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Investigation of triboelectric charging in dry powder inhalers using electrical low pressure impactor (ELPI^{TM})

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Abstract

Electrostatics and triboelectrification phenomena in dry powder inhalers (DPI) are not well understood, but as shown in this study they may play an important role. Using model formulations of albuterol in lactose, the extent of triboelectrification in the operation of DPI was investigated using an electrical low pressure impactor (ELPI^{TM}). An experimental apparatus was developed, the performance of the ELPI^{TM} was evaluated for consistency and reproducibility, and compared to a conventional inertial impactor. Using a statistical experimental design the effects of lactose type, drug load, capsule fill, capsule material, and inhaler were assessed. DPI formulations appear to be subject to strong triboelectric effects. Charge separation can occur between different size fractions, i.e. different fractions can carry charges of different sign. In particular, lactose type, inhaler, and capsule material have a strong effect on the magnitude and polarity of the charge developed during DPI operation. The study suggests that the polarity of the aerosol can be controlled by choice of lactose type, capsule material, and inhaler, which could be exploited for targeting different lung physiologies.

Keywords: Triboelectrification; Dry powder inhaler (DPI); Electrical low pressure impactor (ELPI^{TM}); Formulation

1. Introduction

Electrostatic attraction between particles is a well-known event. It is of particular importance to small particles which have comparatively large surface areas. For particles smaller than 10 μm in size electrostatic forces can be many times larger than gravitational, fluid-dynamic forces, and other forces acting upon them. The property is exploited by various air-cleaning and aerosol sampling equipment, such as the electrostatic precipitator and the electrical mobility analyzer. While particle charging has been studied in a manufacturing and environmental context, its effects on the delivery of therapeutic aerosols have yet to be fully elucidated.

Dry powder inhalers (DPI) are important delivery devices for respirable medicines (Timsina et al., 1994). As the name suggests, DPI formulations consist of dry blends, typically consisting of micronized drug and larger carrier particles (Telko and Hickey, 2005). Carriers, often lactose monohydrate, reduce drug agglomeration and aid in metering and dispersion. For effective delivery to the peripheral lungs, drug particles need to be ≤5 μm in aerodynamic diameter. Particles in this size range have specific surface areas in the order of several square meters per gram. Since charging is a surface phenomenon, particles in the respirable size range can accommodate large charges. In addition, most drugs and pharmaceutical excipients are organic molecules with high resistivity maintained at low humidities, which makes them prone to electrostatic charging.

Deposition in the lungs occurs by inertial impaction, diffusion, interception, and electrostatic deposition (Gonda, 2004). Computer simulations have indicated that electrostatic deposition dominates in the lower lung regions, particularly the alveoli (Balachandran et al., 1997). The alveolar region is the site of most β-adrenergic receptors (Labiris and Dolovich, 2003) as well as the region from which systemic absorption is most efficient, thus it is an important site for targeting therapeutic aerosols.

Aerosol particles can acquire charge by flame charging, static electrification, diffusion charging, and field charging (Hinds,

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1999). Of these mechanisms, static electrification plays the predominant role during DPI actuation. Static electrification occurs when particles are detached from surfaces or the bulk phase resulting in a separation of charges. In DPIs, this takes the form of surface charging, or triboelectrification. When drug and carrier particles are separated from each other or the surfaces of the dosage form or inhaler, charge can be transferred resulting in a net charge on the particles. Particles experience significant friction during DPI discharge which tends to amplify this effect. The extent to which triboelectrical charging in DPIs occurs, however, has not been investigated from a formulation perspective.

The studies described here evaluate the influence of triboelectrical charging of simple two-component DPI model formulations; magnitude and polarity of resulting currents are measured over time and the effects of lactose type, drug load, capsule fill weight, capsule material, and inhaler type are investigated in the framework of a comprehensive experimental design scheme. The experimental setup makes use of the electric low pressure impactor (ELPI^{TM}), a particle sizing device that detects particles by charge (Keskinen et al., 1992).

The ELPI^{TM} has been used primarily in the analysis of environmental effects in the automotive industry (Holmen and Qu, 2004; Lehmann et al., 2004; Maricq et al., 2002; Sanders et al., 2003) and in industrial hygiene applications (Brouwer et al., 2004; Ferge et al., 2004). Only recently it has been applied to the evaluation of metered dose inhaler electrostatics (Kwok et al., 2005).

A detailed discussion and evaluation of the ELPI^{TM} is available elsewhere (Marjamaki et al., 2000). The ELPI^{TM} is composed of a unipolar corona aerosol charger and a low pressure cascade impactor. Deposition inside the impactor is dependent on particle aerodynamic diameter. Unlike conventional cascade impactors which are disassembled and the stages assayed chemically or gravimetrically after operation, ELPI^{TM}s detect deposited particles by measuring the current resulting from dissipation of the particles' electrical charge. The collected particle fractions can be measured simultaneously on all stages using a multichannel electrometer. Thus, when the ELPI^{TM} is operated with charger turned on, it functions as a near real-time particle sizer. However, when operated with the charger off, particle charge is measured (main focus in this paper). The ELPI^{TM} is a low pressure impactor; operation at reduced absolute pressures (10 kPa on the final stage) allows collection of particles down to a size of 30 nm (with filter stage to 7 nm). (By contrast, the Anderson cascade impactor operates at ambient pressures with a pressure drop of ~5 kPa across the device at flowrates of 30 L/min.)

Studies of medicinal aerosol electrostatics have been attempted before. Electrostatic charge carried by a DPI aerosol cloud has been measured using a grid probe (Murtomaa et al., 2003); however, the particles were rather large and the system was of little pharmaceutical relevance. The effects of particle morphology and crystallinity on triboelectrification of dry powder inhalers have also been studied, but particle deposition was not considered (Murtomaa et al., 2004). Moreover, a Faraday cage was used for the charge measurement, which precluded analysis of different size fractions and charge distribution. Use of the ELPI^{TM} for studying DPI electrostatics allows a more comprehensive investigation of the phenomenon, with accurate determination of magnitude and polarity of charges on particles in the respirable size range over time. Furthermore, since each impactor stage is electrically isolated from the next, charges can be measured across individual stages, allowing size specificity of charging to be evaluated.

2. Materials and methods

2.1. Materials

Lactose monohydrate, Respitose^{TM}, was provided by DMV-Fonterra Excipients. One batch of milled (ML001), and one batch of sieved (SV003) lactose, were used. Milled albuterol sulfate (median particle size 2 μm) was supplied by Chemaco (Beetsterzwaag, NL) from drug manufactured by P.F.C. Italiana S.r.1 (Caronno Pertusella, Italy). Hard gelatin capsules (Capsugel Coni-snap^{TM}, lot 70016321) and carrageenan capsules (Capsugel NPcaps^{TM}, lot 38611), both #3 and transparent, were used in the study.

Two different inhalers were tested; both deliver their doses from capsules, but have otherwise different operational principles. The Rotahaler® (GlaxoSmithKline, RTP, NC) is a low resistance device; the capsule is discharged after separation of the cap from the capsule body. The Inhalator® single capsule inhaler (Boerhinger Ingelheim, Germany) is a high resistance device in which drug is removed from the capsule through punctured holes (Dunbar et al., 1998). Specific device resistance of Inhalator® and Rotahaler® are 0.180 and 0.040 cm H_2O 1/2/(L/min), respectively (Clark and Hollingworth, 1993).

2.2. Blending

Four formulations were manufactured in 5.0 g batch sizes using a method that had previously been validated in the laboratory. Drug and lactose were sieved prior to blending using a #125 mesh to promote deagglomeration. Albuterol was geometrically diluted to concentrations of 0.5% or 1% with lactose, then blended for 2 min in a 60 mL vial using a custom made small-scale planetary mixer operating at 150 rpm.

2.3. Blend uniformity

Content uniformity of the blends was ascertained by withdrawing 5 samples (~10 mg each) from different locations in the powder bed using a 1 mm inner diameter sample thief. Four of the locations were at ~90° to one another, close to the vial wall; the fifth sample was withdrawn from the center. Use of the narrow bore thief allowed lateral sampling of small material quantities representing powder from varying bed heights. The samples were weighed and dissolved in water. UV absorbance of the solutions was assessed at a wavelength of 224.6 nm using a Shimadzu 160U spectrophotometer. Lactose has negligible absorbance at this wavelength.

2.4. Capsule filling

Capsules were hand-filled with 15 ± 1 mg or 30 ± 1 mg of formulation. Actual net fill weight averages were 15.2 ± 0.3 mg and 30.2 ± 0.4 mg. Empty capsule and net-fill weights were determined for each capsule. Each capsule was stored in an individual, labeled container. Since capsules were filled immediately prior to dosing, no capsule was stored for more than 2 h. After dosing each empty capsule was removed from the inhaler and placed back into its weigh boat; empty (post-dosing) capsules were weighted and weight delivered was determined. Actual material delivered averages were 14.6 ± 0.7 mg (15 mg nominal fill weight) and 29.2 ± 1.2 mg (30 mg nominal fill weight). When more than 10% of the fill weight was retained in the capsule (select cases), the recorded ELPI^{TM} data were excluded from the analysis. No significant differences in emitted dose were observed between the different inhalers, formulations, or capsules.

2.5. ELPI^{TM} experimental apparatus

The experimental apparatus was developed to overcome two major obstacles: (1) operation at 30 L/min and (2) pre-separation of agglomerates. (1) The ELPI^{TM} (Dekati Ltd., Tampere, Finland) operates at 30 L/min, but inhalers are typically tested at 60 L/min airflow rates; (2) unlike the Anderson cascade impactor (ACI, ThermoAnderson, Smyrna, GA), the ELPI^{TM} does not have a preseparator capable of removing large quantities of material. However, initial work made clear that failure to remove carrier particles and agglomerates from the aerosol prior to introduction into the ELPI^{TM} could result in flooding of the top stages after a single inhaler actuation. The setup that was devised to address these issues is shown in Fig. 1. The DPI is connected to the mouthpiece and standard USP induction port, which is connected to the ACI pre-separator (loaded with 15 mL water) (cut-off size of 8.6 μm at 60 L/min). A custom-manufactured aluminum part connected the pre-separator and split the 60 L/min stream into two; 40 cm Tygon^{TM} tubing (R3603) was used to connect the two outlets with ELPI^{TM} and ACI, each connected to a vacuum pump operating at 30 L/min. Tygon^{TM} tubing is commonly used in aerosol research; unlike other materials, Tygon^{TM} has negligible electrostatic effects (Liu et al., 1985). Deposition of drug in different parts of the experimental setup was determined; deposition in the custom-made part and tubing accounted for <5% of deposition in the ELPI^{TM} and ACI. To prevent particle bounce ACI collection plates were coated with silicon oil. Coated aluminum foils were used with the ELPI^{TM} stages. The apparatus was leak tested prior to each experiment.

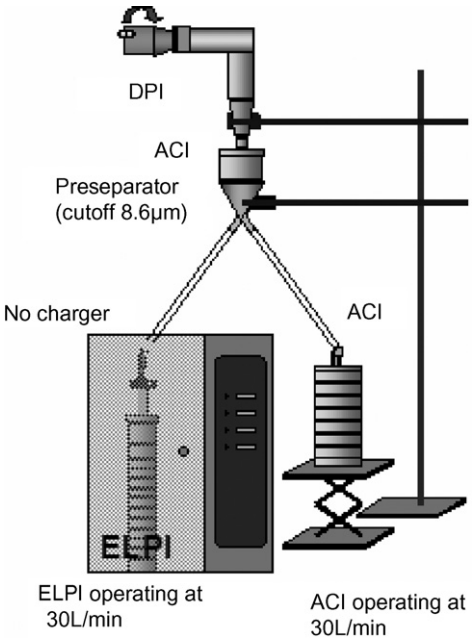

Fig. 1. Experimental set-up.

Both ELPI^{TM} and ACI were used to classify the particles. In accordance with manufacturer recommendations, the ELPI^{TM} was switched on at least 1 h prior to measurement. Inlet air was not filtered and baseline measurements of charge were collected.

2.6. ELPI^{TM} versus ACI comparison

The ELPI^{TM} was operated with corona charger and trap voltages turned off. Using the experimental arrangement described particle size distributions were obtained from ELPI^{TM} and ACI. Capsules (6× 30 mg) containing micronized albuterol, and different formulations (10× 30 mg) were actuated with ELPI^{TM} and ACI operating as described. The equipment was then turned off and disassembled, and the stages assayed gravimetrically (for total deposition) and chemically (for drug deposition).

2.7. ELPI^{TM} output versus gravimetric determination

While it is used here for charge measurements, ELPI^{TM} is primarily used for particle sizing. This function was assessed by comparing the particle size distributions recorded by the device with a gravimetric determination of deposited material. For this purpose the ELPI^{TM} was run with charger, trap, and correction (Virtanen et al., 2001) turned on. Capsules containing different formulations (10× 30 mg) were actuated sequentially and sampled by ELPI^{TM} and ACI. The ELPI^{TM} was then disassembled and the total deposition on each stage was determined gravimetrically. The particle size distributions acquired by the ELPI^{TM} were compared to the particle size distribution obtained from gravimetric data.

2.8. Particle size analysis

After the ELPI^{TM} was validated with respect to the ACI and gravimetric analysis of its stages, it was used to size the ELPI^{TM} fractions (<8.6 μm) from each formulation. These experiments were conducted with the corona charger and trap turned on. Using the Inhalator®, each formulation was dosed in 30 mg-filled capsules in randomized order three times (12 doses). The data collected in each run were used to determine the quanti-

ties and particle size distributions of ELPI™ fractions of the deposited formulations.

2.9. Experimental design

The objective of the experimental design was to quantify the contributions of different formulation variables with respect to magnitude and polarity of triboelectrification during DPI actuation. The experimental design was used to investigate the contribution of several common formulation variables:

(1) *drug load*: 0.5% (w/w) and 1.0% (w/w) albuterol;
(2) *lactose grade*: sieved lactose and milled lactose;
(3) *capsule material*: Carrageenan and Gelatin;
(4) *capsule fill*: 15 mg and 30 mg;
(5) *inhaler type*: Rotahaler® (low resistance) and Inhalator® (high resistance device).

The choice of full-factorial design for the above five variables each at two levels/categories yields $2^5 = 32$ individual data points. Each setting (combination of five factors) was tested at least three times ($n \geq 3$). The experiments were divided into blocks of 16 actuations and the order was randomized. Inhaler and equipment were disassembled and cleaned between blocks.

2.10. Environmental conditions

The extent to which triboelectric charging occurs depends in part on the environmental conditions; triboelectrification is only observed at relative humidities of less than 65% (Hinds, 1999). Hence, conditions must be monitored closely. The data for the experimental design were collected over the course of 2 weeks; the conditions during blending, storage, capsule filling, and actuation were constant at a temperature of $23 \pm 0.5\,^{\circ}C$ and a relative humidity of $39 \pm 1\%$.

2.11. Data analysis

Data were collected by the ELPI™ data acquisition system, ELPI™VI 4.0 (Dekati, Tampere, Finland). Raw data were analyzed using Excel software (Microsoft, Seattle, WA). Each actuation was isolated and charge was integrated over the time the actuation had occurred. This data were fed into statistical software Design-Expert 5 (Stat-Ease Corporation, Minneapolis, MN). Total magnitude and polarity (summed across all stages) were designated as response elements. The influence of each of the five factors was determined.

3. Results and discussion

3.1. Blend uniformity

Blend uniformity was determined by withdrawing five samples (ca. 10 mg each) from each blend and determining the drug content by chemical assay. All blends were within 5% of claim and relative standard deviation of the five samples was <5% in each case.

3.2. ELPI™ versus ACI comparison

Since the ELPI™ is not frequently used for pharmaceutical applications, initial experiments were conducted to assess its ability to classify therapeutic aerosols consistently and in accord with a conventional method, i.e. the ACI. The equipment was validated using micronized albuterol alone and as a component of a 1.0% formulation using two different DPIs. These combinations were chosen to represent scenarios relevant to subsequent studies. After actuations, the equipment was disassembled and stages were weighed or deposition of drug was determined chemically. The details and results of the validation experiments are shown in Table 1. Several capsules were dosed sequentially in each case to ensure sufficient deposition on each stage so discriminating particle size distributions could be obtained. Particle size distributions shown reflect drug deposition only.

The agreement between ELPI™ and ACI was good with almost superimposable particle size distributions for drug (represented by cumulative % fines, since the division of intervals differs) and d_{50} values differing by no more than 0.1 μm. The d_{50} values of approximately 2.0–2.2 μm are consistent with particle size given by the manufacturer. One representative particle size distribution comparison for drug is shown in Fig. 2; 1.0% albuterol in milled lactose produced identical drug particle size distributions in both measurement devices.

3.3. ELPI™ output versus gravimetric determination

The particle sizes acquired by the ELPI™ compared well to the particle size distribution obtained from gravimetric data. This is shown in Fig. 3, where ELPI™ output is compared to the gravimetric determination of its stages. Discrepancy was observed in the lower particle sizes; however, this may be explained by the limited resolution of the gravimetric analysis; deposition on the lower stages (≤0.39 μm) was in the single microgram range, which is the resolution of the analytical balance used. The ELPI™ is thought to be more reliable in this

Table 1
Formulations/device combinations tested for ELPI™ ACI comparison and d_{50} of recovered drug

Formulation	Device	Number of capsules, target fill weight	d_{50}, cumulative undersize
Micronized albuterol	Rotahaler®	5× 6.0 mg capsules	ELPI™: $d_{50} = 2.0$; ACI: $d_{50} = 2.1$
1.0% albuterol in milled lactose	Rotahaler®	10× 30 mg capsules	ELPI™: $d_{50} = 2.1$; ACI: $d_{50} = 2.2$
	Inhalator®	10× 30 mg capsules	ELPI™: $d_{50} = 2.0$; ACI: $d_{50} = 2.1$

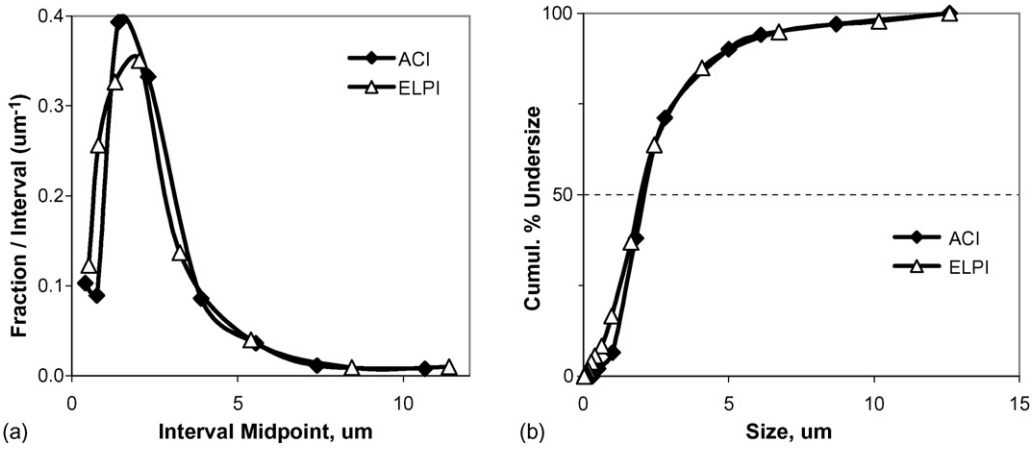

Fig. 2. Particle size distribution of micronized albuterol dosed in 30 mg capsules of 1.0% albuterol in milled lactose via the Inhalator® at 60 L/min (determined chemically): (a) fraction per stage normalized for interval width; (b) cumulative % undersize. White triangles represent data collected with ELPI™, solid diamonds data collected with ACI.

region. Note that chemical analysis was not used, because total deposition (of drug and lactose) was measured.

3.4. Particle size distributions

The ELPI™ was in agreement with the ACI (Section 3.2) and the particle size distributions it generates were consistent with gravimetric analysis of the stages (Section 3.3). Having confidence in its ability to size particles, the ELPI™ was used to determine the particle size distributions of the deposited fines (<8.6 μm) of each of the four formulations. The resulting particle size distributions accounting for both drug and lactose (each the average of three measurements/actuations) are shown in Fig. 4. The particle size distributions are similar, most points are within the standard deviations of the actuations. Standard deviations on the particle size distributions indicate that particle size distribution varies somewhat from one actuation to the next; the largest variability is observed on the lowest stages, where deposition was very low. The amount of material deposited varied for the formulations; the more disperse milled lactose has a larger portion of fine particles compared with sieved lactose (11.8% versus 7.3% below 8.5 μm, internal data), and therefore resulted in higher deposition on all stages. Total relative depositions are given in Table 2. This deposition pattern is considered in subsequent analyses of electrostatics.

3.5. Charge versus particle size

Charge does not appear to be uniformly distributed with respect to particle size or formulation. Fig. 5 shows five actuations of 0.5% albuterol in milled lactose in 30 mg gelatin

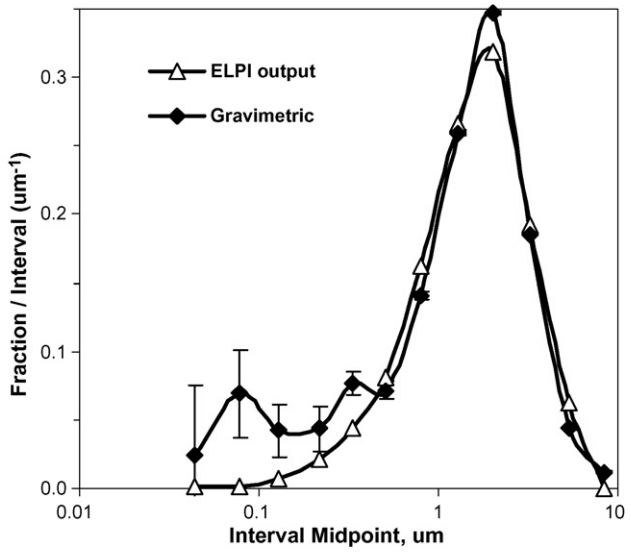

Fig. 3. Particle size distribution of 1.0% albuterol in milled lactose, dosed in 10× 30 mg capsules delivered by Rotahaler® at 60 L/min. Figure shows the size distribution as recorded by ELPI™ (white triangles) and by gravimetric analysis (black diamond). Conformance is good except in lower region, where resolution of gravimetric analysis is highly limited. Error bar gives resolution of analytical balance, ±0.003 mg.

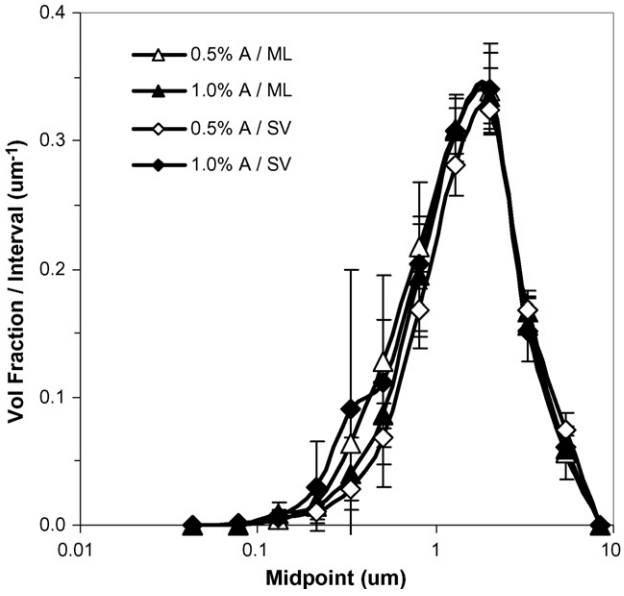

Fig. 4. Particle size distributions of fine particles (<8.6μm) of the four formulations used as recorded by ELPI™ ($n = 3$, mean ± S.D.).

Table 2
Relative deposition of particles <8.6 μm (entire formulation) in ELPI™

Formulation (drug load and lactose)	Amount deposited average of 3× 30 mg capsules
0.5% albuterol/SV lactose	100
1.0% albuterol/SV lactose	102
0.5% albuterol/ML lactose	198
1.0% albuterol/ML lactose	240

Deposits relative to 0.5% A/SV. Total deposit for this formulation was 0.5 mg.

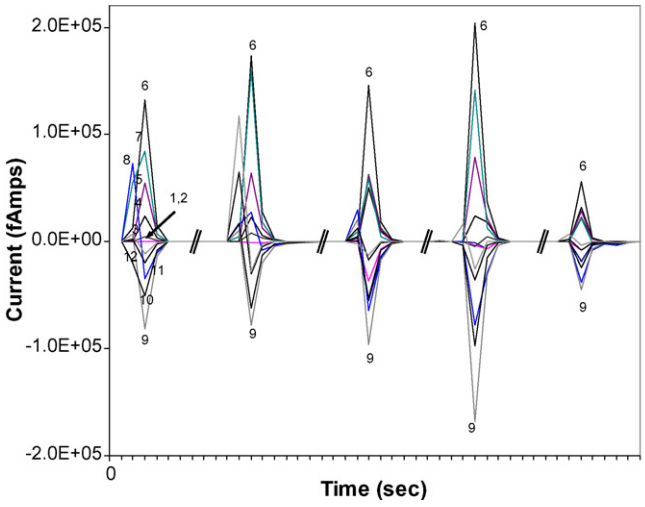

Fig. 5. Five actuations (each performed in different block, i.e. different day, in a different order) of 0.5% albuterol in ML lactose, 30 mg gelatin capsule, dosed via Inhalator®. Double line indicates temporal discontinuity. Capsule emptying and deposition on stages takes about 6 s in each case. The numbers on first actuation indicate the stages on which the electric charge was recorded. While there is some variability, particularly with regards to magnitude, the overall rank/order and polarity is preserved in each trial as shown on the subsequent actuations.

capsules, dosed via Inhalator®. Each actuation was performed in a different experimental block, i.e. on different days (graphs have been merged to facilitate direct comparison). The figure provides insight into formulation delivery by the inhaler. Clearly there is some variability, however there are many common features. The data provide temporal insight into how emission from the device and deposition in the ELPI™ occurs. Capsule emptying and deposition in the ELPI™ takes about 6 s in each case but deposition on the stages does not occur simultaneously. This temporal data might make ELPI™ a useful screening tool to evaluate formulation and device differences in emission; a thorough discussion of this is beyond the scope of this paper. The numbers (shown on first actuation) indicate the stages on which the charge was recorded. While there is variability with regards to magnitude, the overall rank/order and polarity is preserved in each trial. For example, stage 6 (cut-off size 0.39 μm) is highly positive in each actuation, while stage 9 (cut-off size 1.6 μm) delivers a highly negative charge in each actuation. Actuations of the same formulation/capsule/inhaler combination give a consistent charge distribution which differs for other formulation/capsule/inhaler combinations.

Fig. 6 shows the particle size distribution and total charge observed (integrated over the time course of the actuation) during actuations for two formulations (a) 0.5% albuterol in milled lactose, delivered from 15 mg carrageenan capsule and (b) 1.0% albuterol in sieved lactose, delivered from 30 mg gelatin capsules. Each of the charge profiles is the average of five actuations, performed via the Inhalator® on different days. Particle size distributions were determined separately as described in Section 3.4. Note that the charge profiles of the two formulations are very different. Formulation (a) has a large portion of positively charged particles below stage 9 (cut-off size 1.6 μm), but is negatively charged at and above stage 9. This formulation clearly shows that different size particles can carry opposite charges, as observed by Murtomaa et al. (2004). By contrast, the second graph shows an entirely negative charge distribution. In both graphs, and in most cases observed in these experiments, the largest charge (whether positive or negative) was observed at particle size fractions which accounted for the largest portion of particles by surface area, i.e. stages 7 and 8 (cut-off sizes of 0.63 and 0.97 μm, respectively).

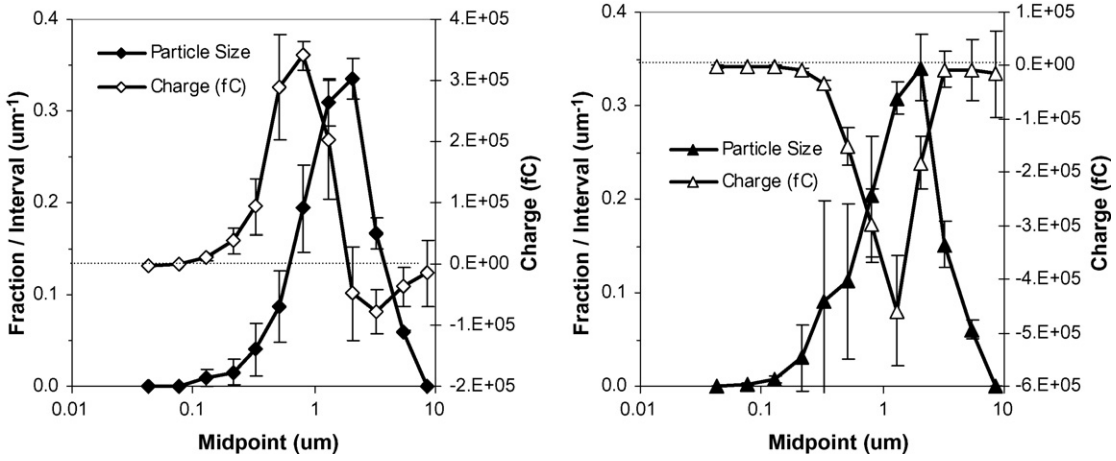

Fig. 6. Particle size distribution ($n = 3$, mean ± S.D.) (solid) and deposited charge per stage (i.e. current flow) ($n = 5 \pm$ S.D.) (white) for (a) 1.0% albuterol in milled lactose, delivered from 15 mg carrageenan capsule and (b) 1.0% albuterol in sieved lactose, delivered from 30 mg gelatin capsules, both delivered via Inhalator®. The dashed line indicates charge neutrality.

3.6. Experimental design analysis

Magnitude and polarity of electrical charge recorded varied widely depending on the combination of formulation, capsule, and inhaler used. To facilitate statistical analysis, the charges were integrated over time and summed across the different stages, and total charges were recorded as response variables. Using the statistical software, the effects of the five factors (inhaler type, drug load, lactose grade, capsule fill, and capsule material) were evaluated with respect to net charge, as well as to magnitude of charge and polarity (−1 was assigned to each actuation that yielded a net negative charge, +1 where the net charge was positive). The important distinction between net charge and charge magnitude is that opposite charges cancel each other when they are summed to obtain net charge, whereas absolute values, i.e. magnitudes, are summed to obtain charge magnitude.

The results of the experimental analysis, with contribution and significance level for each factor are presented in Table 3. The complete data set with net charge and charge magnitude for the 32 different factor combinations is summarized in Table A1 in Appendix A. The average magnitude for all actuations was 0.473 ± 0.337 nC. Note that electrostatic charge had been measured previously using Faraday cage experiments (not shown); the average recorded charges were in the ±0.25 to 2.0 nC/g range for several lactose batches and select drugs. Based on the amount of material recovered on the ELPI™ stages the expected charge captured by the ELPI™ would have been in the 100–1000 fC range. However, the charges recorded were at least four orders of magnitude larger in each case, which strongly suggests that triboelectrification during DPI actuation is the main contributor to overall charge.

As can be observed in Table 3, magnitude and polarity of charge are highly correlated with most factors studied. Despite the inherent variabilities in the data, net charge is highly correlated with all factors except fill weight. There are a number of relevant two-factor interactions. Separation of net charge into absolute magnitude (where negative and positive charges do not cancel each other) and polarity deconvolutes the analysis and allows contributions to be considered separately. Thus, choice of capsule has a large effect on the polarity of the charge but has only a minor (though also statistically significant) effect on the magnitude of the charge. Similarly, fill weight is shown to affect the magnitude (as would be expected) but not the polarity. There are no two-factor interactions that affect polarity, but choice of Inhalator® and milled lactose and/or carrageenan capsules has a synergistic effect on charge magnitude.

The effects of drug load and fill weight on magnitude of charge are predictable since they are tied to the amount of material deposited. The effects of lactose can only partly be explained by mass considerations. Milled lactose has a larger fraction of fine particles, so fraction depositing inside the ELPI™ is greater, but the contribution of lactose exceeds the effects of drug load and fill weight. It is, therefore, likely that the morphology (shape and surface characteristics) of the milled lactose promotes triboelectric charging (compared to sieved lactose). It has been suggested that different morphology could result in change in polarity of charge (Murtomaa et al., 2004) as observed in the present studies. However, the ELPI™ experiments provide additional insight with regards to bipolar charging during single actuations. The effects of inhaler and capsule material cannot be explained by mass considerations alone, since differences in amount of material delivered between the two inhalers were small and there were no differences between the capsules. The increased charge of the Inhalator® is likely tied to the increased friction, since the Inhalator® has a higher pressure drop, which results in a higher rate of shearing and thus more charge separation (Srichana et al., 1998). The effect

Table 3
Calculated effects and standard errors for 2^5 factorial ELPI™ experimental design

Factors (reference level)	Effect on net charge[a] ± standard error	Effect on absolute polarity of charge ± standard error	Effect on charge magnitude[b] ± standard error
Main effects			
Inhaler (Inhalator®)	+0.074 ± 0.025 nC $p = 0.0032$	+0.28 ± 0.064*	+0.246 ± 0.029 nC*
Drug load (1.0%)	−0.049 ± 0.021 nC $p = 0.022$	No effect	+0.124 ± 0.026 nC*
Lactose (milled)	+0.234 ± 0.022 nC*	+0.65 ± 0.055*	+0.143 ± 0.026 nC*
Fill weight (30 mg)	+0.0055 ± 0.021 (no effect)	No effect	+0.134 ± 0.026 nC*
Capsule (carrageenan)	+0.143 ± 0.034 nC*	+0.29 ± 0.055*	+0.081 ± 0.025 nC $p = 0.0017$
Two-factor interactions			
Inhaler × drug load (Inhalator® × 1.0%)	No effect	−0.15 ± 0.057 $p = 0.0116$	+0.098 ± 0.026 nC $p = 0.0003$
Inhaler × lactose (Inhalator® × milled lactose)	+0.178 ± 0.022 nC*	No effect	+0.110 ± 0.026 nC*
Inhaler × fill weight (Inhalator® × 30 mg)	No effect	No effect	+0.082 ± 0.026 nC $p = 0.0021$
Inhaler × capsule (Inhalator® × carrageenan)	+0.094 ± 0.022 nC*	No effect	No effect
Drug Load × lactose (1.0% × milled lactose)	+0.142 ± 0.021 nC*	No effect	No effect
Lactose × fill weight (milled lactose × 30 mg)	+0.117 ± 0.021 nC*	No effect	No effect
Lactose × capsule (milled × carrageenan)	+0.089 ± 0.021 nC*	+0.10 ± 0.055 $p = 0.0634$	+0.149 ± 0.025 nC*
Three-factor and higher interactions	Insignificant		

[a] Net charge refers to the currents summed across stages and integrated over time.
[b] Charge magnitude refers to the absolute values of the currents summed across stages and integrated over time.
* $p < 0.0001$.

of capsule material is perhaps more surprising. Use of capsules made of carrageenan, a carbohydrate polymer, results in higher triboelectric charging than use of gelatin (protein) capsules.

The effects on magnitude of charge are difficult to interpret unequivocally, since they are tied in part to mass deposited inside the ELPI^{TM}, which is variable and was not determined for each individual actuation. The effects on absolute polarity are easier to interpret as they are consistent and independent of mass. Use of the Inhalator®, milled lactose, and/or carrageenan increased the formulation's propensity to acquire a positive charge, while Rotahaler®, sieved lactose, and/or gelatin led to negative charging. These effects are statistically highly significant, and these properties could be exploited for delivery purposes. Several studies have implicated electrical charge in lung deposition and have suggested exploiting charge for enhanced delivery (Bailey, 1997; Bailey et al., 1998; Hashish et al., 1994; Wilson, 1947). The results of this study suggest that polarity can be exploited for delivery purposes as well, since it can be controlled quite well and quite easily. Of course there are limitations to the approach. The current study considers only two devices that use single dose capsules to deliver drug, whereas blister packs and reservoirs are more commonly used. Also, storage effects are not considered, but would be expected to play a role.

This paper considers electrical charges of particles in the <8.6 μm range. Note that charged particles can remain in the inhaler and thus result in poor delivery from the device. Only particles that have been emitted from the device, have separated successfully from the carrier particles, and have cleared the preseparator, i.e. particles smaller than 8.6 μm in aerodynamic size (cut-off size of ACI preseparator) are recorded. Despite the fact that these particles account only for a small fraction of the total, the results can help predict situations (e.g. formulation, device) where electrostatics may either be a design advantage or limitation.

4. Conclusions

Triboelectric charging during DPI actuation was quantitatively assessed using an ELPI^{TM}. DPI actuation gives rise to significant triboelectric charging, which is orders of magnitude larger than the charge predicted from Faraday cage experiments. The charge magnitude and polarity of fine particles deposited in the ELPI^{TM} was measured and correlated with various formulation variables. Choice of lactose grade, inhaler device, and capsule material have a strong effect on both magnitude and polarity of triboelectrification. These properties could be exploited for therapeutic purposes. The ELPI^{TM} is a device that is not regularly used in pharmaceutical aerosol work. The study has assessed the ELPI^{TM} and validated its measurements against chemical and gravimetric analysis of its stages, and against the more commonly used Anderson cascade impactor. A potentially valuable attribute of the ELPI^{TM} is its ability to provide temporal deposition data across the stages; while not analyzed and discussed thoroughly in the context of this study, this data could help evaluate device and formulation emission and deposition characteristics from a temporal perspective.

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Appendix A

See Table A1 .

Table A1
Results of experimental design studies: net charge and charge magnitude, average value ($n \geq 3$) ± standard error

Lactose	Drug load (%)	Inhaler	Capsule fill (mg)	Capsule	Net charge (nC) (rank order)[a]	Charge magnitude (nC) (rank order)[b]
Milled	0.50	Inhalator®	30	Gelatin	0.161 ± 0.195 (7)	0.726 ± 0.259 (6)
Milled	0.50	Inhalator®	30	Carrageenan	0.809 ± 0.248 (2)	1.227 ± 0.331 (3)
Milled	0.50	Inhalator®	15	Gelatin	0.079 ± 0.057 (9)	0.417 ± 0.183 (9)
Milled	0.50	Inhalator®	15	Carrageenan	0.351 ± 0.178 (4)	0.607 ± 0.233 (8)
Milled	0.50	Rotahaler®	30	Gelatin	−0.076 ± 0.092 (19)	0.241 ± 0.139 (17)
Milled	0.50	Rotahaler®	30	Carrageenan	0.073 ± 0.075 (10)	0.325 ± 0.087 (13)
Milled	0.50	Rotahaler®	15	Gelatin	−0.031 ± 0.016 (16)	0.117 ± 0.075 (26)
Milled	0.50	Rotahaler®	15	Carrageenan	0.021 ± 0.052 (12)	0.151 ± 0.117 (21)
Milled	1.00	Inhalator®	30	Gelatin	0.351 ± 0.348 (5)	0.737 ± 0.303 (5)
Milled	1.0	Inhalator®	30	Carrageenan	1.403 ± 0.305 (1)	2.002 ± 0.532 (1)
Milled	1.0	Inhalator®	15	Gelatin	−0.092 ± 0.169 (21)	0.368 ± 0.059 (11)
Milled	1.0	Inhalator®	15	Carrageenan	0.797 ± 0.107 (3)	1.218 ± 0.192 (4)
Milled	1.0	Rotahaler®	30	Gelatin	−0.121 ± 0.050 (24)	0.254 ± 0.035 (14)
Milled	1.0	Rotahaler®	30	Carrageenan	0.176 ± 0.047 (6)	0.250 ± 0.106 (15)
Milled	1.0	Rotahaler®	15	Gelatin	−0.006 ± 0.058 (14)	0.122 ± 0.071 (25)
Milled	1.0	Rotahaler®	15	Carrageenan	0.129 ± 0.019 (8)	0.209 ± 0.111 (20)

Table A1 (*Continued*)

Lactose	Drug load (%)	Inhaler	Capsule fill (mg)	Capsule	Net charge (nC) (rank order)[a]	Charge magnitude (nC) (rank order)[b]
Sieved	0.50	Inhalator®	30	Gelatin	−0.186 ± 0.156 (26)	0.236 ± 0.174 (18)
Sieved	0.50	Inhalator®	30	Carrageenan	0.025 ± 0.062 (11)	0.096 ± 0.042 (27)
Sieved	0.50	Inhalator®	15	Gelatin	−0.113 ± 0.080 (23)	0.144 ± 0.065 (22)
Sieved	0.50	Inhalator®	15	Carrageenan	0.016 ± 0.060 (13)	0.062 ± 0.030 (30)
Sieved	0.50	Rotahaler®	30	Gelatin	−0.106 ± 0.024 (22)	0.131 ± 0.007 (24)
Sieved	0.50	Rotahaler®	30	Carrageenan	−0.067 ± 0.013 (18)	0.074 ± 0.010 (29)
Sieved	0.50	Rotahaler®	15	Gelatin	−0.049 ± 0.025 (17)	0.051 ± 0.026 (31)
Sieved	0.50	Rotahaler®	15	Carrageenan	−0.029 ± 0.013 (15)	0.042 ± 0.009 (32)
Sieved	1.0	Inhalator®	30	Gelatin	−1.170 ± 0.228 (32)	1.265 ± 0.263 (2)
Sieved	1.0	Inhalator®	30	Carrageenan	−0.653 ± 0.373 (31)	0.725 ± 0.359 (7)
Sieved	1.0	Inhalator®	15	Gelatin	−0.356 ± 0.117 (30)	0.379 ± 0.110 (10)
Sieved	1.0	Inhalator®	15	Carrageenan	−0.294 ± 0.139 (29)	0.363 ± 0.197 (12)
Sieved	1.0	Rotahaler®	30	Gelatin	−0.220 ± 0.070 (28)	0.243 ± 0.060 (16)
Sieved	1.0	Rotahaler®	30	Carrageenan	−0.211 ± 0.031 (27)	0.218 ± 0.035 (19)
Sieved	1.0	Rotahaler®	15	Gelatin	−0.132 ± 0.021 (25)	0.141 ± 0.025 (23)
Sieved	1.0	Rotahaler®	15	Carrageenan	−0.082 ± 0.056 (20)	0.090 ± 0.048 (28)

[a] Determined by addition of all charges across the stages; starts with most positive charge.
[b] Determined by addition of absolute value of all charges across the stages; starts with largest charge.

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