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Research Article

Aerosol Electrostatics I: Properties of Fine Powders Before and After Aerosolization by Dry Powder Inhalers

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Purpose. To evaluate the dependence of fine particle dose charge (FPD charge) generated from powder inhalers on physico-chemical properties of the inhalation powder, inhaler type, deaggregation mechanism, dose number and/or retained powder.

Methods. Electrostatic charges were determined on micronized powders and aerosolized fine particle doses withdrawn from two, high efficiency, multidose powder inhalers, Turbohaler™ and prototype Dryhaler™. The behavior of terbutaline sulfate, budesonide, albuterol (sulfate and base), beclomethasone dipropionate and lactose was assessed before and after aerosolization.

Results. Both inhalers conferred triboelectric FPD charges during aerosolization in the range −400 pC through +200 pC. Specific charges (charge/unit mass) on the fine particle doses of budesonide from Dryhaler were significantly less than those from Turbohaler ($p < 0.01$). Electrostatic charges on the potentially respirable cloud of terbutaline sulfate generated by Bricanyl Turbohaler were positive and/or negative and unpredictable. With Pulmicort Turbohaler, FPD charges on budesonide were always positive. Dryhaler was used to determine the chemical dependence of fine particle triboelectrification during the aerosolization of pure materials. A triboelectric series was constructed from the Dryhaler results ranking the powders from positive to negative as budesonide > lactose > albuterol sulfate > terbutaline sulfate ≥ albuterol ≥ beclomethasone dipropionate.

Conclusions. While there was no evidence of FPD charge dependence upon dose number with either inhaler, FPD charges were dependent upon the powder under investigation, as well as the construction and deaggregation mechanism of the inhaler. The specific charge on the fine particle dose of budesonide from Turbohaler corresponded to approximately 200 electronic charges per particle, a value which is known to affect both total and regional aerosol deposition in the human lung. Electrostatic charge effects may be important determinants of aerosol behavior and should not be neglected.

KEY WORDS: dry powder inhaler; aerosol; electrostatic charge; aerosolization; deposition.

INTRODUCTION

Most models of aerosol deposition in the human lung are based on data collected following inhalation of "charge neutralized" aerosol particles (1). As a precaution following their generation, and prior to characterization and inhalation, aerosols in those and other studies were brought into Boltzmann equilibrium by exposure to an ionization source such as ^{85}Kr (2). Thus, many common assumptions concerning the deposition of pharmaceutical aerosols in the lung may require, for their validity, that the aerosols in question are either uncharged or charged negligibly, with respect to studies which have shown dramatic deposition changes as a function of aerosol charge (3–6). Elsewhere, in the pharmaceutical aerosol literature, compelling empirical evidence has been collected showing the importance of the static charge on plastic aerosol reservoir devices, to aerosol drug retention within those devices (7–10). Notably, the importance of aerosol charge upon this retention has not been studied, even though the various processes of aerosolization are known to induce static charge by triboelectrification (frictional contact) on individual aerosol particles or droplets (11).

In this paper, to begin to assess the dependence of aerosol charge on inhaler type and powder deaggregation mechanism, we determined the charge induced on the fine particle fractions of aerosols emitted by two high efficiency, multidose dry powder inhalers. Most drug crystals are organic crystals which behave as insulators under ambient conditions. Because the accumulation and decay of static charge on insulators is material dependent (12), and processes like powder milling, mixing, pouring and metering also induce charges by triboelectrification, we quantified the charge on several micronized drug powders as a function of dosage number before and after aerosolization *in-vitro*. The electrostatic behavior of processed (13), pure micronized terbutaline sulfate and budesonide in commercially obtained Bricanyl and Pulmicort Turbohalers™ was compared to that in two prototype Dryhalers™. Prototype

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Dryhalers were also used to study the behavior of several other micronized compounds.

MATERIALS AND METHODS

Bricanyl and Pulmicort 100 Turbohalers (Astra Draco, Lund, Sweden), containing processed, micronized terbutaline sulphate 500 micrograms, and budesonide 100 micrograms respectively, were obtained commercially as Lot Numbers UL 538 and UL 210. Both batches were tested prior to their expiry dates. Samples of the pure, micronized drug substances terbutaline sulfate (BN 772) and budesonide (BN 527) were donated by Astra Draco. Micronized albuterol base, albuterol sulfate and beclomethasone dipropionate were obtained from Leiras (Batch # 73263501, Turku, Finland), Rhone Poulenc Rorer (Batch # 910119, Dagenham, UK) and Farmabios s.r.l. (Batch # 0029420, Gropello, Cairoli (PV), Italy), respectively. Crystalline α-lactose monohydrate USP was obtained as Microtose (Batch 464, Meggle, Wasserburg, Germany). Commercially blended albuterol sulfate/lactose was purchased as Ventolin Rotacaps™ 400 micrograms (Batch # 51602NC, Allen & Hanbury's, Ware, UK), and tested prior to its expiry date. Powders were stored in well sealed containers over Drierite (W.A. Hammond, Drierite Company, Xenia, OH) at room temperature. Ventolin Rotacaps and Turbohalers were stored at room temperature in accord with their patient instruction leaflets. The electrostatic behavior of these unformulated micronized drug substances, lactose and albuterol blend was reviewed following dispersion by two injection molded prototype Dryhaler devices donated by Dura Pharmaceuticals, San Diego, CA, U.S.A.(14). Turbohaler and Dryhaler were constructed of plastic components—specific details are proprietary information.

The electrostatic properties of 10 marketed inhalers (5 Bricanyl, 5 Pulmicort 100) and seven powders dispersed by two separate Dryhaler devices were reviewed using the apparatus shown diagrammatically in Figure 1. Turbohalers were primed according to the manufacturer's instructions, while Dryhalers were loaded with a nominal 10 mg of powder in the aerosol chamber. Both types of inhalers were individually inserted horizontally into the mouthpiece adapter of the aerosol sampling apparatus shown in Figure 1 (a), and actuated by switching power to the vacuum pump (Model #1423, Gast Manufacturing Inc., Benton Harbor, MI) for 20 seconds. The electrical currents induced by the collection of aerosol particles with aerodynamic diameters <5.8 μm from Turbohaler, or 5 μm from Dryhaler were measured as functions of time, following their collection in the aerosol electrometer (Model 3068, TSI Inc., St. Paul, MN), connected to a chart recorder (Servogor 120, BBSRC, RadioSpares, Corby, UK). Turbohaler devices were tested at 45 l min^{-1}, the maximum flow rate possible through the aerosol electrometer. The coarse aerosol fraction from each puff was collected in a coated impaction stage, identical in cut-off characteristics to the Marple-Miller (Model 160, cascade impactor, MSP Corporation, St. Paul, MN, USA) 5 μm aerodynamic diameter cut-off stage. At 45 l min^{-1}, the 50% cut-off diameter was calculated to be 5.8 μm; cut-off diameters conform to theory with respect to flow rate (15). Powders aerosolized from Dryhaler were collected at a flow rate of 30 l min^{-1} via a coated impaction stage identical in cut-off characteristics to the Marple-Miller (Model 150, cascade impactor, MSP Corporation, St. Paul, MN, U.S.A.) 5 μm aerodynamic diameter cut-off stage. All testing and powder handling was performed in a controlled environment with temperatures between 20.5 and 24°C and relative humidities ranging 56.5 to 60.6%.

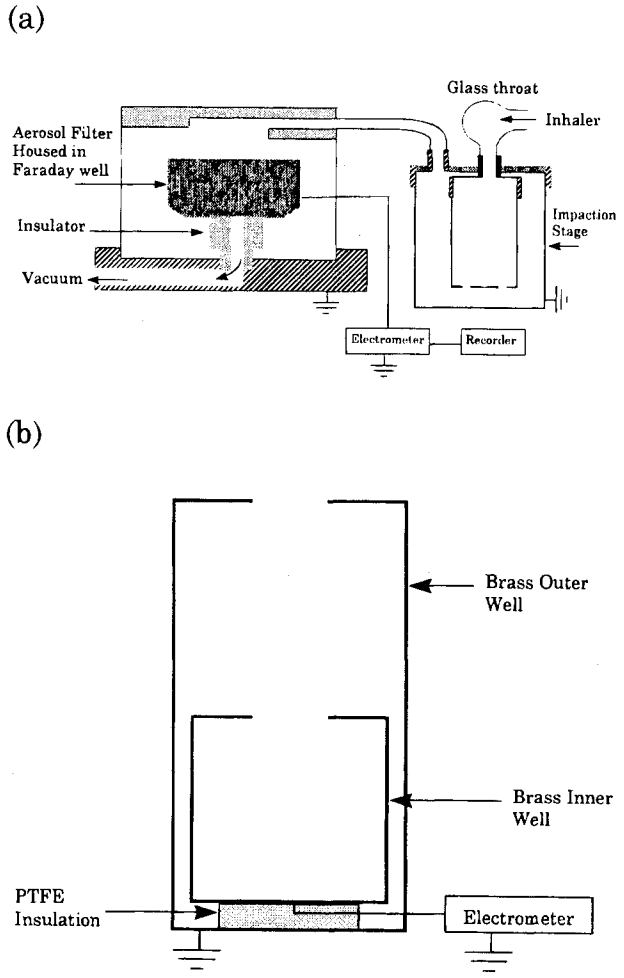

Fig. 1. Diagrammatic representation of (a) Aerosol sampling apparatus for the aerosol electrometer, and (b) Faraday well static charge detector for measurement of specific charges on powders.

Turbohaler Characterization

The electrostatic charges on drug powders held in Turbohaler multidose inhalers were characterized as received. Turbohalers were removed from their original packaging and an 'electrostatic powder history' was constructed for each of 5 separate inhalers containing terbutaline sulfate and budesonide (n = 10) as follows: The doses from actuation numbers 1 through 25 were withdrawn sequentially from each Turbohaler at 45 l min^{-1}, after first coating the receiving cup of the clean, dry impaction stage by spraying with Silicone Release Spray #316 (Dow Corning Corporation, Midland, Michigan, U.S.A.), and evaporating the propellant, to prevent particle re-entrainment (16). Following actuation number 25, the apparatus was disassembled, drug was washed from the impaction stage and glass throat, and assayed as described previously (16,17). A charge sampling probe, in the form of a thin steel needle connected by a co-axial cable to an electrometer (Model 610C, Keithley Instruments, Cleveland, OH), was inserted approxi-

mately 10mm into the spiral channels of the inhaler mouthpiece before the first actuation, and was again inserted immediately after actuation number 25, in order to determine the sign and comparative magnitude of any charge associated with this component, the main site of powder deaggregation and aerosolization in Turbohaler (13). Charges on accumulated powder in Turbohaler devices were not determined (residual powder cannot be easily accessed). The inhaler mouthpiece was then removed and the mean charge was determined on the powder aggregates metered in actuation numbers 26 through 50. This was performed by priming the inhaler, as before, but inverting and tapping the inhaler base to displace each metered actuation into the Faraday well connected to the Keithley 610C electrometer (Figure 1 (b)), prior to repriming and repeating the operation. The mean specific charge (charge per unit mass) on the powder held in the inhaler reservoir was determined by removing the blue plastic plug from its top, and tapping approximately 30 mg of the contents directly into the Faraday well (Figure 1 (b)). The mass of drug displaced into the well during this operation was determined by weight difference. Five separate 'Bricanyl' and 5 'Pulmicort 100' Turbohalers were tested in each case.

Powder Characterization Using the Dryhaler

With the exception of the contents of Ventolin Rotacaps, this investigation was performed on the unformulated pure powders with the aid of two identical injection molded, prototype Dryhaler devices. These devices aerosolize a powder held or delivered into their aerosol chambers by subjecting it to turbulence and shear induced by a high speed rotor; this being actuated by air passage through the chamber, typically at about 30 l min^{-1} (14). The aerosol is simultaneously formed in the chamber and displaced from it in the air passing toward the inhaler mouthpiece (14). Approximately 10 mg of each substance was weighed accurately and introduced into the aerosol chamber prior to connection to, and actuation into the aerosol sampling apparatus (Figure 1 (a)). The receiving cup of the impaction stage was coated, as before (16), and the dose collected following actuation of the Dryhaler at 30 l min^{-1}. The mass delivered as an aerosol (the emitted dose) was determined by inhaler weight difference before and after each actuation. Five sequential doses were loaded and withdrawn from each chamber, cleaned prior to initial loading (washed with solvent and air-dried) but without cleaning between doses ($n = 5 \times 2$ inhalers = 10). As with Turbohaler experiments, this protocol enabled the charge of only the fine particle dose (FPD charge) to be determined in the aerosol electrometer, since the coarse material was collected in the impaction stage. In addition, following dose 5, the Dryhaler was dismantled and the charge sampling probe, connected to the Keithley 610C electrometer, inserted into any adherent powder remaining in the aerosol chamber in an attempt to determine the sign and relative magnitude of any charge associated with this non-aerosolized powder. With the exception of lactose and Ventolin Rotacap blend for which no assays were performed, drug with aerodynamic diameters >5 μm (coarse particle dose collected in the impaction stage) was dissolved and assayed as described previously (16,17). Drug remaining in the Dryhaler was determined gravimetrically. The average fine particle dose per actuation was calculated from the difference between the mean inhaler weight loss and mean coarse particle fraction.

RESULTS AND DISCUSSION

Electrostatic charge measurements were undertaken using the deep Faraday well for bulk powder measurements, and the aerosol electrometer for charge measurements on the fine particle dose of the generated aerosol. The aerosol electrometer contained an absolute filter within a Faraday well of different dimensions and design to that used for specific charge determinations (Figure 1 (b)). Charge measurements in the two systems were shown to be comparable and independent of these design differences. Because of the possibility of further triboelectrification of particles during aerosol passage through the grounded metal impaction stage shown in Figure 1 (a), some experiments were performed with Turbohaler without using the impaction stage. The results of those experiments were consistent only with the discharge of additional charged drug mass into the aerosol electrometer. There were no experimental indications that the aerosol specific charge measurements reported in this paper were a function of this impaction stage.

Emitted and Fine Particle Doses

Nominal, emitted and fine particle doses are summarized for these investigations in Table 1. The method of aerosol capture and charge determination (filtration and retention within the filter of the aerosol electrometer) precluded the analytical determination of the fine particle dose in all cases. With Bricanyl and Pulmicort Turbohalers it was only possible to assay drug collected in the glass throat and impaction stage (Figure 1 (a)). The amounts of coarse aerosol collected per actuation of Turbohaler (Table 1) were consistent with our previous studies of emitted dose from this inhaler and its known deaggregation efficiency (16). When prototype Dryhalers were used to study pure, unformulated, micronized drugs, inhaler emptying was variable. In practice, Dryhaler produced average emitted doses between 45 and 78% of loaded doses. Dryhaler weight changes following actuation were used to determine emitted doses in these cases. Fine particle doses from Dryhaler were determined by difference, following assay of drug collected in the impaction stage. Average deaggregation efficiencies for Dryhaler (fine particle dose/emitted dose) ranged 28–40% and were consistent with literature (14) documenting the high efficiency of this device.

Fine Particle Charge on Aerosols Generated from Turbohaler

Table 2 summarizes the results obtained from Bricanyl and Pulmicort Turbohalers. In addition, typical aerosol current versus time profiles of the different Turbohalers are shown in Figures 2 and 3. The area under each individual aerosol current (pA) vs time (seconds) curve gave charge in picocoulombs (1 coulomb is equivalent to 1 amp sec) and was defined as the fine particle dose charge (FPD charge). Each of these potentially respirable clouds carried net charges of the order of 100 pC. This was true in spite of the fact that the fine particle dose of terbutaline sulfate appeared to be larger than that of budesonide. Estimates of the fine particle dose in these investigations were approximately 0.15 and 0.03 mg for terbutaline sulfate and budesonide, respectively.

For Bricanyl Turbohalers, Figure 2 shows clearly that the charge on the potentially respirable cloud from this inhaler

Table 1. Nominal, Emitted[a] and Fine Particle[b] Doses (Sample Standard Deviation)

Inhaler	Drug	Dose (mg/actuation)				
		Nominal[c]	Loaded[d]	Impaction Stage[e]	Emitted[a]	Fine Particle[b]
Turbohaler	Terbutaline sulfate	0.5	nd	0.201 (0.053)	nd	nd
	Budesonide	0.1	nd	0.029 (0.003)	nd	nd
Dryhaler	Terbutaline sulfate	10.0	10.4 (1.1)	3.46 (0.45)	6.1 (1.7)	2.7 (1.4)
	Budesonide	10.0	9.6 (1.3)	2.94 (0.05)	4.7 (1.2)	1.7 (1.2)
	Albuterol sulfate	10.0	10.9 (1.3)	3.69 (0.01)	5.8 (1.6)	2.1 (1.6)
	Albuterol	10.0	10.0 (1.2)	3.81 (0.30)	6.1 (0.9)	2.3 (0.9)
	BDP	10.0	9.8 (1.1)	2.84 (0.06)	4.4 (1.1)	1.6 (1.1)
	Microtose	10.0	10.2 (1.3)	5.6 (0.00)	8.0 (1.2)	2.4 (1.2)

[a] Change in inhaler weight following actuation; could not be determined accurately for Turbohaler.
[b] Flow rates of 45 and 30 l min^{-1} were used for Turbohaler and Dryhaler aerosol generation respectively. Cut-off diameters of the impaction stage (Figure 1 (a)) were 5.8 μm and 5 μm aerodynamic diameter, respectively. Values are (emitted dose—impaction stage).
[c] Label claim (Turbohaler) and target fill weight (Dryhaler prototype).
[d] nd = not determined. Turbohalers were loaded volumetrically from the powder reservoirs, according to the patient instruction leaflet.
[e] Determined by assay.

could not be predicted. Results for the charge on the fine particle dose could be consistently positive as in inhaler 1, negative as in inhalers 4 and 5, or mixed as in inhalers 2 and 3. There was clear evidence that emitted aerosols contained net positive and negative components which, in some cases were emitted separately with respect to time (time-dependent polarity) (Figure 2: B3). Furthermore, there seemed to be inconclusive correlation between the charge on the fine particle dose and the surface charge on the spiral channels of Turbohaler mouthpiece (compare the trends in aerosol and mouthpiece charge moving from inhaler B1 through B5; Table 2), implying electron transfer upon powder impact with precharged mouthpiece channels.

Table 2. Electrostatic Characteristics of Marketed Bricanyl (B) and Pulmicort 100 (P) Turbohalers

Inhaler[a]	Average charge on mouthpiece (pC)[b]	Charge per actuation (pC):		
		Reservoir[c]	Metered[d]	Aerosol[e]
B1	−1200	−13.6	−20.4 (15.8)	+50.8 (14.9)
B2	−1450	−11.0	−15.4 (7.89)	−1.17 (11.5)
B3	−1700	−8.21	−18.6 (5.57)	−4.23 (14.5)
B4	−1700	−5.14	−14.5 (6.15)	−44.0 (38.5)
B5	−2550	−9.33	−9.20 (2.80)	−43.3 (11.5)
P1	−1950	−0.459	−0.06	+89.2 (30.9)
P2	−2000	−0.503	−0.64	+71.0 (17.8)
P3	−1600	−0.706	−0.89	+77.7 (24.2)
P4	−2500	−0.588	−1.50	+73.8 (6.20)
P5	−1800	−0.653	−0.60	+54.8 (29.0)

[a] B = Bricanyl (terbutaline sulfate 0.5 mg/metered dose); P = Pulmicort (budesonide 0.1 mg/metered dose).
[b] Apparent charge in spiral mouthpiece channels; mean of 2 readings taken before actuation 1 and after actuation 25 (no significant difference between mean readings; n = 5).
[c] Charge per nominal dose (B = 0.5 mg, P = 0.1 mg) of drug sampled from powder reservoir.
[d] Mean charge (Sample SD) of metered doses 26–50 dispensed to Faraday well.
[e] Mean charge (Sample SD) of aerosol fine particle dose (aerodynamic diameter <5.8 μm) for actuations 1–25 collected in aerosol electrometer.

With Pulmicort, electrostatic charges on the fine particle dose were always positive with no evidence of time-dependent polarity charging occurring (Figure 3). Dose metering of budesonide by Turbohaler is known to be less reproducible than that of terbutaline sulfate (17). While individual dose emissions were not monitored in the present investigation, occasional and random doses of budesonide showed multiple electrostatic peaks in the charge profiles (Figure 3: P3). Given the overall negative surface charges in the Turbohaler mouthpiece (Table 2), it was tempting to propose that these pulsatile powder release profiles resulted from sporadic detachment of positively charged powder clumps (due to electrostatic attraction of powder with a high charge per unit mass). In control experiments, in which the aerosol electrometer was dismantled to enable known charges to be added and withdrawn rapidly from it's Faraday well enclosure, the response time of the instrument and chart recorder was shown to be rapid, (one positive through negative full scale deflection in ≤0.25 seconds). Thus, instrument response time was not a determinant of the shape of the profiles shown in Figures 2–4.

For comparative purposes, the charge per actuation on terbutaline sulfate and budesonide are shown in Table 2 for each inhaler. Both compounds are understood to be physically processed following micronization, before their incorporation as chemically pure drug into the Turbohaler powder reservoirs (18). Terbutaline sulfate carried a negative charge within the reservoir of approximately 20 pC/mg. This charge increased in negativity with passage through Turbohaler's metering mechanism to approximately 30 pC/mg (Compare 'reservoir' to 'metered' in Table 2). Similar trends were observed with budesonide. Budesonide carried a very small negative charge within the reservoir, of the order <1 pC/mg, which increased in absolute magnitude to approximately −10 pC/mg, following metering. Following deaggregation and aerosolization within the spiral mouthpiece channels of the inhaler (flow rate = 45 l min^{-1}), triboelectrification of the powder resulted in significantly higher charges. The specific charge for terbutaline sulfate was found to increase approximately 10 fold, while that of budesonide increased some 300 fold when charges were calculated based on the fine particle dose estimates described earlier.

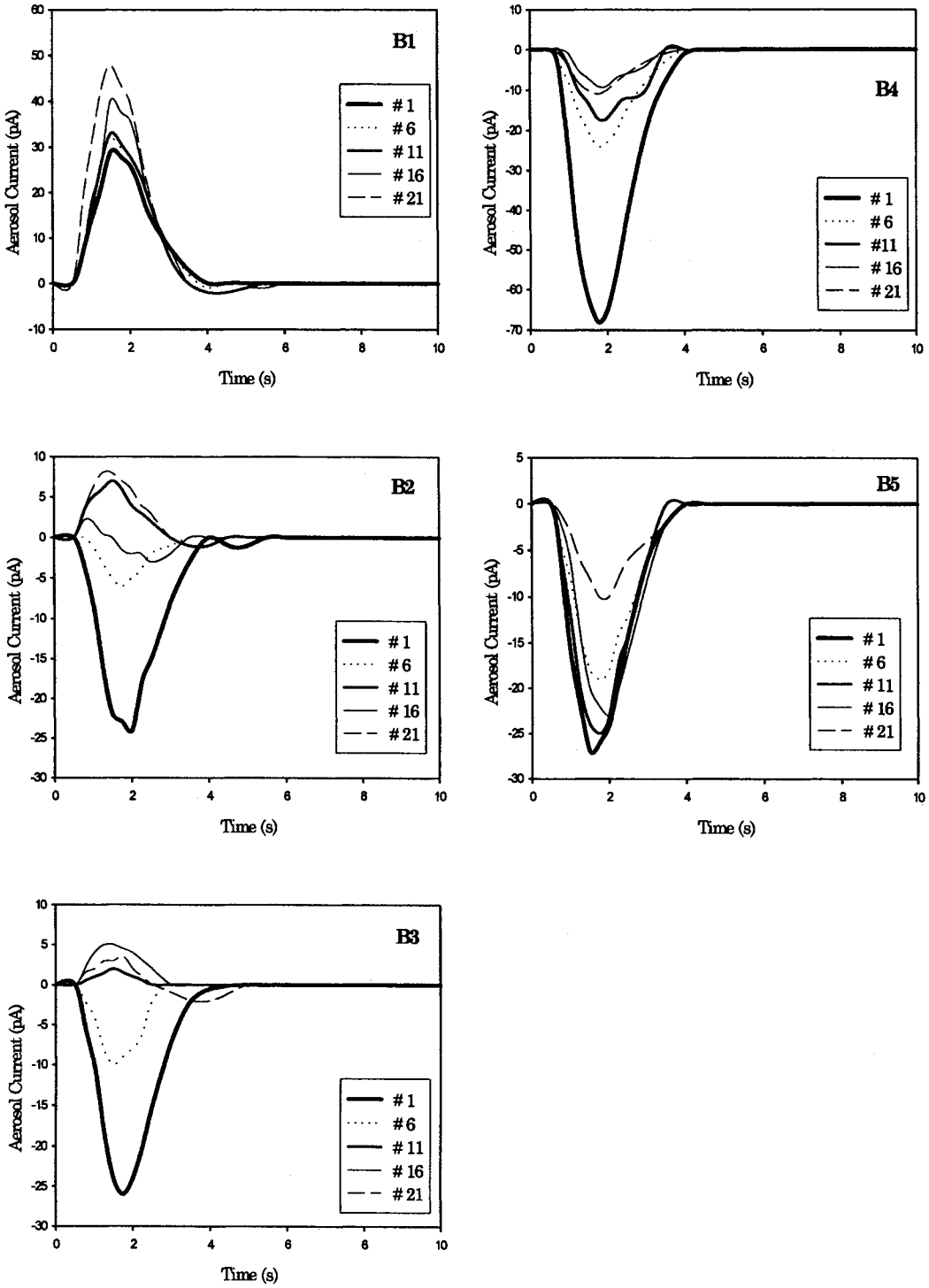

Fig. 2. Typical aerosol current versus time profiles for 5 Bricanyl Turbohalers (B1–B5): Actuations #1, #6, #11, #16, #21 are shown from each sequence of 25 doses.

Charge must be conserved, and as budesonide was shown to develop positive charges, it could be proposed that negative charges be left either on the coarse aggregates collected in the impaction stage, or upon inhaler surfaces. The charge on the drug left in the impaction stage was not determined in this study, and in the case of Pulmicort, there was no evidence of an increasing negative charge on the interior channels of the inhaler mouthpiece. At this stage, however, little is known about the rate of charge decay from these surfaces.

Fine Particle Charge on Aerosols Generated by Dryhaler

Dura Pharmaceutical's Dryhaler was chosen for these investigations because of its reported deaggregation efficiency (14). However, because there were no attempts to formulate the materials which were tested with each of the two prototypes, experiments should be viewed as a determination of the chemical compound dependence of fine particle triboelectrification during the aerosolization of pure compounds.

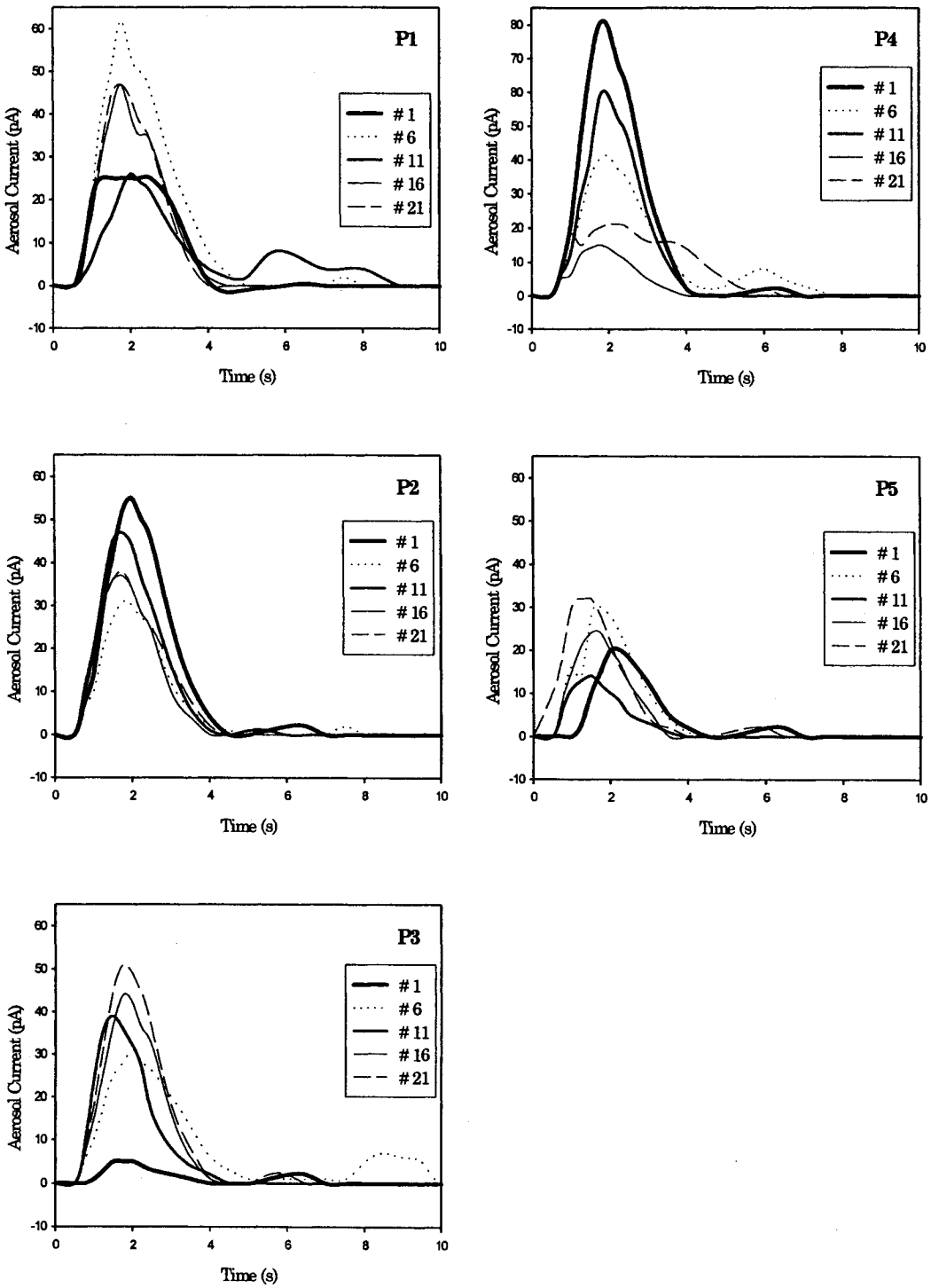

Fig. 3. Typical aerosol current versus time profiles for 5 Pulmicort Turbohalers (P1–P5): Actuations #1, #6, #11, #16, #21 are shown from each sequence of 25 doses.

The results from studies with different pure drugs in Dryhaler are presented in Table 3, and Figure 4. Aerosol current pulses from Dryhaler were similar in shape and magnitude to those from Turbohaler. Like Turbohaler, some compounds always charged positively, some charged negatively, while others displayed clear evidence of time-dependent polarity charging. As expected, the use of unformulated pure compounds resulted in less than ideal inhaler emptying, and a gradual increase in the amount of drug retained by the aerosol chamber of the inhaler over each five dose experiment.

The nominal dose of drug in each of the Dryhaler experiments was 10 mg. Average fine particle doses were about 2 mg in all cases (Table 1), a factor of 10 greater than those from Turbohaler. As a consequence, the fine particle dose charge per unit drug mass was significantly smaller from Dryhaler than Turbohaler, for both terbutaline sulphate and budesonide. It

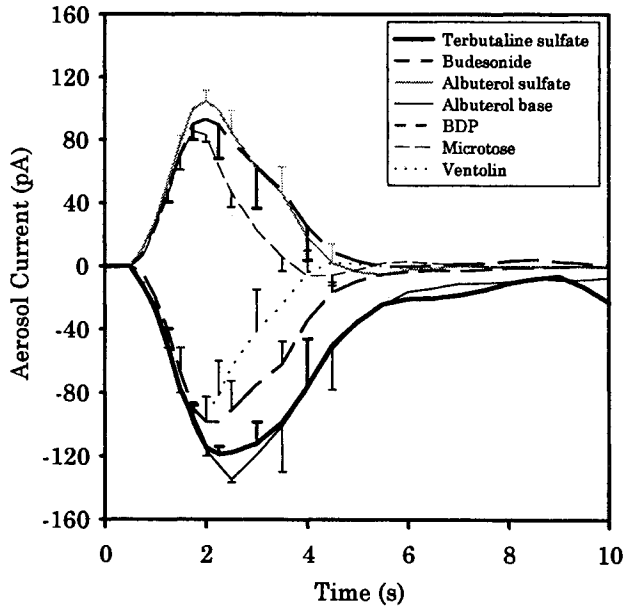

Fig. 4. Mean aerosol current versus time profiles following aerosolization of several micronized powders by a single prototype Dryhaler (n = 5); BDP = beclomethasone dipropionate. Error bars (sample standard deviations) are shown where they do not interfere with the clarity of the profiles.

would appear that the turbulent airstream deaggregation mechanism used by Turbohaler (13) produced greater triboelectrification than the high speed rotor in Dryhaler (14). Furthermore, terbutaline sulphate demonstrated time-dependent polarity charging characteristics following aerosolization from Turbohaler, whereas a consistent net negative charge was observed following its delivery from Dryhaler. Similarly, budesonide developed a consistent net positive charge from Turbohaler, whereas from Dryhaler there was some evidence of time-dependent polarity charging.

Specific charges on all the micronized powders loaded into Dryhaler were small and similar in magnitude to those found in the Turbohaler reservoir. Dryhaler's FPD specific charges (charge per unit drug mass) were much smaller than those from Turbohaler. Even so, its powder deaggregation mechanism still conferred charge onto fine particle doses (Table 3). With the exception of albuterol sulfate, there was an interesting and consistent difference between the charge on the fine particle doses and that on the accumulated powders which remained within Dryhaler following deaggregation of 5 × 10mg doses. It appeared that a charge transfer process had occurred during deaggregation and that the polarity of the retained powder was opposite to that on the primary deaggregated particles.

There was no consistent evidence that FPD charge was dependent upon dose number (Dryhaler, 1–5 doses; Turbohaler, 1–25 doses). Also, because the mass of drug in the fine particle doses from Dryhaler showed no correlation with dose number, there was no reason to believe that time between doses and "charge relaxation" influenced anything other than the FPD charge itself [charge relaxation or charge decay occurs with time in a material and environment—dependent fashion]. Nevertheless, because of the possibility that electrostatic charges on retained powder may influence the emptying and deaggregation of the next dose from multidose inhalers, charge relaxation instructions have been included in the recent compendial update for powder inhalers in Europe (19).

Because the results from Dryhaler (Table 3) were obtained using identical methodology, they enable the construction of a triboelectric series for the FPD of these micronized chemicals. Correcting the results for FPD in column 4 of Table 3 for mass in the fine particle dose, this series ranked the specific charges, from positive to negative, as: budesonide > lactose > albuterol sulfate > terbutaline sulfate ≥ albuterol base ≥ beclomethasone dipropionate [mean specific charges on FPD were +138 (57.6), +85.9 (114), +48.7 (122), −171 (148), −178 (48.1) and −182 (128) pC/mg, respectively]. One further series of experiments was performed with Dryhaler in which the FPD charge on albuterol sulfate was shown to be consistently negative, following loading and aerosolization of 10 mg aliquots of micronized albuterol sulfate—coarse crystalline lactose blend in Ventolin Rotacaps. If the electrostatic behavior of the microtose tested in Dryhaler is considered to be representative of the lactose carrier used in Ventolin Rotacaps, then the FPD charge developed on the micronized drug from the blend could be anticipated from the relative positions of lactose and albuterol sulfate in the triboelectric series above. Because albuterol sulfate was more electronegative than the carrier, we would expect charge transfer on separation to produce a net negative charge on the fine particle dose of the drug. The fact that this occured, producing an opposite net charge to that on albuterol sulfate alone, was consistent with the earlier results of Peart *et al.* (20) for this blend, and demonstrated clearly, the important effect of formulation on FPD charge from powder inhalers.

Net charges on the FPD from Turbohaler and Dryhaler fell in the range 0–800 pC. It is important to recognize that these recorded charges result from the summation of the charges on individual particles. Because separation of any particle pair may result in two particles carrying opposite charges (21), the net charge data shown in this paper may actually underestimate the total charges held by individual particles, in the aerosol cloud. However, even if the aerosols produced in this paper are assumed to be unipolar (a conservative assumption in terms of the likely electrophoretic mobility), the magnitude of the measured charges were frequently quite significant. For exam-

Table 3. Average (n = 10)[a] Electrostatic Characteristics[b] of Micronized Drugs in Two Prototype Dryhalers

	Charge (pC/mg)		Charge per actuation (pC)
Micronized drug	Powder[c]	Retained[d]	<5 μm[e]
Terbutaline sulfate	−8.27 (3.63)	++	−171 (148)
Budesonide	−8.61 (4.91)	−	+138 (57.6)
Albuterol sulfate	−0.96 (0.50)	++	+48.7 (122)
Albuterol	−0.93 (0.75)	+++	−178 (48.1)
Beclomethasone dipropionate	−8.83 (5.55)	++	−184 (128)
Microtose	−0.90 (0.15)	−	+85.9 (114)

[a] 5 actuations from each of 2 prototype Dryhalers.
[b] Values in parentheses are sample standard deviations.
[c] Static charge on bulk powder.
[d] Sign and approximate magnitude of charge on powder remaining in aerosolization chamber after actuation 5.
[e] Measured charge/emitted dose; see Table 1.

ple, in terms of specific charge, the greatest charge per unit mass was seen with budesonide from Turbohaler where, if a 25% fine particle fraction was assumed, the maximum specific charge could have been as high as 4 nC/mg. If the budesonide fine particle aerosol is assumed to be monodisperse, with a mass median diameter (within the fine particle dose) of 2.5 um (16), such a specific charge would correspond to an approximate 200 electronic charges per aerosol drug particle (electronic charge = -1.6×10^{-19} C). According to the literature, this value is certainly sufficient to bring about changes in total and regional lung deposition due to electrostatic attraction between charged aerosol particles and their induced image charges within the lung (3–6). It is also likely that charged particles will adhere readily, following impact with oppositely charged surfaces, and/or electrophoretically migrate short distances toward such surfaces, during a variety of testing and administration circumstances. Indeed, powder inhaler designers who are thinking of adding aerosol holding chambers to their inhalers, would do well to consider the importance of electrostatically—induced powder holdup in those chambers and their associated valves (7–11,22). Aerosol electrostatics is an important but hitherto under-investigated feature of pharmaceutical aerosols. A future manuscript will address the electrostatic charge issues surrounding pressurized metered dose inhaler output and their formulation dependence.

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