase in force caused detachment of the bulk of the powder as one large aggregated mass (Fig. 6b). Figure 6c shows that minimal drug was retained on the surface in the center of the heap and that this surface ("the detachment zone", in which the adhesive bond between drug and surface cleaved more readily than that between drug and drug) was generally cleared of drug following application of forces mildly exceeding the yield force value. Detachment of 2.1–3.3μm AS from polyacetal (Fig. 5b) followed the same mechanism described above, i.e. detachment occurred as one large aggregated mass of drug powder. Data points representing 50% detachment however, did not reflect detachment of half of each impacted heap; rather this indicated that on a single disk, 5 out of the 10

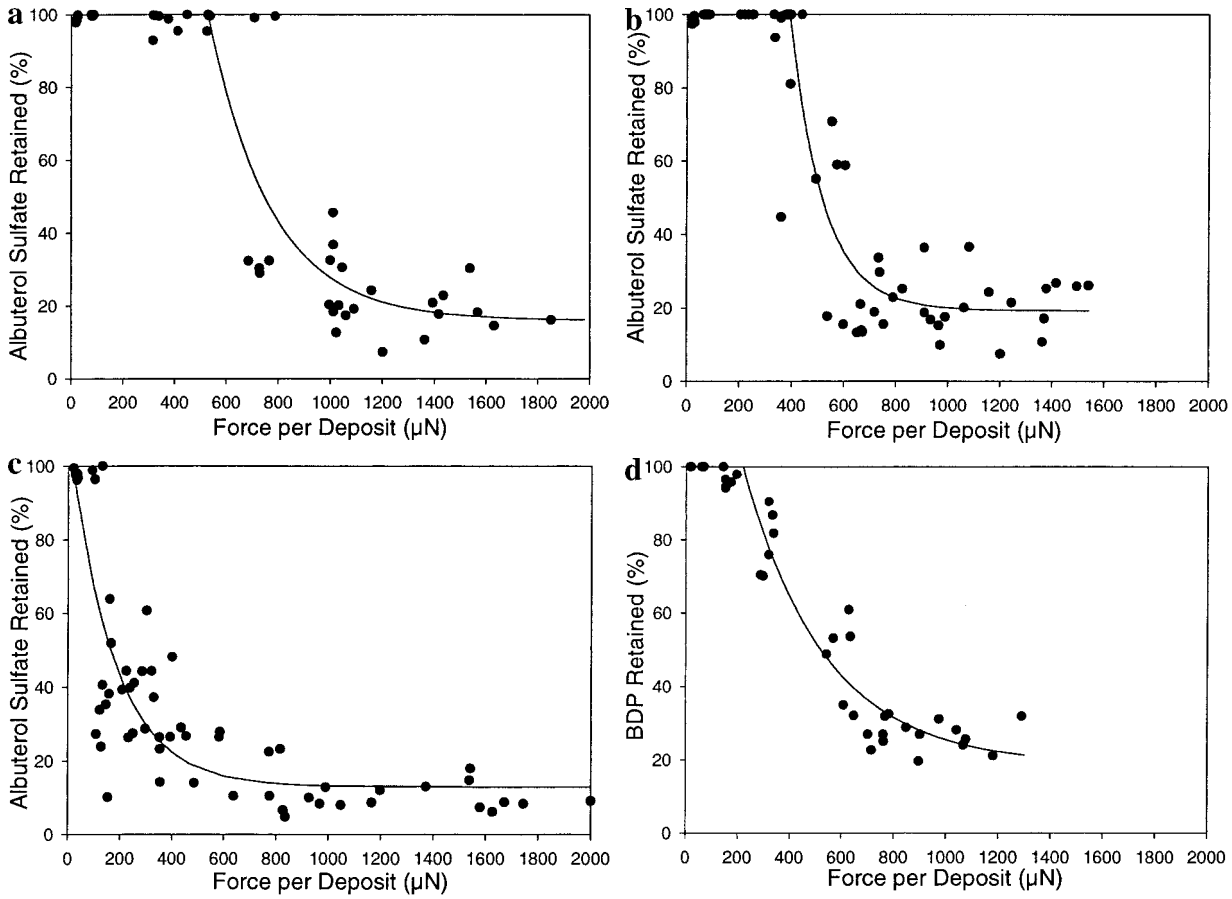

Fig. 5. Adhesion profiles for aerosolized (a) AS 2.1–3.3 μm on aluminum, (b) AS 2.1–3.3μm on polyacetal, (c) AS 4.7–5.8 μm on polyacetal and (d) BDP 2.1–3.3μm on polyacetal.

deposits detached at this force value (Fig. 6a). However, for 2.1–3.3 μm AS, the effective drug heap adhesion force was significantly greater for aluminum (F_{yield}, 532 μN) than polyacetal (F_{yield}, 383 μN) surfaces, possibly because aerosolized albuterol sulfate particles are non-conductive but highly charged, following aerosolization by this method (16), and image charges of opposite sign are readily induced in a conductive material like aluminum. Increasing values of F produced some additional detachment but approximately 20% of the mass [R_{inf}] was virtually impossible to detach in spite of almost tripling the RCF. That was probably because once about 80% of each heap had detached, the true operational force for further powder detachment was reduced to some 20% of that shown on the abscissa (so that all tested forces became less than the yield force in this case). This implied that the true force of adhesion for this drug size fraction, following its deposition by impaction, was given by the product of the apparent yield force in each figure and the fraction of the drug heap cleaving from the surface [true adhesion force = F_{yield} (R_o–R_{inf}) / 100]; since the value of F_{yield} itself was an overestimate in each case. Table II shows estimates of this "true adhesive force' in the case of each drug material and surface studies using CPD. This true adhesion force may provide a more relevant parameter when making inhaler design decisions although, it must be recognized that micronized drug detachment from DPI surfaces may also be induced by factors such as scouring (by larger lactose particles or drug aggregates) and air turbulence.

Table II. Best Estimates of the Variables F_{yield} and R_{inf} (Eq. 1) following Nonlinear Regression Analysis of R vs. F Data Shown in Fig. 5

Drug material	Size fraction (μm)	Contact surface	F_{yield} (μN) [SD]	R_{inf} (%) [SD]	True adhesion force (μN)[a]	Goodness of fit (r^2)
AS	2.1–3.3	Aluminum	532 [25.3]	16.1 [5.29]	446	0.969
AS	2.1–3.3	Polyacetal	383 [12.7]	18.6 [3.64]	312	0.972
AS	4.7–5.8	Polyacetal	18.0 [13.8]	12.5 [3.26]	NA[B]	0.897
BDP	2.1–3.3	Polyacetal	220 [24.8]	18.7 [5.47]	179	0.991

[a] F_{yield} (R_o – R_{inf})/100.
[b] Heap fracture may occur as several small masses therefore, a True Adhesion Force was not calculated.
AS — albuterol sulfate and, BDP — beclomethasone dipropionate.

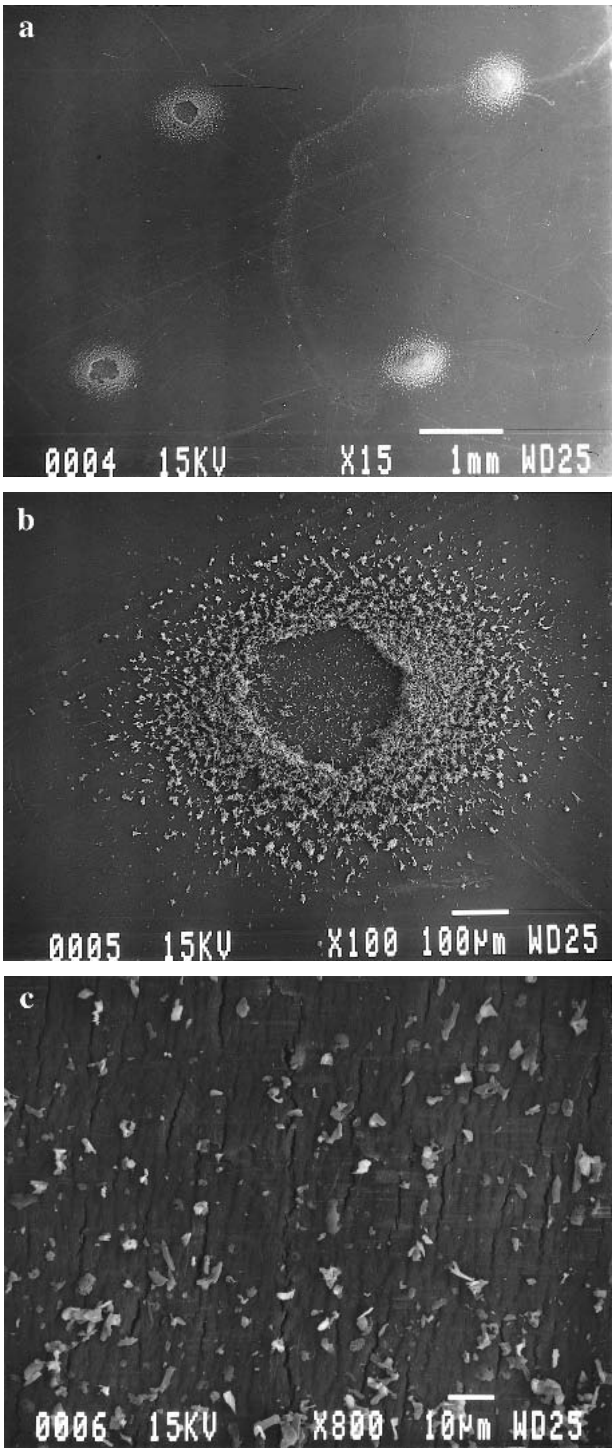

Fig. 6. Scanning electron micrograph as AS 2.1–3.3 μm retained on polyacetal following CPD at RCF = 47 200 g. At (a) low, (b) medium and (c) high magnification. The boxed region is shown in detail in (c).

Effects of Particle Size and Drug Substance

Micronized BDP in the same 2.1–3.3 μm size fraction was less adherent to polyacetal than AS over the range of humidities studied (F_{yield} = 220 vs. 383 μN). The detachment pattern for 4.7–5.8 μm AS from polyacetal revealed a detachment yield force very much smaller (~18μN) than the value for its smaller counterpart. This was almost certainly because the uniform deposition of larger particles reduced the particle surface area in contact with the disc surface, thus reducing the operational force of adhesion. Additionally, deposits didn't always detach as one agglomerated mass, i.e., heap fracture was sometimes observed for this size fraction detaching from polyacetal. Therefore, unlike the 2.1–3.3 μm deposits, 50% detachment of 4.7–5.8 μm material may sometimes correspond to detachment of half of an individual heap (Fig. 5c).

Adhesion Literature and the Results of CPD

Adhesion of micronized powders to different surfaces found in inhalers can be studied using CPD. Podczeck (8) evaluated the adhesion properties of single micronized particles of albuterol sulfate sieved onto surfaces and, we will use these results for comparative purposes during this discussion. Importantly, the technique requires that single particles are generated, "pressed-on" to different surfaces [using centrifugal forces presumed to be representative of collisions with inhaler walls (8)], then detached from those surfaces using CPD. Podczek's detachment forces are functions of the mass assigned to each particulate entity and, while we have been unable to reproducibly distribute single particles using the technique, it was possible for us to relate the reported forces (8) to those determined in the present study. This is illustrated below.

CPD-derived detachment forces are directly proportional to the mass detached (F = mass x acceleration). In our case, following deposition of particles from an aerosol stream, and forced detachment of the agglomerated micronized drug (representative of the situation seen in inhalers), far greater forces were required than those reported by Podczeck. For example, Podczeck (8) quotes a median adhesion force for a single albuterol sulfate particle (Feret's diameter = 2.7 μm) on a PVC contact surface of approximately 5 nN, following the application of a "press-on-force" of 3 nN which was used to initially attach particles to the surface. The present study has shown that for similarly sized albuterol sulfate particles (2.1–3.3 μm), deposited onto polyacetal by impaction, forces > 383 μN were required to remove any of the adherent material and some 500 μN were required to remove the bulk of each 1.2 μg heap. Because detachment occurred most frequently as a large agglomerated mass (Figs. 5b and 6b), overall autohesive (cohesive) forces in each agglomerate were stronger than the adhesive forces responsible for attachment of powder heaps to the surface. Thus, it appeared that values for F_{yield} should be dictated by the sum of the adhesive forces between each individual particle and the adhering surface, across the heap. In practice, for the smaller AS particles adhering to polyacetal, agglomerated particles in each heap which were detachable as a mass {1.2 μg x $[(R_0-R_{inf})/ R_0]$; Tables I and Fig. 5} contained about 9.5×10^4 particles (2.7 μm monodisperse spherical particles of unit density were assumed to represent the 2.1–3.3 μm aerodynamic size range) of which about 3.4×10^4 particles (contact surface area of heap in detachment zone/ projected area of one particle), or 36% of the total, were actually in contact with the surface in the detachment zone. Thus, the adhesive force of interest in the present study was dictated by the surface-attractive forces operating between "n" 2.7 μm AS particles and the contact

surface area in the detachment zone = 2.0×10^5 μm^2 (Fig. 6b). Assuming that the particle–surface interactions in each heap were additive, this gave an average attractive force per particle = $[F_{yield} \times (R_o - R_{inf})/ 100$ n], where n is the number of particles in contact with the surface detachment area = 9.2 nN, a value which was remarkably similar to that reported by Podczeck for the same drug's adhesion to PVC.

Applying the same computation technique to the data for BDP in this size range gave an average attractive force per particle = 5.3 nN (polyacetal); AS on aluminum computed to 13.1 nN per particle. It was notable however, that the required detachment force for agglomerated AS in the larger particle size range was much smaller than that for 2.1–3.3 μm material (Fig. 5 and Table II), indicating that the attractive force between the larger particle agglomerates and the surface was much smaller (detachment was much easier). However, a similar data transformation for AS 4.7–5.8 μm was not performed since, if the heap fractured as several small aggregates (of unknown mass), the force acting on the detached material can not be calculated. Provided however, that a reproducible impaction technique is employed to deposit particle agglomerates, comparative values of F_{yield} enable a much more relevant assessment of the likely detachment of different drug substances from surfaces found in powder inhalers.

CONCLUSIONS

Values for drug retention ranging 2–30% for different powder inhalers (25–26) create concerns over inhaler construction and formulation variations that prove difficult to evaluate systematically. Using the standardized CPD technique described in this paper however, comparative effects of particle size and inhaler construction materials on the adhesion of different micronized drug substances can be studied fairly readily. Drugs could be accumulated reproducibly in small size range agglomerates by cascade impaction on different surfaces. For the smaller 2.1–3.3 μm size fraction, forces of autohesion (cohesion) were greater in impacted agglomerates than forces of adhesion between the agglomerate and the surface on which it was formed, causing powder detachment as an agglomerated mass. This was not always the case for the larger 4.7–5.8 μm size fraction where, autohesive and adhesive fracture of the heap (possibly due to less efficient packing of the larger particles/aggregates), caused detachment of several small aggregates.

However, all materials detached with distinctive profiles for percent remaining vs. applied centrifugal force. Each profile showed reproducible values for the minimum force required to initiate drug detachment, F_{yield}, thereby providing a realistic parameter by which to compare the effects of material properties on the adhesion of micronized drug powders to inhaler surfaces.

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