

Chapter 1

Introduction

1.1 Aim

This thesis aims to contribute a clearer understanding on the electrostatic properties of pharmaceutical inhalation aerosols, in particular those generated from metered dose inhalers and dry powder inhalers, which are the two most popular forms of medical aerosol delivery. Although the influence of electrostatic forces on particle deposition in the lungs has been theorised, little is known hitherto about the charge characteristics of these particles. The experimental objectives are to measure the charge and mass profiles *in vitro* using a modified electrical low pressure impactor and investigate the effects of various physicochemical factors of the formulation and the environment in which the aerosols are administered on the charging process. The new knowledge gathered would facilitate future *in vitro* and *in vivo* electrostatic research and applications in pharmaceuticals.

Most of the material in this chapter was published in the *Encyclopedia of Pharmaceutical Technology*¹. Some modifications to the text had been added here.

1.2 Natural Charging of Solids

Electrostatic effects on solids have been known for a long time. The ancient Greeks in the six or seventh century BC already observed that amber attracts small objects after rubbing. In fact, the term ‘electricity’ is derived from the Greek word for amber, *ηλεκτρον*² (pronounced as ‘ilektron’).

Charging in the absence of electric fields occurs by contact or friction between two solid surfaces. Contact charging involves the direct contact and subsequent separation of two surfaces without rubbing, whereas frictional charging involves relative movements of two contacting surfaces². However, these two modes of charging are difficult to be discerned independently in physical interactions. Thus the term triboelectrification is conventionally used to describe the overall process, even though the prefix ‘tribo’ literally means rubbing^{2,3}.

Metal-metal contact charging is the most thorough model for solid electrification and serves as the basis for understanding charging of other materials. The valence electron energy state of a metal atom is designated as the Fermi level² (Figure 1.1). The vacuum energy level is that of an electron infinitely far from the atom, and serves as a reference point for energy considerations⁴. The difference between the Fermi level and vacuum energy level equals the work function (Φ), which is unique to a particular metal.

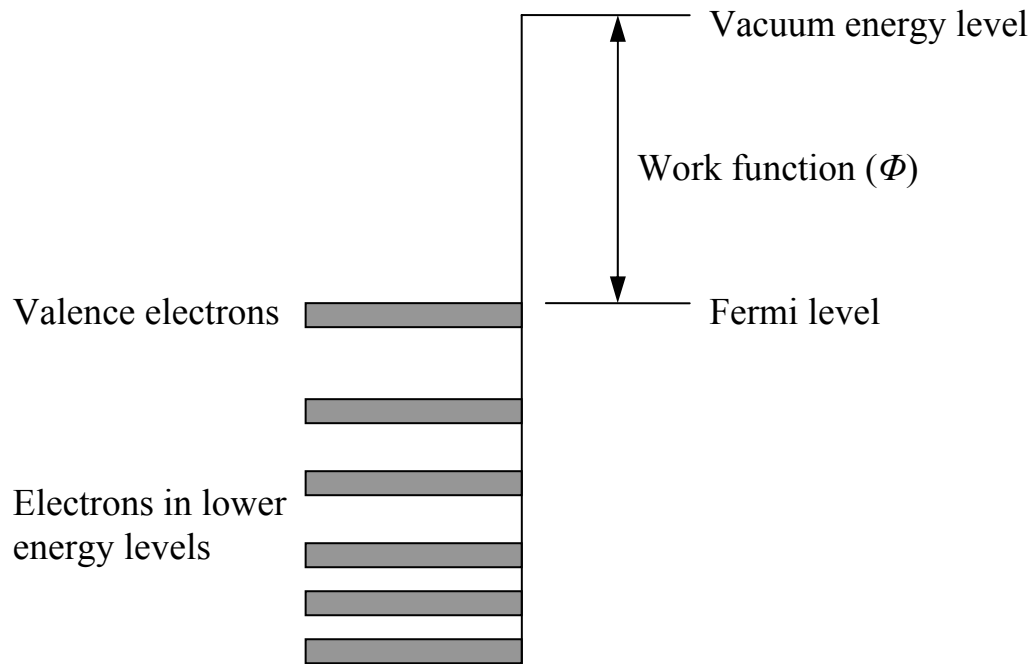


Figure 1.1. Energy diagram for a metal.

When two different metals establish contact, electrons flow from the metal with the lower work function (Φ_1) to that with the higher (Φ_2) until the Fermi levels become equal (Figure 1.2). Consequently a potential difference ($\Phi_2 - \Phi_1$), called contact potential, is generated across the metal surfaces. Oppositely charged metals are obtained when the two parts are separated in an insulated system.

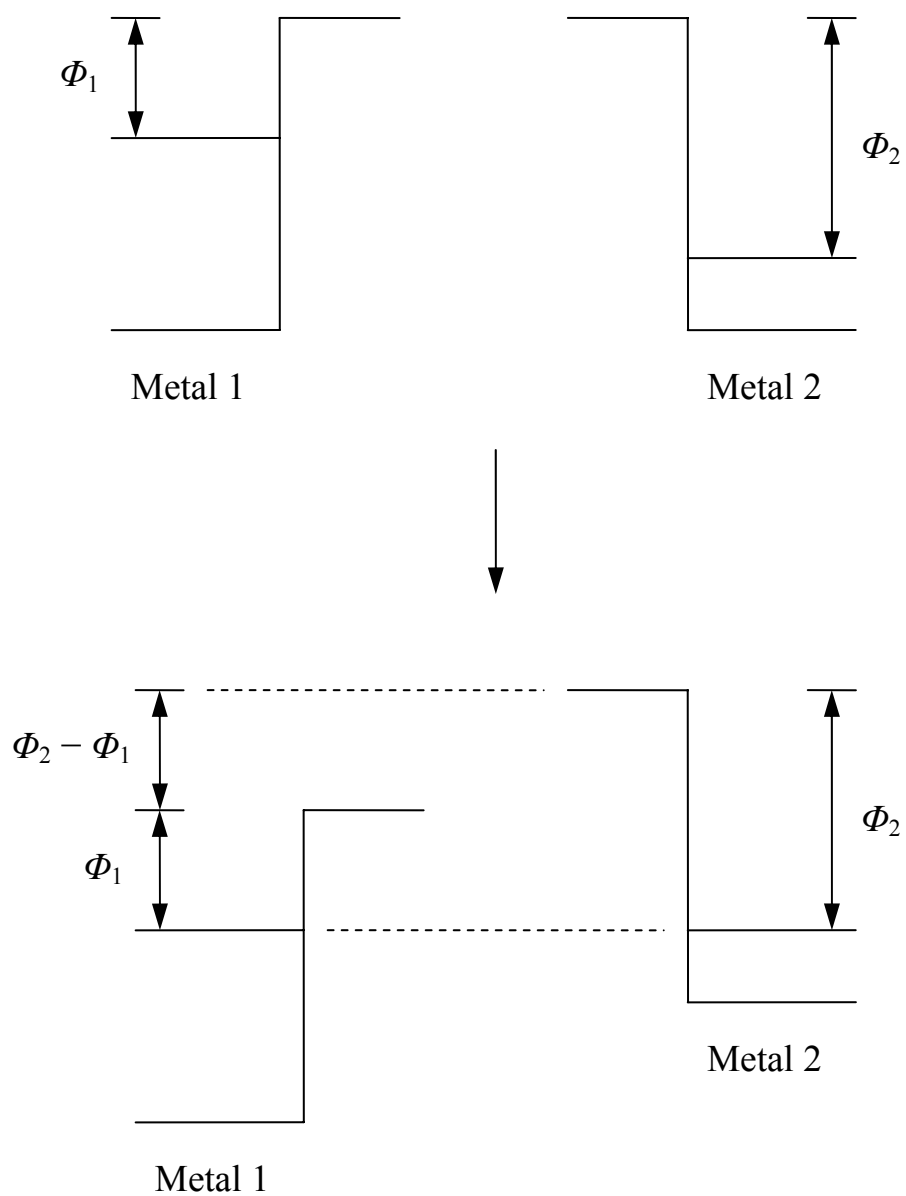


Figure 1.2. Establishment of a contact potential between two metals.

Most pharmaceutical solids are insulative³. However, the charging mechanisms in metal-insulator and insulator-insulator contacts are poorly understood despite of extensive research. This is because insulator surfaces are difficult to characterise clearly and the electron energies are ill-defined². Valence electrons in insulators are

bound to ionic or molecular structures thus are not free to conduct, yet charge exchange is still possible. If this is indeed due to the exchange of electrons then only those very near contacting surfaces will contribute in the charging². An charging model for insulator adopting principles of that for metal-metal contact was proposed⁵. Certain chemical functional groups have also been identified and ranked according to their electron donating properties during contact charging, as follows in decreasing order of donor tendency: $\text{OH} > \text{OCOR} > \text{C}_6\text{H}_5 > \text{COOH} > \text{CN}$ ⁶. Other postulated theories include the transfer of ions or surface material between the two bodies⁵. Despite the complexities of insulator charging on the atomic scale, triboelectric series have been constructed to describe the charging of materials on the macroscopic scale. Substances are ranked according to the polarity and magnitude of charges obtained, as shown in Table 1.1.

Table 1.1. A typical triboelectric series².

Positive	Lucite
	Bakelite
	Cellulose acetate
	Glass
	Quartz
	Mica
	Wool
	Silk
	Cotton
	Wood
	Amber
	Resins
	Metals
	Polystyrene
	Polyethylene
	Teflon
	Cellulose nitrate
Negative	

Materials should become positively charged when contacted with those positioned below in the series. The magnitude of charge transfer is also related to the extent of

their separation in the table⁷. Different experimental conditions generate triboelectric series with different ordering, which are rarely reproducible². Triboelectrification is sensitive to ambient relative humidity, temperature, surface impurities, surface roughness, area of contact, and other physicochemical factors, thus it is difficult to control^{4,7,8}. In addition, frictional charging also generates heat, thus reduces the predictability of the outcome⁷.

Although the metal-metal charging model is not directly applicable to insulators, the concept of work function facilitates interpretation of charging phenomena in non-metals. Theoretical relationships between work function, dielectric constant, and particle size were explored by Gallo and Lama⁹. The work function was found to decrease with increasing dielectric constant or increasing particle size. This has two main implications. Firstly, when two substances with different dielectric constants establish contact, the one with the higher dielectric constant (i.e. lower work function) would donate electrons to the other and thus become positively charged⁹. This was supported by one exemplified triboelectric series in which the materials followed the order of decreasing dielectric constants⁹. Secondly, charges can be transferred between particles of different sizes, even if both are of the same material⁹. In particular, the larger particle would be the electron donor and become positively charged. This may explain the occurrence of bipolar charging during powder handling⁸. It was noted that the work function model only provides a simplified analysis of triboelectrification from an energetic perspective. As mentioned above, many other physicochemical factors contribute to and influence the actual charging process.

1.3 Natural Charging of Liquids

Liquid droplets produced in nature, such as those from the sea, rain, and waterfalls, spontaneously carry electrostatic charges¹⁰. The larger droplets in waterfall mists are mainly positively charged, while the smaller ones negatively charged¹⁰. This size dependence of polarity also conforms to the model of Gallo and Lama⁹. Spray charging can occur for both organic and aqueous liquids¹¹. The charges are generated solely from the atomisation process in the absence of applied electric fields. Liquids can also be charged by flowing against a solid surface¹¹. Yatsuzuka et al^{12,13} and Matsui et al¹⁴ reported the electrification of water droplets through dripping and sliding on an inclined polytetrafluoroethylene (PTFE or Teflon) plate. The potential power of natural charging was appreciated when charged mists accumulated in large oil cargo tanks during washing with water jets caused explosions from accidental discharge¹⁰. The charges generated on pure water droplets flowing down an insulating surface were also sufficiently high to produce luminous sparks¹⁴. Although no conclusive liquid charging theory has been developed hitherto, a number of models had been proposed from fundamental studies. Since most pharmaceutical liquids are aqueous-based, only these shall be considered below.

Mason et al conducted a series of studies on the mechanism of natural charging of water and various aqueous ionic solutions^{15,16}. Negative charges were measured on droplets of water and dilute ionic solutions and low positive charges at higher concentrations ($> 10^{-4}$ M). Mason et al theorised that the surface of a liquid, including pure water, consists of an electrical double layer, with an outer layer of anions and a

diffuse inner layer of cations¹⁵. The negative charging at low concentrations was due to the separation of anions from the double layer as droplets are formed from the surface and detach from the bulk. At higher concentrations, the charge relaxation time of the double layer is shortened to less than the time taken for droplet formation and ejection (10^{-5} s), thus the jet formed is initially neutral. However, as the jet is disturbed by the propagation of varicose waves, liquid inside the neck of the jet carries cations into the growing head (Figure 1.3), resulting in the detachment of a positively charged droplet.

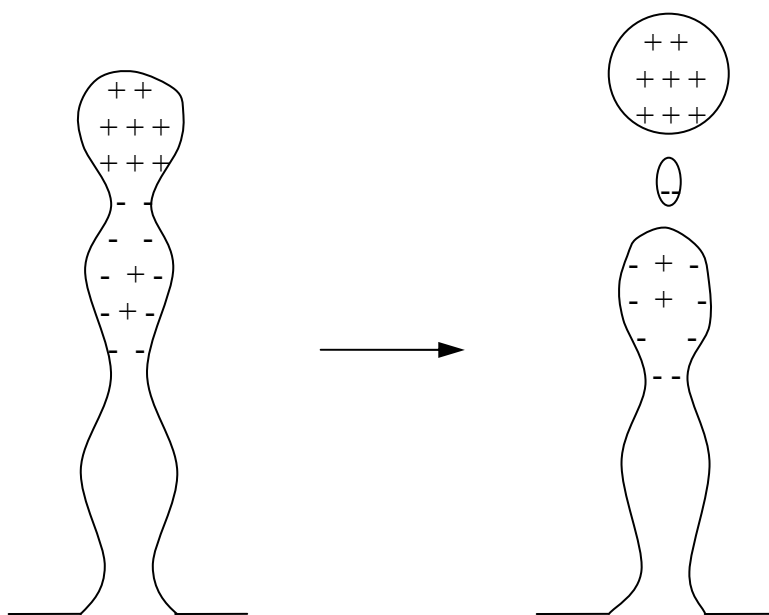


Figure 1.3. Positive charging of aqueous droplets during the break-up of a jet.

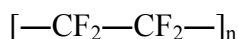
Matteson¹⁷ disagreed with the theory of electrical double layer disruption of Mason et al. It was observed that the charge detected on the droplets produced by spraying carry the same polarity as that on the larger ions in solution. Another mechanism was thus

proposed based on the assertion that droplet production involves the sudden formation of new liquid surfaces. Instead of occupying the surface, ions were thought to compose a double layer situated deeper underneath, separated by size with small ions on the upper layer. When a new surface is formed upon spraying, ions in the double layer would be attracted into the bulk of the liquid. Since the smaller ions are more mobile, these travel more rapidly inwards, thus leaving the large ions at the surface. If the rate of surface renewal is sufficiently fast, as in the case of spraying, the larger ions would be removed from the liquid and carried away by the droplets, hence the generation of charged sprays.

Lopatenko et al¹⁸ suggested a charging model similar in some features to that of Matteson¹⁷ but does not explicitly involve any electrical double layers. An undisturbed liquid is proposed to have an equilibrium surface potential value of χ . Likewise, a new surface formed has a nonequilibrium potential of χ_1 . Thus a potential difference $\Delta\chi = \chi - \chi_1$ is established along the old and new surfaces on the liquid. This in turn causes a movement of ions across the two regions for charge compensation. A disruption of the liquid bridging these areas during dispersion would produce charged droplets.

Yatsuzuka et al^{12,13} observed that after dripping and sliding a droplet of electrically neutral deionised water on an uncharged Teflon ramp, the droplet became positively charged and the polymer surface bipolar in charge. The Teflon plate was highly negatively charged at the dripping point and slightly positively charged downstream. The specific charge of the droplets decreased with an increase in the electrical conductivity of the water^{12,13}. This relationship between conductivity and droplet

charging is also evident in liquid sprays (Section 1.9). Yatsuzuka et al^{12,13} proposed that the highly electronegative fluorine atoms in the molecular structure of Teflon



adsorb anions in the water droplet onto the polymer surface upon initial contact. These anions were believed to be OH⁻ ions or a complex of OH⁻ ions and H₂O molecules. As a droplet travelled down the ramp, more anions were left behind on the polymer surface and the droplet progressively became positively charged (Figure 1.4). When a critical limit of positive charge had accumulated on the droplet, the excess cations diffused to the water surface and adsorbed onto the Teflon (Figure 1.4). As the conductivity was increased by the presence of electrolytes, such as NaCl, KCl, or HCl, the adsorption of OH⁻ ions or OH⁻/H₂O complexes might be prevented by these foreign ions, consequently the charging was dampened¹³. However, the details of the ionic interaction were not discussed in the studies.

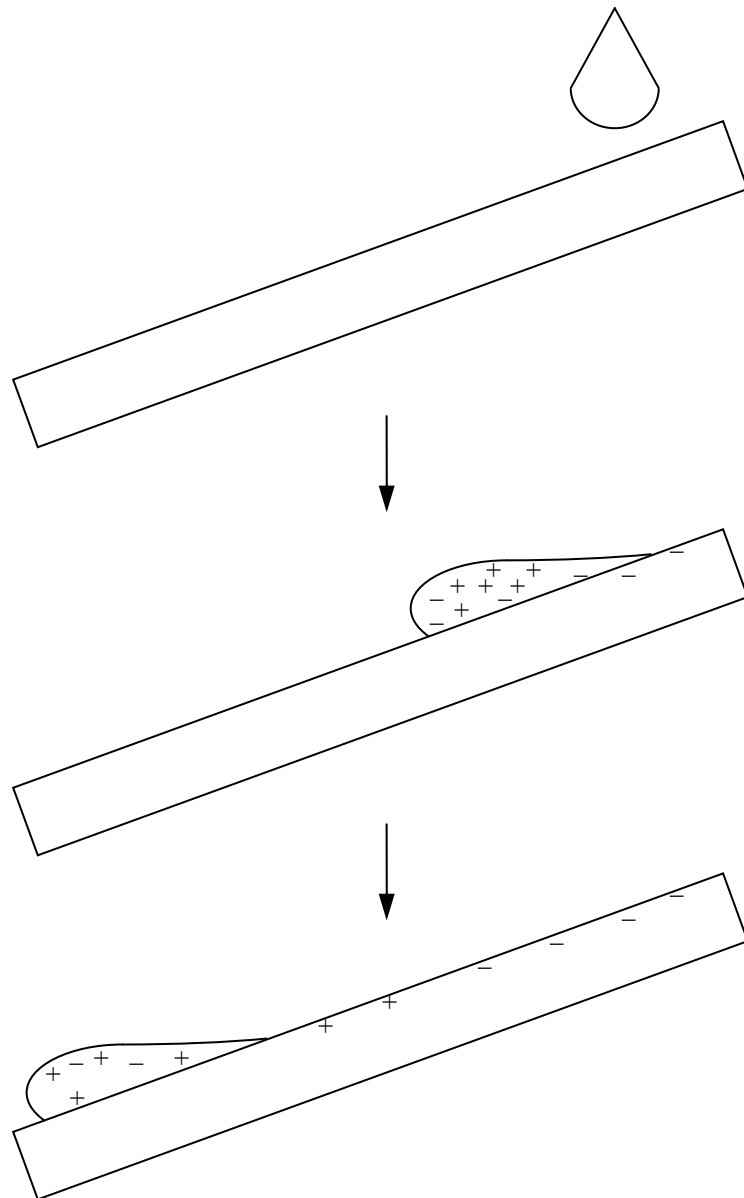


Figure 1.4. Charging of a droplet of deionised water dripping and sliding on an inclined Teflon plate.

1.4 Powder Processing

Many pharmaceutical solids are organic materials that have high resistivities ($> 10^{13} \Omega\text{m}$)^{3,19} and charge relaxation times of minutes to hours⁸. Since the rates of charge decay from particle surfaces depend on the relaxation time^{7,8}, these solids have high tendencies to accumulate charges during industrial processing. Pharmaceutical processing inevitably involves relative movements of particles against solid surfaces of equipments, thus providing ample opportunities for triboelectrification. Operations including micronisation, fluidisation, sieving, conveying of powders through pipes, bags, and hoppers, transfer into silos, and spray drying invariably generate charges^{8,20,21}. Usually, the higher the energy involved in a procedure the greater is the resultant charging⁷.

1.4.1 Problems from Powder Charging

The charges generated from triboelectrification often leads to problems in industrial processing. The accumulation of charges in a silo during powder loading may develop high surface electric potentials on the growing heap, resulting in electrostatic discharges. The heap may self-ignite if the discharge energy is greater than the minimum ignition energy of the powder⁸. Discharges are especially dangerous when flammable vapors or dust clouds are present in the vicinity⁷. Attractive forces produced from particle charging cause particle agglomeration and adhesion to surfaces of processing equipments, which in turn alters particle size and reduces or even clogs powder flow⁷. On the other hand, electrostatic repulsive forces reduce bulk

powder density. Consequently, the filling of containers and metering of formulation doses during manufacture are affected⁷. Repulsion between particles also decreases the physical stability of powder blends²².

1.4.2 Physicochemical Factors Affecting Powder Charging

The aforementioned problems of powder charging may be prevented through more detailed understanding of triboelectrification. Unfortunately, particle charging is a complex phenomenon that is fundamentally dependent on the contact area, pressure, duration, and contacting frequency between surfaces, all of which are difficult to quantify²³. A number of more easily controlled physicochemical parameters have been identified to affect powder charging during processing and are discussed below.

Powder Constitution and Pre-Treatment

The constitution and pre-treatment of a material affects its charging. Gold and Palermo examined the charging of various acetaminophen tableting formulations flowing through a hopper²⁴. The charging of fine crystalline acetaminophen was reduced when wet-granulated with ethylcellulose, starch paste, or sucrose syrup. The addition of excipients such as fillers and lubricants also decreased charging²⁴.

Surfaces of Processing Equipment

Since triboelectrification arises from interactions between surfaces, the state and composition of equipment surfaces would directly affect charging. Eilbeck et al

investigated the charging of lactose particles by blowing through a cyclone apparatus with interchangeable internal surface materials²⁵. Polyvinylchloride (PVC) generated positively charged particles whereas acetal and stainless steel produced negative charges. Smooth stainless steel produced slightly higher charges than rough stainless steel but the difference is smaller than that between different material types. Polypropylene imparted minimal charge on the particles and thus was suggested to be a suitable material for avoiding charges during processing²⁵.

Contamination of surfaces by particulate material also affects charging. Using the same cyclone setup mentioned above, Eilbeck et al demonstrated that the charging of lactose particles against stainless steel decreased with use of the apparatus without cleaning²⁶. This effect was more significant on the smaller size fractions (99-125 μm). Although not quantified, the amount of adhered lactose inside the cyclone was observed to increase after each run. The particle deposits promoted lactose-lactose and decreased lactose-metal interactions. These two modes of charging were thought to generate bipolar charges that reduced the net charge measured and the predictability of particle size effects²⁶ (see below). Washing with dilute ammonia solution and water restored the charging capacity of the cyclone.

Detergent residues left after cleaning are also potential contaminants on manufacturing equipments²⁷. The charging of microcrystalline cellulose and polystyrene particles flowing through detergent-coated stainless steel pipes and the effect of rinsing these pipes with distilled water were measured by Murtomaa et al²⁷. The specific charges obtained on the particles depended on the type and concentration of detergent in the coating. Detergent residues remaining in the pipe after rinsing

changed the charging, the trend of which differed between the detergents²⁷. These results show that triboelectrification is affected by detergent residues and related to the extent of the contamination.

Particle Size

Using the cyclone charger (see above) on lactose particles, Rowley et al investigated the effects of particle size on triboelectrification^{23,25,26}. The specific charges were inversely related to the size fractions above 90 μm in all experiments, regardless of the cyclone surface material. Adhesion was negligible for these particles thus charges originate mainly from particle-wall interactions. It was argued that the higher specific charges of the lower size fractions were due to the increased surface area available for charge transfer²⁶. Charging of particles < 90 μm was more complex, with specific charges from the 53-75 μm fraction comparable to those from the 250-355 μm fraction²³ due to the increased particle adhesion to cyclone walls in the lower size fraction providing bipolar charging (see above).

The addition of fine lactose particles (< 10 μm) to coarse crystalline and spray-dried lactose was found to dampen charging^{23,28}. Furthermore, this effect increased with the concentration of fines in the powder mixes. It was found that a portion of the fine particles separated from the blend and adhered to the cyclone during triboelectrification, thus produces charge reduction effects similar to that from particulate contamination (see above). This property of fines was also demonstrated in blends of respirable salbutamol with a coarse lactose carrier at various concentrations²³.

Relative Humidity

Particle charging decreased with increasing ambient relative humidity (RH) in the hopper and cyclone experiments conducted by Gold and Palermo²⁴ and Eilbeck et al²⁶, respectively. It was suggested that moisture reduced surface contact, changed the conductivity or other bulk properties of the particles, and facilitated charge neutralisation²⁶. More fundamental explanations were derived from other studies measuring electrical properties of solids^{19,29,30}. The volume resistivity and charge decay half-life of several pharmaceutical powder compacts decreased with increasing RH¹⁹. The improvement of surface conductivity of the particles through moisture adsorption was the major factor, but changes to bulk conductivity also occurred via water absorption at high humidities¹⁹. Similarly, the time constant for charge relaxation decreased with increasing RH on ferrite particles coated with silicone resin³⁰. This trend also corresponded with the amount of adsorbed water on the powder³⁰. Recently, it was found that RH had negligible effects on the charging of solids with low hygroscopicity, such as α -lactose monohydrate²⁹. On the contrary, the charging of sodium starch glycolate, a hygroscopic compound, is inversely related to RH²⁹. These indicate that adsorbed and absorbed water are the determinants of charge reduction.

1.4.3 Applications of Powder Electrostatics

Despite the potential problems of triboelectrification, controlled charging is applicable to facilitate processing operations such as powder mixing and coating. Ordered powder mixes can be obtained by blending two powders charged to opposite polarities.

This was achieved by blending in a container with a suitable surface that charges one powder positively and the other negatively²². The charges increase particle cohesion and reduce segregation thus enhancing the physical stability of the blend^{22,31}. In another study, lactose carriers and respirable salbutamol sulfate particles charged negatively and positively against a metal surface, respectively, but both were electropositive against plastic³². Thus an ordered mix for dry powder inhalers may be prepared using metal equipments. Furthermore, detachment of the drug from the carrier is promoted when the mix is dispersed from the plastic inhaler due to their same charge polarity^{3,32}.

Electrostatic powder deposition is an efficient coating process that has been applied to novel oral dosage forms. Accudep[®] is such a process developed by Delsys Pharmaceutical^{33,34}. The drug powder is triboelectrified with acoustic energy and then deposits onto an ingestible polymer substrate about 30 μm thick. Dose uniformity and deposition are tightly controlled since the charged particles are attracted to uncoated areas on the substrate and repelled by charged deposits. The substrate is sealed with a cover film and a thicker external coating applied to become a basic dosage unit³⁴.

1.5 Deposition of Charged Aerosols in Lung Airways

Five mechanisms govern particle deposition in lung airways, namely, inertial impaction, gravitational sedimentation, diffusion, interception, and electrostatic attraction³⁵. Electrostatic charges enhance deposition by increasing attractive forces to airway surfaces. Melandri et al^{36,37} found that the deposition of monodisperse

carnauba wax particles in human subjects increased with the amount of charges carried, up to about 200 elementary charges per particle. However, since only the net deposition was measured in these experiments, the specific location of deposition was unclear. It was assumed from the submicron particle sizes that the enhancements in deposition occurred in the alveoli³⁶. Enhanced deposition was also measured for monodisperse nanoparticles carrying a single positive elementary charge than for neutralised ones *in vitro* using a tubular tracheal model³⁸ and a hollow airway cast prepared from an adult human cadaver³⁹.

Computational models of the deposition of charged particles within the lungs have been developed employing a dichotomous model of pulmonary airways originally proposed by Weibel⁴⁰⁻⁴². In this lung model, the trachea is referred to as Generation 0, which bifurcates into two bronchi of Generation 1. This branching continues, culminating to 23 generations. Generations 0-15 represent the tracheo-bronchial region and Generations 16-23 the alveolar region⁴⁰. The basic physical parameters involved in the calculation of deposition efficiency are the particle size and charge. Bailey's model^{40,41,43,44} examines the complete respiratory cycle, including inhalation, pause, and exhalation. It is also applicable to the administration of aerosol boli. Thus the breathing pattern and delivery conditions can be more precisely defined. On the contrary, the deposition model of Balachandran et al⁴² only considers the inhalation phase.

Electrostatic charges affect deposition in two ways, via the space charge force and the image charge force. The space charge force is the repulsion between charged particles in an aerosol cloud⁴⁵. The image charge force is the attraction between a charged

particle and its image charge on a surface. Although human airways are normally neutral, image charges with equal magnitude and opposite polarity to charged particles may be induced on the surfaces, especially inside small airways in the peripheral lung^{40,42}. Balachandran et al found that the deposition of 2.2 μm particles was increased in all airway generations when the number of elementary charges per particle was increased from 1 to 200⁴². Space charge forces are predominant in the upper airways and image charge forces in the lower airways. As the amount of charge is increased to half of the Gauss' limit (the maximum charge a particle can hold), space charge forces overwhelm and most particles deposit in the first ten generations of the respiratory tract⁴². Similar effects of electrostatic forces on deposition were obtained by Bailey et al⁴⁰ for 0.5 μm and 5 μm particles, but contributions from the space charge force were not considered as it was deemed unimportant.

Bailey et al compared their model to human inhalation scintigraphy results of uncharged radiolabelled droplets from a nebuliser⁴¹. Although the total deposition and deposition in the 'head' agreed between experimental and simulation data, *in vivo* alveolar deposition was more than that predicted. The model was used to demonstrate the efficiency of the use of charged aerosol boli in targeting specific sites in diseased airways^{43,44}. Generations 10-16 within the respiratory tract were designated as target sites to treat bronchoconstriction. Particle deposition in this region was enhanced by increasing the particle charge and size of up to 2.5 μm , reducing the delay of bolus administration after onset of inhalation, and increasing the pause duration before exhalation^{43,44}.

The electrostatic effects on particle deposition illustrated by computational simulation may have implications on charged aerosol delivery. However, more clinical research is needed since these models have not been validated hitherto by *in vivo* data using charged aerosols.

1.6 Dry Powder Inhalers

Dry powder inhalers (DPIs) have been widely used to deliver aerosolised medicinal powders into the lungs for local or systemic treatments. These portable devices provide single- or multi-doses via oral inhalation, depending on the design of the powder reservoir and metering components⁴⁶. Particles inevitably undergo triboelectrification (Section 1.2) from contacts with each other and with solid surfaces inside the inhaler during aerosolisation.

Electrostatic profiles of drugs before and after aerosolisation from commercial Turbohalers[®] and prototype Dryhalers[®] were characterised by Byron et al⁴⁷. Fine particle (< 5.8 μm) charges of budesonide (Pulmicort[®]) aerosols from Turbohalers[®] were reproducibly positive and charges measured on the mouth pieces negative after dispersion. On the other hand, terbutaline sulfate (Bricanyl[®]) aerosols from devices of the same design showed inter- and intra-inhaler variations in charge polarity. In addition, time-dependent polarity was observed on one particular Bricanyl[®] inhaler from which positive and negative charges were produced separately in time. However, both of these DPIs produced fine particle charges in the order of 100 pC. The specific charge, expressed as the net charge per unit mass of powder, was lowest in the drug

reservoir, rose slightly after dose metering, and increased 10- and 300-fold in the fine particle aerosol for Bricanyl[®] and Pulmicort[®], respectively. The electrostatic charges measured on powder samples in the inhaler reservoir may originate from micronisation during formulation processing before packaging. More charges were developed as a portion of powder was dispensed from the reservoir into the metering cavity. Triboelectrification during dispersion generated the highest amount of charges on the particles. A 2.5 μm particle from Pulmicort[®] was estimated to carry 200 elementary charges⁴⁷, which is high enough to affect deposition in the lung, according to computational models⁴⁰ (Section 1.5).

Various compounds aerosolised from prototype Dryhalers[®] showed drug-dependent charging, with differing polarities and magnitudes of specific charges⁴⁷. However, all charges produced were significantly lower than those from Turbohalers[®]. This suggests that deaggregation using turbulent airstreams in the Turbohaler[®] produced more extensive triboelectrification than that provided by the high-speed rotor in the Dryhaler[®]. In addition, terbutaline sulfate charged negatively and budesonide displayed time-dependent polarity from Dryhaler[®]. The different profiles of these two drugs obtained from the Turbohaler[®] and Dryhaler[®] indicate that charging is influenced by interactions between the formulation and the inhaler⁴⁷.

The charges on the fine particles ($< 5 \mu\text{m}$) of most drugs from Dryhaler[®] followed in magnitude, but are of opposite polarity, to those on particles retained in the inhaler, indicating that charges are separated from powder aggregates upon dispersion⁴⁷. Since the Dryhaler[®] experimental conditions were identical for the various drugs tested, a

triboelectric series was constructed by ranking the magnitudes of the fine particle dose charges from positive to negative, as shown below⁴⁷.

budesonide > lactose > salbutamol sulfate > terbutaline sulfate $\geq$ salbutamol base $\geq$ beclomethasone dipropionate

Theoretically, each compound within the series should be charged negatively with respect to those preceding it when the powders are aerosolised as a blend from the Dryhaler[®]. This was supported by the negatively charged salbutamol sulfate fine particles obtained from the dispersion of Ventolin Rotacaps[®], which contain a mixture of the drug with a lactose carrier⁴⁷.

Palonen and Murtomaa⁴⁸ also investigated a lactose carrier system containing beclomethasone dipropionate aerosolised from Easyhalers[™]. The lactose particles were found to be positively charged whereas the drug particles mostly negatively charged. Although the magnitude of charges did not balance between the carrier and the drug, the opposing polarities suggest charge separation resulted from the dislodgement of the beclomethasone dipropionate from large lactose particles during dispersion.

The energy of powder dispersion from most DPIs is derived solely from the air flow generated by inhalation through the device⁴⁶. However, it may be difficult for respiratory disease patients to inhale with sufficient effort to generate high enough air flow for efficient aerosolisation⁴⁹. In view of this, electrostatic technologies have been applied to enhance powder dispersion in novel battery-operated DPIs. In an inhaler

designed by Sun et al⁴⁹, metered powder deposits are stored on a substrate composed of an insulative material, such as polyimide. Two electrodes, one in the form of a mesh overhanging the powder and the other as a backing underneath the substrate, are connected by an electrical power source. A short voltage pulse of 0.5-2 kV across the electrodes lasting for 0.3-1 ms is triggered by inhalation. The brief, but intense, electric field created thus releases the powder from the substrate, disperses it through the top mesh, and subsequently inhaled by the patient.

High electric fields are also employed in another novel DPI with a more elaborate setup⁵⁰. Two compartments are separated by a rotatable drum. The inner chamber serves as a powder depot that also holds an electrode, which charges to a high voltage of approximately 10 kV when triggered by inhalation. The powder becomes charged by induction from the resultant electric field and deposit onto the neutral drum. The drum rotates and carries the powder into the outer compartment, which contains another highly charged electrode of opposite polarity to the first one. The electric field here is thus inverted and the particles are released from the drum. The aerosolised particles subsequently pass through an electric dosage regulator grid and mix with an inhaled airstream inside the inhaler. A deionising element located near the mouthpiece neutralises the particles before they enter the patient. The electronic and dosage regulatory functions of the inhaler are controlled by an in-built microprocessor.

Instead of inducing charges on particles with electric fields, Noakes et al⁵¹ proposed the direct application of a high voltage to the powder bulk. A multi-dose blister strip containing discrete amounts of powder is mounted on a roller system inside an inhaler with an upright opening for nasal or oral administration. The lower backing of the

strip is composed of a conductive material. A blister is fed into place at the opening when a dose is needed and is then opened by a conductive plunger pushed from below. The plunger simultaneously charges from an electric power source and applies a high voltage (3-25 kV) directly to the exposed powder mass. This leads to the repulsion amongst and hence the dispersion of the charged particles. The whole sequence of operation may be breath-actuated.

1.7 Metered Dose Inhalers

Metered dose inhaler (MDI) has been the most popular aerosol delivery device for the treatment of respiratory diseases, which is attributable to its portability and simple operation. Although seemingly easy to use, the MDI has a sophisticated design. The drug(s) are suspended or dissolved in a liquefied propellant system, which may also contain excipients such as cosolvents or surfactants. The formulation is kept pressurised in a small canister, sealed with a metering valve. Upon actuation through an actuator, the valve opens and the metered dose is dispensed as an aerosol spray from the expansion and vaporisation of the propellant under ambient pressure⁵². The inhalers may be used alone or with spacer devices, the electrostatic issues of which are considered in Section 1.8. The present discussion focuses on the inherent charging of particles produced from MDIs.

Since the MDI possesses multiple components of differing compositions and the fact that the formulation must travel through and contact these parts in the process of atomisation, generation of electrostatic charges in the aerosol particles would be

expected. Both the chlorofluorocarbon (CFC)-based Ventolin[®] and the hydrofluoroalkane (HFA)-based Airomir[®] produced net charges of approximately -160 pC per puff, which was estimated to be equivalent to 300 and 490 elementary charges per respirable particle from each of the respective inhalers^{53,54}. According to computer simulated results, these charge levels may be high enough to affect particle deposition in lung airways⁴⁰ (Section 1.5).

It has been reported that the charging of MDI aerosols may be dependent on interactions between the formulation and the materials of various inhaler components. The active ingredients, salbutamol base and salbutamol sulfate, were the major contributors of charging in Ventolin[®] and Airomir[®], respectively⁵⁴. Salbutamol sulfate and fluticasone propionate particles from HFA-based Ventolin[®] and Flixotide[®] MDIs were also highly charged as measured by an electrical low pressure impactor (Section 1.11.3). The droplets of propellant (HFA-134a) were found to be responsible for charges in the lower size fractions⁵⁵. The charge profile of a HFA-134a formulation was altered by a sequential addition of absolute ethanol and dissolved beclomethasone dipropionate to the propellant⁵⁶. Similarly, the low positive charges of HFA-134 droplets became highly negative after the addition of salbutamol sulfate particles to the MDI⁵⁷. Therefore, each ingredient in the formulation contributes to the charging of the final product. The presence of water as an impurity in MDIs may also influence the electrostatic properties of the aerosol by inverting the polarity of the net charge⁵⁸. Repackaging of propellant blends, and salbutamol sulfate and levalbuterol sulfate MDI suspensions with various combinations of valve components showed that elastomer and valve stem materials may affect aerosol charging⁵⁹. CFC-11/12 propellant blends generated charge profiles of differing magnitudes and polarities

when packaged in various combinations of valve body and stem materials⁵⁹. CFC albuterol sulfate aerosols were charged more electronegatively with stainless steel valve stems than with acetal ones⁵⁹. On the other hand, the levalbuterol sulfate counterparts produced net negative charges with nitrile (BK 356) elastomers and net positive charges with nitrile RB 190NT (BK 357) elastomers. Composition of MDI actuators may also play a role in aerosol charging. By charging polymeric substances used in actuators with a corona charger and monitoring the charge decay with a Faraday pail, Carter et al⁶⁰ observed that the materials have varying degrees of electrostatic charge accumulation and decay properties.

The charging of MDI aerosols clearly has a physicochemical basis. It is related to interactions between the contents of the formulation (propellant, actives, and other excipients) and the compositions of the inhaler components (metering valve, valve stem, and actuator). Research in this area is progressing and a clearer understanding on MDI aerosol charging may enhance the design and use of these products, especially when coupled to spacers.

1.8 Spacer Devices

Spacer devices, also known as holding chambers, are used with MDIs to overcome problems in coordinating inhalation with actuation, especially in children, and minimise oropharyngeal deposition of drug particles⁶¹. These devices may be broadly classified into three groups according to their design, namely, tube spacers, holding chambers, and reverse-flow devices⁶¹. The general term ‘spacers’ is used to describe

these devices collectively in this thesis. Essentially, a spacer serves as a reservoir to hold the aerosol cloud for the patient to inhale through a one-way valve at a natural pace.

Most spacers are plastic⁶¹, usually made of polycarbonate, which is an insulative material. Thus electrostatic charges may be generated and accumulated on spacer surfaces through handling. High charges exist even on new spacers that had been stored in their original packaging⁶²⁻⁶⁴. Interactions between these charges and the charged particles from a MDI (Section 1.7) may decrease the drug output from a spacer. Conversely, reduction or elimination of electrostatic charges on spacer surfaces improves drug delivery⁶¹. In fact, the respirable fraction (particles < 6.8 μm) of an albuterol aerosol delivered from a spacer was found to be inversely related to the measured surface charge⁶⁵. Spacer charges may be significantly decreased by various types of treatments through increasing the conductivity of the spacer surface, especially the inner walls. O'Callaghan et al found that the fine particle doses (< 5 μm) of sodium cromoglycate⁶⁶ and budesonide⁶⁷ from MDI aerosols were significantly increased *in vitro* when delivered through a spacer coated with a commercial antistatic lining. However, since the toxicity profiles of antistatic sprays on humans are questionable, other methods are needed for spacer surface charge reduction.

Priming a spacer with a medicated⁶⁸ or placebo⁶⁹ MDI aerosol before use was also found to decrease surface charge. After repeated actuation from a sodium cromoglycate inhaler, the surface charge inside the Fisonair[®] spacer was greatly reduced⁶⁸. In an *in vivo* scintigraphic study⁶⁹, priming plastic spacers (Nebuhaler[®] and

Volumatic[®]) with a placebo aerosol containing surfactants increased whole lung deposition of a radiolabelled budesonide aerosol (

Table 1.2). Drug retention in the primed spacers was also significantly lower than that in their unprimed counterparts. It was proposed that the surfactant from the MDI coated on the spacer surface acting as a conductive lining to reduce charges and enhance drug output⁶⁹.

Table 1.2. Mean whole lung deposition of radiolabelled Pulmicort[®] MDI from primed and unprimed spacers. Adapted from Kenyon et al⁶⁹.

	Plastic Nebuhaler [®] (%)	Plastic Volumatic [®] (%)	Metal Nebuchamber [®] (%)
Unprimed	26.7	22.1	32.9
Primed	37.7	32.0	33.5

Coating spacers with surfactants is a popular method for reducing surface charge. Ionic surfactants were found to be more effective than non-ionic ones in this role⁶². Commercial detergents, most of which are anionic, significantly reduced surface charges on spacers, even at very low concentrations (1:10000 in water)⁶⁴. The optimal procedure was to soak the spacer in detergent solution followed by drip-drying, without rinsing with water or wiping with towel. The *in vitro* fine particle doses from detergent-coated spacers and new spacers with high charges were 55-70% and 30%, respectively⁶². Charge reduction also counteracted the negative impacts of increased aerosol residence time on drug delivery⁷⁰ presumably by reducing electrostatic deposition. Detergent treatment decreased drug retention in spacers from 76.7% to 33.1% and increased mean lung deposition of radiolabelled albuterol *in vivo* from 11.5% to 45.6%⁶⁴, along with significantly improved bronchodilator response⁷¹.

Being a conducting material, metal has been used to construct non-electrostatic spacers. The half-life of aerosol disappearance in a steel spacer prototype was > 30 s, whereas that in a non-coated Nebuhaler[®] was 9 s⁷². The lengthened half-life was comparable to that achieved by coating the Nebuhaler[®] with a cationic surfactant, benzalkonium chloride⁷². *In vivo* drug delivery to infants and children was higher from the steel spacers than that from various plastic ones^{72,73}. This steel spacer prototype was subsequently developed by AstraZeneca into a commercial product, the Nebuchamber[®], which showed similar *in vitro* antistatic properties to detergent-coated plastic spacers⁷⁰. It also increased *in vivo* drug delivery from a budesonide MDI^{74,75}. Since metal surfaces dissipate electrostatic charge very rapidly, priming is unnecessary and does not significantly affect the performance of Nebuchamber[®] (Table 1.2). Similarly, drug deposition in metal cylindrical spacers (stainless steel, anodised aluminium, and nickel-coated aluminium) was observed to be less than that in plastic ones (polycarbonate, styrene-butadiene copolymer, and polyester) for two types of MDIs⁷⁶.

Recently, spacers manufactured from charge-dissipative polymers are available. These materials are physically similar to the usual plastics but their electrical conductivity is higher. Thus the spacer walls retain low electrostatic charges. Detergent-coating was deemed unnecessary for the non-electrostatic AeroChamber Max[™] and AeroChamber Z-STAT Plus[™] to improve the drug output⁷⁷. The AeroChamber Max[™] was also shown to perform better than the polycarbonate OptiChamber[®] and the aluminium Vortex[™]⁷⁸. Zerostat V, a non-electrostatic spacer made with a different polymer to those of AeroChamber Max[™] and AeroChamber Z-

STAT Plus™, significantly prolonged the half-life of MDI aerosols inside the chamber⁷⁹.

A consequence of the improved delivery efficiency of all types of antistatic spacers is that MDI doses may need to be adjusted. This is particularly relevant to the administration of corticosteroids, which are used regularly in asthmatic children⁶⁷. A lower dose would reduce adverse effects and enhances the control of the disease but more clinical research is needed to address this issue^{69,72}.

1.9 Liquid Sprays

Charging of polydisperse droplets from a wet scrubber nozzle used in industrial cleaning was characterised by Vaaraslahti et al⁸⁰. Positively charged droplets were resulted from the spraying of distilled water, ionic solutions, and diluted scrubber liquid, whereas negative charges were measured on undiluted scrubber liquid droplets. Although the exact constituents of the scrubber liquids tested were not disclosed, these products generally contain lime, limestone, sodium hydroxide, or sodium carbonate, together with other soluble and insoluble impurities collected through recirculation during cleaning⁸⁰. Varying the nozzle material between stainless steel, brass, and polyvinylidene fluoride had no significant effect on charging. The specific charge, expressed as the net charge per unit volume of sprayed liquid, was found to be inversely related to the electrical conductivity of, and hence the concentration of ionic species in, the liquid⁸⁰. This effect of conductivity on charging was also observed by Yatsuzuka et al^{12,13} (Section 1.3).

The inverse relationship between ionic concentration and resultant charges on atomised droplets was exploited to suppress the charging of inhalation aerosols produced from a novel atomiser, AERx[®] ⁸¹. The rationale for reducing aerosol charging is to avoid premature droplet deposition in the oropharynx during inhalation. Ionic salts such as sodium chloride or potassium chloride are added to increase the conductivity of the solution. Droplets of deionised water and Water for Injection USP produced from the AERx[®] atomiser carried high positive charges, whereas those of sodium chloride (5 mM and 10 mM) and sodium cromoglycate (30 mg/mL) solutions had much lower charges⁸¹. In addition, the output of a non-ionisable drug (details undisclosed) from the same atomiser was increased with the sodium chloride concentration, reaching a maximum plateau at 7.7 mM ⁸¹. Thus low levels of added electrolytes to aqueous solutions are sufficient to reduce droplet charging significantly.

1.10 Electrosprays for Inhalation

Electrospray, also called electrohydrodynamic (EHD) or electrostatic spray, is an atomization technique in which liquids are dispersed solely by the application of high voltages^{10,82}. A simple electrospray setup is shown in Figure 1.5. A liquid flows into a metal capillary tube charged to the kilovolt range and emerges from the tip as a conical meniscus, known as a Taylor cone¹⁰, due to the intense electric field (Figure 1.6). An unstable jet extends continuously from the apex of the cone and disperses into charged droplets further downstream^{10,83}. Electrosprays have been used in

industrial and agricultural applications such as ink-jet printing, paint coating, and crop spraying for controlled deposition of charged droplets onto specific targets¹⁰.

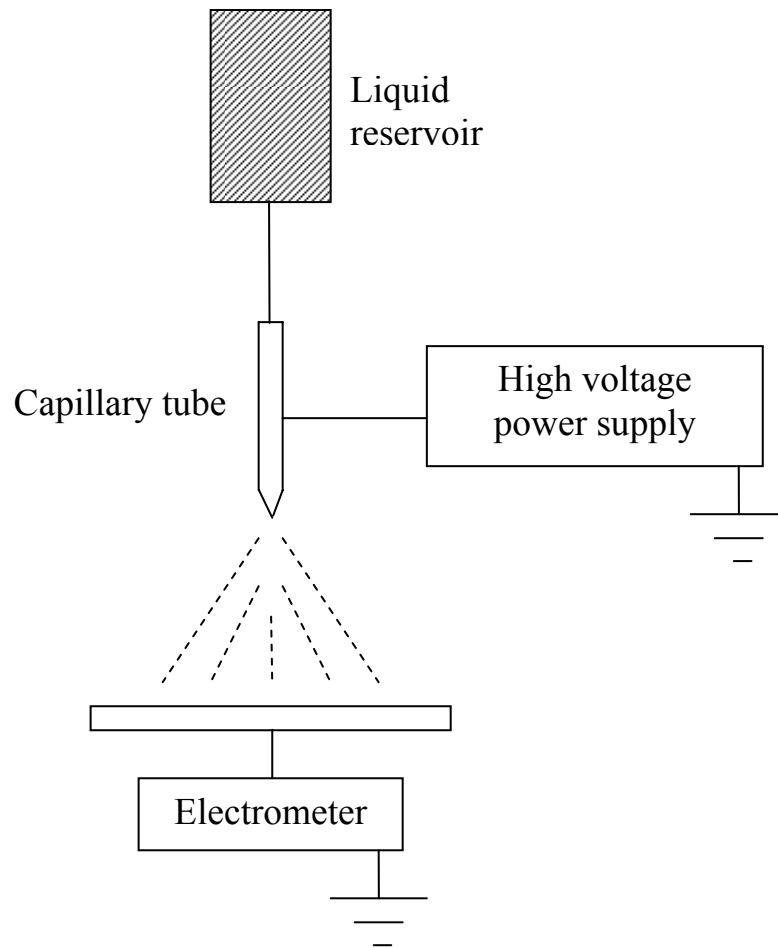


Figure 1.5. Schematic diagram of an electrospray setup.

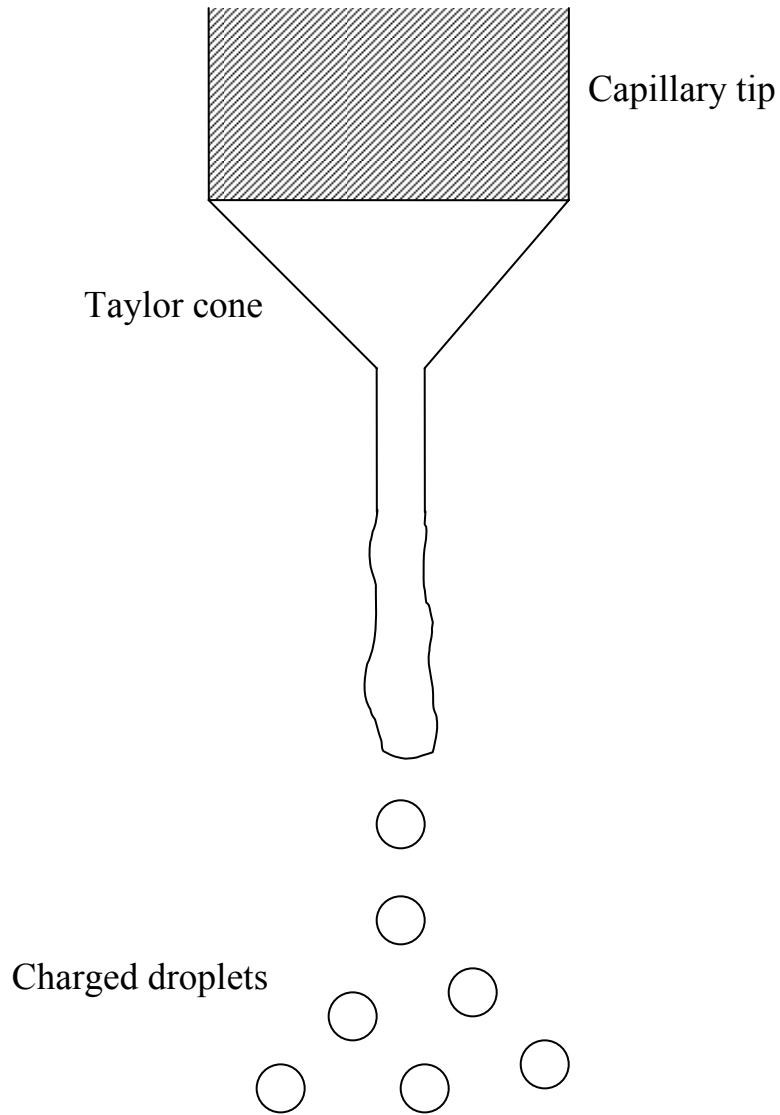


Figure 1.6. The droplet production zone of an electrospray.

The size of electrosprayed droplets can be tightly regulated, depending on the applied voltage, liquid flow rate, and physicochemical characteristics of the liquid such as the dielectric constant, conductivity, surface tension, and viscosity⁸². Thus the system has been employed to produce monodisperse droplets and particles in size ranges potentially suitable for respiratory delivery^{84,85}. Tang and Gomez⁸⁴ generated normally distributed saline droplets with a mean diameter of 1.4 μm and a relative standard deviation of 0.14. Gomez et al⁸⁵ also electrosprayed an insulin solution and

yielded particles between 90 and 110 nm after solvent evaporation. The technique is also suitable for dispersing suspensions without clogging the system, due to the relatively large caliber of the capillary tubes (typically 100 μm)^{82,85}.

More sophisticated electrospray devices have been designed to produce aerosols for patient use. However, the droplets must be discharged before inhalation to avoid premature deposition from image forces in the oropharynx (Section 1.5). The capillary nozzle of the electrospray apparatus devised by Noakes et al⁸⁶ is charged to the opposite polarity to a needle discharge electrode (Figure 1.7).

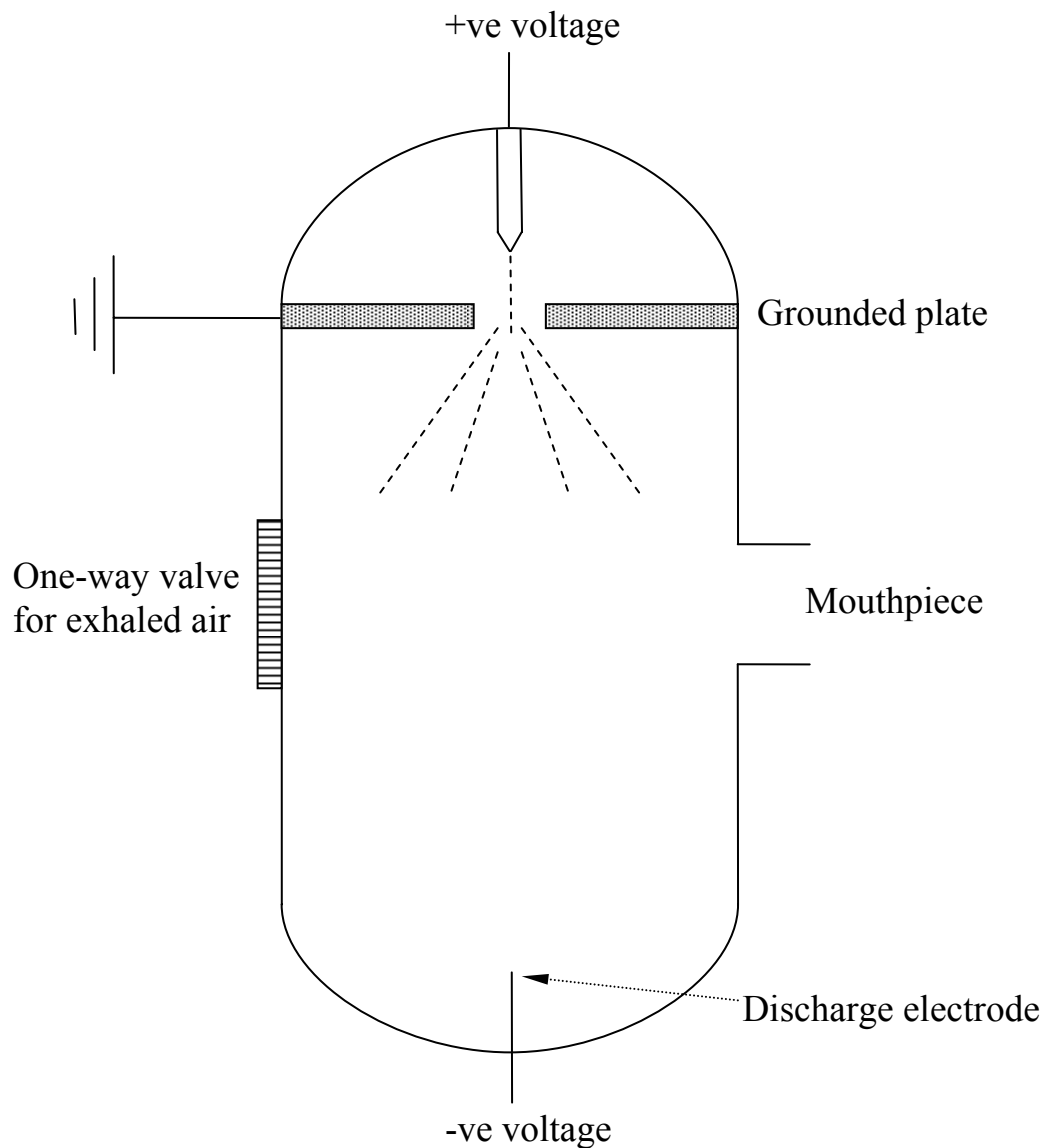


Figure 1.7. Schematic diagram of the electrospray inhaler.

The ions produced from the needle electrode through corona charging neutralise the charges on the droplets. A grounded plate shields the capillary to prevent corona ions from discharging the nozzle and interfering with the electrostatic dispersion. The shield contains a small orifice through which charged droplets pass into the aerosol chamber for neutralisation. A similar mechanism for discharging droplets is used in the breath-actuated electrospray nebulisers recently developed by BattellePharma,

including battery-operated portable and bench-top prototypes⁸². Although a high voltage is applied upon atomization, the nebulisers are claimed to be safe for patient self-operation due to the low electric currents involved⁸⁴. The manufacturing cost of these devices is also relatively inexpensive. Multiple nozzles are used to achieve an optimal drug output. Respirable fractions of nebulised triamcinolone acetonide, albuterol, and cromolyn were close to 100%, with narrow geometric standard deviations between 1.2-1.5⁸². The average lung deposition was 78% of the emitted dose from a prototype Battelle inhaler in a Phase I scintigraphic study on human subjects⁸⁷. The oropharyngeal deposition was also significantly lower compared to that from a dry powder inhaler (16% vs 67%), thus the electrospray nebuliser has high respiratory delivery efficiency.

Drug molecules should gain no charge upon electrospray atomization because it is believed that only the liquid carrier, rather than the drug, is charged during the process⁸². Furthermore, the droplets are discharged after their dispersion, thus it is improbable that charges should remain on the drug. Since no heat is applied during electrospraying, heat-labile substances such as proteins may be aerosolized without molecular fragmentation⁸². Owing to this advantage, the technique is used to inject macromolecules into mass spectrometers for analyses⁸⁵. However, a concern for electrospraying macromolecules for inhalation is their potential denaturation due to interferences from intensifying electric fields resulted from the evaporation of highly charged liquid droplets⁸⁵. This may happen without the occurrence of fragmentation and result in altered molecular conformations, as well as loss of biological activities. Nevertheless, the receptor binding ability of electrosprayed insulin was not found to

be altered in an *in vitro* assay⁸⁵. Further investigations are needed to evaluate the suitability of the electrospray atomisation for other macromolecules.

1.11 Electrostatic Charge Measurement Techniques

A diverse range of electrostatic measurement devices have been described in the literature for powders and aerosolised particles. For instance, the electrical single particle aerodynamic relaxation time (E-SPART) analyser determines the numerical size and charge distributions of airborne particles using a laser Doppler velocimeter coupled to an applied electric field⁸⁸. Less well-known examples include the differential charge-to-mass apparatus³, the airstream Faraday cage³, the bipolar charge measurement system⁸⁹, and other techniques with no formal nomenclature^{20,90,91}. These devices were individually designed by separate research groups and operate on different mechanistic principles. The instruments relevant to the research reported in subsequent chapters of this thesis are the Faraday pail, the aerosol electrometer apparatus by Peart et al^{54,58,59,92}, and the electrical low pressure impactor (ELPI). Although the aerosol electrometer apparatus was never utilised in the work of the thesis, some of the data obtained by the author using the Faraday pail and ELPI are compared with those obtained by Peart et al in later discussions. Thus a brief description of it is provided in this section.

1.11.1 Faraday Pail

The simplest instrument for measuring electrostatic charge is the Faraday pail or Faraday well (Figure 1.8). It consists of two metal containers, one situated inside the other. The outer well is grounded to provide shielding from interferences by stray charges or electric fields in the vicinity. The inner well, connected to an electrometer, is electrically insulated to prevent charge leakage. A charged object in the inner well induces a flow of electrons to or from earth through the electrometer to balance the charge in the well. This results in a charge imbalance across a capacitor in the electrometer and is measured to derive the charge in the inner well³.

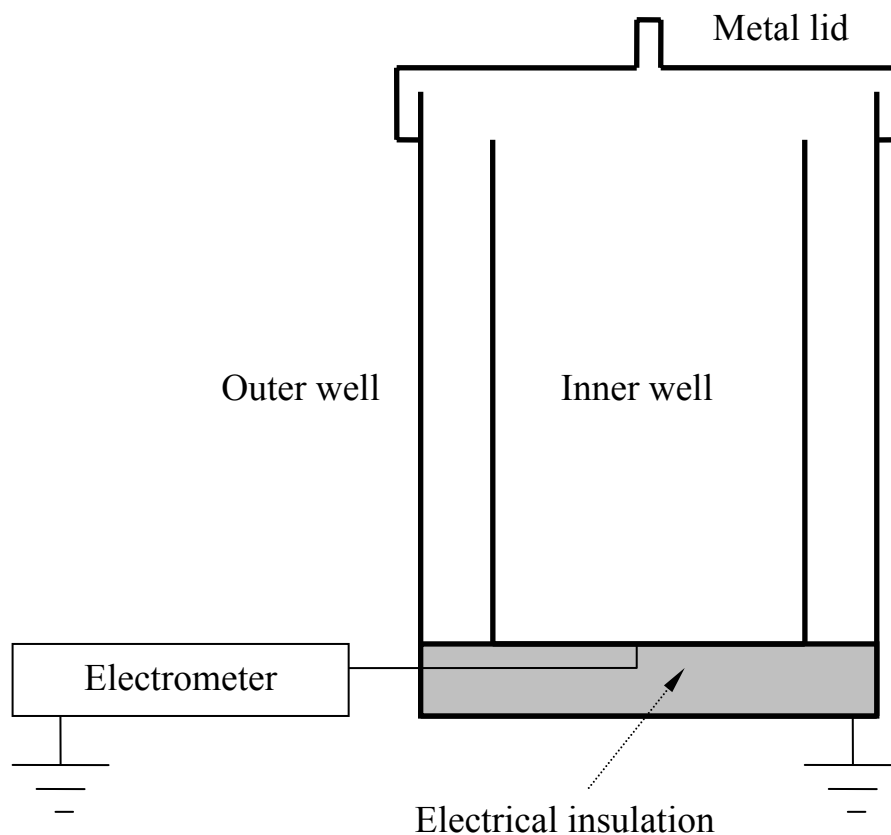


Figure 1.8. Schematic diagram of a Faraday pail.

1.11.2 Aerosol Electrometer Apparatus

Electrostatic charge distribution studies of MDIs and DPIs were previously conducted by Peart et al using an aerosol electrometer apparatus that was built in-house^{54,58,59,92}. The instrument is essentially a two-stage impactor with a Faraday pail serving as the second stage for collecting fine particles $< 5\ \mu\text{m}$ (Figure 1.9)⁹². The net charge on the fine particle mass was measured with an electrometer. The limitation of this setup is that while the net charge of the fine particles was measured the charges among different size fractions could not be discerned. Thus if an aerosol carries bipolar charges, the two polarities would mask each other as only the overall charge is detected.

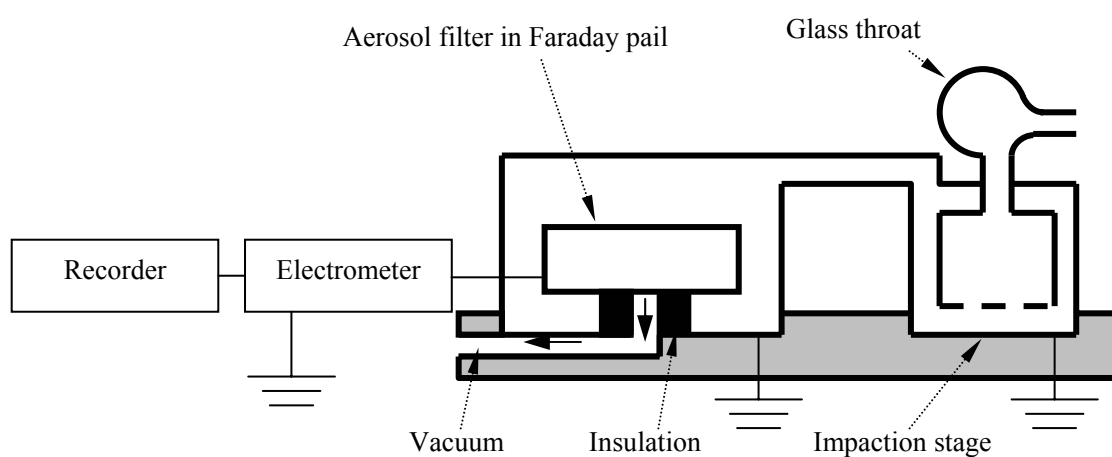


Figure 1.9. Schematic diagram of the aerosol electrometer apparatus by Peart et al⁹².

1.11.3 Electrical Low Pressure Impactor

The ELPI was originally designed for near real-time sizing of airborne particles by electrical detection^{93,94}. It consists of a 13-stage Berner multijet low pressure impactor with a diode-type corona charger situated directly above the top stage⁹³ (Figure 1.10). The size range covered by conventional cascade impactors is usually 0.3 to 10 μm ⁹⁴. By operating the impactor stages below atmospheric pressure the lower size limit can be extended down to about 30 nm, as it is for the ELPI⁹⁴ (Figure 1.10). In its original mode of operation, the corona charger is charged to +5 kV⁹⁵, and the resulting high electric field imparts a known, size-dependent level of charge to the particles introduced into the impactor by vacuum suction. The jet plate of Stage 1 functions as a critical orifice for establishing the flow rate⁹⁴. All the impactor stages are electrically insulated from each other with the last twelve stages connected individually to individual electrometers with sensitivity at femtoampere levels. The particles subsequently deposit onto the stages according to their aerodynamic sizes with their charges measured by the respective electrometers. Particle size distribution is then derived from the electric current measurements according to the corona charger efficiency⁹³. The computer data collection software has an algorithm to correct for fine particle losses due to space-charge forces (Appendix A). Further details on the theoretical background and electronics of the ELPI were given by Keskinen et al⁹³.

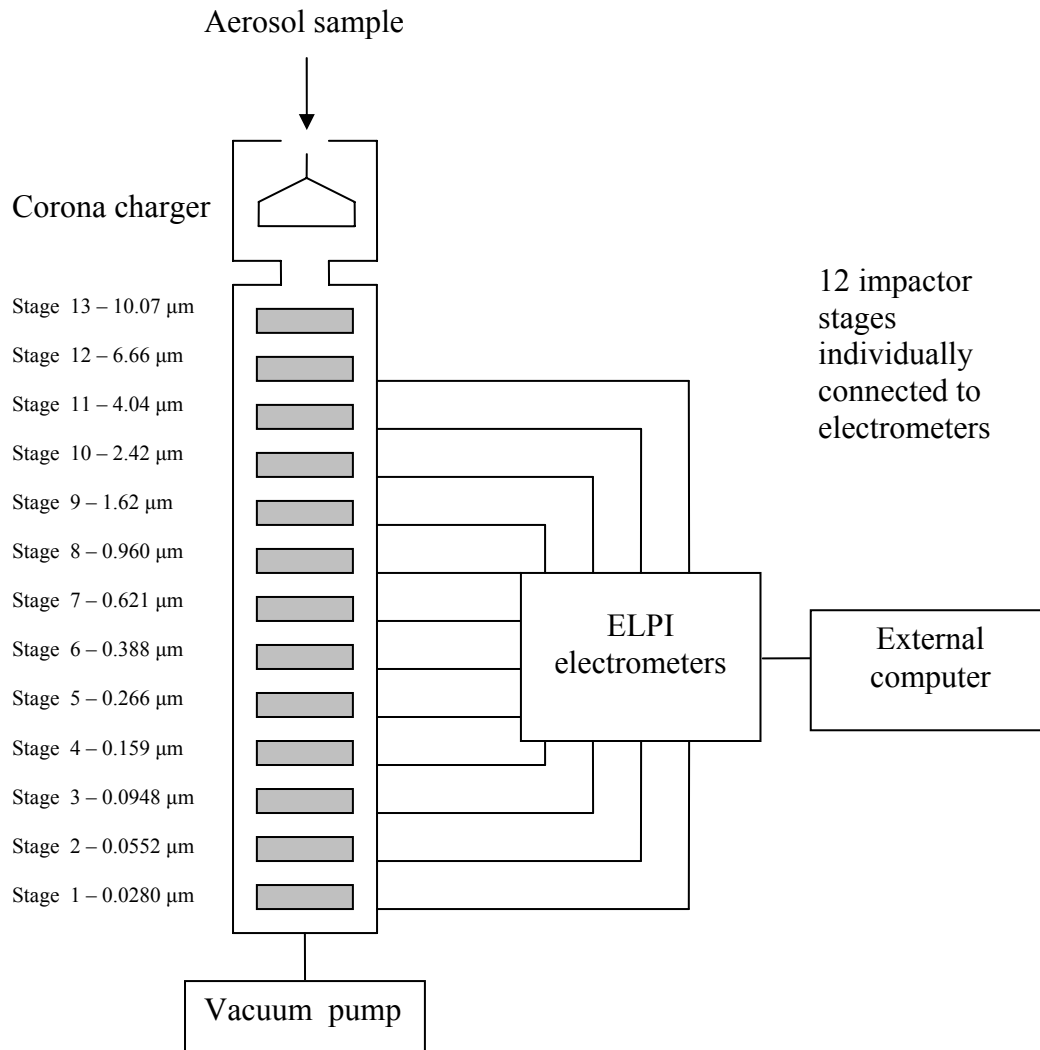


Figure 1.10. Schematic diagram of the ELPI in its original configuration.

Diagram not drawn to scale.

Particle sizing via corona charging and electrical derivation with the ELPI is an indirect method but it is fast and convenient because no gravimetric or chemical analyses are required⁹⁶. These additional assays may still be conducted afterwards if desired. The ELPI has mostly been applied in measurements or real-time monitoring of industrial and environmental aerosols. These include particulate emissions from diesel engines⁹⁷⁻¹⁰², vehicles¹⁰³, burning incense¹⁰⁴, smoke particles attached with

radon decay products¹⁰⁵, and general atmospheric airborne particles¹⁰⁶⁻¹⁰⁸. Aerosols generated from MDIs¹⁰⁹ and DPIs¹¹⁰ had also been sized by ELPI electrical detection but in general pharmaceutical applications are relatively few.

In all the aforementioned studies aerosol samples were charged with the corona charger. The primary interest was to derive size distributions from electrical signals. However, inherent charges on aerosol particles may also be measured by the ELPI without corona charging. Palonen and Murtomaa measured DPI aerosol charges with the corona charger in place but switched off⁴⁸. However, no drug mass was determined. Glover and Chan found no significant difference in the charge measurement of MDI aerosols with the corona charger in place but switched off and with the charger removed⁵⁵. The charger was thus unnecessary and was removed to eliminate the possibility of artefacts in charge and mass measurements due to unwanted triboelectrification and deposition of particles on the charger block⁵⁵. The electrometer reading from each stage of this modified setup represents the net charge contributed by all particles collected on the individual stages. The deposited drug on each stage may be assayed chemically using high performance liquid chromatography (HPLC) to obtain the particle size distribution by mass⁵⁵. The charge and mass data may be combined to yield charge-to-mass ratios (q/m), or specific charges, for the various size fractions.

An advantage of using the modified ELPI to measure particle charges over Peart's aerosol electrometer apparatus (Section 1.11.2) is the higher resolution of size and charge classifications. Variations in both the mass and net charge within the different size fractions can be discerned. This is needed for gaining a detailed understanding on

the electrostatic properties of aerosols. The modified configuration of the ELPI was hence adopted in the studies reported in this thesis.

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Chapter 2

Electrostatic Charge Characteristics of Metered Dose

Inhaler Aerosols

2.1 Introduction

Since its first development in the mid-1950s¹, the metered dose inhaler (MDI) has been the most popular drug delivery device for the treatment of respiratory diseases. MDIs are portable and relatively easy to operate by the patient for self-administration. Although the aerosol characteristics such as particle size and output of MDIs have been measured extensively over the years, the electrostatic properties of these particles are poorly studied. It is well known that electrostatic deposition is one of the five major mechanisms of aerosol deposition in the lungs². Computer modelling and limited *in vivo* inhalation studies conducted on human subjects indicate that electrostatic charges may affect total and regional deposition in the lung³⁻⁸.

Electrostatic charge distribution studies of MDIs were previously conducted using an aerosol electrometer apparatus that was built in-house⁹⁻¹². The instrument is essentially a two-stage impactor with a Faraday pail as the second stage for collecting fine particles ($< 5 \mu\text{m}$)¹⁰. The net charge on the fine particle mass was measured with an electrometer. The limitation of this setup is that while the net charge of the fine particles was measured the charges among different size fractions could not be discerned. Thus if an aerosol carries bipolar charges, the two polarities would be

masked by each other as only the overall charge is detected. The drawback has been overcome with a modified setup of the electrical low pressure impactor (ELPI) described by Glover and Chan¹³. The instrument is conventionally used for near real-time size measurements of airborne particles¹⁴⁻¹⁷. The ELPI consists of a 13-stage impactor with a corona charger situated directly above the top stage. In its conventional operation, the corona charger is charged to +5 kV¹⁸, and the resulting electric field imparts a known amount of charges to the particles introduced into the impactor by vacuum suction. All the impactor stages are electrically insulated from each other with the last twelve stages connected individually to twelve electrometers with sensitivity at femtoampere levels. The particles subsequently deposit onto the stages according to their aerodynamic sizes with their charges measured by the respective electrometers. Particle size distribution is then derived from the electric current measurements. Further details on the theoretical background and electronics of the ELPI were given by Keskinen et al¹⁶. Instead of charges imparted by the corona charger, inherent charges on aerosol particles produced from MDIs were measured in the present study. The corona charger was thus unnecessary and was removed since its presence may potentially cause artefact in the measurement due to contact charging of the particles. The deposited mass on each stage was assayed using HPLC. The electrometer reading from each stage represented the net charge (sum of both positive and negative charges) contributed by all particles collected on the individual stages. The ELPI provides a high resolution of size classification and can detect variation of net charge within the different particle size fractions.

Most of the material in the chapter was published in the *Journal of Pharmaceutical Sciences*¹⁹. Some modifications to the text and previously unpublished data are included here.

2.2 Aim

The aim of the present study was to employ this novel technique to investigate charge profiles of aerosols generated from commonly used MDIs.

2.3 Materials and Methods

2.3.1 Metered Dose Inhalers and Sampling Protocol

Five types of widely available MDIs were examined in the study, including Ventolin[®] (100 µg salbutamol sulphate; Allen & Hansburys, Australia), QVAR[®] (100 µg beclomethasone dipropionate, 3M Health Care, UK), Flixotide[®] (250 µg fluticasone propionate; Allen & Hansburys, Australia), Intal[®] Forte (5 mg sodium cromoglycate; Aventis Pharma, UK), and Tilade[®] (2 mg nedocromil sodium; Aventis Pharma, UK). All of these MDIs are hydrofluoroalkane (HFA) products. QVAR[®] is a solution MDI, whereas the other four are suspensions (Table 2.1).

Table 2.1. MDI formulations evaluated²⁰.

Inhaler	Drug (dose per puff)	MDI type	Propellant	Formulation excipients	Valve stem material*
Intal [®] Forte	Sodium cromoglycate (5 mg)	Suspension	HFA-227	Povidone Macrogol 600	Plastic
Tilade [®]	Nedocromil sodium (2 mg)	Suspension	HFA-227	Povidone Macrogol 600 Menthol	Plastic
Flixotide [®]	Fluticasone propionate (250 µg)	Suspension	HFA-134a	None	Plastic
Ventolin [®]	Salbutamol sulphate (100 µg)	Suspension	HFA-134a	None	Plastic
QVAR [®]	Beclomethasone dipropionate (100 µg)	Solution	HFA-134a	Ethanol	Metal

* Specific details were not available as this is proprietary information of the manufacturers.

Three inhalers of each type were tested for measuring both charge and mass characteristics. All inhalers were used before the expiry date and were primed to waste by actuation according to the instructions specified on the consumer medicine information leaflets. After priming, five single puffs (#1-5) from each inhaler were individually determined for the charge and mass profiles. There was a lapse of an hour or longer between actuations to allow mass assay procedures to follow. These aerosol samples are referred to as ‘discrete puffs’. The next ten puffs (#6-15) were actuated continuously (about 30 seconds apart) into the ELPI and their charge profiles measured sequentially. No mass was assayed for these ten puffs. The ELPI was cleaned and reassembled. Immediately after actuating the MDI twice to waste, a

single puff (#18) was collected in the ELPI for charge and mass determinations. This puff is referred to as a ‘continuous puff’.

2.3.2 *Electrostatic Charge Measurement*

A modified ELPI (Dekati, Finland) was used in the electrostatic measurements. The corona charger was removed from the instrument so that innate charges on the particles could be measured. The performance of the ELPI was not found to be altered significantly by this modification¹³. Aerosol samples were introduced via a USP throat. Tight-fitting adaptors flush with the MDI mouthpieces were used to ensure complete aerosol sampling. The presence of the adaptors was not found to affect the electrostatic charge profile of the MDI aerosols. 90 µL of a 15 g/mL solution of silicone fluid (200 Fluid/60000 cSt; Dow Corning, Australia) in cyclohexane (Ajax Finechem, Australia) was applied to each ELPI impactor stage to minimise particle bounce and re-entrainment during sampling. The cyclohexane was allowed to fully evaporate before the stages were assembled. A Sogevac[®] model SV25 vacuum pump (Leybold, France) provided air flow at 30 L/minute through the ELPI. The electric currents induced on the impactor stages were measured and recorded by the ELPIVI 3.1 software from Dekati. The current range setting for charge measurement was 40,000 fA. The experimental setup is shown schematically in Figure 2.1.

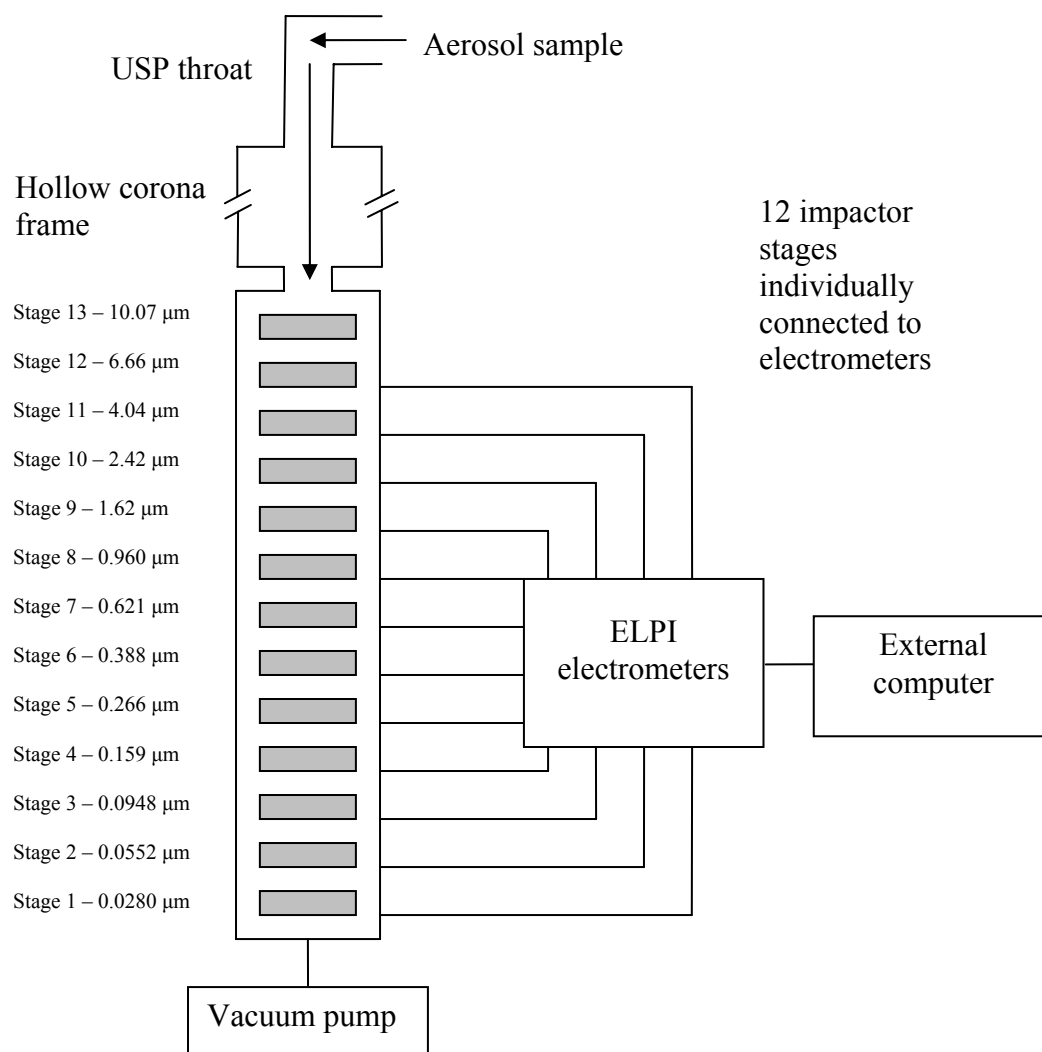


Figure 2.1. Schematic of the modified ELPI instrument setup. Diagram not drawn to scale.

Before the present aerosol sampling procedure described above was adopted, an earlier method had been used but was subsequently rejected due to its shortfalls. The charge and mass profiles of multiple puffs instead of single puffs were measured. Six actuations from Intal[®] Forte and ten actuations from the other four MDI types were introduced into the ELPI each time. The ELPI stages were covered with aluminium foil discs without grease coating. The sampling was performed in triplicates (six puffs

× three runs or ten puffs × three runs). The charge and mass determined for each ELPI stage were averaged to obtain the mean profiles (Appendix B). This method was less laborious than the present one because drug deposits from multiple puffs were collectively assayed. However, a major disadvantage was that variations in the mass distribution between actuations could not be discerned. Consequently, any variations in the charge profiles of individual puffs, as measured by the ELPI, could not be meaningfully related to the mean mass profiles. Furthermore, the lack of grease coating on the stages may increase the risk of particle bounce on the impactor stages and introduces error in the sizing. The typical recommended load of an ELPI stage is 1 mg²¹. Since the HPLC methods employed were of sufficient sensitivity to quantify drug deposits from single puffs, all experiments were redone using the present procedure on individual puffs with silicon-coated stages. Aluminium foil discs were not used in this method lest the particle impaction stopping distances, and hence the cutoff sizes, be affected.

2.3.3 Mass Quantification of Deposited Drug Particles

In all mass assays the actuators and valve stems were not washed (hence the drug deposited on these parts not quantified) to avoid possible effects of cleaning on charge generation and to partly resemble patient use. Drug particles deposited on the adaptor, USP throat, hollow corona frame, and ELPI stages were assayed chemically using high performance liquid chromatography (HPLC). Chromatographic conditions for the assays are summarised in Table 2.2. Fresh standard solutions were prepared to generate standard curves before each HPLC run. The Waters HPLC system (USA)

consisted of a 515 mobile phase pump, a 717 auto-injector, and a 2487 dual wavelength UV-visible detector.

Ventolin[®]

The adaptor, throat, and corona frame were each washed exhaustively with 5 mL of the mobile phase (Table 2.2). The impactor stages were ultrasonicated for 10 minutes in beakers containing 5 mL of the mobile phase and 5 mL of cyclohexane, which was used to dissolve the silicon fluid to allow the extraction of the drug into the mobile phase. The liquid mixtures were centrifuged at 3080g for 15 minutes to separate the two phases. Samples were taken from the aqueous phase for assay.

Intal Forte[®] and Tilade[®]

The drug extraction method was similar to the one for Ventolin[®], except the appropriate mobile phase (Table 2.2) used was 10 mL instead of 5 mL.

QVAR[®] and Flixotide[®]

Drug extraction by sonication was carried out in 5 mL of the respective mobile phase (Table 2.2). For QVAR[®], 10 µg/mL triclosan was also present in the mobile phase as an internal standard. The samples were not centrifuged as no cyclohexane was used, hence no phase separation required.

Table 2.2. Chromatographic conditions for the chemical assays.

Inhaler	Mobile phase ^a	Column ^b	Mobile phase flow rate (mL/min)	UV Detection (nm)	Injection volume (μL)	Limit of quantitation (LOQ; μg/mL)	Accuracy at LOQ (%)	Concentration range for standards (μg/mL) ^c
Ventolin [®]	300 mL methanol 200 mL deionised water 0.5 g sodium lauryl sulphate	Waters Nova-Pak [®] C18	1.5	276	100	0.05	95-105	0.04-10 ($r^2 = 0.9996$)
Intal [®] Forte	260 mL acetonitrile 140 mL phosphate buffer	Phenomenex Luna [®] 5μm Amino-propyl	2.0	320	20	0.5	97-103	0.06-500 ($r^2 = 0.9998$)
Tilade [®]						0.1	99-100	0.06-500 ($r^2 = 0.9994$)
QVAR [®]	350 mL methanol 150 mL deionised water	Waters Nova-Pak [®] C18	1.0	240	100	0.1	98-112	0.02-20 ($r^2 = 0.9996$)
Flixotide [®]	250 mL methanol 190 mL deionised water 50 mL acetonitrile 8.5 mL acetic acid	Waters Nova-Pak [®] C18	1.0	242	50	1	104-105	0.02-200 ($r^2 = 0.9992$)

^a All mobile phases were filtered through a 0.45 μm filter by vacuum prior to the HPLC runs.

^b Column temperature was 30°C.

^c Standard curves for all HPLC runs were linear in the concentration range measured. Coefficients of determination are in parentheses. Precision for all assays were < 1% relative standard deviation between 10-50 μg/mL.

2.3.4 Data Analysis

The charge on each impactor stage was derived from the electric current data by calculating the area under the curve in the current versus time plot for that particular stage. The *net charge* was calculated from the sum of charges on all stages. The *fine particle dose charge* was taken as the sum of charges on all particles of size < 6.66 µm, corresponding to those on Stage 11 and below. Likewise, the *ex-actuator dose* was the total drug mass recovered without the actuator and the *fine particle dose (FPD)* was the sum of drug mass deposits on Stage 11 and below. The *charge per mass of drug, or charge-to-mass ratio (q/m)*, for a given size fraction was calculated for the discrete puffs by dividing the charge by the mass in that size fraction. This was only derived for the size fractions containing detectable amounts of drug, corresponding to Stages 8 to 10 for suspension MDIs and Stages 4 to 9 for QVAR[®] solution MDIs. Likewise, the number of elementary charges (*n*) per drug particle in these particular size fractions was estimated for the discrete puffs by the following equation:

$$n = \frac{q}{m} \cdot \frac{\rho V}{e} \quad (\text{Equation 2.1})$$

where ρ is the true density of the particles, V the volume of a particle, and e the elementary charge (1.602×10^{-19} C). The particles were assumed to be spherical and have an average true density of 1.5 g/cm^3 . For a given ELPI stage, V was calculated from the cutoff diameter.

2.3.5 Faraday Pail Charge Measurement for Ventolin[®] MDIs

The Faraday pail method was also employed to measure the net charge of the Ventolin[®] aerosol for comparison (see later discussion). Single puffs were discharged through an USP throat into the inner well of a Faraday pail (Model 284/22B, Monroe Electronics, Lyndonville, NY) connected to a NanoCoulomb Meter (Model 284, Monroe Electronics, Lyndonville, NY). The net charge of particles that exited the throat was thus measured. Six puffs from each of the three Ventolin[®] inhalers were sampled.

2.4 Results

Typical electric current profiles of the aerosols from which the charge data were derived are displayed in Figure 2.2. Figures 2.3 to 2.5 show the mass and charge distributions of the aerosols. The ex-actuator dose, FPD, net charge, and fine particle dose charge are summarised in Table 2.3. Substantial differences in the charge profiles were observed among the five types of inhalers. Bipolar charges were produced from Intal[®] Forte, Tilade[®], and Flixotide[®], irrespective of discrete or continuous puffs. Ventolin[®] produced bipolar charges in the discrete puffs, but the continuous puffs were unipolar negative (Figure 2.4). However, after lapsing for an hour or longer the Ventolin[®] inhalers produced bipolar aerosols again. In contrast, discrete puffs from QVAR[®] were unipolar positive with high variation, while the continuous puffs were only very lightly charged. The charges from Ventolin[®] measured with the Faraday pail were -2.57 ± 0.31 , -2.99 ± 0.26 , -2.55 ± 0.70 nC for

inhalers V1, V2, and V3, respectively (mean $\pm$ standard deviation; $n = 6$). Tables 2.4 and 2.5 show the charges per mass of drug and estimated number of elementary particles per drug particle, respectively. The charges per mass of drug of the MDIs were between -20 and +12 $\mu\text{C/g}$. A particle in these size fractions was estimated to carry up to several hundred elementary charges.

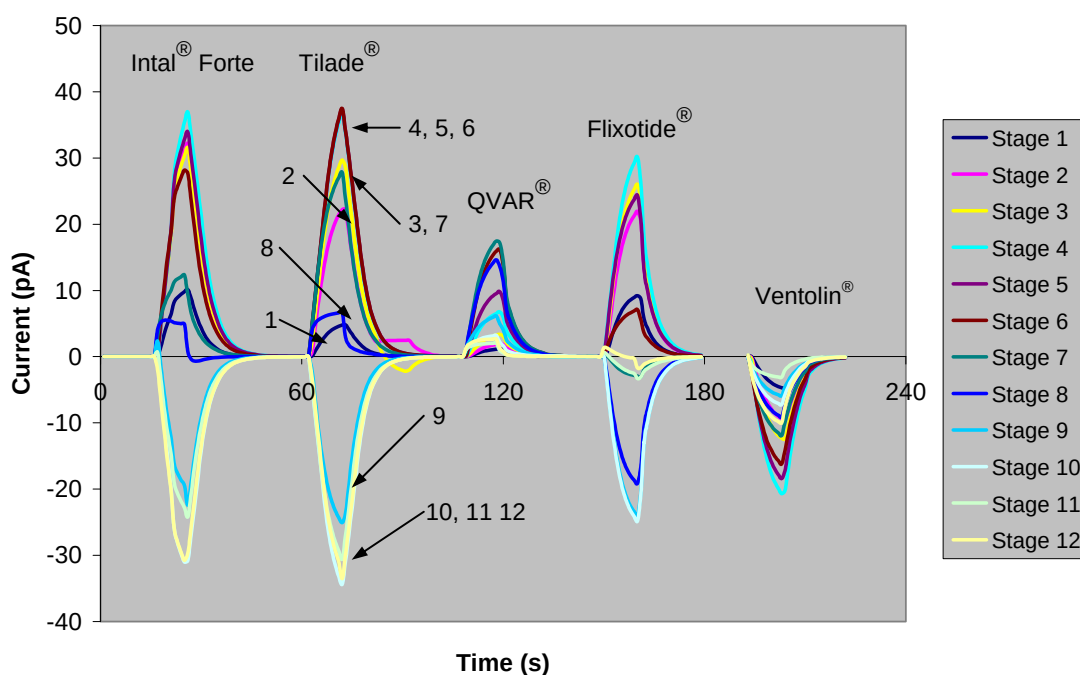


Figure 2.2. Typical current profiles of aerosol per actuation of the MDIs. Numbers labelling the Tilade[®] profile indicate the ELPI stages.

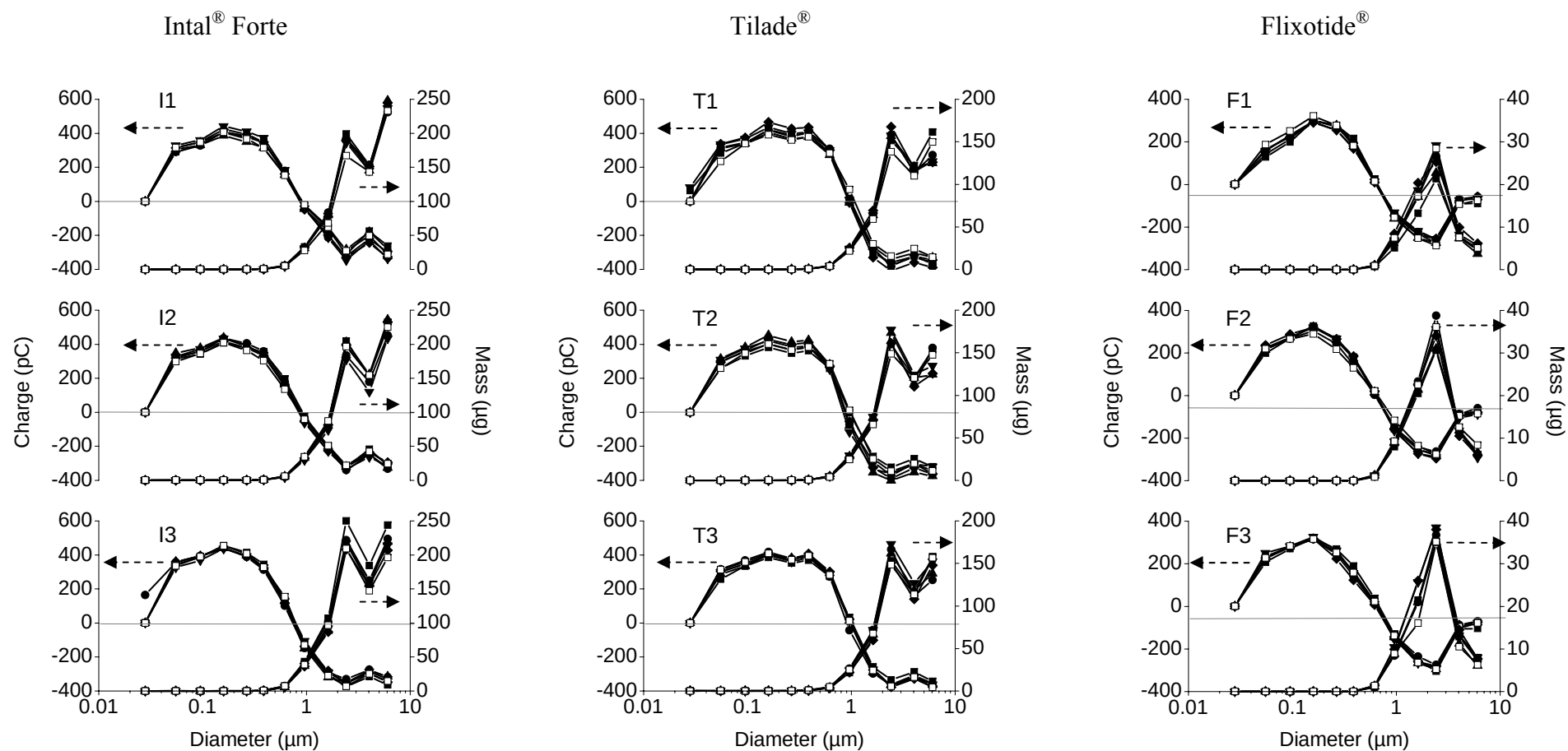


Figure 2.3. Charge and mass profiles of Intal[®] Forte (I1-I3), Tilade[®] (T1-T3) and Flixotide[®] (F1-F3) inhalers. Actuations #1 to #5, and #18 are shown for each MDI (■#1, ●#2, ▲#3, ▼#4, ◆#5, □#18).

Ventolin[®]

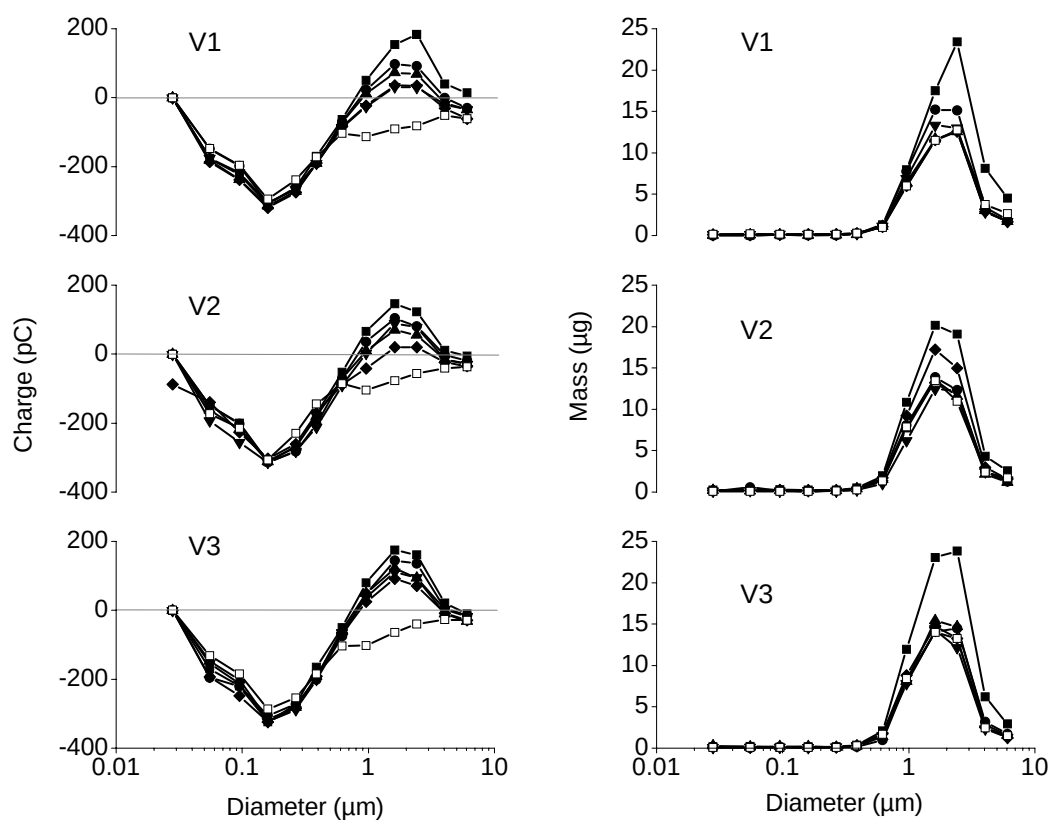


Figure 2.4. Charge and mass profiles of Ventolin[®] (V1-V3) inhalers. Actuations

#1 to #5, and #18 are shown for each MDI (■#1, ●#2, ▲#3, ▼#4, ◆#5, □#18).

QVAR[®]

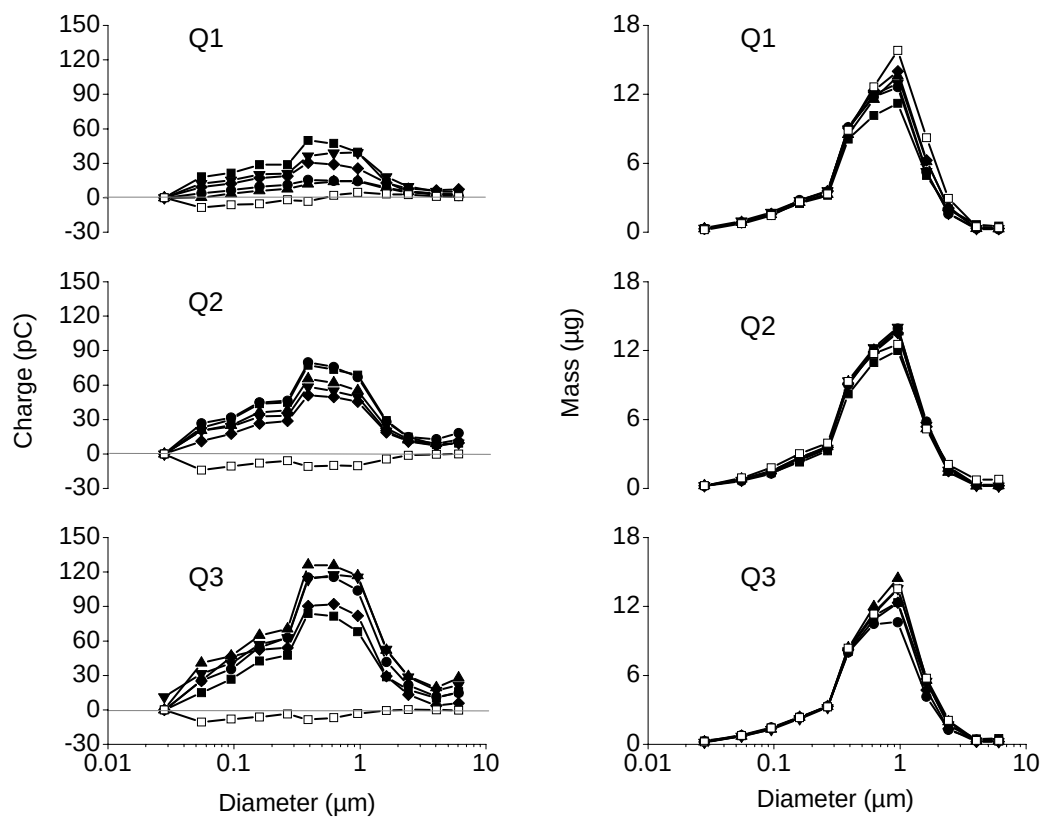


Figure 2.5. Charge and mass profiles of QVAR[®] (Q1-Q3) inhalers. Actuations #1 to #5, and #18 are shown for each MDI (■#1, ●#2, ▲#3, ▼#4, ◆#5, □#18).

Table 2.3. Mean ex-actuator and fine particle doses; mean net and fine particle dose charges (n = 18)*.

Inhaler	Ex-actuator dose (µg)	Fine particle dose (µg)	Net charge (nC)	Fine particle dose charge (nC)
Intal [®] Forte	4332.62 (38.15)	480.25 (10.03)	+0.80 (0.03)	+1.12 (0.03)
Tilade [®]	1844.18 (26.54)	373.22 (4.57)	+0.79 (0.02)	+1.15 (0.02)
Flixotide [®]	198.47 (4.71)	72.74 (2.74)	+0.38 (0.01)	+0.45 (0.01)
Ventolin [®]	97.22 (4.41)	43.13 (2.21)	-1.13 (0.06)	-1.10 (0.05)
QVAR [®]	74.26 (3.28)	49.60 (0.76)	+0.30 (0.06)	+0.29 (0.05)

* 6 actuations from each of 3 MDIs. Standard errors are in parentheses.

Table 2.4. Mean charges per mass of drug of the MDIs (µC/g) (n = 15)*.

Stage	4	5	6	7	8	9	10
Size (µm)	0.159	0.266	0.388	0.621	0.960	1.62	2.42
Intal [®] Forte	N/A	N/A	N/A	N/A	-2.00 (0.29)	-2.73 (0.11)	-1.65 (0.03)
Tilade [®]	N/A	N/A	N/A	N/A	-0.61 (0.42)	-4.37 (0.09)	-2.28 (0.04)
Flixotide [®]	N/A	N/A	N/A	N/A	-18.19 (0.89)	-12.27 (0.49)	-8.96 (0.43)
Ventolin [®]	N/A	N/A	N/A	N/A	+2.48 (1.01)	+6.33 (0.64)	+5.68 (0.56)
QVAR [®]	+14.73 (2.06)	+11.44 (1.56)	+7.90 (1.15)	+5.81 (0.83)	+4.71 (0.69)	+4.88 (0.73)	N/A

* 5 discrete actuations from each of 3 MDIs. Standard errors are in parentheses.

N/A: Not applicable for derivation of charge per mass of drug.

Table 2.5. Estimated number of elementary charges per drug particle for the MDIs calculated by Equation 2.1 (n = 15)*.

Stage	4	5	6	7	8	9	10
Size (µm)	0.159	0.266	0.388	0.621	0.960	1.62	2.42
Intal [®] Forte	N/A	N/A	N/A	N/A	-9 (1)	-57 (2)	-115 (2)
Tilade [®]	N/A	N/A	N/A	N/A	-3 (2)	-91 (2)	-158 (3)
Flixotide [®]	N/A	N/A	N/A	N/A	-79 (4)	-256 (10)	-623 (30)
Ventolin [®]	N/A	N/A	N/A	N/A	+11 (4)	+132 (13)	+395 (39)
QVAR [®]	0 (0)	+1 (0)	+2 (0)	+7 (1)	+20 (3)	+102 (15)	N/A

* 5 discrete actuations from each of 3 MDIs. Standard errors are in parentheses. Calculations based on an average true density of 1.5 g/cm³; pharmaceutical powders generally have true densities between 1.0 and 2.0 g/cm³²².
N/A: Not applicable for derivation of elementary charges per drug particle.

2.5 Discussion

The results indicated that aerosols produced from the MDIs carried electrostatic charges and the charge is MDI-dependent. The charge levels measured for the various particle size fractions may depend on i) the level of innate charges on the particles and/or ii) the amount of charged particles in a specific size fraction. The mass of deposited drug measured by HPLC will help to differentiate these two factors (see later discussion). The charge profile and net charge produced per actuation were reproducible for Intal[®] Forte, Tilade[®], and Flixotide[®], while those from QVAR[®] showed a large inter- and intra-inhaler variation (Figures 2.3 and 2.5; Table 2.3). Although the charge profiles obtained over six actuations from three QVAR[®] inhalers

were similar in trend they differed in magnitude over the entire particle size range. However, the size distributions showed little change (Figure 2.5). Ventolin[®] displayed some mass and charge variation (Figure 2.4). Most noticeably are i) the first puff being always the highest in dose, and ii) the continuous puffs being negatively charged in the size range 0.960-4.04 μm as opposed to the positive charge of the discrete puffs. Since the mass distributions of the continuous and discrete puffs were similar, the variations in their charge profiles were not due to dose non-uniformity, but other MDI aspects. Flixotide[®], Ventolin[®], and QVAR[®] use 1, 1, 1, 2-tetrafluoroethane (HFA-134a or norflurane) as the propellant but QVAR[®] also contains ethanol (Table 2.1). In addition, QVAR[®] is the only MDI used in this study that has a metal valve stem, while all the others have plastic ones. These differences are most likely the source of variation in QVAR[®] as ethanol may interact with the rest of the formulation system, including the valve stem material. Furthermore, water ingress into MDI formulation is well documented²³. It is likely that water may also be present as an impurity in the formulation and affect the charging^{9,24}. The results also indicate that it is the propellant-drug combination rather than the propellant itself that determines the charge in the aerosol, since both Flixotide[®] and Ventolin[®] contain HFA-134a without excipients, yet the former produces bipolar charges reproducibly and the latter bipolar or unipolar negative charges (depending on discrete or continuous puffs). The puff-dependent charging of Ventolin[®] indicates that charge relaxation may influence the charging of salbutamol sulphate from this formulation. Upon actuation, as electrostatic charges are produced on the emitted particles, counter-charges must reside in the actuator, valve components and/or drug deposits in these locations. These residual charges take time to decay and their presence may affect charging of the particles in the subsequent actuation. A similar mechanism may

apply to QVAR[®] between the discrete or continuous puffs. The lack of this effect in Intal[®] Forte, Tilade[®], and Flixotide[®] suggests different electrostatic characteristics of these drugs and formulations. Future investigation is necessary to understand these charging mechanisms.

The charge profiles of Intal[®] Forte, Tilade[®], and Flixotide[®] share a similar trend, with positive charges measured below 0.6 μm and negative charges above that size (Figure 2.3). The charge polarity of Intal[®] Forte and Tilade[®] changed over between Stages 8 and 9, corresponding to particle cutoff diameters of 0.960 and 1.62 μm , respectively. The FPDs of Intal[®] Forte (480 μg) and Tilade[®] (373 μg) are comparable which can account for their similar fine particle dose charges (Table 2.3). However, a difference in the FPD did not yield a proportional difference in the fine particle dose charge for the other three MDIs. Any dose dependency of charging between different types of MDIs should be apparent from the charges per mass of drug (charge-to-mass ratios). The charges per mass of drug and estimated number of elementary charges per particle in the upper size fractions of Intal[®] Forte and Tilade[®] were comparable, but differed for the other MDIs (Tables 2.4 and 2.5). This suggests that the similar charging of Intal Forte[®] and Tilade[®] aerosols is due to their similar formulations. Both MDIs contain povidone, and macrogol 600 in the propellant 1, 1, 1, 2, 3, 3, 3-heptafluoropropane (HFA-227) (Table 2.1). These results support earlier reports that the charge of an MDI aerosol may be controlled by its formulation^{11,12}. Another possible reason for the similar charge levels may be due to the limitation of current detection with the 40,000 fA range setting. Thus the higher charges produced from these two products (due to their higher doses) could not be measured and consequently the charge profiles were truncated. This is discussed further in Chapter 3.

The average FPDs obtained from Ventolin[®] and Tilade[®] (Table 2.3) agreed with those reported in other studies^{25,26}. The fine particle fractions from HFA Flixotide[®] inhalers in the present study were consistent with those from chlorofluorocarbon (CFC) Flixotide[®] inhalers²⁷, both of which are suspension formulations. The same applied to those from QVAR[®] 100 µg MDIs in the present study and QVAR[®] 50 µg MDIs used by Leach et al²⁸. The results of mass measurements in the present study show a large proportion of drugs deposited in the inhaler mouthpiece and USP throat. The mass profiles of Intal[®] Forte, Tilade[®], Flixotide[®], and Ventolin[®] show similar trends, with progressively less drugs deposited down successive ELPI stages and negligible amounts past Stage 7, corresponding to a cutoff diameter of 0.621 µm (Figures 2.3 and 2.4). This is consistent with the fact that micronised particles used in suspension-type MDIs generally range from 1-5 µm²⁹. However, the QVAR[®] mass profile shows more particles in the lower size fractions, which is due to QVAR[®] being a solution formulation^{20,28}. A comparison of the charge and mass profiles of Intal[®] Forte, Tilade[®], and Flixotide[®] shows that while an increased level of charge (+ve or -ve polarity) followed a higher amount of deposited drug, an increased charge was also found in the lower stages where only very little drug was detected (Figures 2.3 and 2.4). These MDIs show high levels of positive charges measured without much drug particles below 0.6 µm, and negative charges were detected for drug particles above 1.0 µm. In contrast, Ventolin[®] reveals significant negative charges below 0.6 µm, and the charge level is diminishing above 0.6 µm where more drug particles are present. The high charges measured on the lower stages may be mainly contributed by propellant/excipients (and water as an impurity), rather than the drug itself. Thus the charge to mass ratios for the submicron fractions may be confounded by the excipient

charge and may not truly reflect the specific charges of the drug particles. This may contribute to large errors so the charge per mass of drug and the number of elementary charge per particle were only calculated for stages with substantial drug deposits (Tables 2.4 and 2.5). It is well known that for the suspension-type formulations the smaller droplets may not contain any solid drug particles³⁰. Thus the droplets that deposit on the lower stages may contain only excipients contributing to the charge measured. The contribution of excipients to the charge of MDI aerosols had been alluded to by Glover and Chan (2004) and earlier by Peart et al¹¹ on reformulated MDIs. The small droplets may also be produced from the evaporation and/or bursting of larger droplets. Charges are known to remain on a droplet during evaporation, hence the repulsive forces between the charges increase as the droplet size decreases³¹. The droplet explodes to generate smaller charged droplets when a critical size is reached at which the repulsive electrostatic forces overcome the surface tension of the droplet³². Evaporation and bursting may continue to occur on the daughter droplets. For suspension MDIs, droplets originally containing drug particles may burst asymmetrically to yield droplets with and without particles. For those containing the drug, charges from the propellant remain on the particles after evaporation. Thus the resultant charges on these particles are net charges contributed by both the excipients and the drug. On the other hand, the empty droplets would only carry charges from the excipients. This may account for the different charging between the upper and lower size fractions of the aerosols.

Unlike the four suspension-type inhalers, QVAR[®] shows a different trend with charge following the mass closely (Figure 2.5). QVAR[®] is a solution MDI containing ethanol and HFA-134a, both being volatile. Droplets actuated from the inhaler would contain

the dissolved drug, with an amount directly proportional to the size of the droplet. Also, the mass ratio of drug to excipients is constant for droplets of all sizes, even for those undergo or produced from evaporation and explosion. Thus the charge contribution by the excipients is likely to follow the drug mass according to the droplet size, resulting in the resemblance in the trend of the charge and mass profiles.

Besides the physicochemical properties of the drug and formulation, interactions of the drug and formulation with materials composing the metering valve and stem of the inhaler may be responsible for the charging, as had been investigated by Peart et al¹² on reformulated MDIs. Since charging of particles originates from their interactions with surfaces, the valve stem being the exit of MDI aerosols would be the site of significant charging of particles as they are blasted out of the canister with the propellant. Hence the material and design of valve components may play a crucial role.

In the present study the number of elementary charges per drug particle was estimated from the charge per mass of drug (Table 2.4 and 2.5). For all of the MDIs, larger drug particles carry more charge, presumably due to more surface area per particle for charging through triboelectrification and other physicochemical interactions. It is worth to note that based on the computer simulation results by Bailey et al⁸, these magnitudes of charge on the particles are high enough to affect particle deposition in the airways. Thus, the electrostatic properties of the aerosol may need to be examined in addition to other quality control routines (such as dose output and particle size) for MDIs. The findings may also have regulatory implications for generic aerosol products. For example, aerosols produced from MDI generic products using

formulation and/or components non-identical to the innovator product may have different charge profiles. Since aerosol particles from MDIs carrying high enough charges may affect deposition in the airways, different charges from generic products may potentially generate different lung deposition patterns. Clinical studies involving both therapeutic effect and lung deposition are necessary to fully address the potential effects of aerosol charge.

The fine particle dose charge of the HFA formulation of Ventolin[®] measured earlier by Peart et al¹⁰ was -230 pC compared with -1.10 nC from the present study (Table 2.3). The difference in the definitions of the fine particle fraction (5 μm vs 6.66 μm) does not account for this five-fold difference. This prompted the charge measurements of Ventolin[®] aerosols using the USP throat/Faraday pail setup. The charges determined from this procedure were slightly over -2.5 nC (Section 2.4). The higher magnitude of these results is partly because ELPI does not measure the large particles deposited in the corona frame and stage 13 but the Faraday pail measurements include these particles. Hence, the ELPI and Faraday pail results from the present study are comparable, both being consistently higher than the earlier value by Peart et al. The difference in instrumental design may account for the discrepancy between results from the present study and those by Peart et al¹⁰. The aerosol electrometer apparatus³³ is simpler in design, more akin to a two-stage impactor with an electrometer connected to a Faraday pail that serves as the fine particle stage. In contrast, the ELPI has a more intricate design with sensitive electrometers connected to each impactor stage. Furthermore, the aerodynamic environments within the two instruments may vary and not be completely congruent. In those studies^{11,12} only the net charge of the whole fine aerosol particle dose was measured. Thus the charge profiles derived did

not show charges on the particles within the various size fractions. More detailed profiles are desirable since charges of opposite polarities as functions of particle size may mask each other and detailed information on the specific charge versus the aerodynamic diameter cannot be discerned from an impactor with a low size resolution. This shortfall was overcome with ELPI, which provides more details illustrating relationships between the size and charge of aerosol particles.

2.6 Conclusion

The electrostatic characteristics of aerosols produced from a number of commercial MDIs were successfully examined using a modified ELPI. The aerosol charge profile was found to be MDI-dependent. The results are ascribable to differences in the drug, formulation, and the valve stem material of the MDI. The calculated number of elementary charges per particle of size $\leq 6.66 \mu\text{m}$ ranged from zero to several ten thousands. The high charge levels on particles may have a potential effect on the deposition of the aerosol particles in the lung when inhaled.

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Chapter 3

Effect of Spacers on the Electrostatic Charge Properties of Metered Dose Inhaler Aerosols

3.1 Introduction

Spacer devices are used with metered dose inhalers (MDIs) to overcome problems in coordinating inhalation with actuation, especially in children, and reduce throat deposition of drug particles¹. A spacer serves as a reservoir to hold the aerosol cloud for the patient to inhale through a one-way valve at a natural pace. It also provides a chamber in which MDI droplets may decelerate and evaporate to a smaller size before inhalation to reduce throat deposition and enhance penetration into the lungs².

Most spacers are constructed with lightweight plastic materials for portability and durability. Plastics are electrical insulators, thus electrostatic charges may be generated and accumulated on spacer surfaces through contact and friction, or triboelectrification³, during handling. Many studies have shown that spacer charges adversely affect drug output and consequently lung deposition due to particle retention inside the spacer⁴⁻⁸. Conversely, a reduction in spacer surface charges counteracts this effect. This suggests that spacer drug retention is due to electrostatic particle deposition on the internal walls. Methods of varying degrees of effectiveness have been reported for the reduction or elimination of surface charges on plastic

spacers^{5,9-12}. A radical method is to construct the spacer with a conducting material such as metal, which does not hold charges. The Nebuchamber[®] is a commercial steel spacer developed by AstraZeneca that showed similar *in vitro* antistatic properties to detergent-coated plastic spacers⁷. Recently, spacers manufactured from charge-dissipative polymers are also available¹³⁻¹⁵. However, the most popular method for charge reduction is coating the electrostatic spacers with dilute surfactant solutions^{7,8,10}. Ionic surfactants were found to perform better than nonionic ones¹⁰. This supports the hypothesis that a conductive surfactant coating on the spacer surface is effective in dissipating charges¹². The optimal treatment was to immerse the spacer in a detergent solution followed by drip-drying without rinsing with water⁸. The use of commercial detergents is simple, economical, and relevant to patient use in the community setting, and thus this procedure was adopted in the present study.

Particles emitted from MDIs are known to be charged (Chapter 2). Electrostatic interactions between charges on these particles and those on spacer surfaces may contribute to spacer deposition⁶⁻¹⁰. However, the electrostatic properties of MDI aerosols delivered via spacers have not been studied hitherto. Although many studies had been conducted on the effect of spacer charges on MDI aerosol drug output by cascade impaction^{5,7-10}, only the mass profiles were measured. The aerosol charge profiles were a major aspect missing from these studies because charge data cannot be obtained using conventional impactors. The modified ELPI overcomes this drawback and was employed in the present study to acquire a more complete understanding of the effects of spacers on aerosol charges.

Most of the material in this chapter was published in the *Journal of Aerosol Science*¹⁶. Some modifications to the text are included here.

3.2 Aim

The aim of the present study was to employ the modified ELPI to investigate charge and mass profiles of MDI aerosols sampled through new and detergent-coated plastic spacers. The AeroChamber[®] Plus spacer was used because it has a soft adaptor universal for the MDIs to provide a common sampling system.

3.3 Materials and Methods

3.3.1 Metered Dose Inhalers, Spacers, and Sampling Protocol

The four types of MDIs examined in the study were Ventolin[®] (100 µg salbutamol sulphate; Allen & Hanburys, Australia), Flixotide[®] (250 µg fluticasone propionate; Allen & Hanburys, Australia), Tilade[®] (2 mg nedocromil sodium; Aventis Pharma, UK), and QVAR[®] (100 µg beclomethasone dipropionate, 3M Health Care, UK). All are HFA products, with QVAR[®] being a solution formulation and the other three being suspensions. Nine new inhalers of each type were used before expiry, three without a spacer, three with new spacers and three with detergent-coated spacers. All MDIs were primed to waste prior to use according to the consumer medicine information leaflets. In the case of MDIs without spacer coupling, three single puffs

from each inhaler after priming were individually sampled for the charge and mass profiles, whereas only the first puff after priming was sampled in the spacer experiments.

New AeroChamber[®] Plus Valved Holding Chambers with Mouthpiece (Trudell Medical International, Canada) were used as new spacers upon removal from their packaging. After the first aerosol sampling and drug assay, these spacers were thoroughly cleaned and coated with detergent by soaking in a 1:5000 aqueous solution of Palmolive[®] (Colgate-Palmolive, Australia) for five minutes, followed by drip-drying under room conditions for 12-24 hours.

3.3.2 Measurement of Spacer Wall Surface Potential

The surface potential on the internal spacer wall was measured with a side-view probe (Model 1017AS, Monroe Electronics, USA) connected to an Isoprobe[®] electrostatic voltmeter (Model 244A, Monroe Electronics, USA). This feedback-type voltmeter was used because measurements can be conducted without contacting the probe with the surface under examination. This is desirable because surface potentials may be disturbed through electrostatic discharge or charge transfer if the probe touches that surface. The principle of operation is that the voltmeter drives the probe to the same voltage as that on the spot of interest to nullify the unknown electric field when the detection aperture is positioned close to, but not contacting, the surface. The voltage reached thus is recorded as the surface potential.

The voltmeter was first zeroed and the probe-to-surface spacing insensitivity was adjusted as specified in the manual. This minimises the effect of minor variations in the probe-to-surface distance on the voltage reading. All new spacers were kept in the original packaging until measurement. Charges were measured on all spacers immediately before and after aerosol sampling. The rubber inhaler adaptor (Figure 3.1a) was removed from the spacer before measurement to allow close positioning of the electrostatic probe to the internal wall. A sheet of aluminium foil was wrapped tightly around the external surface and placed onto a grounded metal plate (Figure 3.1b). The aluminium wrapping contacted the metal plate thus was also grounded. The detection aperture of the probe was positioned inside the spacer, approximately 5 cm from the inhaler end and 3 mm above the internal surface (Figure 3.1c). This is the mid-section of the spacer. The spacer was rotated about its longitudinal axis for one revolution. The surface potential along the inner circumference was measured by the electrometer and recorded by an oscilloscope (Model 54621A, Agilent Technologies, USA). The measurement was repeated at another position 10 cm from the inhaler end (Figure 3.1c). This is in the far end of the spacer close to the mouthpiece. The same procedure was applied to the detergent-coated spacers. The surface potential at the inhaler end was not measured because the action of removing the rubber adaptor from the spacer would generate surface charges in this region and thus confound the readings. The adaptor was replaced onto the spacer after each surface potential measurement and before aerosol sampling.

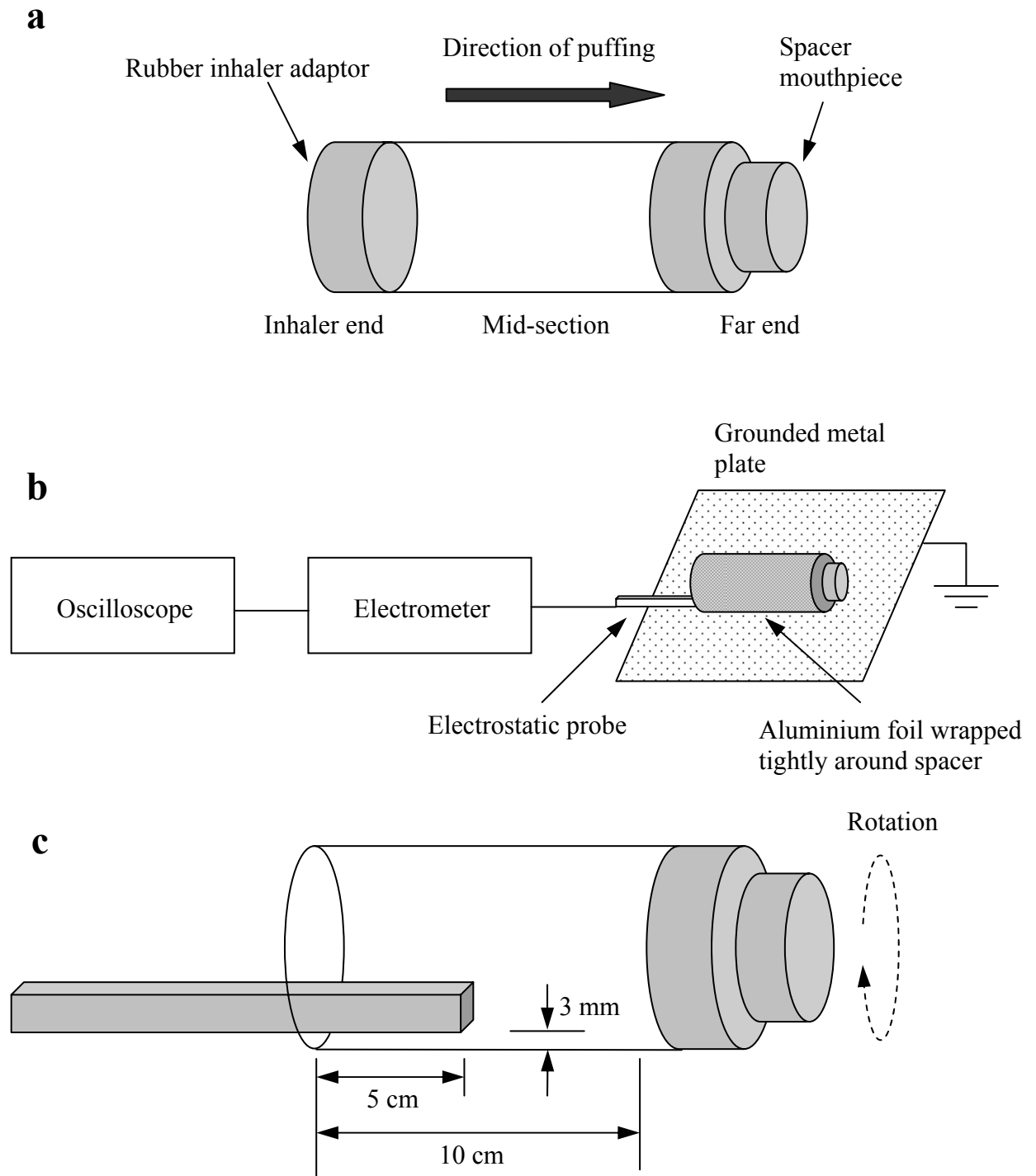


Figure 3.1. (a) Nomenclature of the spacer parts. (b) Schematic of the spacer surface potential measurement setup. (c) Probe-to-surface distances inside the spacer. Diagrams not drawn to scale.

3.3.3 Measurement of Aerosol Electrostatic Charge

A modified ELPI (Dekati, Finland) with the corona charger removed and a USP throat attached was used to measure the inherent aerosol charges¹⁷. Tight-fitting adaptors for the MDI and spacer mouthpieces were employed for complete aerosol sampling. Particle bounce and re-entrainment were minimised by the application of 90 μ L of a 1 g/15 mL solution of silicone fluid (200 Fluid/ 60000 cSt; Dow Corning, Australia) in cyclohexane (Mallinckrodt, USA). The solvent was allowed to evaporate before the assembly of the impactor stages. The air flow through the ELPI was 30 L/minute, generated with a Sogevac[®] model SV25 vacuum pump (Leybold, France). The aerosol charges were measured and recorded using the Dekati ELPIVI 4.0 software with the current range set at 400,000 fA. This software is a newer version provided by the manufacturer than the one used previously (Section 2.3.2). All the essential data collection functions are the same for both versions. The experimental setup is shown in Figure 3.2.

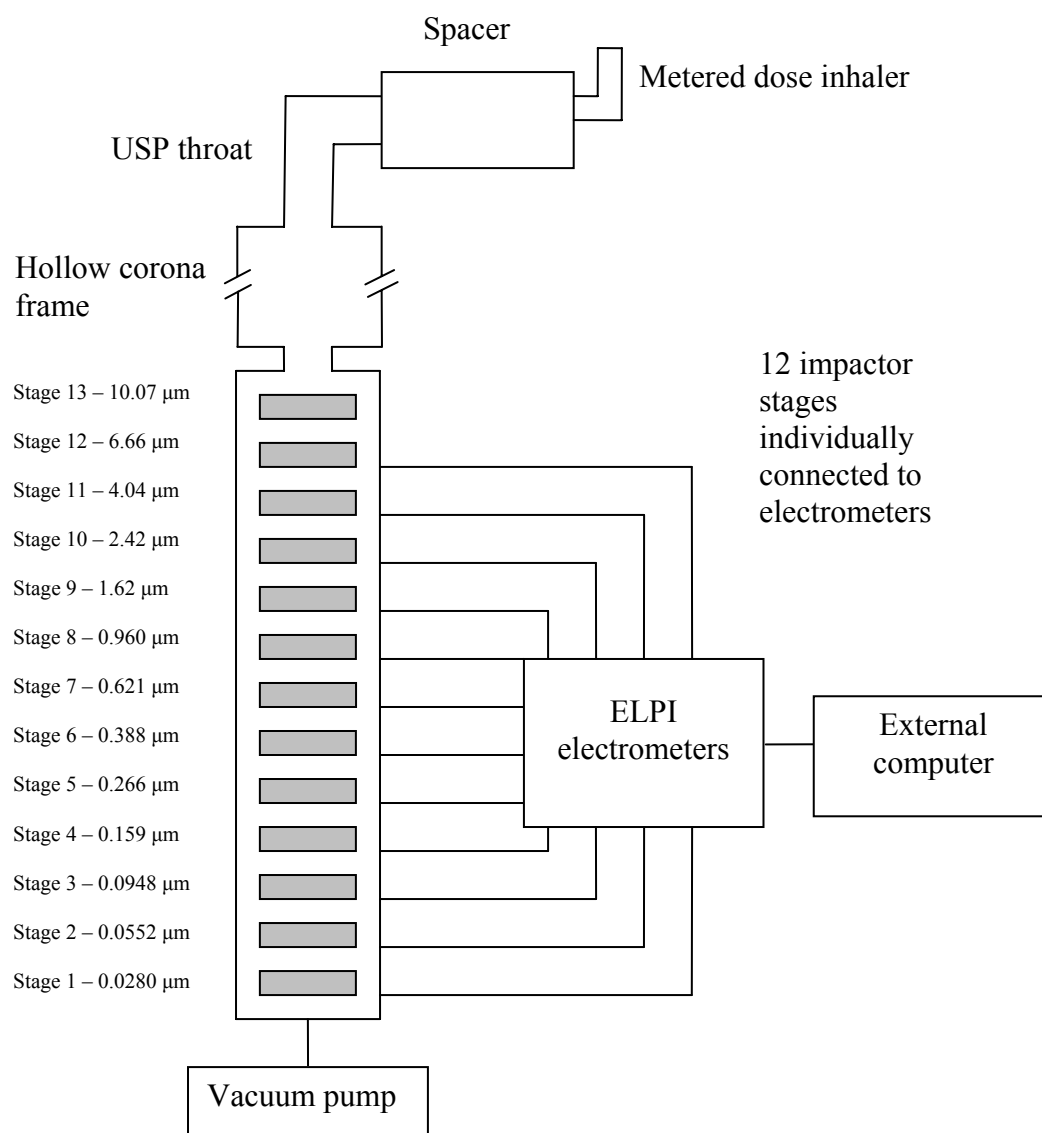


Figure 3.2. Schematic of the ELPI setup the MDI/spacer measurement. For the MDI-alone experiments the inhaler was connected directly to the throat. Diagram not drawn to scale.

All MDIs were shaken by hand for a few seconds before aerosol sampling. In the experiments without spacers, the vacuum pump was switched on to establish the air flow and the electric current signals zeroed before inhaler actuation into the ELPI. In the spacer experiments, the spacer was first connected to the USP throat with the

vacuum pump switched off. The air flow was then started immediately after MDI actuation into the spacer. This was done to ensure that tight connection and alignment of the spacer to the throat was in place. The difference in the experimental protocols was found to have no effect on the drug mass recovered for the MDI aerosols. This is because a steady flow (which takes 400 ms) is already established before the aerosol entered the impactor stages (which takes > 900 ms). It was observed that the background electrical signals were always temporarily disturbed upon the commencement and termination of air flow through the impactor. These disturbances were low in magnitude relative to the sample signals and lasted only for a few seconds, after which a stable zero baseline was obtained. Before each spacer experiment the vacuum pump was switched on and off three times to generate the blank signals, the mean of which was calculated and subtracted from the aerosol measurements to account for these noises.

3.3.4 Mass Assays of Drug Deposits

The drug deposits on the MDI actuators and valve stems were not assayed since the priming shot(s) also contributed to the deposits in these components. Furthermore, this allows the comparison of mass recoveries obtained with those from Chapter 2 using similar assaying procedures. Deposits inside the spacer, on the adaptor, USP throat, hollow corona frame, and ELPI stages were quantified chemically using HPLC.

3.3.5 Sample Preparation for HPLC

The drug extraction methods and chromatographic conditions were identical to those used previously (Section 2.3.3) except that in the present study no internal standard was used in the QVAR[®] assays and 5 mL of a 20:80 v/v water-in-methanol mixture was used for drug extraction in the QVAR[®] and Flixotide[®] assays.

3.3.6 Data Analysis

The charge on each impactor stage was derived from the electric current data by calculating the area under the curve in the current versus time plot for that particular stage. The *net charge* was calculated from the sum of charges on all stages. The *fine particle dose charge* was taken as the sum of charges on all particles of size < 6.66 μm , corresponding to those on Stage 11 and below. Likewise the *fine particle dose* (FPD) was the sum of the drug mass deposits on Stage 11 and below. The *ex-actuator dose* is the total drug mass recovered from all the components assayed. The *spacer* and *throat depositions* are the masses of drug deposited in these parts. The *mass median aerodynamic diameter* (MMAD) was calculated from the ELPI drug assay data. The *charge per mass of drug*, or *charge-to-mass ratio* (q/m), for a given size fraction was calculated by dividing the charge by the drug mass in that size fraction. This was only derived for the size fractions containing detectable amounts of drug, corresponding to Stages 8 to 10 for suspension MDIs and Stages 4 to 9 for QVAR[®] solution MDIs. Likewise, the number of elementary charges (n) per drug particle in a these size fractions was estimated by Equation 2.1 (Chapter 2). The ex-actuator dose, spacer deposition, throat deposition, FPD, MMAD, net charge, and the fine particle

charge were analysed statistically using one-way analysis of variance (ANOVA), followed by the Tukey multiple comparisons post hoc test ($\alpha = 0.05$) to determine differences between the means. All statistical procedures were performed with Minitab™ Statistical Software 13.31.

3.4 Results

Figure 3.3 shows examples of surface potentials at the two measurement regions inside new and detergent-coated spacers. Before aerosol firing and sampling, high surface potentials were measured on the new spacers, the magnitude and distribution of which were non-uniform within and between spacers. Detergent-coated spacers showed minimal surface potentials that were fairly close to zero. The surface potentials on the new spacers were slightly altered after aerosol actuation and sampling. While the readings at some locations decreased in magnitude, those at other sites increased both in the positive and negative polarities. The extent of change was also unequal. On the other hand, the surface potentials on detergent-coated spacers remained low after aerosol actuation.

The charge and mass profiles of the four types of MDIs with and without spacers are shown in Figure 3.4. For MDIs used alone, the first puff after priming was not characteristically different in charge and mass to the two subsequent puffs, except for Ventolin[®], the first puff (after priming) was higher in mass, as was also observed in the previous chapter. Most drug deposits were on Stages 8 to 10 (0.960 to 2.42 μm) for the three suspension-type MDIs. On the other hand, QVAR[®], being a solution

formulation, produced smaller particles that deposited mainly on Stages 4 to 9 (0.159 to 1.62 μm). For the suspension MDIs, high charges were measured on the lower stages where only very little drug was detected. As discussed in the previous chapter, these charges are believed to originate from propellant/excipient droplets containing no drug particles. Since patients are instructed by consumer medicine information leaflets to prime new MDIs before initial use, only the results from the first puff in the MDI-alone experiments were compared with those with spacers, from which only the first puff of an inhaler was sampled. Figure 3.4 shows that both charge and mass outputs were decreased when a spacer was used. Of the two types of spacers, the new spacer gave the lowest charge and mass levels. However, the charge profiles were not qualitatively altered by the presence of a new or detergent-coated spacer. The charges were merely decreased in magnitude compared to those directly from a MDI.

The ex-actuator dose and various particle size and charge parameters are summarised in Table 3.1. Spacer retention was generally the highest when a new spacer was used. This in turn led to lower throat deposition, FPD, and net aerosol and Fine particle dose charges comparing to MDI-alone (Table 3.1) as fewer particles were available for sampling by the ELPI. These trends were counteracted by the detergent-coated spacer, with result values being intermediate in magnitude between those with MDI-alone and with a new spacer.

Tables 3.2 and 3.3 show the charges per mass of drug and estimated number of elementary particles per drug particle, respectively. In the size fractions containing major drug deposits (Section 3.3.6), both the charge per mass of drug and number of elementary charges per drug particle generally follow the order of “new spacer”,

“detergent-coated spacer”, and “MDI-alone” in increasing magnitude. This is the same trend as that indicated in Table 3.1. In the size fractions with minimal drug deposition, the charges per mass of drug are high in both magnitude and variability. This is due to the low drug mass in the q/m ratio, along with the high charges being mainly contributed by the propellant and/or excipients.

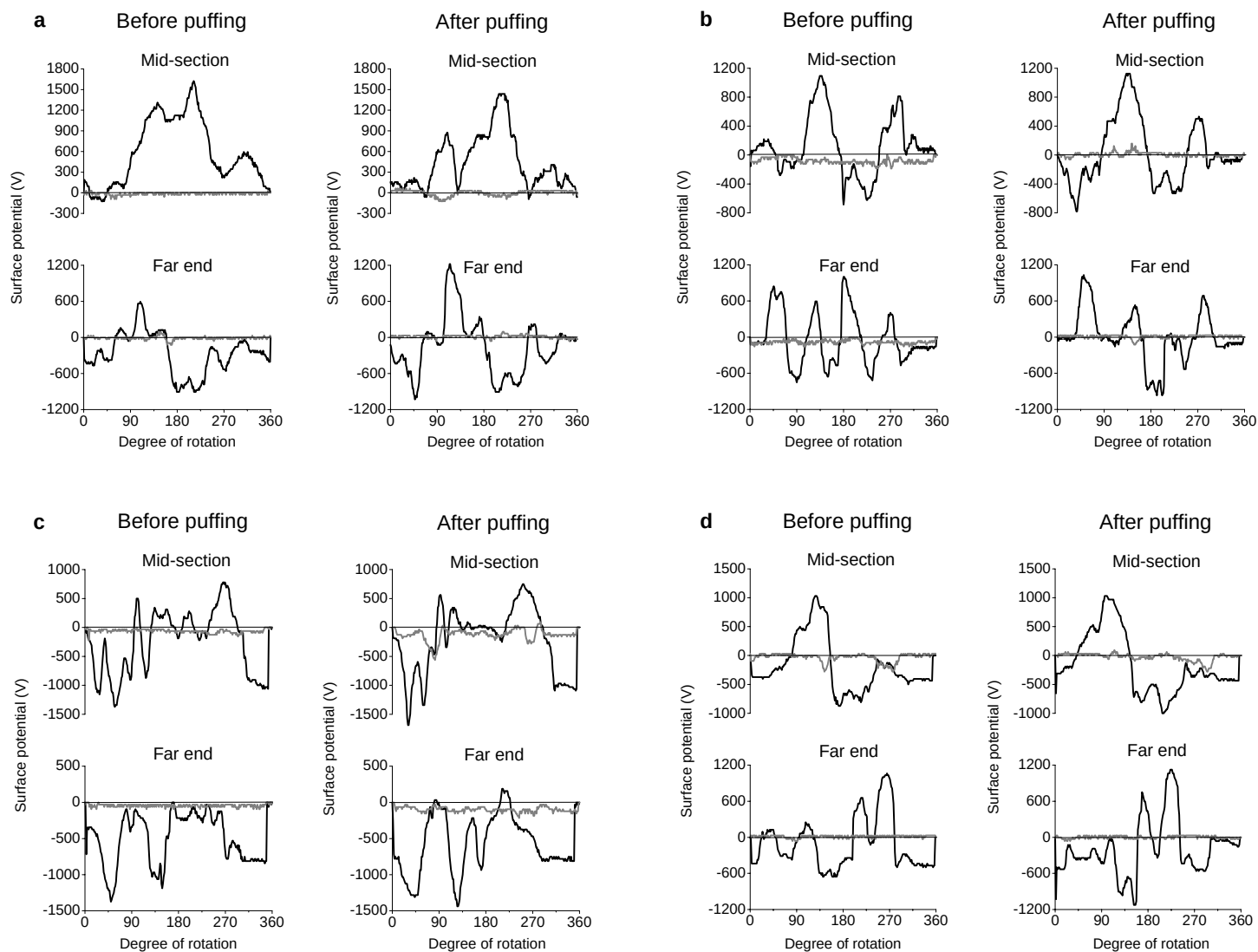


Figure 3.3. Surface potentials on the internal wall at two locations inside a new (black line) and a detergent-coated (grey line) AeroChamber Plus® spacer before and after aerosol puffing and sampling from (a) Ventolin®, (b) Flixotide, (c) Tilade®, and (d) QVAR®.

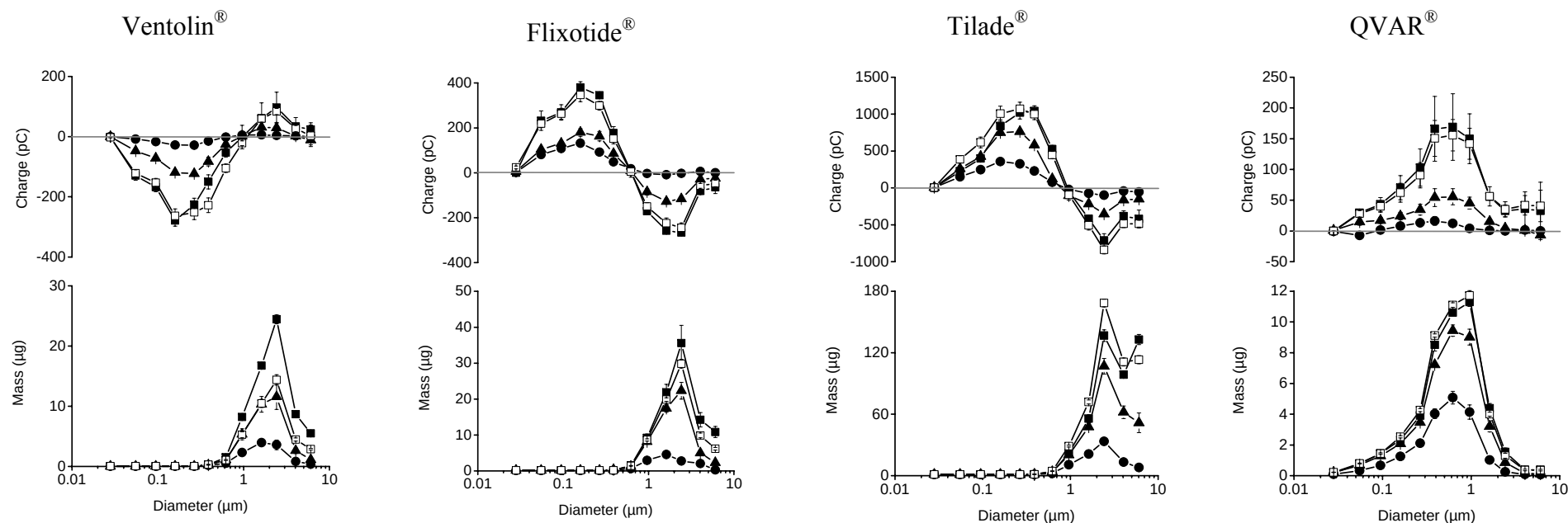


Figure 3.4. Charge and mass profiles of Ventolin[®], Flixotide[®], Tilade[®], and QVAR[®] (■ MDI-alone, Puff #1; □ MDI-alone, Puffs #2 and #3; ● with new spacer, Puff #1; ▲ with detergent-coated spacer, Puff #1). Error bars represent standard errors ($n = 3$ for ■, ●, ▲; $n = 6$ for □).

Table 3.1. Ex-actuator dose, deposition, particle size, and charge parameters for the aerosols emitted from MDIs with and without a spacer.

		Ex-Actuator Dose (µg)	Spacer Deposition (µg)	Throat Deposition (µg)	Fine Particle Dose (µg)	MMAD (µm)	Net Charge (pC)	Fine Particle Dose Charge (pC)
Ventolin®	MDI-Alone	150.80 (9.03)	N/A	70.20 (6.11) ^{ab}	60.08 (1.74) ^{ab}	1.82 (0.01) ^{ab}	-792.23 (150.34) ^a	-815.81 (135.73) ^{ab}
	New Spacer	127.84 (26.01)	113.62 (23.70)	0.65 (0.11) ^a	11.61 (2.16) ^{ac}	1.42 (0.04) ^a	-81.08 (32.18) ^a	-81.50 (33.32) ^a
	Detergent-Coated Spacer	104.43 (15.25)	66.04 (13.62)	2.07 (0.55) ^b	31.37 (4.75) ^{bc}	1.56 (0.05) ^b	-417.27 (50.43)	-406.15 (34.23) ^b
Flixotide®	MDI-Alone	280.19 (41.46)	N/A	160.21 (28.78) ^{ab}	83.35 (10.29) ^a	1.95 (0.02) ^{ab}	+567.61 (83.92)	+632.44 (61.83) ^a
	New Spacer	250.41 (17.17)	233.72 (16.50) ^a	0.84 (0.20) ^a	13.87 (1.84) ^{ab}	1.34 (0.06) ^{ac}	+472.74 (87.77)	+473.01 (81.14)
	Detergent-Coated Spacer	223.88 (19.93)	156.46 (13.92) ^a	5.86 (0.37) ^b	55.17 (4.85) ^b	1.65 (0.02) ^{bc}	+297.52 (20.77)	+321.60 (22.77) ^a
Tilade®	MDI-Alone	1920.60 (52.98)	N/A	1215.23 (53.28) ^{ab}	322.92 (12.67) ^{ab}	3.75 (0.17) ^{ab}	+2070.24 (92.36) ^a	+2491.10 (171.46) ^a
	New Spacer	2014.53 (93.77)	1893.50 (103.79) ^a	14.17 (1.28) ^a	88.06 (8.73) ^{ac}	1.78 (0.03) ^a	+1105.13 (51.83) ^{ab}	+1160.53 (58.78) ^{ab}
	Detergent-Coated Spacer	1800.60 (38.92)	1379.97 (9.40) ^a	74.08 (1.47) ^b	247.41 (15.88) ^{bc}	2.23 (0.07) ^b	+1917.59 (69.94) ^b	+2068.94 (83.50) ^b
QVAR®	MDI-Alone	77.45 (2.05)	N/A	28.28 (2.85) ^{ab}	45.36 (1.27) ^{ab}	0.50 (0.01) ^a	+888.22 (257.20) ^a	+855.47 (225.75) ^a
	New Spacer	66.86 (4.45)	45.77 (3.80) ^a	0.98 (0.15) ^a	19.13 (1.34) ^{ac}	0.43 (0.01) ^a	+50.90 (50.68) ^a	+29.78 (30.65) ^a
	Detergent-Coated Spacer	63.95 (4.57)	22.23 (3.36) ^a	1.83 (0.26) ^b	37.64 (1.41) ^{bc}	0.47 (0.01)	+261.08 (61.06)	+267.66 (64.07)

Data are presented as mean with standard error in parenthesis ($n = 3$). Results for MDI-alone experiments were derived from Puff #1 of each of the three inhalers. Means within a cell labelled with common letter(s) in the superscript are statistically different ($p \leq 0.05$).

MMAD: mass median aerodynamic diameter; N/A: Not applicable for MDI-alone experiments.

Table 3.2. Charges per mass of drug for the MDIs ($\mu\text{C/g}$).

Stage		4	5	6	7	8	9	10
Size (μm)		0.159	0.266	0.388	0.621	0.960	1.62	2.42
Ventolin [®]	MDI-Alone	N/A	N/A	N/A	N/A	-0.50 (4.69)	+3.50 (3.03)	+3.83 (2.01)
	New Spacer	N/A	N/A	N/A	N/A	+2.42 (1.03)	+1.72 (0.71)	+1.29 (0.63)
	Detergent-Coated Spacer	N/A	N/A	N/A	N/A	+0.85 (1.61)	+3.13 (1.37)	+2.37 (1.15)
Flixotide [®]	MDI-Alone	N/A	N/A	N/A	N/A	-19.01 (2.03) ^a	-12.05 (1.29) ^a	-7.80 (1.15)
	New Spacer	N/A	N/A	N/A	N/A	-2.13 (2.46) ^a	-1.68 (1.26) ^{ab}	-3.18 (3.89)
	Detergent-Coated Spacer	N/A	N/A	N/A	N/A	-10.72 (2.25)	-7.42 (0.83) ^b	-5.23 (0.41)
Tilade [®]	MDI-Alone	N/A	N/A	N/A	N/A	-2.33 (1.48)	-7.56 (0.71) ^a	-5.21 (0.64) ^a
	New Spacer	N/A	N/A	N/A	N/A	-1.92 (0.91)	-3.33 (0.76) ^a	-2.82 (0.50) ^a
	Detergent-Coated Spacer	N/A	N/A	N/A	N/A	-5.20 (1.33)	-4.57 (0.82)	-3.33 (0.18)
QVAR [®]	MDI-Alone	+30.10 (7.89) ^a	+26.39 (7.63)	+19.92 (6.54)	+16.00 (5.16) ^a	+13.50 (3.83) ^a	+12.93 (1.87) ^{ab}	N/A
	New Spacer	+6.12 (4.39) ^a	+6.12 (2.82)	+3.86 (1.63)	+2.27 (0.81) ^a	+0.99 (0.16) ^a	+0.94 (0.31) ^a	N/A
	Detergent-Coated Spacer	+11.48 (2.79)	+9.98 (2.53)	+7.49 (1.95)	+5.84 (1.30)	+4.98 (0.96)	+4.86 (1.02) ^b	N/A

Data are presented as mean with standard error in parenthesis ($n = 3$). Results for MDI-alone experiments were derived from Puff #1 of each of the three inhalers. Means within a cell labelled with common letter(s) in the superscript are statistically different ($p \leq 0.05$).

N/A: Not applicable for derivation of charge per mass of drug.

Table 3.3. Estimated number of elementary charges per drug particle for the MDIs calculated by Equation 2.1.

Stage		4	5	6	7	8	9	10
Size (µm)		0.159	0.266	0.388	0.621	0.960	1.62	2.42
Ventolin®	MDI-Alone	N/A	N/A	N/A	N/A	-2 (20)	+73 (63)	+266 (140)
	New Spacer	N/A	N/A	N/A	N/A	+10 (4)	+36 (15)	+90 (44)
	Detergent-Coated Spacer	N/A	N/A	N/A	N/A	+4 (7)	+65 (29)	+164 (80)
Flixotide®	MDI-Alone	N/A	N/A	N/A	N/A	-82 (9)	-251 (27) ^a	-542 (80)
	New Spacer	N/A	N/A	N/A	N/A	-9 (11)	-35 (26) ^{ab}	-221 (270)
	Detergent-Coated Spacer	N/A	N/A	N/A	N/A	-47 (10)	-155 (17) ^b	-364 (29)
Tilade®	MDI-Alone	N/A	N/A	N/A	N/A	-10 (6)	-158 (15) ^a	-362 (44) ^a
	New Spacer	N/A	N/A	N/A	N/A	-8 (4)	-70 (16) ^a	-196 (35) ^a
	Detergent-Coated Spacer	N/A	N/A	N/A	N/A	-23 (6)	-95 (17)	-231 (12)
QVAR®	MDI-Alone	+1(0)	+2 (1)	+6 (2) ^a	+19 (6) ^a	+59 (17) ^{ab}	+270 (39) ^{ab}	N/A
	New Spacer	0 (0)	0 (0)	0 (0) ^a	+1 (1) ^a	+3 (2) ^a	+11 (8) ^a	N/A
	Detergent-Coated Spacer	0 (0)	0 (0)	+1 (1)	+4 (2)	+12 (6) ^b	+55 (29) ^b	N/A

Data are presented as mean with standard error in parenthesis ($n = 3$). Results for MDI-alone experiments were derived from Puff #1 of each of the three inhalers. Means within a cell labelled with common letter(s) in the superscript are statistically different ($p \leq 0.05$).

N/A: Not applicable for derivation of number of elementary charges per drug particle.

3.5 Discussion

The charge profiles from the MDI-alone experiments are comparable to those obtained previously (Chapter 2) except for those of Tilade[®]. A range of 400,000 fA was used on the ELPI in the present study instead of the 40,000 fA setting used before. This increase in the electrometer range enabled the detection of higher charges present in the Tilade[®] aerosol that were missed in the earlier study. Ventolin[®], Flixotide[®], and QVAR[®] have lower charges so the 40,000 fA range used before was sufficient and no extra charges were detected on these aerosols at the higher range. The difference in the charge levels may be due to the high dose of Tilade[®], which is one order of magnitude higher in mass per actuation than the other three MDIs. The electrometers might be overloaded as the dense aerosol cloud of charged particles deposited on the ELPI stages. Indeed, even with the range set to the highest at 400,000 fA in the present study, the electric currents on certain stages still appeared to be over the range. Thus the charges measured for Tilade[®] in this study may not be complete, but the charge profiles are still valid in showing semi-quantitative trends with respect to particle size. However, in view of the limitations of the ELPI electrometers, dense aerosols of such kind may need to be diluted before measurement in the future.

The AeroChamber Plus[®] is a commonly used small volume (149 mL)^{18,19} cylindrical spacer with a rubber universal adaptor that may be fitted snugly with a variety of MDI actuator mouthpieces. Some other spacers are designed by MDI manufacturers to be specific for their own inhaler products. For instance, the plastic adaptor on the large volume (750 mL)¹ Volumatic[®] spacer from GlaxoSmithKline is only complementary

to Ventolin[®] and Flixotide[®] actuators. Likewise, Fionair[®] (750 mL)¹ from Fisons is made to fit Tilade[®] and Intal[®] Forte mouthpieces. On the other hand, QVAR[®] does not have a spacer specific for it. Since the volume and dimensions of a spacer are known to affect drug output characteristics^{2,20}, all MDIs in this study were used with the same type of spacer to avoid such variables.

The main body of AeroChamber Plus[®] is made of clear copolyester¹⁸, which is a non-conducting plastic. New spacers are individually packaged in a sealed plastic bag and stored in a cardboard box. As these are all insulators, charges are expected to be generated from physical interactions between the spacer and packaging materials before usage, such as during manufacturing, shipment, and storage. Thus charges are expected to be generated and retained on the surfaces^{4,8,10}, as shown in the high, non-uniformly distributed surface potentials on the internal wall of spacers freshly removed from their original packaging (Figure 3.3). The charges are non-uniformly distributed due to the insulating nature of the copolyester. Similar observations were noted in other studies on new polycarbonate Volumatic[®] spacers^{4,8,10} and those deliberately rubbed with a thin piece of clear plastic¹⁰.

Upon visual inspection after aerosol sampling, powder deposits were formed on the internal wall of new spacers in irregular, branch-like patterns. On the contrary, deposits in detergent-coated spacers were thin and more uniform. The patterns were probably trails of highly charged streaks on the spacer surface that attracted drug particles. The changes in surface potential after aerosol sampling must be due to the deposition of charged drug particles and propellant droplets inside the spacer. The charges carried on the particles and droplets would coat the spacer surface after

deposition and evaporation thus alter the original surface potential. However, the changes in surface potentials after aerosol puffing appeared to be irregular and unpredictable. For example, locations with higher surface potentials were not preferentially dampened, as they would if particle charges of the opposite polarity were attracted to the site. The situation with detergent-coated spacers was simpler with the low surface potentials not affected by aerosol puffing. This is probably due to the conductive nature of the detergent-coating on the spacer surface that dissipated away the charges of deposits.

Methods of varying degrees of effectiveness have been reported for the reduction or elimination of surface charges on plastic spacers. O'Callaghan et al^{5,9} used a commercial antistatic lining for coating spacers. However, since the toxicity profiles of antistatic sprays on humans are unclear, other methods should be considered. Lining the inside of a spacer with aluminium foil is effective in eliminating charges¹⁰ but is impractical and tedious in the clinical setting. Priming a spacer with a medicated¹¹ or placebo¹² MDI aerosol before use was also found to decrease surface charge. After repeated actuations from a disodium cromoglycate inhaler, the surface charge inside the Fisonair[®] spacer was greatly reduced¹¹. It was proposed that surfactants from the MDI formulation coated on the spacer surface and acted as a conductive lining to dissipate charges¹². Although charge reduction by priming is feasible, it is an inefficient method because the surfactant coating may be easily washed off during cleaning, after which drug retention would become high again¹². Consequently, drug delivery would be variable and unpredictable, depending on the frequency of cleaning of the spacer. Frequent priming is also a waste of the MDI formulation. Rinsing spacers in water followed by towel- or drip-drying was found to

be unreliable as it resulted in variable surface charges¹⁰. The most popular method for charge reduction was coating spacers with dilute surfactant solutions. Ionic surfactants performed better than nonionic ones in this role¹⁰. The effectiveness of ionic surfactants supports the hypothesis of a conductive lining mentioned above. Several anionic commercial detergents were found to significantly reduce surface charges at very low concentrations in water⁸. The optimal treatment was to immerse the spacer in a detergent solution followed by drip-drying without rinsing with water. The antistatic effect lasted for at least four weeks⁸. The use of commercial detergents is simple, economical, and relevant to patient use in the community setting. Thus the procedure was adopted in the present study. Palmolive[®] is a common household dishwashing detergent containing anionic surfactants⁸ and effectively reduced the surface potential on the AeroChamber Plus[®] spacers (Figure 3.3). The lowering of surface potentials by detergent-coating signified a reduction of electrostatic charges on spacer surfaces.

Although non-electrostatic metal and polymeric spacers have been devised and marketed (Section 1.8), the aim of the present study was to investigate the effect of spacer wall charges on the electrostatic properties of sampled aerosols. Since several MDI products were examined, a common spacer device must be employed. As stated in the introduction, the Aerochamber Plus[®] was chosen because it has a soft adaptor universal for the different mouthpieces. The two essential conditions tested were spacers with and without surface charges, which could be achieved by using new (i.e. unused) and detergent-coated Aerochamber Plus[®] spacers, respectively. Thus the Aerochamber Plus[®] was a sufficiently complete aerosol sampling system providing all necessary variables to fulfill the experimental aim. Additional experiments on the

non-electrostatic spacers would not contribute further to the study. Firstly, the effect of surface charge elimination on aerosol charges was already addressed and tested in the detergent-coated Aerochamber Plus[®]. Secondly, the difference in volume between Aerochamber Plus[®] and other spacers may introduce another variable in the interpretation on the results. Thirdly, the comparison of performance between the Aerochamber Plus[®] and another spacer device is not the aim of the present study. Repeated experiments using non-electrostatic spacers are therefore not needed.

One of the objectives of spacer usage with MDIs is to minimise oropharyngeal deposition¹, thereby reducing systemic adverse effects due to swallowing and gastrointestinal absorption of the medication. Thus the spacer becomes the major site of deposition of drug particles instead of the throat. This is evident from the results in this study. The throat deposition of new AeroChamber[®] Plus spacers was > 96% lower than that of MDI-alone (Table 3.1). However, the consequence of this is the high drug retention in the spacer, which implies a significant decline in the delivered dose. Coating the spacers with detergent almost halved the spacer deposition for all MDIs, except for Tilade[®] (Table 3.1). This is because the elimination of spacer surface charges by the detergent coating reduced electrostatic attraction between drug particles and the spacer wall, thus deposition was decreased. Although throat deposition of detergent-coated spacers was increased slightly compared to that of new ones, it was still > 93% lower than that of MDI-alone. Thus the overall effect is increasing the drug output. Barry and O'Callaghan⁵ reported an increase in the dose of budesonide available to the patient from 47.5 to 110.9 µg with antistatic-lined Nebuhaler[®] spacers. Piérart et al⁸ also found that spacer drug retention decreased from 76.7% to 33.1% of the actuated dose when the spacer was detergent-coated. This

consequently increased the mean lung deposition of radiolabelled salbutamol *in vivo* from 11.5% to 45.6% of the actuated dose⁸. Similarly, the bronchodilator response was significantly improved as a reflection of an increased available dose when salbutamol was administered via detergent-coated spacers²¹.

In the current study, both the new and detergent-coated spacers generated lower FPDs than those from MDI alone (Table 3.1). This is due to the small volume of the AeroChamber[®] Plus. It is known that large volume spacers such as the Nebuhaler[®] and Fisonair[®] deliver higher respirable doses than MDI alone and smaller spacers such as the AeroChamber[®], the precursor to AeroChamber[®] Plus². Nevertheless, the positive effect of detergent-coating, i.e. reduction of spacer charges, on enhancing drug delivery was demonstrated in an increase in FPD compared to those from new spacers (Table 3.1). This effect is supported by the inverse relationship found between the respirable fraction and the static voltage on the Volumetric[®] spacer⁶. O'Callaghan et al^{5,9} also observed that the amount of particles < 5 µm was increased with antistatic-lined spacers.

The shift in the FPD between MDI-alone, new spacers, and detergent-coated spacers was also paralleled by a corresponding change in the net and Fine particle dose charges (Table 3.1). One apparent exception was Flixotide[®], which gave lower net and Fine particle dose charges from detergent-coated spacers than those from new ones. This is due to the bipolar nature of the aerosol cloud (Figure 3.4). The negative portion of the charge profile was contributed by the drug particles whereas the positive portion by empty propellant droplets. Since the net charges for Flixotide[®] were positive, this implies that there were more charges from propellant droplets in

the aerosol. Although both the positive and negative portions in the charge profile were dampened when spacers were used, the reduction of one polarity did not yield a proportional decline in the other. This resulted in more positive charges obtained from the new spacer and/or more negative charges from the detergent-coated one, as shown in the apparent anomaly in the order of net and Fine particle dose charges.

Another objective of spacer usage in respiratory therapy is to reduce particle sizes¹. Spacers provide an enclosed chamber in which the deceleration and evaporation of MDI droplets may occur before inhalation^{1,2}. This also lowers oropharyngeal deposition. New AeroChamber[®] Plus spacers decreased the MMAD of QVAR[®], Ventolin[®], Flixotide[®], and Tilade[®] by approximately 15%, 20%, 30%, and 50%, respectively compared to MDI alone (Table 3.1). However, detergent-coated spacers raised the MMAD slightly but it is still lower than that of MDI alone. This is understandable because the reduction in spacer drug retention by eliminating surface charges may allow more large particles to exit from the spacer, thus increasing the MMAD. This was also shown as the small difference in throat deposition between detergent-coated and new spacers discussed above.

The decrease in charge levels from the spacers seen in Figure 3.4 may be due to: (i) the lowering of inherent charges on the particles and/or (ii) the reduction in the amount or mass of charged particles in a specific size fraction. For further analyses the charge per mass of drug and the number of elementary charges per drug particle need to be considered. From Table 3.2, the charge per mass of drug is generally the lowest for the new spacers in size fractions having the most drug deposits (Stages 4 to 9 for QVAR[®], 8 to 11 for the suspension MDIs), followed by detergent-coated

spacers and MDI-alone. Likewise, the estimated number of elementary charges per drug particle displayed the same trend (Table 3.3). This implies that the particles that exited from a new spacer, hence sampled by the ELPI, possessed lower inherent charges. Furthermore, particles carrying higher charges became available by reducing the spacer surface potential with detergent and even more so without a spacer. Thus the spacer acts like an electrostatic filter and particles carrying a higher charge (i.e. more elementary charges) appeared to be more susceptible to the effects of spacer surface charges and become retained. This phenomenon may be interpreted using Coulomb's Law:

$$F \propto \frac{q_1 q_2}{r^2} \quad \text{(Equation 3.1)}$$

where F is the electrostatic force between two charged bodies, q_1 and q_2 their charges, and r the distance between them. If q_1 represents the charge of a particle and q_2 the charge on a small section of the spacer surface, then at a given q_2 on a new spacer and a set r , the electrostatic force exerted on the particle would simply be directly proportional to q_1 . Hence particles carrying a higher charge would have a higher tendency for electrostatic deposition inside the spacer. Conversely, if q_2 is greatly reduced or eliminated by detergent-coating, then for a given q_1 , the particle would experience a low electrostatic force and would be more likely to be delivered from the spacer. However, Coulomb's Law has its limitations in providing a full explanation on the data obtained. The equation describes both electrostatic attractive and repulsive forces, depending on the polarities of the charged bodies. Same polarities repel whereas opposites attract. From the ELPI charge profiles, it appears that all drug particles from a specific inhaler are charged to the same polarity. For instance, those from Flixotide[®] and Tilade[®] were all negatively charged (with positive charges from the propellant/excipients), and those from QVAR[®] were all positively charged (Figure

3.4). From such data, it may be surmised that particular types of MDIs should experience more attraction or repulsion from the spacer wall than others if the surface potentials were predominantly of one polarity.

The calculation of the actual deflection of a charge in the presence of the electric field caused by a charged cylinder is very complex. In this thesis, no attempt is made to determine precisely how the moving charges will be deflected due to fixed charge on the spacer. However, some qualitative conclusions about the nature of charge transmission through the spacer can be drawn from simple arguments. Consider, for example, the situation if the spacer surface is charged with a uniform distribution of negative charges. Although by symmetry the electric field within a very long uniformly charged cylindrical spacer will be zero at points distant from the ends, the spacers considered here are not very long relative to their diameter. There will thus be a significant non-zero radial component of the electric field at all off-axis points near the entrance and exit of the spacer. The effect of this fringing electric field at the entrance to the spacer will be to repel negatively charged drug particles, deflecting their trajectories towards the axis of the spacer, and thus enhancing the output of these particles, such as those from Flixotide[®] and Tilade[®]. Conversely, the fringing electric field near the entrance of the spacer will attract positively charged particles, such as from Ventolin[®] and QVAR[®], deflecting them away from the axis of the system towards the internal surface of the spacer, and particles of this polarity will tend to be retained within the spacer, thus decreasing their emission. The reverse would be expected to occur if the surface of the spacer was positively charged. The extent of particle repulsion and attraction would be directly related to the magnitude of surface charges. The internal spacer wall could accidentally or artificially be charged in a

clinical setting by wiping the surface with a fabric, such as a towel for drying or cleaning. Electrons would be transferred between the spacer wall and the fabric by triboelectrification. The polarity of charging depends on the relative positions of the spacer and fabric materials in the triboelectric series³. A fundamental relationship between aerosol and spacer wall charges may be examined in a similar manner by wiping the spacer interior with a tissue (wetted with a slightly conductive volatile liquid such as ethanol) connected to an electrode of a variable DC voltage source. The magnitude and polarity of charging could subsequently be controlled by selecting the voltage and charging electrode, respectively, to obtain a uniform surface charge distribution.

In the present study with non-uniform surface charge potentials, all MDI aerosols tested were prone to spacer retention, which could be alleviated by a reduction in surface potentials regardless of the polarity of charges on the drug particles, so the situation is more complex than it seems. Although it is certain that fundamentally Coulomb's Law is obeyed on the microscopic level, macroscopically many factors may confound the observation. Firstly, the ELPI measures the net charge in each specific size fraction. The charge on individual particles could not be distinguished, thus the heterogeneity in charge polarity might be masked. Secondly, the surface potentials on new spacers were non-uniformly distributed and were different within and between the spacers. This makes generalisation on surface charges and particulate behaviour inside the spacers difficult. Thirdly, aerosols are emitted from MDIs at very high velocities (30 to 50 m/s)²². Inertial impaction inside the spacer may overcome electrostatic deposition, especially for the larger particles. This effect is expected to be compounded in small volume spacers such as the AeroChamber[®] Plus.

It is interesting to note the action of the spacer as an electrostatic filter and the particles it delivers carry lower charges than those directly from a MDI (Table 3.3). This may affect particle deposition in the lungs. Computational modelling on charged particle deposition in the airways showed that the deposition of 0.5 μm particles was increased in the lower airways when the number of elementary particle was increased from 0 to 200²³. The trend is similar for larger particles but progressively more charge is required for the effect. Since the magnitude of particle charges delivered from spacers fall within this range (Table 3.3), lung deposition may be affected by charge alteration, in addition to the already well-established effect of particle size reduction. Particle deposition by electrostatic forces becomes a significant mechanism in the lower airways owing to the small dimensions in these pulmonary areas^{23,24}, in which r in Equation 3.1 becomes small. Thus a change in the aerosol charges may have an impact on the deposition pattern. The elimination of spacer charges in the present study increased not only the FPD, but also the Fine particle dose charge (Table 3.1). The higher charges suggest that the deposition in the lower airways may be increased. It is well known that particle deposition from non-static spacers is improved *in vivo*^{8,12}. Although this observation has been generally attributed to the increase in the FPD available, the contribution of electrostatic forces to the resultant deposition may also play a role. The findings from the present study are relevant to the design and use of spacers, which have influence on particle charges and possibly deposition. Clinical studies investigating the influence of charges on therapeutic effect and lung deposition are necessary to fully address these potential issues.

3.6 Conclusion

New AeroChamber[®] Plus spacers were found to possess high surface potentials on the internal walls. Coating the spacers with detergent successfully removed the surface charges. The electrostatic characteristics of commercial MDI aerosols delivered via the new and detergent-coated spacers were successfully measured using a modified ELPI and compared with those from MDIs alone. Both types of spacers reduced the aerosol charges, throat deposition, FPD, and MMAD. Detergent-coated spacer had less spacer drug retention than the new ones because the low surface charges minimised electrostatic particle deposition. Consequently, drug output through these spacers was enhanced. Particles delivered from spacers carried lower inherent charges than those directly from MDIs. Those with higher charges might be susceptible to electrostatic forces inside the spacers and were thus retained. The altered charge levels on drug particles administered via a spacer may have a potential effect on lung deposition when inhaled.

3.7 References

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Chapter 4

Effect of Relative Humidity on the Electrostatic Charge

Properties of Dry Powder Inhaler Aerosols

4.1 Introduction

Dry powder inhalers (DPIs) are popular for delivering pharmaceutical aerosols to the lungs. There are many marketed products with different device designs and formulations covering a wide range of drugs. Although the aerosol characteristics of DPIs such as particle size and mass output have been evaluated extensively for many years, their electrostatic properties are poorly studied. Electrostatic deposition is one of the five major mechanisms of aerosol deposition in the lungs¹. Computer modelling and limited *in vivo* inhalation studies conducted on human subjects indicate that electrostatic charges may affect total and regional deposition in the lung²⁻⁷.

Aerosol dispersion from DPIs is a mechanical process in which particles inevitably undergo electrification through contact with and friction against solid surfaces. This charging process is termed triboelectrification. However, the fundamental charging mechanism of insulators, such as pharmaceutical solids, is poorly understood. On the other hand, contact charging between metals is the most thorough model for solid electrification and often serves as the basis for understanding charging of other materials. Each metal has a unique work function, the energy required by a valence

electron to leave the atom^{8,9}. When two different metals establish contact, electrons flow from the metal with the lower work function to that with the higher. A potential difference, called contact potential, is thus generated across the metal surfaces. Oppositely charged metals are obtained when the two parts are separated in an insulated system⁹.

Although the metal-metal charging model is not directly applicable to insulators, the concept of work function facilitates interpretation of charging phenomena in non-metals. The charging mechanisms of insulators are poorly understood because their surfaces are difficult to characterise clearly and the electron energies are ill-defined⁸. Valence electrons in insulators are bound to ionic or molecular structures thus are not free to conduct, yet charge exchange is still possible. If this is indeed due to the exchange of electrons then only those very near contacting surfaces will contribute in the charging⁸. Other postulated theories include the transfer of ions or surface material between the two bodies¹⁰. Triboelectrification is a very complex surface phenomenon. It is sensitive to ambient relative humidity, temperature, surface impurities, surface roughness, area of contact, and other physicochemical factors, thus it is difficult to control^{9,11,12}. In addition, frictional charging also generates heat, which reduces the predictability of the outcome¹¹.

Electrostatic charges generated from DPIs have been previously conducted using an aerosol electrometer apparatus built in-house by Peart et al (Section 1.11.3). The limitation of this setup is that while the net charge of the fine particles was measured the charges among different size fractions could not be discerned. Thus if an aerosol carries bipolar charges, the two polarities would mask each other as only the overall

charge is detected. The drawback has been overcome with a modified setup of the ELPI, as described in previous chapters. Although the ELPI has been applied to measure DPI charges before, the dispersion flow rate used was not specified^{13,14}. No drug assays were reported in these experiments either. The current ELPIs marketed by Dekati, Finland, only operate at 10 or 30 L/min, which are too low for common pharmaceutical DPIs. For the study of DPIs the ELPI setup was further modified to aerosolise at 60 L/min.

This chapter focuses on the Pulmicort[®] and Bricanyl[®] Turbuhalers[®], both of which are drug-only formulations with no carriers or excipients. They represent the simpler DPI formulations in terms of understanding of their charging behaviour, as compared with binary systems with carriers. Further, they are two of the few drug-only DPI products on the market. Lastly, the two products have the same inhaler design and share the same dispersion mechanism for the powders. This eliminates one variable and facilitates data interpretation when comparing the charging of the two drugs.

The Turbuhaler[®] (also called Turbohaler[®] in some countries) is a breath-actuated, multi-dose DPI with a powder reservoir marketed by AstraZeneca, Sweden. To protect the powder in the reservoir from moisture, the Turbuhaler[®] has an internal dessicant compartment and an external tight-fitting screw cap covering the whole device¹⁵. The firmly fastened cap makes the inhaler waterproof. Its performance was not affected after undergoing a routine wash-dry cycle at 60°C in a domestic washing machine¹⁶. Conversely, exposure of Turbuhalers[®] without the cap at 30°C / 75% RH reduces the respirable fraction¹⁷. Thus patients are instructed by the manufacturer to keep the cap tightly closed when the inhaler is not in use. The dispersion performance

had been shown to be efficient *in vitro* and *in vivo*. The delivered and fine particle doses of budesonide and formoterol fumarate from Symbicort Turbuhalers were not affected by storage at 40°C / 75% RH for three months¹⁸. The plasma concentration profile of budesonide after inhaling from the same inhalers also remained unchanged¹⁸. Drugs delivered from Turbuhalers[®] were clinically effective in hot and humid environments such as Bangkok¹⁹ and tropical Queensland²⁰. The formulations consist of agglomerates of 2-4 µm primary particles²¹. Metered doses are individually dispensed from the reservoir with an internal scraper and dosing unit prior to each inhalation¹⁵. The resistance to airflow of Turbuhaler[®] is ranked as medium^{22,23}. The maximum inhalation flow rates through the Turbuhaler[®] were found to be 81.8 and 55.6 L/min by healthy male and female subjects, respectively²⁴. In another clinical study, the mean peak flow rates achieved by asthmatic adult patients were 60-70 L/min²⁵. Thus 60 L/min is a suitable flow rate for the *in vitro* dispersions as it is readily achievable *in vivo* using this inhaler.

Relative humidity (RH) has long been recognised to affect triboelectrification. Many humidity studies have been conducted on the charging of bulk powders²⁶⁻²⁹ but few have been done on aerosols. Since the mass and size output from DPIs can be affected by RH³⁰⁻³², it is important to investigate the electrostatic properties. At present, there is no published data examining the effect of relative humidity on the electrostatic charges of dry powder inhaler aerosols.

4.2 Aim

The aim of this study was to investigate the charging of particles from Pulmicort[®] and Bricanyl[®] Turbuhalers[®] dispersed at different RHs.

4.3 Materials and Methods

4.3.1 Dry Powder Inhalers and Aerosol Electrostatic Charge Measurement

The two types of DPIs examined in the study were Pulmicort[®] (400 µg budesonide; AstraZeneca, Australia; Batch 1420061C00) and Bricanyl[®] (500 µg terbutaline sulfate; AstraZeneca, Australia; Batch 3520210B00) Turbuhalers[®], both of which are drug-only formulations with no carriers or excipients. 12 inhalers of each type were used before expiry. All were kept in their original packaging under ambient conditions until experimentation.

The ELPI (Dekati, Finland) connected to a vacuum pump normally operates at an airflow of 30 L/min because the jet plate of Stage 1 is the flow-limiting critical orifice³³. The setup was modified to disperse the DPIs at 60 L/min in this study. The corona charger frame was removed from the ELPI and was replaced with a stainless steel straight tube, a Y-piece, and USP throat (Figure 4.1). A plastic unit dose sampler coupled to a vacuum pump was also connected to the Y-piece to provide the

additional airflow at the throat inlet (Figure 4.1). A 47 mm glass fibre type A/E filter (Pall, USA) was placed inside the unit dose sampler to capture drug particles.

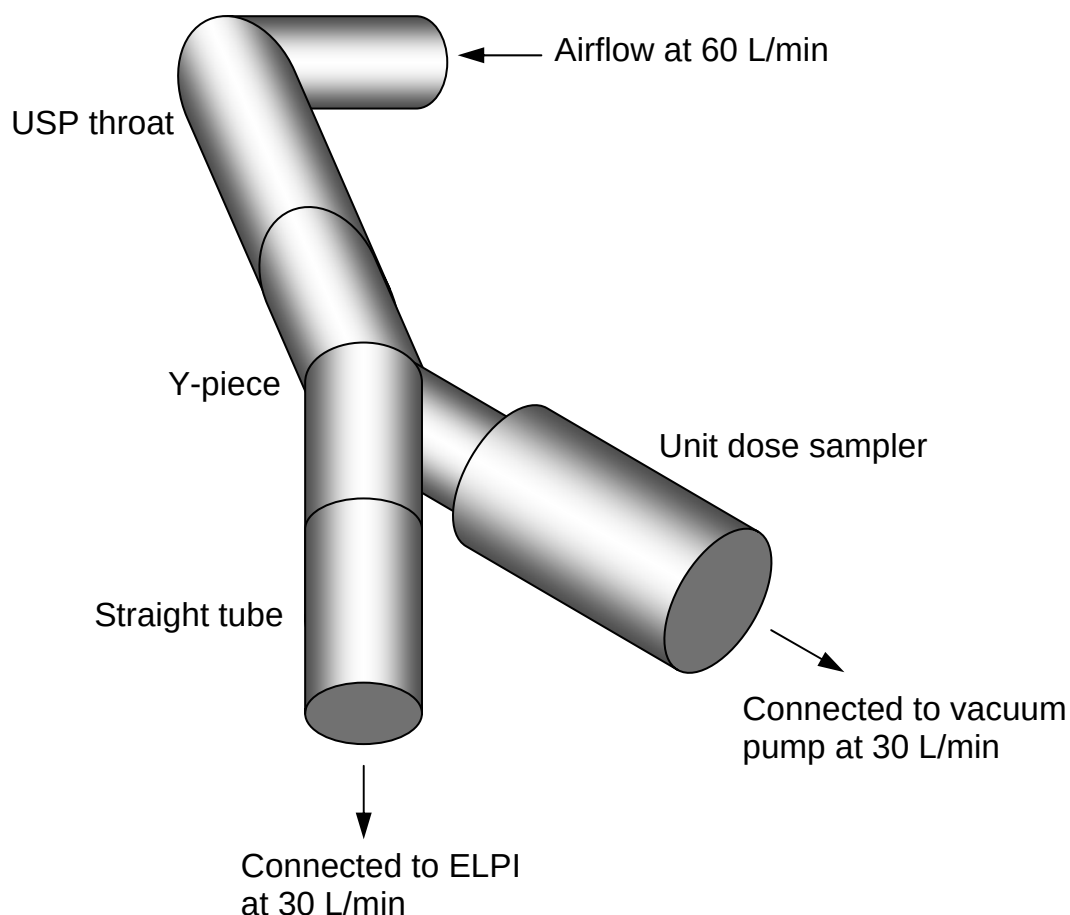


Figure 4.1. Three-dimensional representation of the modified ELPI setup suitable for DPIs operating at 60 L/min. Diagram not drawn to scale.

Before each experiment, the flow rate through a blank Turbuhaler at the throat was checked and adjusted to 60 L/min with both pumps operating at 30 L/min. A silicone rubber adaptor ring was fitted onto the DPI mouthpieces for airtight sealing during aerosol sampling. Particle bounce and re-entrainment were minimised by the application of 90 μ L of a 1 g/15 mL solution of silicone fluid (200 Fluid/60000 cSt;

Dow Corning, Australia) in cyclohexane (Mallinckrodt, USA). The solvent was allowed to evaporate before assembling the impactor stages. The aerosol charges were measured and recorded using the Dekati ELPIVI 4.0 software with the current range set at 400,000 fA.

The ELPI was enclosed in a polycarbonate box with a controller (Vaisala HMD60Y temperature and RH transmitter coupled to two Shimaden SR71 controllers; custom made by Active Instrument Services, Australia) to establish and maintain the relative humidity (RH) at the ambient temperature (24 ± 2 °C). The temperature and RH accuracies are $\pm 0.1\%$ and 2.2% , respectively. Four RHs were chosen in this study for the dispersions (15%, 40%, 65%, and 90%). Three new inhalers of each DPI product were randomly assigned for each RH and four doses were individually sampled from each inhaler for both charge and mass determinations. Prior to dispersion, each inhaler was put inside the box upright with the cap closed to condition for one hour at the experimental RH before the first aerosol sampling.

For dispersion, the ELPI electrometers were zeroed. Then the inhaler cap was removed, the rubber adaptor fitted onto the mouthpiece, and both vacuum pumps were switched on. When a stable zero baseline was obtained the inhaler was inserted into the throat and kept there until all aerosol charges from the dose were measured. It was observed that the background electrical signals were always temporarily disturbed upon the insertion of the inhaler to the throat. These disturbances were relatively low in magnitude and lasted only for a few seconds, after which the signals returned to a stable zero baseline. Immediately after dose sampling the inhaler was reinserted into and removed from the throat three times to generate the blank signals, the mean of

which was calculated and subtracted from the aerosol measurements to account for these noises. The rubber adaptor was removed from the mouthpiece for chemical assay after the dispersion and the cap was replaced tightly. The ELPI stages were then disassembled and the drug deposits on which were extracted with solvents for quantification.

4.3.2 Mass assays of drug deposits

Drug deposits were quantified chemically using high performance liquid chromatography (HPLC), the conditions for which are summarised in Table 4.1. Fresh standard solutions were prepared to generate standard curves before each HPLC run. New Pulmicort® and Bricanyl® inhalers of the same batches as the tested ones were sacrificed to obtain the drugs for making the standard solutions.

Table 4.1. Chromatographic conditions for the chemical assays.

Inhaler	Mobile Phase ^a	Column ^b	Mobile Phase Flow Rate (mL/min)	UV Detection (nm)	Injection Volume (µL)
Pulmicort®	600 mL methanol 400 mL deionised water	Waters Nova-Pak® C18	1.5	240	50
Bricanyl®	600 mL methanol 400 mL deionised water 1 g sodium lauryl sulfate	Waters Nova-Pak® C18	1.0	218	100

^a All mobile phases were filtered through a 0.45 µm filter by vacuum prior to the HPLC runs.

^b Column temperature was 30°C.

Pulmicort[®]

The adaptor, USP throat, Y-piece, straight tube, and unit dose sampler were each washed exhaustively with 5 mL of a 20:80 v/v water-in-methanol mixture. The impactor stages were sonicated for 5 min in beakers containing 5 mL of the same solvent. The unit dose sampler washing was centrifuged at 12045g for 15 min to separate out the filter fibres before loading into HPLC vials.

Bricanyl[®]

The drug extraction method was similar to that for Pulmicort[®] except that 5 mL of water was used instead of water-in-methanol for the adaptor, USP throat, Y-piece, straight tube, and unit dose sampler. The stages were sonicated for five minutes in 5 mL of water and 5 mL of cyclohexane, which was used to dissolve the silicone fluid to allow the extraction of the drug into the mobile phase. The liquid mixtures were centrifuged at 3080g for 15 min to separate the two phases. Samples were taken from the aqueous phase for assay.

4.3.3 Data analysis

The charge on each impactor stage was derived from the electric current data by calculating the area under the curve in the current-versus-time plot for that particular stage. The *net charge* was calculated from the sum of charges on all stages. The dose splitting by the modified ELPI setup was assessed by considering drug deposition downstream from the Y-piece. The percentage of the total amount deposited in the

ELPI and that in the unit dose sampler to the sum of these two (which denotes the post Y-piece dose) were calculated. The ideal dose split ratio is 50:50 between the ELPI and the unit dose sampler. The *emitted dose* is the total drug mass recovered from all the components assayed. The *fine particle dose (FPD)* is the sum of drug mass deposits on Stage 11 and below divided by the percentage of the post Y-piece dose in the ELPI to account for the fine particles deposited in the unit dose sampler. The *fine particle fraction (FPF)* is the percentage of the FPD in the emitted dose. The *specific charge*, or *charge-to-mass ratio (q/m)*, for a given size fraction is the quotient of the charge and drug mass in that size fraction. The *FPD net specific charge* was derived by dividing the net charge (i.e. arithmetic sum of charges) from Stage 11 and below by the FPD. The *FPD absolute specific charge* was obtained in a similar manner except that the absolute magnitude of charges from Stage 11 and below was used instead. This parameter reveals the level of real charges without charge neutralisation by opposite polarities, as in the case of the FPD net specific charge. The *number of elementary charges per drug particle (n)* in a particular size fraction was estimated by Equation 2.1. The data were analysed statistically using one-way analysis of variance (ANOVA), followed by the Tukey multiple comparisons *post hoc* test ($\alpha = 0.05$) to determine differences between the means unless specified otherwise. All statistical procedures were performed with Minitab™ Statistical Software 13.31.

4.3.4 Dynamic water vapour sorption

The hygroscopicity of powders from Pulmicort® and Bricanyl® were tested using a dynamic vapour sorption (DVS) analyser (Surface Measurement Systems, UK) equipped with a Cahn D-200 microbalance (ATI Instruments, USA). All experiments

were conducted at 25 °C. The flow of dry nitrogen bubbling through deionised water was controlled to obtain the various RHs. Samples (30-40 mg) of powder tapped out from the drug reservoir of Pulmicort[®] and Bricanyl[®] inhalers were loaded directly into the DVS sample pan. The powders were subjected to two sorption-desorption cycles from 0 to 90% RH in 10% RH steps. The step-change criterion was the rate of mass change (dm/dt) ≤ 0.0002 % of the initial mass per minute over five minutes. The data were analysed with the DVS Analysis Suite Version 3.6 (Advanced) (Surface Measurement Systems, UK).

4.3 Results

The charge and mass profiles of Pulmicort[®] and Bricanyl[®] are shown in Figure 4.2. Both products generated bipolar charges, with the larger particles charging negatively and the smaller ones positively. The particle size at which the polarity changed over is different for the two DPIs, despite the similarity in their mass distributions. Particles larger than 2 μm and 0.9 μm were negatively charged for Pulmicort[®] and Bricanyl[®], respectively. Interestingly, high positive charges from Bricanyl[®] were measured below 0.6 μm , where negligible drug mass was detected. Since the DPI contains no excipients, these charges must be due to the presence of a very small amount of highly charged ultrafine terbutaline sulfate particles in the aerosol. The Pulmicort[®] charge profiles remained the same at different RHs, whereas those of Bricanyl[®] reduced in magnitude with increasing RH. The mass profiles for both inhalers remained unchanged from 15% to 65% RH, only slightly lowered at 90% RH.

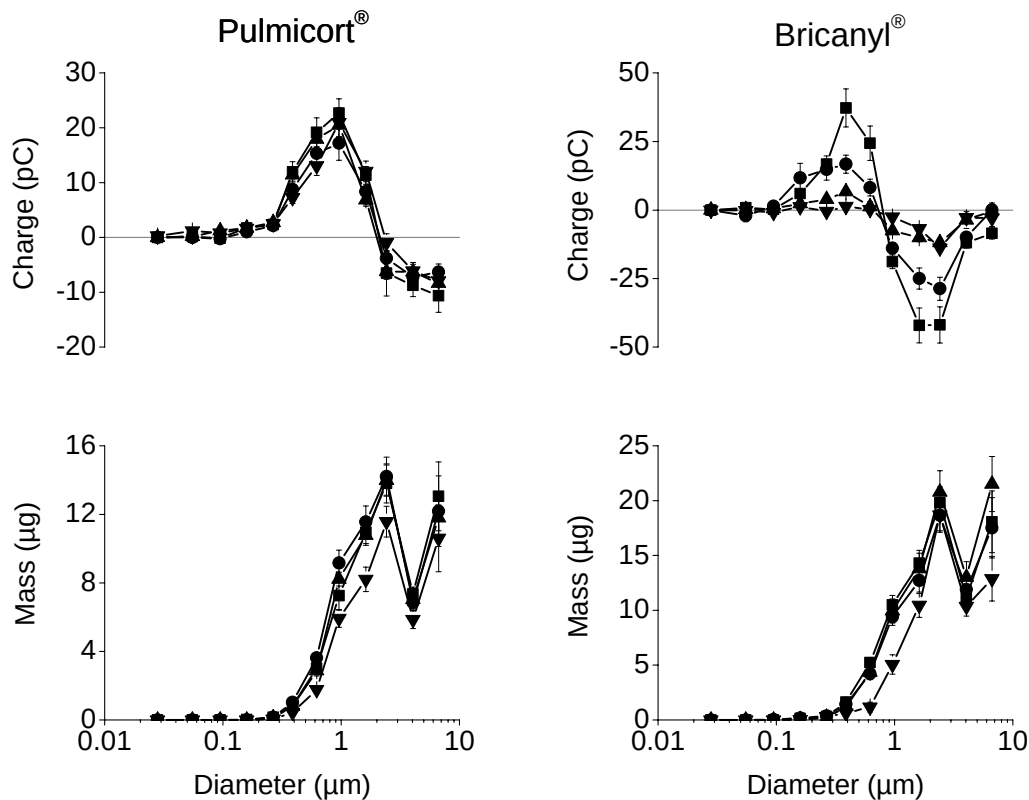


Figure 4.2. Mean charge and mass profiles of Pulmicort® and Bricanyl® Turbuhalers® at different RHs (■15%, ●40%, ▲65%, ▼90%). Error bars represent standard errors ($n = 12$).

The dose split ratios between the ELPI and the unit dose sampler for most of the dispersions were better than 60:40 in either direction. Thus the aerosols can be considered as evenly divided by the Y-piece. Figure 4.3 shows the emitted doses, FPDs, FPFs, and FPD absolute specific charges across the different RHs. Except for the FPD of Pulmicort®, the mass output of both DPIs were not significantly affected by the RH.

The effect of RH on the FPD absolute specific charges was distinctly different for the two inhalers (Figure 4.3). The Pulmicort[®] FPD absolute specific charge showed a trough at 40% RH but increased at higher RHs. In contrast, the trend for Bricanyl[®] was simpler, the FPD absolute specific charge decreased with increasing RH.

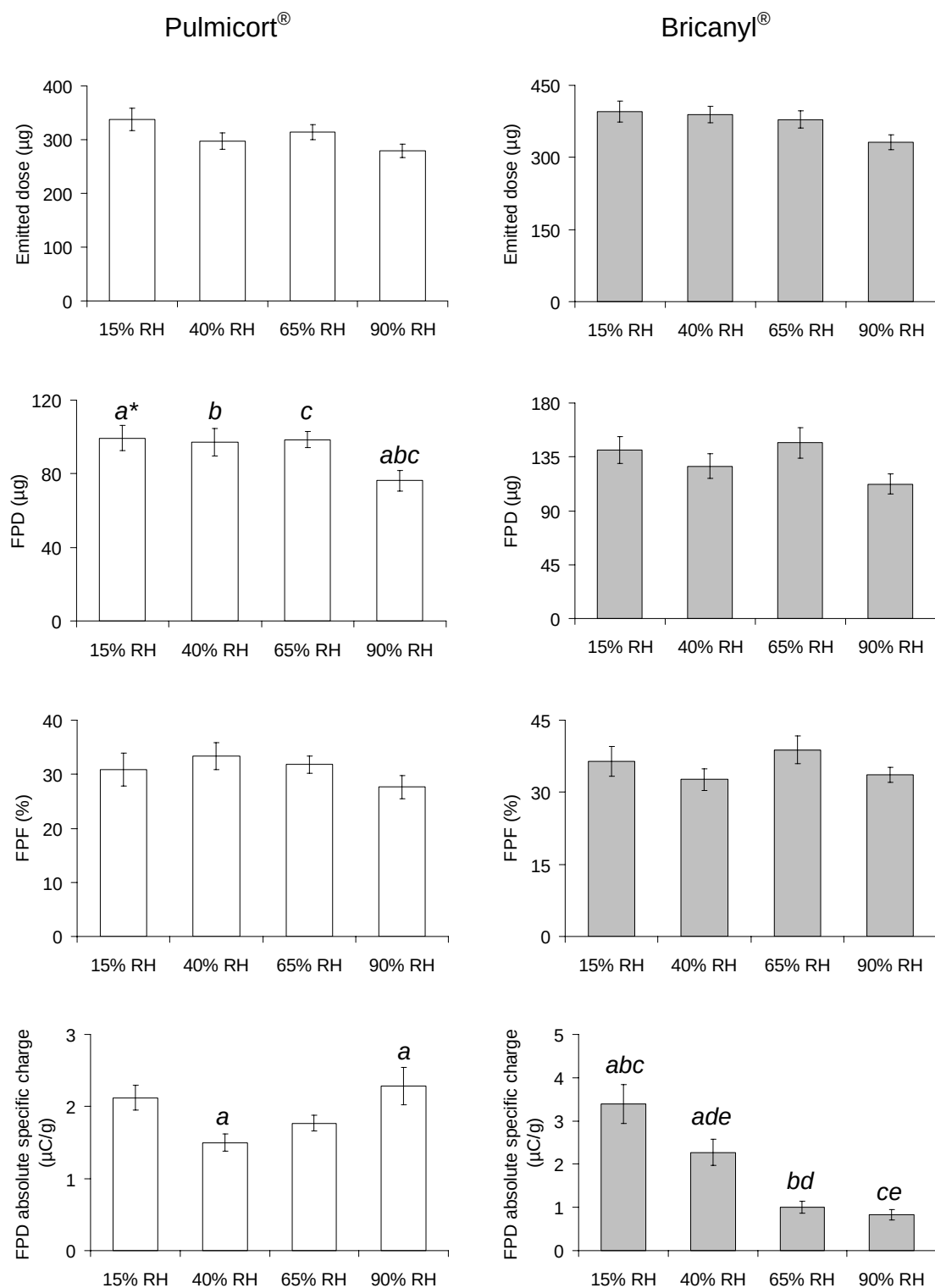


Figure 4.3. Mean emitted dose, FPD, FPF, and FPD absolute specific charge of Pulmicort® (white bars) and Bricanyl® (grey bars). Error bars represent standard errors ($n = 12$).

*** Means in a plot labelled with common letter(s) are statistically different ($p \leq 0.05$). All statistical differences were determined using ANOVA followed by the Tukey multiple comparisons test ($\alpha = 0.05$) except that the Fisher test ($\alpha = 0.05$) was used on the Pulmicort® FPD plot.**

The specific charges and the estimated number of elementary charges per drug particle in the size fractions with detectable drug mass are presented in Tables 4.2 and 4.3. The FPD net specific charges of Pulmicort® were all positive and those of Bricanyl® were low negative, due to the relative amount of positive and negative charges in their charge profiles (Figure 4.2). A substantial amount of charges from both polarities were cancelled out when the net charges of Bricanyl® were calculated. For both inhalers, the specific charges and the number of elementary chargers per drug particle in each size fraction (Tables 4.2 and 4.3) show the same order of magnitude ranking with respect to RH as that of the FPD absolute specific charges (Figure 4.3). This indicates that the RH affected particle charging in all size fractions.

The sorption isotherms and mass change profiles for budesonide and terbutaline sulfate powder samples from Turbuhalers® are shown in Figures 4.4 and 4.5. Moisture adsorption was very low for (0.17%) budesonide while that of terbutaline sulfate was higher (0.25%) (Figure 4.4). There was a slight gross mass loss (< 0.01%) for budesonide after the first sorption-desorption cycle (Figure 4.5). Terbutaline sulfate showed evidence of recrystallisation in the first cycle from the sequential weight losses at each RH step from 50% to 90% RH (Figure 4.5) and the 0.1% gross mass loss after desorption (Figure 4.4).

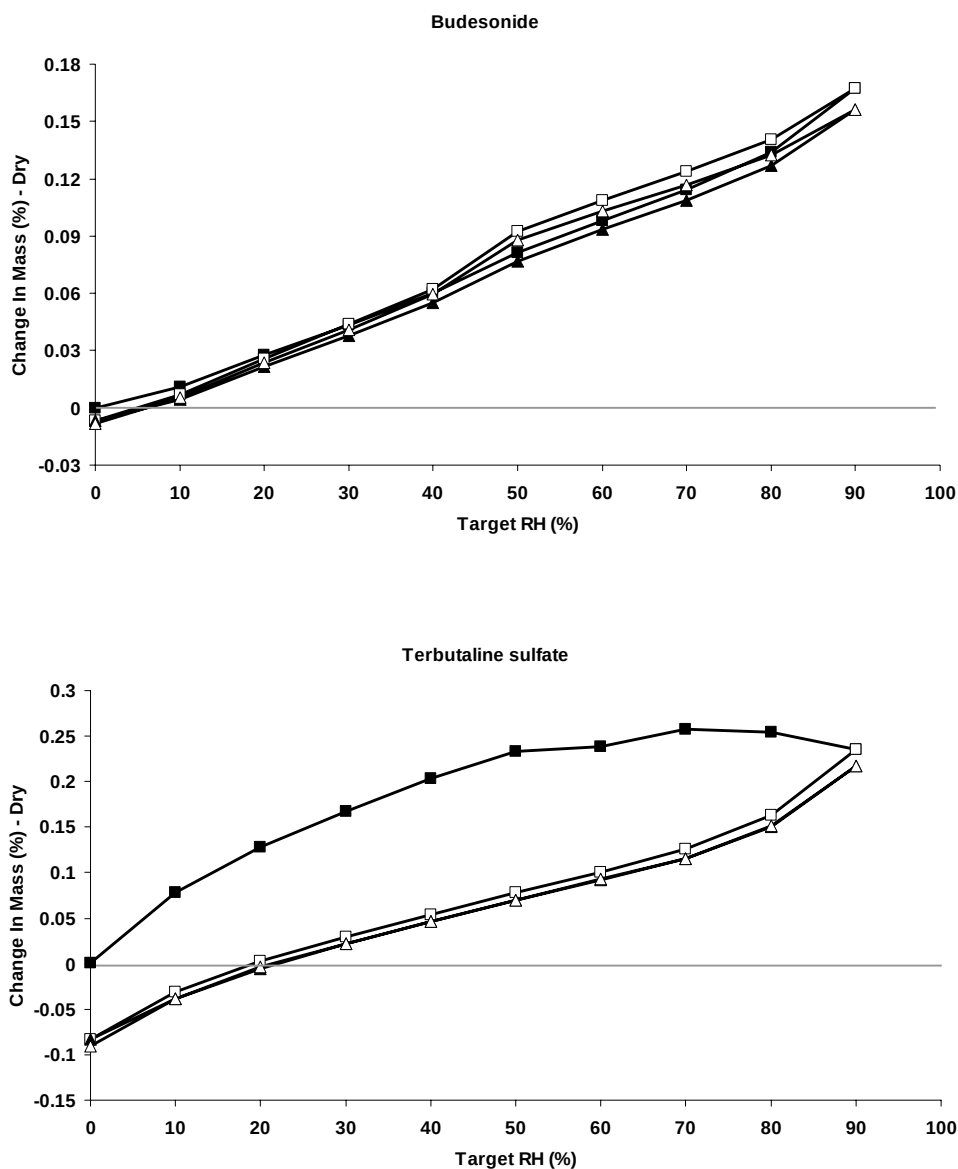


Figure 4.4. Dynamic vapour sorption isotherms of budesonide and terbutaline sulfate powders taken from Pulmicort[®] and Bricanyl[®] Turbuhalers[®] (■ Cycle 1 sorption; □ Cycle 1 desorption; ▲ Cycle 2 sorption; △ Cycle 2 desorption). Gray line represents the dry weight baseline.

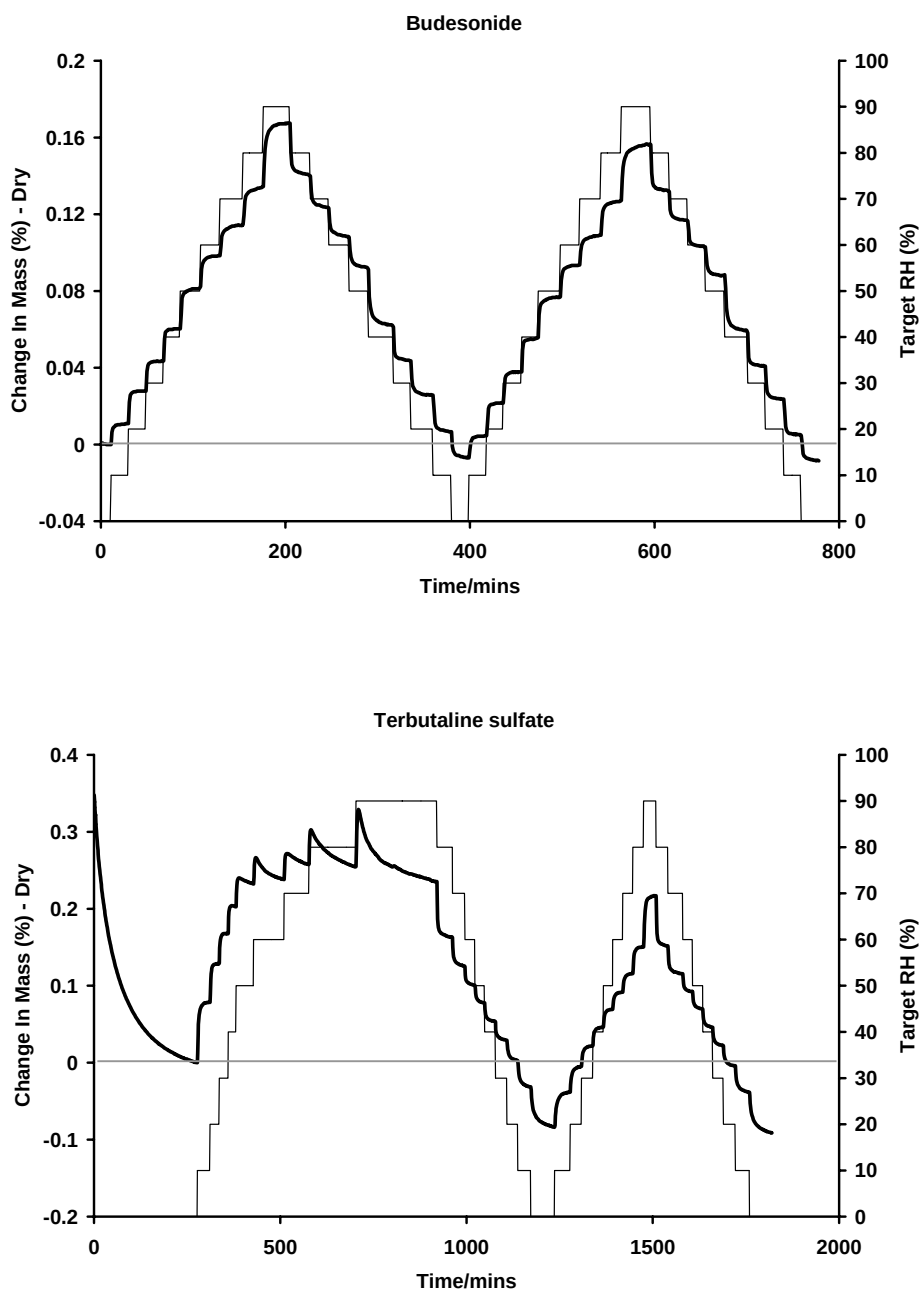


Figure 4.5. Dynamic vapour sorption mass change profiles of budesonide and terbutaline sulfate powders taken from Pulmicort[®] and Bricanyl[®] Turbuhalers[®]. Bold line represents the percent change in mass with respect to the dry weight. Thin line represents the target RH steps. Gray line represents the dry weight baseline.

Table 4.2. Specific charges for the DPIs at different RHs ($\mu\text{C/g}$).

	Stage	6	7	8	9	10	11	12	FPD net*
	Size (μm)	0.388	0.621	0.960	1.62	2.42	4.04	6.06	< 6.06
Pulmicort®	15% RH	+23.36 (8.62)	+7.17 (1.30)	+4.71 (1.56)	+1.15 (0.21)	-0.32 (0.24)	-1.17 (0.29)	-1.10 (0.46)	+1.34 (0.15)
	40% RH	+9.91 (1.93)	+4.27 (0.53)	+1.90 (0.34)	+0.70 (0.21) ^a	-0.27 (0.16)	-1.10 (0.20)	-0.62 (0.17)	+0.86 (0.19) ^a
	65% RH	+22.17 (7.01)	+7.97 (1.89)	+2.48 (0.21)	+0.63 (0.10) ^b	-0.43 (0.10)	-0.87 (0.19)	-0.79 (0.19)	+1.16 (0.09)
	90% RH	+21.34 (4.05)	+8.13 (1.17)	+3.94 (0.62)	+1.65 (0.29) ^{ab}	-0.06 (0.14)	-1.13 (0.32)	-0.92 (0.25)	+1.68 (0.22) ^a
Bricanyl®	15% RH	+23.18 (3.01) ^a	+4.59 (1.00) ^{ab}	-1.95 (0.29) ^{ab}	-2.99 (0.32) ^{abc}	-2.12 (0.24) ^{ab}	-1.08 (0.18) ^{ab}	-0.72 (0.25)	-0.51 (0.14)
	40% RH	+15.12 (3.15)	+1.81 (0.63) ^a	-1.47 (0.15) ^c	-1.91 (0.20) ^{ade}	-1.53 (0.16) ^{cd}	-0.90 (0.16) ^c	-0.06 (0.19)	-0.47 (0.16)
	65% RH	+8.18 (2.20) ^a	+0.35 (0.62) ^b	-0.78 (0.14) ^a	-0.74 (0.10) ^{bd}	-0.64 (0.12) ^{ac}	-0.14 (0.28) ^{ac}	-0.05 (0.16)	-0.27 (0.07)
	90% RH	N/A	N/A	-0.64 (0.24) ^{bc}	-0.65 (0.16) ^{ce}	-0.79 (0.09) ^{bd}	-0.33 (0.15) ^b	-0.59 (0.46)	-0.61 (0.13)

Data presented as mean with standard error in parenthesis ($n = 12$). N/A: not calculated due to negligible drug mass detected. Means within a DPI type labeled with common letter(s) in the superscript are statistically different for a given impactor stage ($p \leq 0.05$).

* FPD net specific charge.

Table 4.3. Estimated number of elementary charges per drug particle for the DPIs calculated by Equation 2.1.

	Stage	6	7	8	9	10	11	12
	Size (μm)	0.388	0.621	0.960	1.62	2.42	4.04	6.06
Pulmicort®	15% RH	+7 (4)	+8 (3)	+20 (12)	+24 (8)	-22 (29)	-377 (161)	-1593 (1151)
	40% RH	+3 (1)	+5 (1)	+8 (3)	+15 (8) ^a	-19 (19)	-355 (111)	-902 (416)
	65% RH	+6 (3)	+9 (4)	+11 (2)	+13 (4) ^b	-30 (12)	-283 (104)	-1140 (482)
	90% RH	+6 (2)	+10 (2)	+17 (5)	+34 (10) ^{ab}	-4 (7)	-366 (178)	-1333 (638)
Bricanyl®	15% RH	+7 (1) ^a	+5 (2) ^{ab}	-8 (2) ^{ab}	-62 (11) ^{abc}	-147 (29) ^{ab}	-350 (99) ^{ab}	-1037 (636)
	40% RH	+4 (2)	+2 (1) ^b	-6 (1) ^c	-40 (7) ^{ade}	-107 (19) ^{cd}	-290 (88) ^c	-84 (467)
	65% RH	+2 (1) ^a	0 (1) ^a	-3 (1) ^a	-16 (4) ^{bd}	-45 (15) ^{ac}	-46 (156) ^{ac}	-67 (407)
	90% RH	N/A	N/A	-3 (2) ^{bc}	-14 (6) ^{ce}	-55 (11) ^{bd}	-108 (88) ^b	-852 (1146)

Data presented as mean with standard error in parenthesis ($n = 12$). N/A: not calculated due to negligible drug mass detected. Means within a DPI type labeled with common letter(s) in the superscript are statistically different for a given impactor stage ($p \leq 0.05$).

4.5 Discussion

Pulmicort[®] and Bricanyl[®] generated aerosols with bipolar charges but their charging behaviour differed: the absolute specific charges of fine particles from Bricanyl[®] decreased monotonously with increasing RH, whereas the fine particles from Pulmicort[®] carried the highest specific charges at 15 and 90% RH but lowest at 40% RH. The charges generated per particle were sufficiently high to potentially influence particle deposition in the lungs.

In the present study, the inhalers were kept under the specified RH with the cap closed to mimic normal patient use in the same environment. Dispersion at 60 L/min was successful with the modified ELPI setup using a Y-piece and an extra vacuum pump. The 50:50 split ratio was aimed at to obtain a representative sample with the ELPI. The experimental results show that the dose splitting was acceptable. Moreover, the emitted dose and FPF yielded were comparable to those from other studies using conventional impaction methods on the Turbuhaler[®] at 60 L/min^{22,34}. Thus the modified setup was suitable for measuring charges of DPI aerosols dispersed at a higher flow rate

Both Pulmicort[®] and Bricanyl[®] generated bipolar charges but the profiles were different. This must be due to the different physicochemical properties of the drugs as the two products employ the same inhaler. In both formulations the larger size fractions were negatively charged and the smaller ones positively charged. In a theoretical study by Gallo and Lama³⁵, the work function decreases with increasing

particle size. This implies that charges can be transferred between particles of different sizes, even if both are of the same material³⁵. In particular, the larger particle would be the electron donor due to its lower work function and become positively charged. However, the charge profiles from the present study showed the opposite trend. It must be noted that the work function model only provides a simplified analysis of triboelectrification from an energetic perspective. The model also assumes that the only interaction that occurs is the contact between two spherical particles under idealised conditions. As mentioned in the Introduction, many physicochemical factors contribute to and influence the actual charging process. During aerosol dispersion, the deaggregation of drug agglomerates and the subsequent movement of particles in the turbulent airstream create numerous physical interactions inside the inhaler. Drug particles come into contact with each other, as well as with the interior surfaces of the device, from the powder reservoir through to the mouthpiece channels. Indeed, powders became charged immediately after metering from the reservoir, before aerosolisation³⁶. Furthermore, the Turbuhaler[®] consists of many components made from different plastics, which add even more physicochemical variables to the triboelectrification. The aerosol charging process is therefore very complex and the results do not necessarily conform to the predictions of the work function model. Fundamental studies, such as those examining single impact charging of a particle^{37,38}, would be propitious for unravelling the elementary factors that are likely to be involved.

Charges produced from Pulmicort[®] 100 µg and Bricanyl[®] 500 µg Turbuhalers[®] had been measured by Byron et al³⁶ using the aerosol electrometer apparatus. The fine particles dispersed from Pulmicort[®] under ambient temperature and RH were

positively charged³⁶. Despite the difference in the dose of budesonide used, the polarity agrees with that measured in the present study where most of the fine particle size fractions were highly positively charged. Byron et al³⁶ reported that Bricanyl[®] displayed high inter- and intra-inhaler variations in charge polarity. Electrostatic measurements in the present study were more reproducible, as indicated by the short error bars in Figure 4.2. However, the ELPI also provided more detailed information, owing to the finer divisions of size ranges for charge measurement. Substantial levels of positive and negative charges $< 5.8 \mu\text{m}$ were measured by the ELPI (Figure 4.2). It is likely that Byron et al³⁶ reported low specific charges of terbutaline sulfate because the bipolar nature of the aerosol could not be discerned by their setup, hence the net charge of fine particles would be low in magnitude due to neutralisation by opposite polarities, as evident from the low FPD net specific charges derived from ELPI data in the present study. In addition, the specific charges of budesonide determined by the aerosol electrometer apparatus was $2\text{--}3 \mu\text{C/g}$ ³⁶, which is in the same order of magnitude as the FPD net specific charges obtained in the present study.

The drawback of describing bipolar charging in terms of net specific charges is overcome by expressing the data as absolute charges. From the plots of the FPD absolute specific charge, Pulmicort[®] and Bricanyl[®] showed distinctly different fine particle charging behaviours with increasing RH. Triboelectrification generally decreases with increasing RH²³ but Pulmicort[®] did not follow the expected pattern. The statistical differences indicated for the values in Tables 4.2 and 4.3 showed that Bricanyl[®] was more sensitive to RH than Pulmicort[®] in particle charging. An explanation of this apparent anomaly is attempted below.

The dielectric constant of air increases with RH, but the effect is negligible. Under ambient temperature (22°C) and pressure (760 mmHg), the dielectric constant of air only increases by 0.017% if the RH increases from 15% to 90%³⁹. Rather, moisture adsorption on a powder is thought to be a major factor as it reduces interparticulate contacts and increases the particle surface conductivity, thus facilitating charge dissipation^{23,26,27,29}. Changes to the bulk conductivity also occur via water absorption at high RHs²⁷. Conversely, RH has negligible effects on the charging of solids with low hygroscopicity²⁸.

In the present study, the Turbuhalers[®] have been kept dry by being tightly capped¹⁶. Exposure of the device and powder surfaces to the specified RH only occurred shortly before and during the dispersion while the cap was removed, which lasted for less than a minute, before the cap was replaced. It is well known that aerosolisation performance can worsen if a powder was stored for hours under high RH^{16,32,40}. However, during short exposures, humidity equilibrium was unlikely to have been reached, and thus capillary forces or interparticulate liquid bridging would not have fully developed⁴¹. The relatively stable mass profiles of Pulmicort[®] and Bricanyl[®] (Figure 4.2) supported that particle deaggregation was not adversely affected by capillary forces. Nevertheless, moisture adsorption on particulate and inhaler surfaces would have begun after the cap was removed. Indeed, a brief 3-minute exposure of powders prior to their dispersion at various RHs was found adequate to reduce the aerosolisation performance^{30,31} and the degree of influence of RH was dependent on the salt form of the drug³⁰. Furthermore, the work functions of budesonide and terbutaline sulfate may have different sensitivities to RH, as has been reported on

other materials⁴². These observations suggest that the interactions between the humidified air and the drug are likely to have contributed to the aerosol triboelectrification.

The absolute FPD charging profile of budesonide particles from Pulmicort[®] may be the result of two concomitant processes with increasing RH: 1) enhanced charge dissipation rate; and 2) increased cohesion of particles in the agglomerates. At 15% RH, the charge was high due to the low charge dissipation rate so the particles retained the charges generated from aerosolisation. At 40%, the higher moisture adsorption increased charge dissipation, hence the lower specific charge. When the RH reached 65% and above, the high moisture level rendered the agglomerates progressively more difficult to deaggregate. Consequently, the particles that were successfully dislodged from the agglomerates and became dispersed would be those carrying higher charges to counteract the cohesive forces, particularly at the high RH of 90%. The similar FPDs between 40% and 65% RH were associated with comparable FPD absolute specific charges at these RHs. This supports the premise that the amount of fine particles dispersed is related to the level of charges they carry. The charge dissipation rate would still increase from 65% RH onwards, but budesonide may be sufficiently insulating to retain enough charges to be measured after dispersion. This charging model may also be applicable to terbutaline sulfate from Bricanyl[®] but this compound is more hygroscopic than budesonide (Figures 4.4 and 4.5) and may be electrically conductive because it is a salt. Thus the charges generated on the dispersed fine particles would dissipate quicker than those on budesonide, hence only low charges were measured at 65% and 90% RH.

The DVS data indicated that the terbutaline sulfate particles are likely to be amorphous since signs of recrystallisation occurred upon initial moisture adsorption at high RHs. Most of the amorphous regions had recrystallised in the first sorption-desorption cycle since there was no appreciable gross mass loss in the second cycle (Figure 4.4). The sequential recrystallisation at progressively increasing RH indicated that the particles may have amorphous regions of different surface energy levels such that different regions interact with the adsorbed water to different extents (Figure 4.5). On the other hand, budesonide was relatively non-hygroscopic so amorphicity may not be obvious since there was limited interaction with water for recrystallisation to occur. Nevertheless, there was a slight gross mass loss after the first cycle (Figure 4.4), indicating that certain amorphous regions may exist on the particles. Since amorphous surfaces have higher surface energy than crystallised ones⁴³, these types of surfaces may have different electrostatic properties. This would affect electron transfer with other surfaces during triboelectrification and the resultant charges developed. Discontinuous amorphous domains distributing over particle surfaces has been reported⁴⁴. This implies that a particle may be inherently heterogeneous in charge, depending on the nature of the surface region concerned. More particle surface characterisation is needed to confirm this hypothesis.

In the present study, the number of elementary charges per drug particle was estimated from the specific charge. Comparing these with those obtained from MDIs in a previous study⁴⁵ reveal that for particles in a given size fraction, those from DPIs generally carry lower charges. This may be due to the high shear stress (force per unit area) experienced by the particles blasting out from the confined spaces in the metering valve, valve stem, and the actuator block. The dimensions of the inhalation

and mouthpiece channels in the Turbuhaler[®] are comparatively much larger so the shear stress should be lower. Consequently triboelectrification would be less intense in the DPI.

Based on computer simulation results by Balachandran et al⁴ and Bailey et al^{5,7}, the magnitudes of charge on the DPI particles, especially those on Stages 10 and 11 (Table 4.3), are high enough to affect particle deposition in the airways. Particles from Pulmicort[®] were also estimated by Byron et al³⁶ to carry charges in this range. This implies that lung deposition of particles inhaled from Bricanyl[®] may possibly be altered by environmental RH, but less so for Pulmicort[®]. Findings from the present study may be relevant to the individualised design of DPI devices and formulations for particular drugs to control particle charging at different RHs. Clinical studies investigating the influence of charges on *in vivo* deposition and therapeutic effect are needed to fully address these potential issues.

4.6 Conclusion

The size and charge distributions of Pulmicort[®] and Bricanyl[®] aerosols dispersed at 60 L/min were measured successfully using a modified ELPI. The DPIs showed drug-specific responses to particle charging at different RHs. Bricanyl[®] was more susceptible to RH, showing decreased charges with increasing RH. In contrast, particle charges from Pulmicort[®] decreased at 40% RH but increased at higher RHs. A dual mechanistic charging model was proposed to explain the charging behaviours.

The charge levels on drug particles delivered from these inhalers were sufficiently high to potentially affect deposition in the airways when inhaled.

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Chapter 5

Effect of Moisture on the Electrostatic Charge Properties of Metered Dose Inhaler Aerosols

5.1 Introduction

The charging of drug particles generated from commercial MDI products had been measured with the ELPI and discussed in Chapters 2 and 3. It is appropriate to study the electrification phenomena further to examine the underlying mechanisms. Naturally, the charging of the simplest MDI system containing only the propellant should be the first subject to be explored. The knowledge gained would serve as the foundation for understanding the charging of more complex MDI formulations.

It is well-known that organic liquids with low electrical conductivity, such as hydrocarbons and fuels, acquire electrostatic charges after flowing through pipes or undergoing aerosolisation¹⁻⁴. These have been studied in detail, especially by the petroleum industry, because the resultant accumulation of charge can potentially cause explosions or fires through electrostatic discharge. It is believed that low concentrations of ionic impurities, in the range of parts per billion, are present even in organic liquids that are considered to be of high purity^{2,4,5}. These impurities adsorb on the solid/liquid interface when the liquid is at rest in a pipe or container, forming an electric double layer of positive and negative charges^{4,6,7}. When this interface is

disturbed, either by motion of the liquid or by spraying, ionic species having higher affinity for the liquid would be swept along with the flow, leaving the other ions behind on the solid wall. Thus the electric double layer is separated and the liquid becomes charged. A similar electrification mechanism may apply to the liquefied propellant in MDIs. Since droplet formation and dispersion from these inhalers involve high shear flow of the propellant⁸, there are ample opportunities for charge generation.

Due to the concern of ozone depletion by chlorofluorocarbons (CFCs), these are now gradually being replaced by hydrofluorocarbons (HFAs) as the preferred MDI propellant⁹. Since HFAs are more polar than CFCs, they are more hygroscopic^{10,11}. For example, water solubility in CFC-11/12 blend, HFA-227, and HFA-134a are 100, 610, and 2200 ppm, respectively. This implies that water ingress is more significant in HFA MDIs. Moisture from the environment can diffuse into the MDI through the valve gaskets^{10,12,13} and adversely affect the physical stability of MDI formulations by promoting drug particle growth and aggregation^{14,15}.

Water ingress was also reported to affect HFA propellant charging. Using the aerosol electrometer apparatus (Section 1.11.2), Kulphaisal et al¹⁶ found that the fine particle dose charge polarity of HFA-134a MDIs inverted from negative to positive when the water content > 300 ppm after storing under ambient conditions for two weeks. HFA-227 also charged negatively but the water content of these inhalers only increased slightly after storage and was not high enough to significantly alter the charge¹⁶.

Valve component materials may also affect aerosol charging because the MDI formulation contacts these surfaces during the course of dispersion. CFC-11/12 blends generated different charge profiles when packaged in various combinations of valve body and stem materials¹⁷. Albuterol sulfate in CFC charged more electronegatively when steel valve stems than with acetal stems¹⁷. On the other hand, levalbuterol sulfate charged negatively with nitrile (BK 356) elastomers and positively with nitrile RB190NT (BK 357) elastomers¹⁷.

The aforementioned MDI charge studies were carried out with the aerosol electrometer apparatus. Since only the net fine particle charges were measured any bipolarity and particle size dependency of the aerosol charges would not be detected. The rationale of using the ELPI in the study described in this chapter is to obtain detailed data of such kind on custom-made HFA propellant MDIs.

5.2 Aim

The aim of this study was to investigate the effect of propellant water content, metering valve component material, and actuator moisture level on the charging of HFA droplets generated from drug-free MDIs.

5.2 Materials and Methods

5.3.1 *Drug-Free Metered Dose Inhalers for Electrostatic Charge Measurement*

The MDIs were crimped and pressure-filled at ambient temperature with 1, 1, 1, 2-tetrafluoroethane (HFA-134a; Ineos Fluor, UK) and 1, 1, 1, 2, 3, 3, 3-heptafluoropropane (HFA-227; DuPont, USA) in 19 mL uncoated aluminium canisters (Presspart, UK) using the Pamasol Laboratory Plant P 2016 (Pamasol, Switzerland). All inhaler components were stored in desiccators containing a mixture of molecular sieves (3 Å pore size; Sigma, USA) and silica gel (Livingstone, Australia) before use. Two types of HFA-compatible valves (Valois, France) were used, one with Hostaform core components (body, lower stem, metering chamber, upper stem) and the other with polybutylene terephthalate (PBT). Both valve types had ethylene propylene diene (EPDM) rubber gaskets and aluminium external ferrules, with a nominal metering volume of 63 µL. The actuators (Model NMX; Nemo, Spain) were made with polypropylene (100-GB25 homopolymer resin; BP, UK) and a beige pigment (Remafin PP 36328; Clariant, Spain). Ten puffs from a placebo HFA-134a MDI were fired to waste through these new actuators to flush out any possible contaminants on the actuator block surfaces.

The MDIs were filled with 14 g of HFA propellant. Various amounts of deionised water were added to the canisters using a microlitre syringe (Hamilton, USA) immediately before crimping and filling to obtain different aerosol water contents. The constituents and number of the MDIs made are shown in Table 5.1.

Table 5.1. Constituents of the MDIs used for charge measurement.

HFA propellant	Valve type	Spiked water (mg)	# of canisters
134a	Hostaform	0	3
		4.2	3
		8.4	3
	PBT	0	3
		4.2	3
		8.4	3
227	Hostaform	0	3
		4.2	3
		8.4	3
	PBT	0	3
		4.2	3
		8.4	3

After propellant filling the MDIs were shook vigorously by hand, ultrasonicated for 5 minutes, then rotated horizontally on a roller mixer (Ratek Instruments, Australia) for one hour to ensure complete mixing of the spiked water with the propellants. Finally the inhalers were left inverted for another hour for valve equilibration. The MDIs and actuators were stored in desiccators before testing.

5.3.2 Metered Dose Inhaler Water Content Measurement

The moisture contents of the MDIs were measured using an automatic Karl Fischer Coulometer (Model 737KF; Metrohm, Switzerland). The titration cell did not have a diaphragm thus only one titrating reagent (Hydranal[®]-Coulomat AG; Riedel-de Haën, Germany) was needed. The coulometer was calibrated by injecting 0.1 μL of deionised water with a microlitre syringe (Hamilton, USA) into the titration cell. The

mass of water dispensed, obtained by weighing the syringe before and after the injection, was compared against that measured by the coulometer ($n = 7$).

For aerosol sampling, the setup was adapted from that described by Kim et al¹⁸ with some modifications (Figure 5.1). A 1 mL plastic syringe barrel with a MDI valve stem adaptor was attached to the needle to provide additional space for aerosol deceleration before entering the titration cell (Figure 5.2). More titration reagent was also used to maximise aerosol capture.

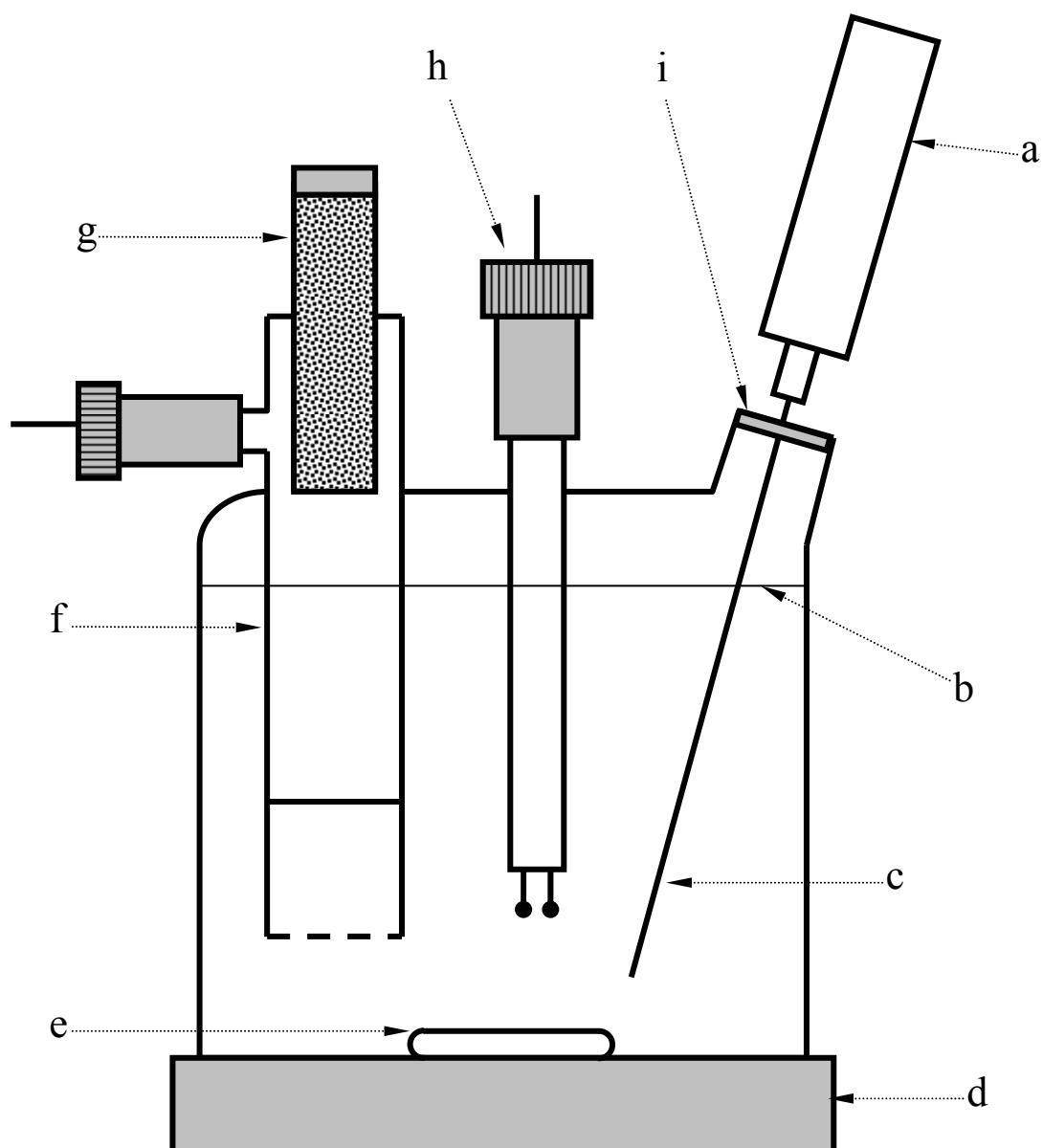


Figure 5.1. Schematic diagram of the Karl Fischer titration cell. a) Syringe adaptor; b) Titration reagent fill line; c) Needle; d) Magnetic stirrer; e) Stirrer bar; f) Generator electrode; g) Drying tube with desiccant; h) Indicator electrode; i) Septum.

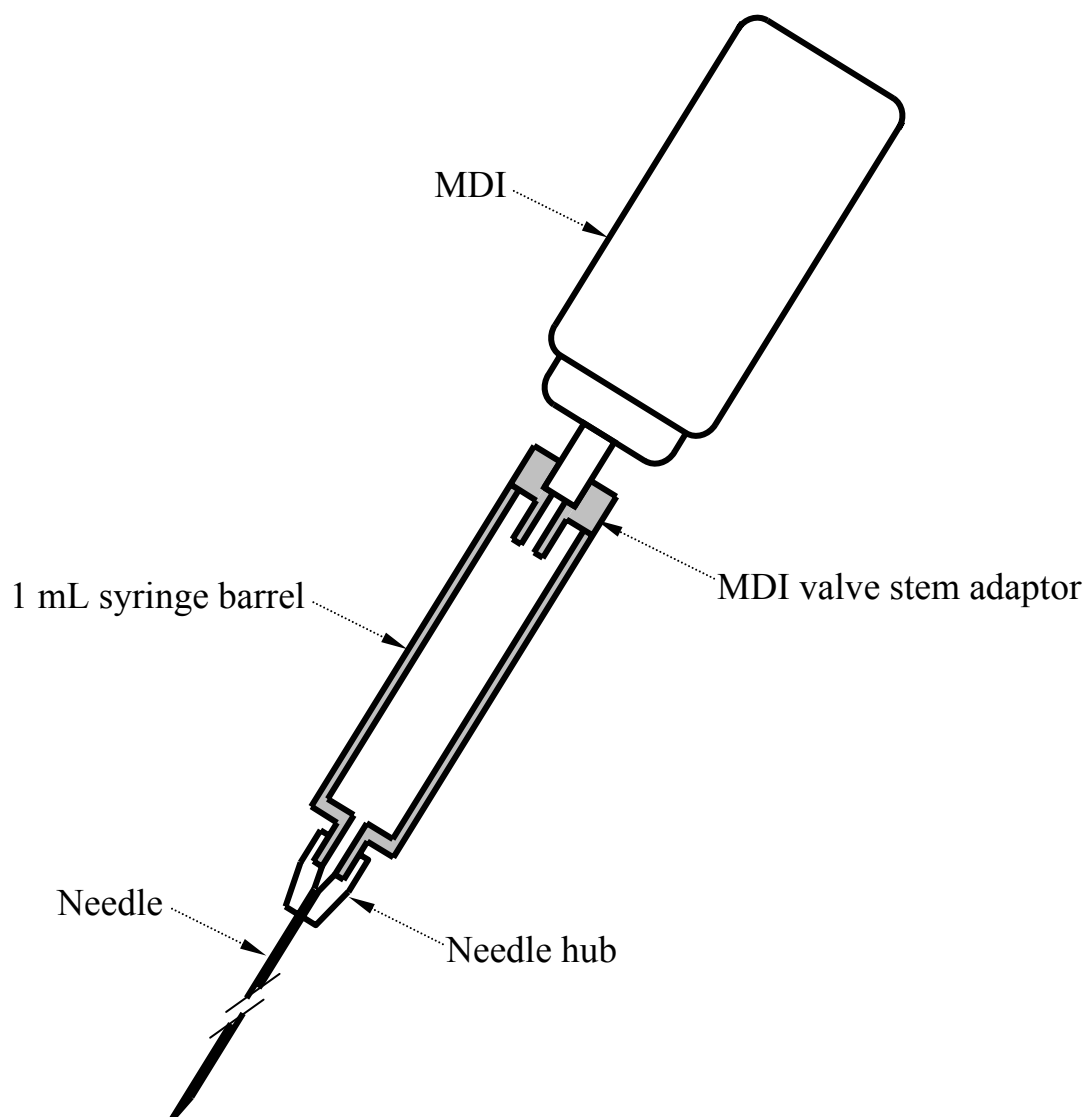


Figure 5.2. Cross-sectional view of the syringe needle adaptor.

The water contents of the MDIs were measured after propellant filling and also after the completion of all ELPI charge measurements. The inhalers were weighed before and after the measurement to obtain the sample mass. After a canister was shaken for several seconds three puffs were actuated into the Karl Fischer titration cell through the syringe needle adaptor. The concentration of water in the aerosol sample was then

calculated in the unit of parts per million (ppm) from the coulometer measurement. The measurement was performed in triplicates.

5.3.3 *Measurement of Aerosol Electrostatic Charge*

The ELPI setup for aerosol charge measurement was the same as that described in Section 2.3.2 except that the hollow corona charger frame was replaced by the stainless steel straight tube described in Section 4.3.1. The substitution was to avoid artificial influence on the aerosol charges due to possible turbulence from abrupt expansion of the air entering the spacious charger frame. The impactor was operated at an air flow of 30 L/min. The ELPI was enclosed in a polycarbonate box with a controller (Vaisala HMD60Y temperature and RH transmitter coupled to two Shimaden SR71 controllers; custom made by Active Instrument Services, Australia) to establish and maintain the relative humidity (RH) at the ambient temperature (24 ± 2 °C).

The actuators were conditioned to be dry or wet by storing them in desiccators or in boxes saturated with water vapour for over 20 hours before an experiment. These were prepared to examine the effect of moisture on the actuator surface on charging. Since charges of multiple puffs were to be measured, moisture would condense in the actuator block due to cooling by the aerosols. Thus the level of moisture on the actuator should be kept relatively constant during the measurement by controlling the RH of the air. Three RHs were chosen for the study, 5%, 50%, and 92%. A compressed air dryer (Model CP 0045 AX; Quality Air, Germany) and several conventional jet nebulisers introducing water mists into the humidity control box were

employed to maintain the low and high RHs, respectively. The experimental design thus consisted of four conditions:

- A) Dry actuators / Dry air ($5 \pm 1\%$ RH)
- B) Dry actuators / Ambient air ($50 \pm 1\%$ RH)
- C) Wet actuators / Ambient air ($50 \pm 1\%$ RH)
- D) Wet actuators / Humidified air ($92 \pm 1\%$ RH)

The MDI canisters were always stored in desiccators when not in use to prevent moisture ingress. Charge measurements were conducted after the target RH was established in the humidity control box. Ten puffs from each MDI were sampled by the ELPI, the procedure of which was similar to that described in Section 2.3.2. No chemical assays were done on these because the inhalers contained no viable compounds for this.

5.3.4 Sizing Tests with the ELPI Corona Charger

Size distributions of the aerosols must be determined in order to calculate the charge-to-mass ratios of the droplets, thus the feasibility of sizing solution MDI aerosols with the ELPI corona charger was tested. It was envisaged that the droplet innate charges and sizes could be measured with and without corona charging, respectively. For this technique to be valid the charging process must not affect deposition on the impactor stages.

Three puffs from a QVAR[®] solution MDI were individually sampled with the charger removed from the ELPI, with the charger in place but switched off, and with it

switched on. The belomethasone dipropionate deposits from each puff were chemically assayed as described in Section 3.3.5.

5.3.5 *Crystal Violet Metered Dose Inhalers for Size Measurement*

Since corona charging was deemed to be unsuitable for sizing (Section 5.4), another set of MDIs were made containing crystal violet as a marker for chemical assays. 140 μL of a 0.4 mg/mL aqueous crystal violet solution was added to empty canisters, which were subsequently dried in a 60°C oven. Thin patches of crystal violet coating the inner surface resulted. Spiked water and propellant were added to these canisters in the same amounts as for those for charge measurements (Table 5.1). Two canisters of each propellant/valve/water content combination were made for the chemical assays instead of three. The water contents of these MDIs were not measured.

The effect of the chemical marker on propellant droplet sizes was observed by laser diffraction using Spraytec (Malvern, UK). Five puffs of propellant aerosols with and without crystal violet were sized by spraying horizontally across the laser beam. The refractive indices of HFA-134a and 227 were 1.17 and 1.22, respectively¹⁹. The imaginary refractive index used was 0.00 for both propellants.

The ELPI mass assays of the crystal violet MDIs followed the same conditions and setup as those for the charge measurements (Section 5.3.3). The MDIs were weighed before and after puff to obtain the sample mass. Twenty puffs and thirty puffs from HFA-134a and 227 inhalers were assayed at a time, respectively. More puffs were needed for HFA-227 because it was found in preliminary experiments that the

solubility of crystal violet was lower in this propellant than in HFA-134a. Each ELPI part and stage were washed or sonicated with 5 mL deionised water and assayed by HPLC. The mobile phase was a 90:10 v/v methanol-water mixture, the pH of which was adjusted to 3.5 with phosphoric acid, pumped at 1.5 mL/min through a Waters Nova-Pak[®] C18 column. The injected sample volume was 100 μ L. Fresh standard solutions were prepared to generate standard curves before each run. The limit of detection of the HPLC assay was 10 ng/mL.

5.3.6 Data Analysis

The charge on each impactor stage was derived from the electric current data by calculating the area under the curve versus time plot for that particular stage. The *net charge* was calculated from the sum of charges on all stages. The *fine particle dose (FPD) charge* was taken from the sum of charges on all particles of size < 6.66 μ m, corresponding to those on Stage 11 and below. The concentration of crystal violet in a MDI was obtained by dividing the total mass of crystal violet assayed from that inhaler by the sample mass of 20 or 30 puffs introduced into the ELPI. The amount of formulation (propellant + crystal violet) deposited on a given stage was calculated by dividing the mass of crystal violet on that stage by the concentration of the chemical marker in the propellant (see above). Subsequently, the mass of crystal violet on that stage was subtracted from this result and then divided by the number of actuations sampled (20 for HFA-134a and 30 for HFA-227) to yield the mass of propellant per actuation on that stage. The *mass median aerodynamic diameter (MMAD)* was calculated from the ELPI drug assay data. The *charge-to-mass ratio (q/m)* or *specific charge* for a given size fraction was calculated by dividing the mean charge by the

mean propellant mass in that size fraction. This was only derived for the size fractions containing detectable amounts of crystal violet, corresponding to Stages 1 to 7 for measurements at 5% and 50% RH and Stages 1 to 13 for those at 92% RH. The number of elementary charges (n) per drug particle in these size fractions was estimated by Equation 2.1, with ρ as the density of the propellant concerned (1.226 and 1.408 kg/dm³ at 20°C for HFA-134a and 227, respectively)²⁰.

5.4 Results

Calibration of the Karl Fischer coulometer showed that the measurements were on average 28.92% lower than the expected values ($n = 7$). All the drug-free MDI aerosol water contents (Table 5.2) were adjusted accordingly by this factor. Although the spiked water successfully increased the moisture level of the MDIs the values obtained were lower than expected. The target medium and high levels should be 300 ppm and 600 ppm, respectively (4.2 or 8.4 mg water in 14 g propellant).

Table 5.2. Water contents of the MDIs for electrostatic charge measurement ($n = 18$ unless otherwise noted)^a.

		MDI water content (ppm)		
		Low level	Medium level	High level
HFA-134a	Hostaform	170.77 (11.49)	246.33 (10.06)	333.33 (11.30)
	PBT	129.21 (6.68)	271.14 (14.11)	434.75 (16.38)
HFA-227	Hostaform	115.77 (10.04)	238.34 (14.60)	321.60 (18.57) ^b
	PBT	80.24 (5.34)	278.19 (8.81)	416.60 (6.06)

Data are presented as mean with standard error in parenthesis.

^a Six measurements from each of three MDIs.

^b $n = 15$ due to three missed measurements.

The raw charge profiles of drug-free MDIs measured by the ELPI showed very high intra- and inter-inhaler variability under all four experimental conditions, especially for HFA-134a (Appendix D). The aerosols were bipolar in charge for both propellants but the point/s of polarity inversion varied between actuations. The effect of inhaler valve type and water content on droplet charging was difficult to discern from these variable profiles. Generally, charges were detected on all ELPI stages but when wet actuators were used in humidified air these were predominantly in the upper size fractions for all MDIs.

Distinctive trends were more obviously gleaned from the mean charge profiles (Figures 5.3 to 5.6). One canister of low water content HFA-227 with a PBT valve consistently charged ten times higher than the other two replicate MDIs (Appendix D), thus it was considered as an outlier and was not included in the data analysis. Despite

the bipolar nature of the individual puffs, most of the aerosols were, on average, negatively charged. HFA-227 produced less charge than HFA-134a. Aerosols actuated from PBT valves also charged less than those from Hostaform valves. Charges were not affected by an increase in the RH from 5% to 50% (Figures 5.3 and 5.4), nor by the moisture on actuators except that the charging of HFA-134a from Hostaform valves increased when wet actuators were used (Figures 5.4 and 5.5). Increasing the RH from 50% to 92% dramatically changed the charge distributions, but the charges remained in the same magnitudes, except for the further increase in negative charges for HFA-134a from Hostaform valves. In general, the charge profiles of all MDI types shifted in the positive direction, i.e. towards neutrality, with increasing water content. Furthermore, the polarity of HFA-134a droplets inverted at the highest water content thus became positively charged.

Dry actuators / Dry air

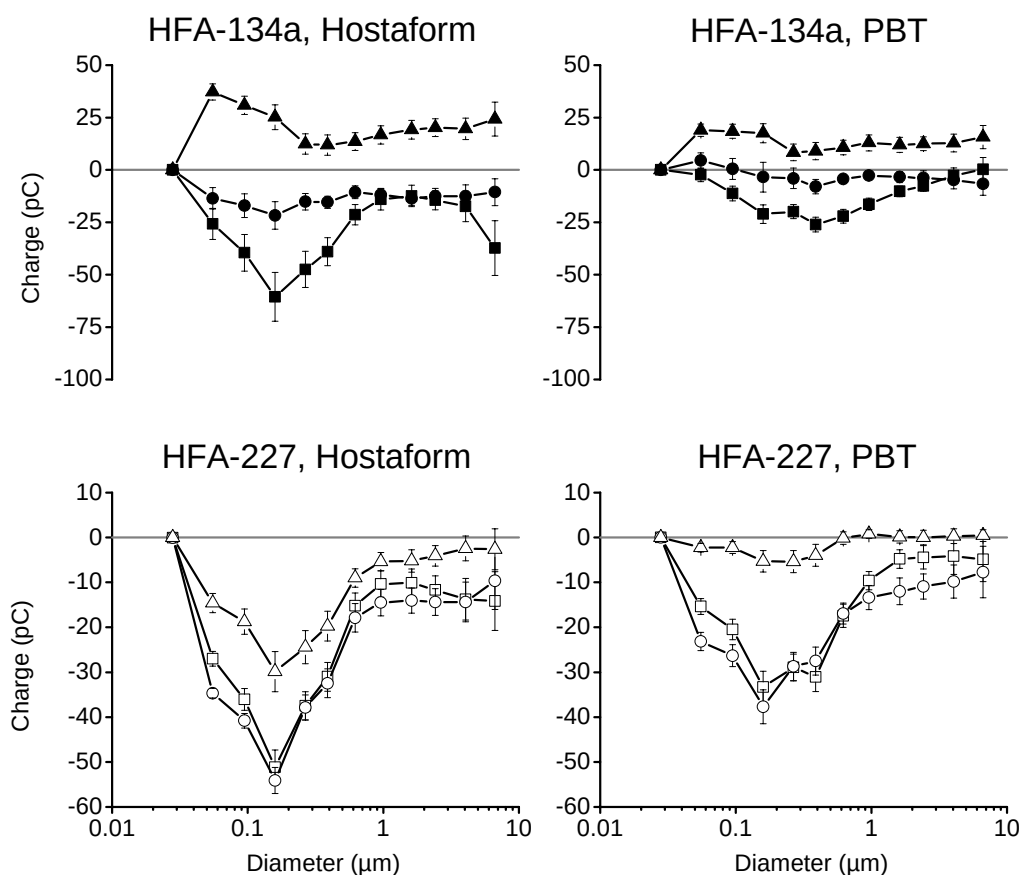


Figure 5.3. Mean charge profiles of HFA-134a (closed symbols) and HFA-227 (open symbols) MDIs used with dry actuators in dry air. (■, □ low water content; ●, ○ medium water content; ▲, △ high water content). Error bars represent standard errors ($n = 30$ for all except $n = 20$ for □ of HFA-227, PBT).

Dry actuators / 50% RH

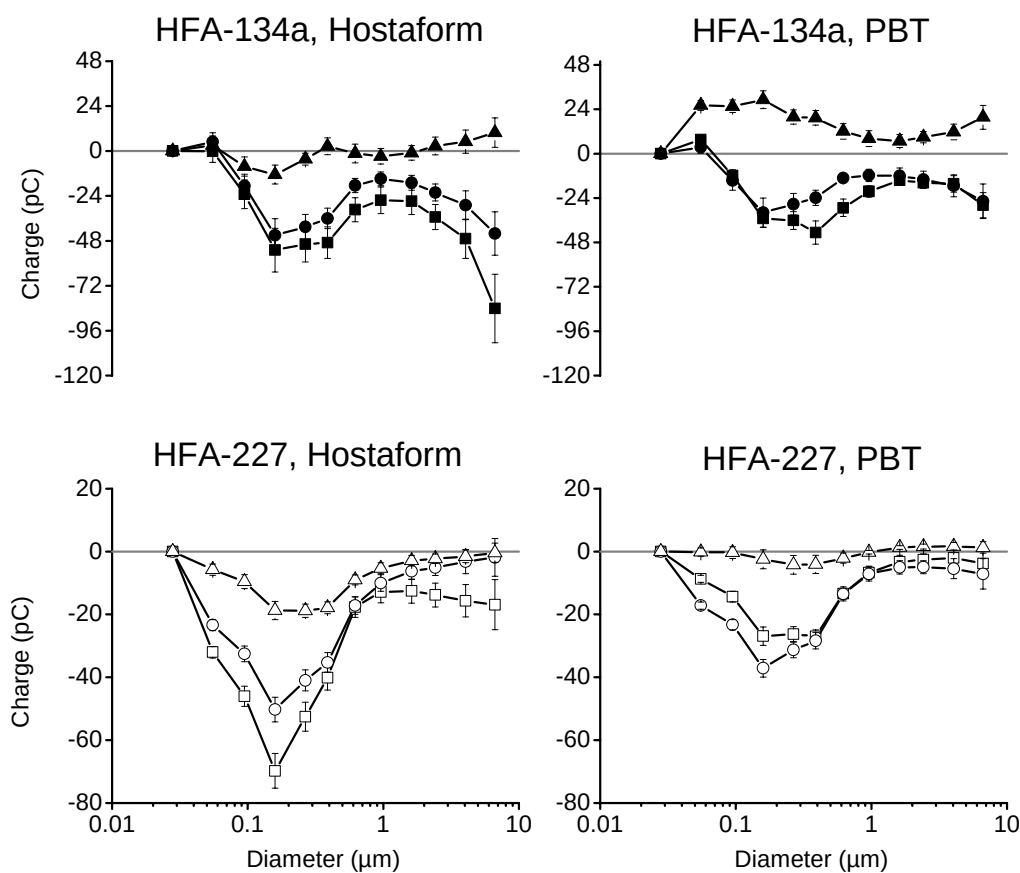


Figure 5.4. Mean charge profiles of HFA-134a (closed symbols) and HFA-227 (open symbols) MDIs used with dry actuators in 50% RH air. (■, □ low water content; ●, ○ medium water content; ▲, △ high water content). Error bars represent standard errors ($n = 30$ for all except $n = 20$ for □ of HFA-227, PBT).

Wet actuators / 50% RH

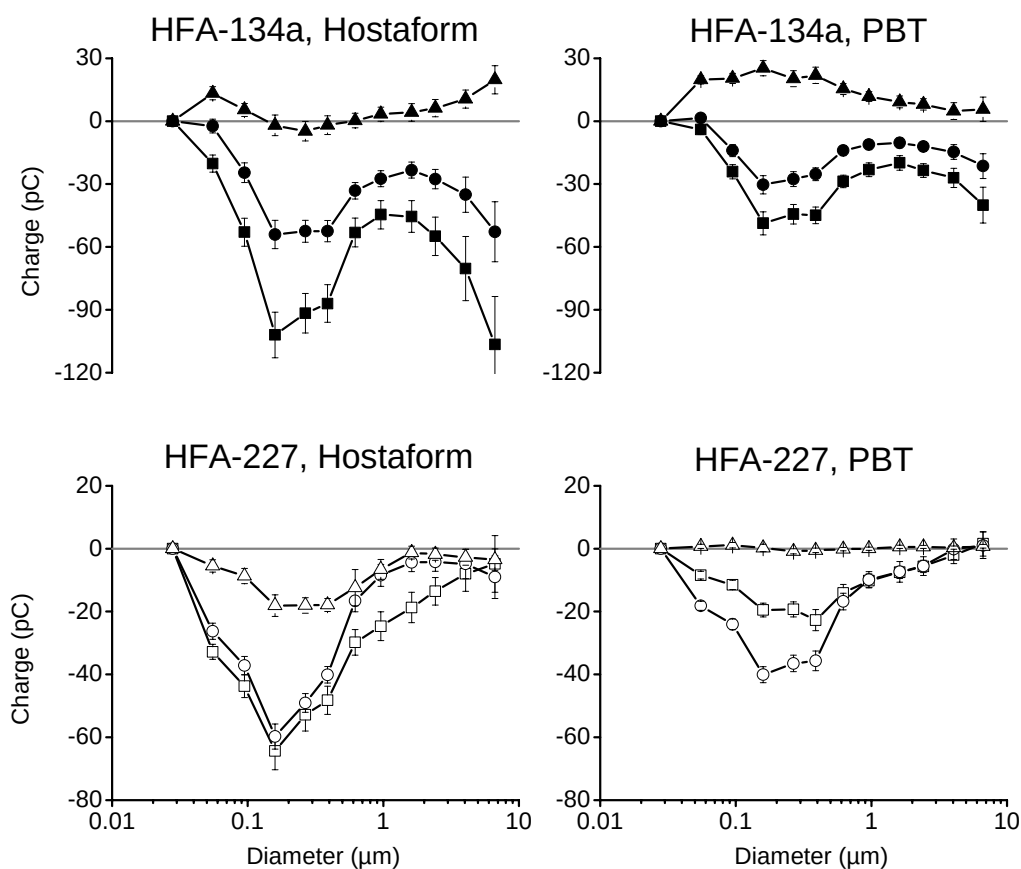


Figure 5.5. Mean charge profiles of HFA-134a (closed symbols) and HFA-227 (open symbols) MDIs used with wet actuators in 50% RH air. (■, □ low water content; ●, ○ medium water content; ▲, △ high water content). Error bars represent standard errors ($n = 30$ for all except $n = 20$ for □ of HFA-227, PBT).

Wet actuators / Humidified air

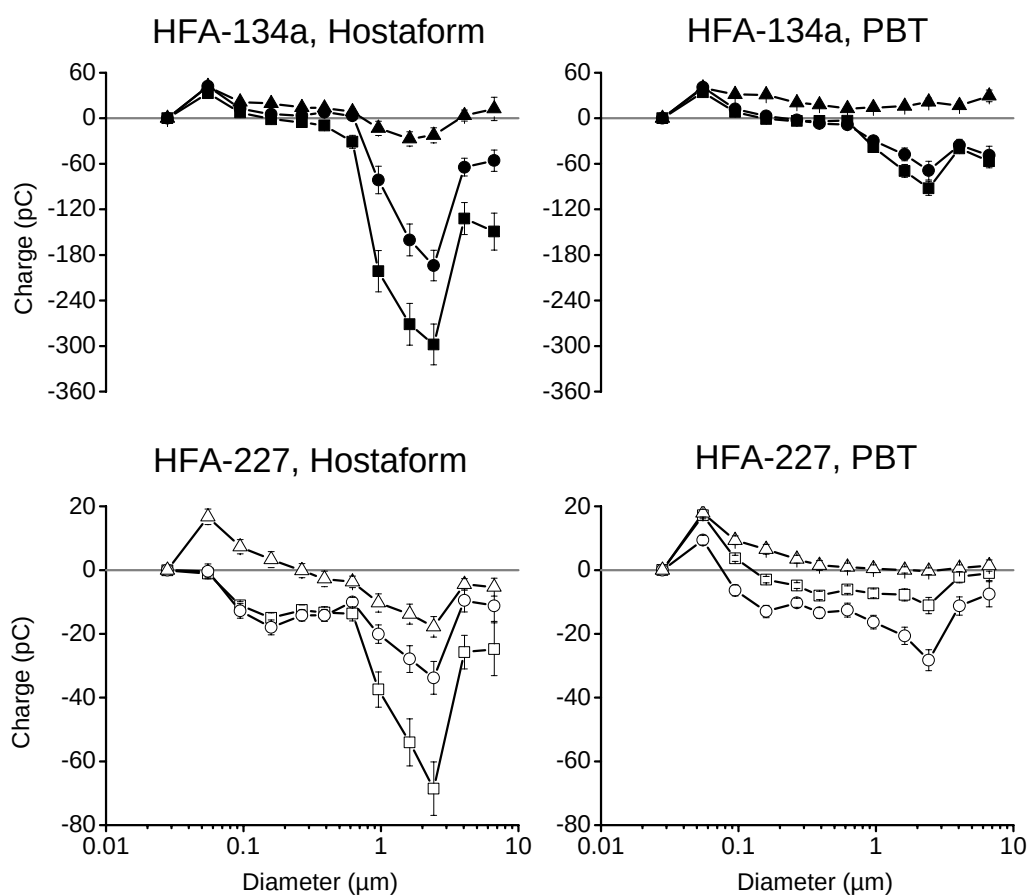


Figure 5.6. Mean charge profiles of HFA-134a (closed symbols) and HFA-227 (open symbols) MDIs used with wet actuators in humidified air. (■, □ low water content; ●, ○ medium water content; ▲, △ high water content). Error bars represent standard errors (n = 30 for all except n = 20 for □ of HFA-227, PBT).

The net and FPD charges showed the same trends with water content as those discussed above in relation to the mean charge profiles (Figures 5.7 and 5.8). The two charges were similar numerically because the charges on Stage 12 were relatively low and did not contribute much to the net charge. HFA-134a charged net positively beyond 300 ppm water. HFA-227 displayed the same tendency and, by extrapolation,

should invert polarity when the water content reaches 400 ppm. Overall, the net and FPD charges of the HFA-227 were not greatly affected by the experimental conditions.

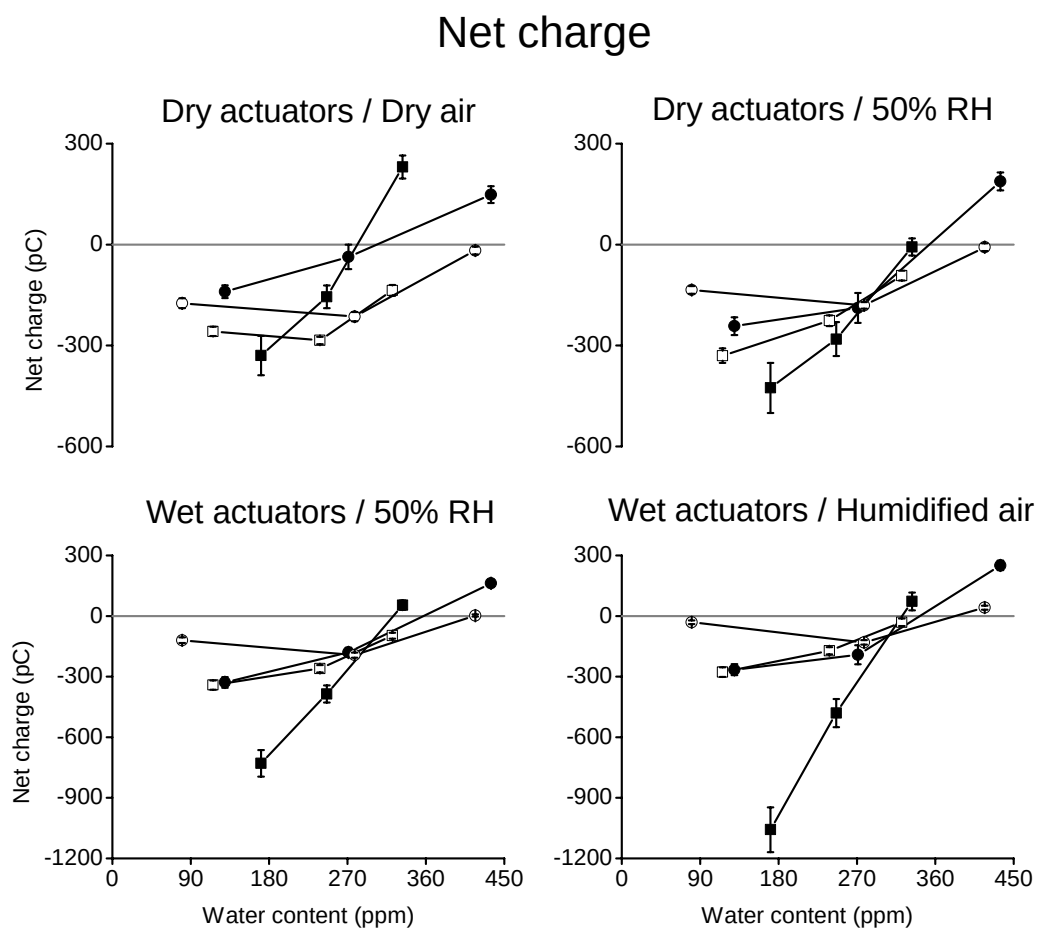


Figure 5.7. Mean net charges produced from HFA-134a (closed symbols) and HFA-227 (open symbols) MDIs. (■, □ Hostaform; ●, ○ PBT). Error bars represent standard errors ($n = 30$ for all except $n = 20$ for ○ of HFA-227 at 80.24 ppm).

FPD charge

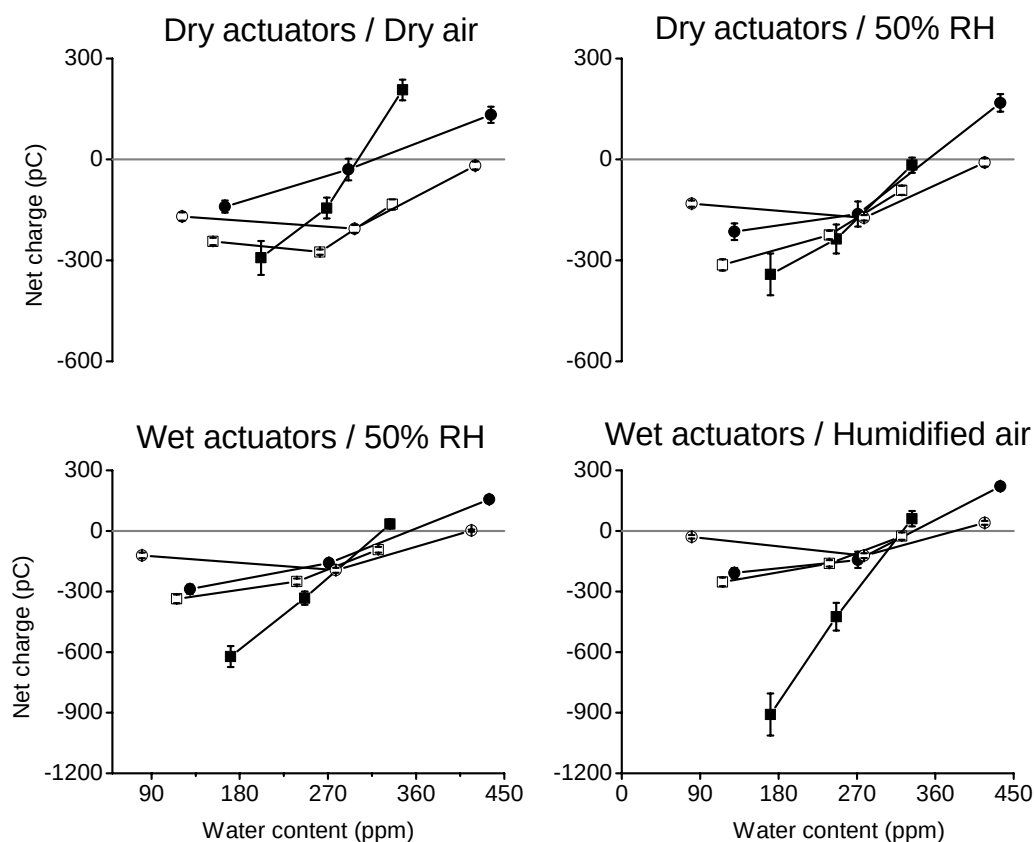


Figure 5.8. Mean FPD charges produced from HFA-134a (closed symbols) and HFA-227 (open symbols) MDIs. (■, □ Hostaform; ●, ○ PBT). Error bars represent standard errors ($n = 30$ for all except $n = 20$ for ○ of HFA-227 at 80.24 ppm).

The sizing of QVAR[®] with the ELPI corona charger indicated that the size distribution was not significantly affected by the physical presence of the charger. Rather, it was the high electric field from the corona charging that greatly reduced particle deposition on the stages. This was due to the four-fold increase in drug

deposition on the charger when it was switched on (6.06 μg vs. 24.36 μg ; $n = 3$). Thus corona charging was deemed unsuitable for sizing drug-free propellant MDIs.

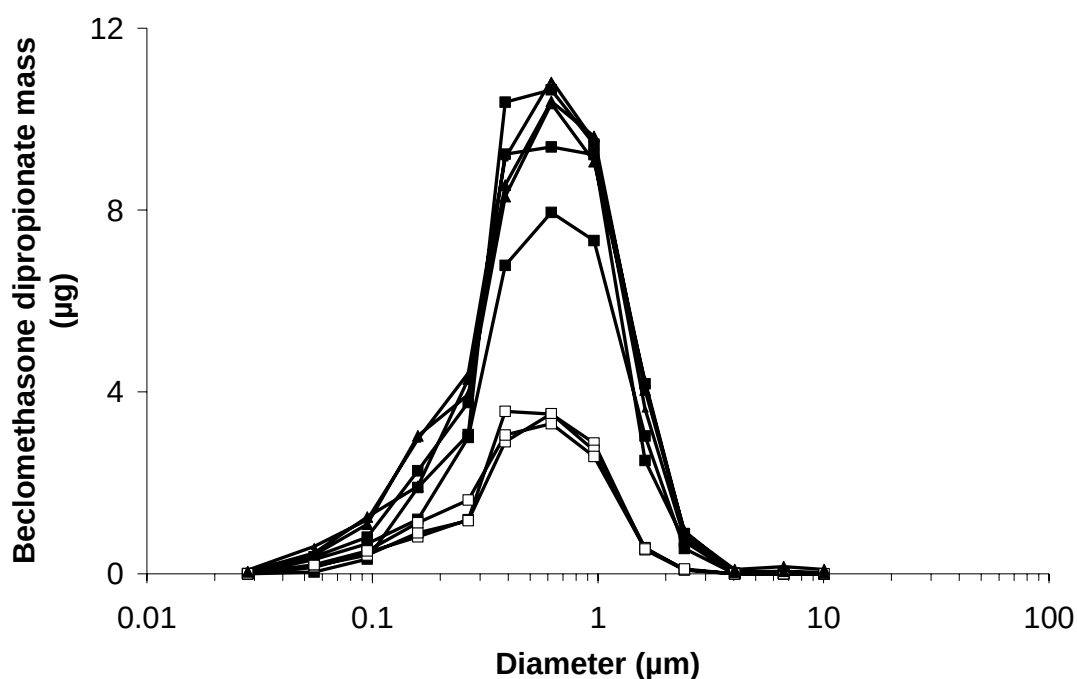


Figure 5.9. Particle size distributions of QVAR[®] from ELPI measured by chemical assay with the corona charger removed ($\blacktriangle$), with the charger in place but switched off ($\blacksquare$), and with the charger switched on ($\square$). Three puffs for each setup.

Laser diffraction measurement of crystal violet MDIs showed that the chemical marker did not alter the HFA droplet sizes since the distributions overlapped (Figure 5.10). HFA-227 produced larger droplets than HFA-134a. The short error bars from both plots indicate that the valves generated reproducible droplet sizes. Thus crystal violet was a suitable and sensitive marker for sizing by impaction and chemical assay.

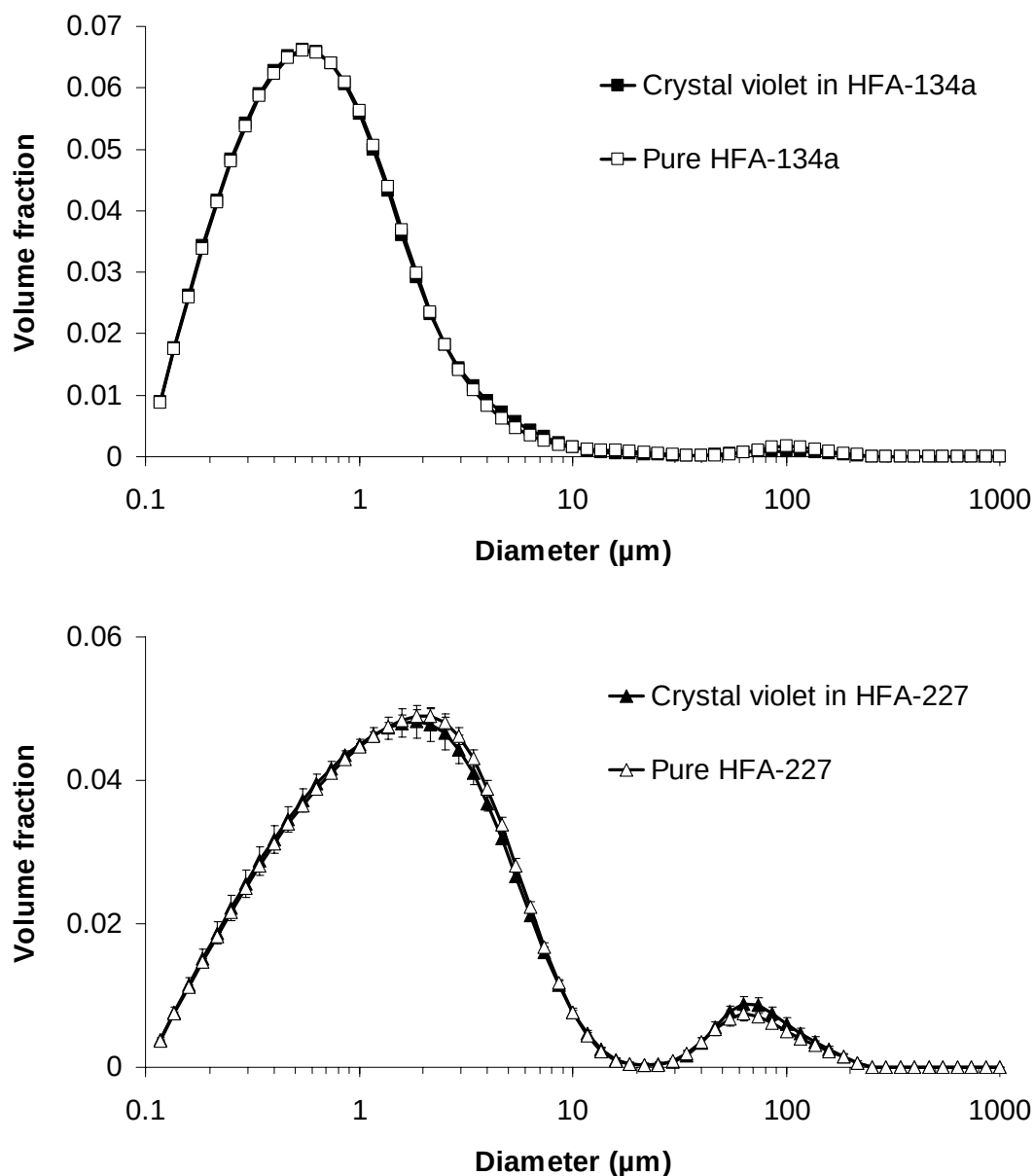


Figure 5.10. Mean droplet size distributions of HFA-134a and HFA-227 with and without crystal violet ($n = 5$). Error bars represent standard errors.

The mean mass of propellant dispensed per actuation from crystal violet-containing HFA-134a and 227 MDIs were 72.8 ± 0.6 and 81.7 ± 0.6 mg (mean $\pm$ standard error; $n = 48$), respectively. These conform to the 65 μ L nominal metering valve volume. No detectable crystal violet was assayed on the adaptor, the throat, and the straight tube in any of the ELPI runs. This conforms to the small size of the propellant

droplets. Size distributions of crystal violet measured by impaction (Figure 5.11) and the corresponding derived distributions of propellant droplets (Figure 5.12) indicated that MDIs of different constitutions yielded similar droplet sizes under a given condition. Droplet sizes were in the submicron range at 5% and 50% RH. However, the MMAD increased by approximately ten-fold at 92% RH (Figure 5.13) as evident from a shift in the size distribution (Figure 5.12).

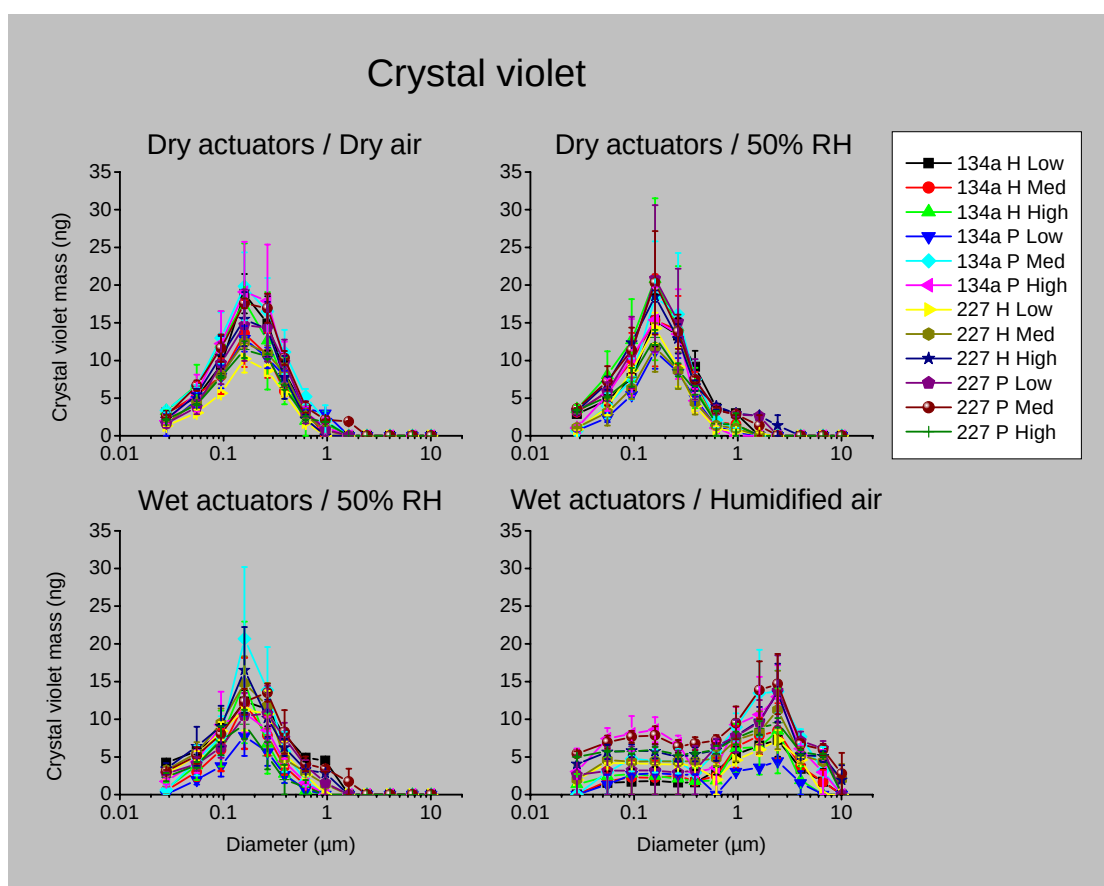


Figure 5.11. Mean size distributions of single puffs of crystal violet from MDIs measured with the ELPI (n = 2). Full error bars represent ranges. Legend key: 134a = HFA-134a, 227 = HFA-227; H = Hostaform valves; P = PBT valves; Low, Med, High = Low, medium, and high water content, respectively.

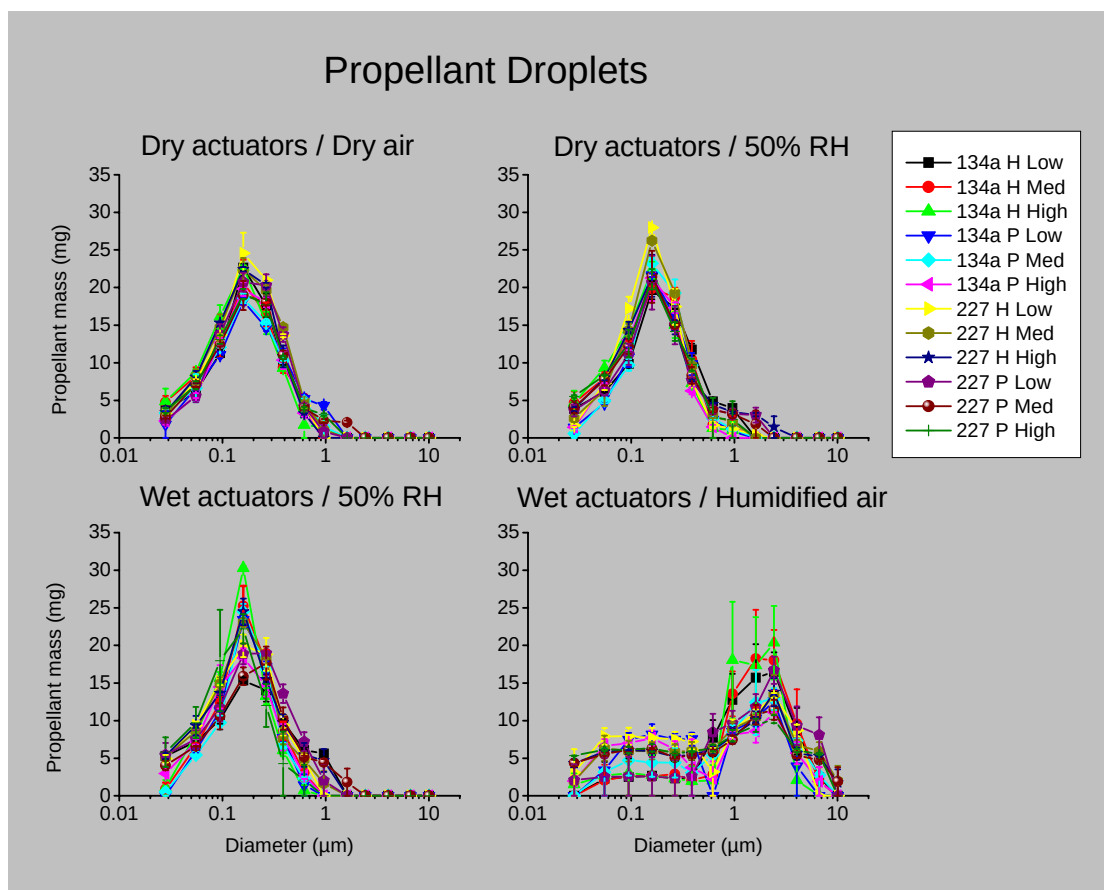


Figure 5.12. Mean size distributions of single puffs of propellant droplets from MDIs calculated from the crystal violet size distributions ($n = 2$). Full error bars represent ranges. Legend key: 134a = HFA-134a, 227 = HFA-227; H = Hostaform valves; P = PBT valves; Low, Med, High = Low, medium, and high water content, respectively.

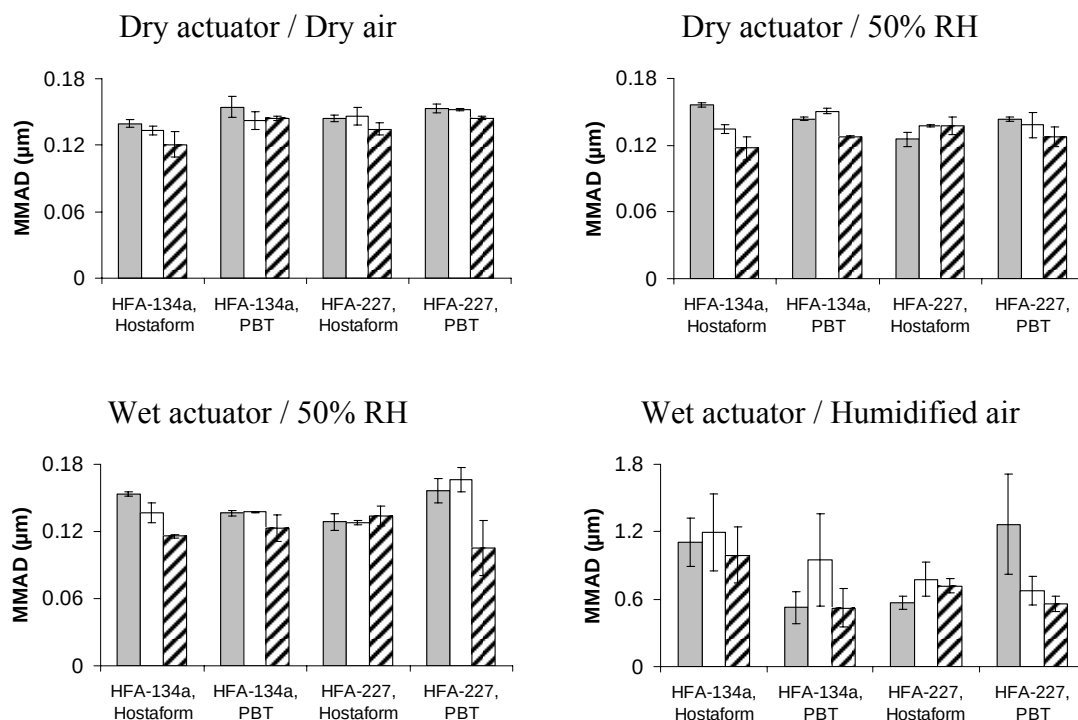


Figure 5.13. MMAD of propellant droplets from MDIs with low (grey bar), medium (white bar), and high (hatched bar) water contents ($n = 2$). Error bars represent ranges of the duplicate runs.

The specific charges of propellant droplets measured under various experimental conditions are shown in Tables 5.3 to 5.6. HFA-134a droplets carried higher specific charges than HFA-227. These values are low in magnitude thus the estimated number of elementary charges per droplet are zero in the lower size fractions with crystal violet detection for measurements at 5% and 50% RH (Tables 5.7 to 5.9). Data for propellant droplets in the upper size fractions at 92% RH (Table 5.10) could be calculated due to the presence of the chemical marker there. It is evident that the amount of charge held by a droplet decreases with droplet size.

Table 5.3. Specific charge of HFA-134a and 227 droplets generated with dry actuators in dry air (nC/g).

Stage	Cutoff diameter (μm)	HFA-134a						HFA-227					
		Hostaform			PBT			Hostaform			PBT		
		Low water content	Medium water content	High water content	Low water content	Medium water content	High water content	Low water content	Medium water content	High water content	Low water content	Medium water content	High water content
1	0.0280	-0.01 (0.00)	0.00 (0.00)	+0.01 (0.00)	0.00 (0.00)	0.00 (0.00)	+0.01 (0.00)	-0.01 (0.00)	-0.01 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
2	0.0552	-4.22 (1.31)	-1.65 (0.85)	+4.26 (0.66)	-0.36 (0.50)	+0.67 (0.75)	+3.37 (0.73)	-3.63 (0.41)	-4.26 (0.64)	-1.81 (0.45)	-2.76 (0.72)	-3.26 (0.40)	-0.32 (0.16)
3	0.0948	-3.51 (0.91)	-1.40 (0.63)	+1.91 (0.46)	-1.02 (0.36)	+0.04 (0.41)	+1.45 (0.33)	-2.63 (0.19)	-2.78 (0.45)	-1.23 (0.19)	-1.49 (0.31)	-2.13 (0.24)	-0.17 (0.11)
4	0.159	-2.67 (0.57)	-1.05 (0.47)	+1.11 (0.27)	-1.16 (0.28)	-0.19 (0.39)	+0.88 (0.27)	-2.08 (0.39)	-2.42 (0.30)	-1.33 (0.22)	-1.61 (0.27)	-1.99 (0.40)	-0.28 (0.13)
5	0.266	-2.69 (0.72)	-0.93 (0.33)	+0.81 (0.40)	-1.36 (0.27)	-0.27 (0.32)	+0.47 (0.24)	-1.79 (0.17)	-1.93 (0.21)	-1.20 (0.20)	-1.43 (0.25)	-1.59 (0.21)	-0.30 (0.17)
6	0.388	-3.92 (0.77)	-1.65 (0.44)	+1.28 (0.54)	-2.33 (0.47)	-0.78 (0.34)	+0.86 (0.50)	-2.28 (0.27)	-2.21 (0.28)	-1.82 (0.55)	-2.26 (0.39)	-2.49 (0.41)	-0.37 (0.23)
7	0.621	-5.14 (1.68)	-2.03 (0.79)	+7.83 (10.26)	-4.24 (1.08)	-0.88 (0.46)	+3.23 (1.50)	-3.54 (0.92)	-3.71 (0.75)	-2.78 (0.66)	-4.22 (1.11)	-4.23 (0.84)	-0.03 (0.36)

Data are presented as the ratio of mean charge to mean mass for each stage with the resultant error in parentheses.

Table 5.4. Specific charge of HFA-134a and 227 droplets generated with dry actuators in 50% RH (nC/g).

Stage	Cutoff diameter (μm)	HFA-134a						HFA-227					
		Hostaform			PBT			Hostaform			PBT		
		Low water content	Medium water content	High water content	Low water content	Medium water content	High water content	Low water content	Medium water content	High water content	Low water content	Medium water content	High water content
1	0.0280	+0.01 (0.00)	+0.01 (0.00)	0.00 (0.00)	+0.01 (0.00)	+0.01 (0.02)	+0.01 (0.00)	-0.02 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
2	0.0552	-0.01 (0.97)	+0.61 (0.68)	+0.34 (0.57)	+1.66 (0.62)	+0.71 (0.66)	+3.65 (0.43)	-4.40 (0.80)	-3.66 (1.50)	-0.72 (0.25)	-1.37 (0.33)	-2.23 (0.37)	-0.02 (0.16)
3	0.0948	-2.35 (0.90)	-1.44 (0.50)	-0.57 (0.39)	-1.11 (0.43)	-1.50 (0.65)	+1.97 (0.46)	-2.67 (0.43)	-2.28 (0.31)	-0.67 (0.21)	-1.29 (0.32)	-1.92 (0.29)	-0.03 (0.15)
4	0.159	-2.70 (0.76)	-2.27 (0.49)	-0.56 (0.26)	-1.62 (0.23)	-1.37 (0.39)	+1.37 (0.42)	-2.49 (0.22)	-1.92 (0.17)	-0.87 (0.25)	-1.30 (0.37)	-1.73 (0.41)	-0.12 (0.15)
5	0.266	-2.89 (0.57)	-2.16 (0.51)	-0.29 (0.24)	-2.25 (0.37)	-1.42 (0.43)	+1.15 (0.27)	-3.01 (0.68)	-2.13 (0.17)	-1.28 (0.23)	-1.75 (0.46)	-2.08 (0.21)	-0.30 (0.24)
6	0.388	-4.17 (1.00)	-3.45 (1.33)	+0.35 (0.64)	-4.34 (1.28)	-2.47 (0.66)	+3.09 (0.87)	-5.29 (0.88)	-3.68 (0.64)	-2.34 (0.28)	-3.51 (0.44)	-3.41 (0.78)	-0.42 (0.33)
7	0.621	-6.44 (1.94)	-10.53 (12.72)	-0.99 (4.83)	-12.02 (3.30)	-5.13 (1.12)	+8.21 (4.42)	-10.40 (4.75)	-5.81 (1.61)	-2.01 (0.38)	-3.56 (0.99)	-3.59 (0.90)	-0.78 (1.39)

Data are presented as the ratio of mean charge to mean mass for each stage with the resultant error in parentheses.

Table 5.5. Specific charge of HFA-134a and 227 droplets generated with wet actuators in 50% RH (nC/g).

Stage	Cutoff diameter (μm)	HFA-134a						HFA-227					
		Hostaform			PBT			Hostaform			PBT		
		Low water content	Medium water content	High water content	Low water content	Medium water content	High water content	Low water content	Medium water content	High water content	Low water content	Medium water content	High water content
1	0.0280	0.00 (0.00)	+0.03 (0.03)	+0.02 (0.03)	N/A	+0.02 (0.02)	+0.01 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
2	0.0552	-2.82 (0.63)	-0.36 (0.52)	+1.64 (0.46)	-0.66 (0.43)	+0.27 (0.40)	+2.76 (0.41)	-3.51 (0.47)	-3.06 (0.31)	-0.59 (0.29)	-1.12 (0.34)	-2.76 (0.23)	+0.08 (0.09)
3	0.0948	-5.23 (0.94)	-1.97 (0.51)	+0.34 (0.22)	-2.14 (0.32)	-1.44 (0.43)	+1.41 (0.45)	-2.87 (0.34)	-2.50 (0.34)	-0.64 (0.19)	-0.99 (0.28)	-2.28 (0.54)	+0.06 (0.07)
4	0.159	-6.65 (0.87)	-2.14 (0.49)	-0.07 (0.17)	-2.08 (0.29)	-1.24 (0.23)	+1.38 (0.30)	-3.23 (0.54)	-2.59 (0.23)	-0.74 (0.20)	-1.03 (0.19)	-2.52 (0.35)	+0.01 (0.06)
5	0.266	-6.54 (1.37)	-2.96 (0.57)	-0.36 (0.38)	-2.59 (0.39)	-1.64 (0.24)	+1.39 (0.40)	-2.81 (0.60)	-2.69 (0.18)	-1.17 (0.21)	-1.02 (0.14)	-2.07 (0.40)	-0.07 (0.09)
6	0.388	-8.83 (1.22)	-6.13 (1.48)	-0.31 (0.79)	-5.83 (0.91)	-3.78 (0.65)	+2.81 (1.12)	-5.13 (1.22)	-5.30 (0.85)	-1.84 (0.41)	-1.67 (0.40)	-3.48 (0.82)	-0.12 (0.29)
7	0.621	-8.75 (1.19)	-10.88 (5.16)	+0.38 (5.21)	-20.11 (22.22)	-6.16 (1.77)	+5.67 (1.91)	-6.14 (1.65)	-3.46 (1.43)	-2.28 (1.72)	-1.96 (0.72)	-3.25 (0.60)	-0.07 (0.33)

Data are presented as the ratio of mean charge to mean mass for each stage with the resultant error in parentheses.

N/A: Not calculated due to negligible mass detected.

Table 5.6. Specific charge of HFA-134a and 227 droplets generated with wet actuators in humidified air (nC/g).

Stage	Cutoff diameter (µm)	HFA-134a						HFA-227					
		Hostaform			PBT			Hostaform			PBT		
		Low water content	Medium water content	High water content	Low water content	Medium water content	High water content	Low water content	Medium water content	High water content	Low water content	Medium water content	High water content
1	0.0280	N/A	N/A	0.00 (0.00)	N/A	N/A	-0.02 (0.02)	-0.01 (0.01)	-0.01 (0.02)	0.00 (0.00)	0.00 (0.00)	-0.01 (0.00)	0.00 (0.00)
2	0.0552	+14.55 (16.56)	+20.37 (22.00)	+15.53 (17.13)	+10.16 (10.75)	+12.91 (13.56)	+5.99 (1.17)	-0.14 (0.20)	-0.06 (0.38)	+2.84 (0.44)	+6.78 (7.21)	+1.69 (0.33)	+2.90 (0.29)
3	0.0948	+3.09 (4.74)	+4.81 (5.71)	+7.04 (8.02)	+1.09 (0.31)	+2.56 (1.67)	+4.47 (0.56)	-1.40 (0.35)	-2.15 (0.89)	+1.21 (0.38)	+1.43 (1.80)	-1.03 (0.34)	+1.53 (0.33)
4	0.159	-0.50 (1.77)	+2.07 (2.82)	+7.18 (8.27)	-0.12 (0.21)	+0.67 (1.01)	+4.03 (0.94)	-1.95 (0.55)	-3.00 (0.97)	+0.55 (0.42)	-1.15 (1.54)	-2.06 (0.34)	+1.03 (0.32)
5	0.266	-2.20 (3.35)	+1.29 (1.91)	+6.11 (7.28)	-0.49 (0.29)	-0.49 (0.82)	+3.30 (0.95)	-1.66 (0.43)	-2.42 (0.72)	-0.03 (0.42)	-2.06 (2.44)	-2.02 (0.33)	+0.61 (0.23)
6	0.388	-4.07 (5.84)	+3.81 (5.04)	+6.96 (8.57)	-0.49 (0.36)	-2.23 (3.20)	+4.71 (5.31)	-1.85 (0.52)	-2.37 (0.79)	-0.50 (0.45)	-3.06 (3.54)	-2.48 (0.39)	+0.25 (0.26)
7	0.621	-4.00 (2.33)	+1.17 (3.01)	+4.29 (6.30)	N/A	-1.55 (0.63)	+5.64 (6.55)	-4.29 (5.00)	-1.60 (0.39)	-0.60 (0.35)	-0.72 (0.35)	-2.17 (0.52)	+0.15 (0.20)
8	0.960	-15.79 (6.42)	-5.99 (2.67)	-0.73 (0.83)	-4.48 (0.76)	-3.49 (1.02)	+1.75 (0.46)	-4.30 (1.36)	-2.26 (0.56)	-1.29 (0.52)	-0.75 (0.28)	-2.19 (0.44)	+0.06 (0.15)
9	1.62	-17.29 (6.71)	-8.78 (4.27)	-1.56 (1.13)	-6.75 (1.54)	-3.83 (2.01)	+1.83 (0.72)	-4.86 (0.82)	-2.68 (0.50)	-1.36 (0.36)	-0.66 (0.25)	-1.91 (0.48)	0.00 (0.11)
10	2.42	-18.07 (4.46)	-10.75 (3.51)	-1.09 (0.75)	-7.33 (1.63)	-5.36 (1.56)	+1.95 (0.48)	-5.13 (0.75)	-2.51 (0.87)	-1.29 (0.41)	-0.66 (0.22)	-2.47 (0.58)	-0.03 (0.11)
11	4.04	-15.38 (8.01)	-6.71 (4.42)	1.78 (5.35)	-10.10 (11.36)	-4.85 (1.24)	+2.98 (1.56)	-2.96 (0.87)	-1.39 (0.67)	-0.80 (0.43)	-0.23 (0.26)	-2.09 (0.68)	+0.10 (0.18)
12	6.66	-60.14 (70.00)	-29.31 (36.66)	N/A	N/A	-17.67 (21.91)	+15.37 (19.44)	N/A	-1.91 (1.23)	-1.01 (0.55)	-0.12 (0.32)	-1.59 (0.89)	+0.25 (0.32)

Data are presented as the ratio of mean charge to mean mass for each stage with the resultant error in parentheses.

N/A: Not calculated due to negligible mass detected.

Table 5.7. Estimated number of elementary charges per droplet of HFA-134a and 227 generated with dry actuators in dry air calculated by Equation 2.1.

Stage	Cutoff diameter (μm)	HFA-134a						HFA-227					
		Hostaform			PBT			Hostaform			PBT		
		Low water content	Medium water content	High water content	Low water content	Medium water content	High water content	Low water content	Medium water content	High water content	Low water content	Medium water content	High water content
1	0.0280	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
2	0.0552	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
3	0.0948	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
4	0.159	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
5	0.266	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
6	0.388	-1 (0)	0 (0)	0 (0)	-1 (0)	0 (0)	0 (0)	-1 (0)	-1 (0)	0 (0)	-1 (0)	-1 (0)	0 (0)
7	0.621	-5 (2)	-2 (1)	8 (10)	-4 (1)	-1 (0)	3 (1)	-4 (1)	-4 (1)	-3 (1)	-5 (1)	-5 (1)	0 (0)

Data are presented as the number of elementary charges per droplet derived from the corresponding mean specific charge for each stage with the resultant error in parentheses.

Table 5.8. Estimated number of elementary charges per droplet of HFA-134a and 227 generated with dry actuators in 50% RH calculated by Equation 2.1.

Stage	Cutoff diameter (μm)	HFA-134a						HFA-227					
		Hostaform			PBT			Hostaform			PBT		
		Low water content	Medium water content	High water content	Low water content	Medium water content	High water content	Low water content	Medium water content	High water content	Low water content	Medium water content	High water content
1	0.0280	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
2	0.0552	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
3	0.0948	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
4	0.159	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
5	0.266	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
6	0.388	-1 (0)	-1 (0)	0 (0)	-1 (0)	-1 (0)	+1 (0)	-1 (0)	-1 (0)	-1 (0)	-1 (0)	-1 (0)	0 (0)
7	0.621	-6 (2)	-10 (12)	-1 (5)	-12 (3)	-5 (1)	+8 (4)	-11 (5)	-6 (2)	-2 (0)	-4 (1)	-4 (1)	-1 (2)

Data are presented as the number of elementary charges per droplet derived from the corresponding mean specific charge for each stage with the resultant error in parentheses.

Table 5.9. Estimated number of elementary charges per droplet of HFA-134a and 227 generated with wet actuators in 50% RH calculated by Equation 2.1.

Stage	Cutoff diameter (μm)	HFA-134a						HFA-227					
		Hostaform			PBT			Hostaform			PBT		
		Low water content	Medium water content	High water content	Low water content	Medium water content	High water content	Low water content	Medium water content	High water content	Low water content	Medium water content	High water content
1	0.0280	0 (0)	0 (0)	0 (0)	N/A	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
2	0.0552	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
3	0.0948	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
4	0.159	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
5	0.266	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
6	0.388	-2 (0)	-1 (0)	0 (0)	-1 (0)	-1 (0)	+1 (0)	-1 (0)	-1 (0)	0 (0)	0 (0)	-1 (0)	0 (0)
7	0.621	-8 (1)	-10 (5)	0 (5)	-19 (21)	-6 (2)	+5 (2)	-7 (2)	-4 (2)	-3 (2)	-2 (1)	-4 (1)	0 (0)

Data are presented as the number of elementary charges per droplet derived from the corresponding mean specific charge for each stage with the resultant error in parentheses.

N/A: Not calculated due to negligible mass detected.

Table 5.10. Estimated number of elementary charges per droplet of HFA-134a and 227 generated with wet actuators in humidified air calculated by Equation 2.1.

Stage	Cutoff diameter (μm)	HFA-134a						HFA-227					
		Hostaform			PBT			Hostaform			PBT		
		Low water content	Medium water content	High water content	Low water content	Medium water content	High water content	Low water content	Medium water content	High water content	Low water content	Medium water content	High water content
1	0.0280	N/A	N/A	0 (0)	N/A	N/A	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
2	0.0552	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
3	0.0948	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
4	0.159	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
5	0.266	0 (0)	0 (0)	0 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
6	0.388	-1 (1)	+1 (1)	+2 (2)	0 (0)	-1 (1)	+1 (1)	0 (0)	-1 (0)	0 (0)	-1 (1)	-1 (0)	0 (0)
7	0.621	-4 (0)	+1 (3)	+4 (6)	N/A	-1 (1)	+5 (6)	-5 (6)	-2 (0)	-1 (0)	-1 (0)	-2 (1)	0 (0)
8	0.960	-56 (23)	-21 (9)	-3 (3)	-16 (3)	-12 (4)	+6 (2)	-18 (6)	-9 (2)	-5 (2)	-3 (1)	-9 (2)	0 (1)
9	1.62	-295 (114)	-150 (73)	-27 (19)	-115 (26)	-65 (34)	+31 (12)	-95 (16)	-52 (10)	-27 (7)	-13 (5)	-37 (9)	0 (2)
10	2.42	-1026 (253)	-610 (199)	-62 (42)	-416 (92)	-304 (89)	+111 (27)	-335 (49)	-164 (57)	-84 (27)	-43 (15)	-161 (38)	-2 (7)
11	4.04	-4063 (2117)	-1773 (1168)	+470 (1413)	-2667 (3002)	-1282 (328)	+788 (412)	-898 (265)	-423 (203)	-241 (131)	-69 (79)	-635 (205)	+30 (56)
12	6.66	-71187 (82861)	-34689 (43400)	N/A	N/A	-20912 (25936)	+18192 (23011)	N/A	-2591 (1672)	-1377 (748)	-165 (437)	-2157 (1206)	+346 (440)

Data are presented as the number of elementary charges per droplet derived from the corresponding mean specific charge for each stage with the resultant error in parentheses.

N/A: Not calculated due to negligible mass detected.

5.5 Discussion

Karl Fischer titration is a well-established pharmacopoeial method for water determination in solid and liquid samples²¹⁻²³. The United States Pharmacopeia²⁴ also reported its use on slow-flowing propellant gas streams fed into the reagent at 100 mL/min. Although the technique has been applied to MDI formulations^{11,14-16,18,25}, its accuracy in quantifying water in rapidly evaporating boli of pressurised gas is not satisfactorily reported hitherto. The aerosol might bubble too fast through the liquid reagent and vaporise into the titration cell headspace without sufficient mixing. Consequently some of the water carried by the escaping gas would be missed in the titration. An early report by Kim et al¹⁸ showed the reproducibility of the measurement on MDI puffs and its accuracy on anhydrous ethanol spiked with water. However, these two sampling procedures are inherently different so accuracy for liquid ethanol samples does not imply the same for aerosol boli. Furthermore, this concern had not been addressed in the studies in which this method was employed^{11,14-16,25}. Since Karl Fischer titration is the only reported technique for quantifying water in MDI aerosols, modifications, such as adding the syringe barrel adaptor and filling the titration cell with more reagent, were implemented in the present study to maximise aerosol capture.

Despite the extra precautions taken with the Karl Fischer coulometer setup and that the amount of water titrated in each run was within the practical determination range (10-10,000 µg)²⁶ the water contents measured for the water-spiked MDIs were consistently lower than expected. This may imply that the aerosol capture was still

inefficient. Another possibility is that part of the spiked water was absorbed by the polymer components in the MDI valves. The aluminium canister is not expected to be water absorbent, while certain organic polymers are known to be hygroscopic^{27,28}. Since the valves were dried in desiccators before use the tendency for water absorption would be enhanced and reduced the propellant moisture level. Nevertheless, the resultant water contents obtained were sufficiently high to affect aerosol charging. MDIs spiked with known amounts of water had also been made by Williams III et al¹¹. However, the amount of HFA-134a filled was not specified in the study thus it could not be ascertained whether similar discrepancies in the water contents occurred in that study.

Since reproducible doses and droplet sizes were generated from the valves (Section 5.4) these were not the causes for the high variability in the raw charge profiles. The amount of charges produced from these drug-free MDIs was obviously much lower than those from MDIs containing suspended drug particles (Figure 3.4). Thus these may be considered as the ‘baseline charges’ from the propellant itself. It should also be noted that the solution-based QVAR[®] also produced lower (and more variable) charges than the suspension products. All these evidence suggest that the charging ability of solution formulations, including the propellant-water MDIs in the present study, is lower than that of suspensions. The higher charges produced from suspension MDIs thus dominate and overwhelm the inherent variability of the baseline propellant charges.

The mean charges of both HFA-134a and 227 were negative at low water contents, with HFA-134a generating higher charges (Figures 5.3 to 5.6). The charges may be

generated from the contact and shear of the propellant against the MDI valve and actuator components during aerosolisation. The negative charging propensity of both propellants may be explained by their molecular structure (Figure 5.14).

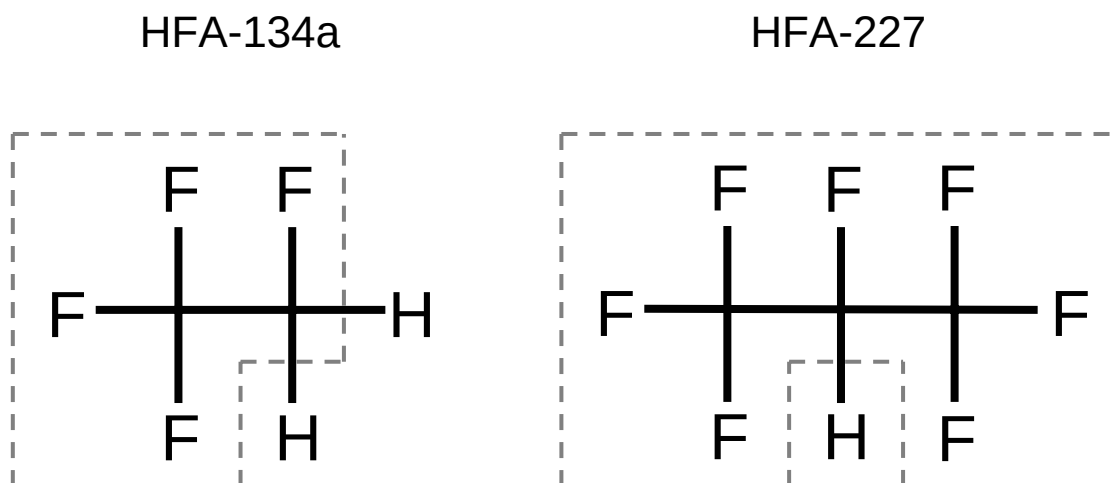


Figure 5.14. Molecular structures of HFA-134a and HFA-227. Regions with fluorine atoms are highlighted. Carbon atoms are not labelled for better clarity.

The two molecules have simple structures composed of hydrogen, carbon, and fluorine atoms. Since fluorine is highly electronegative, it should attract electrons or anions and renders the molecule negatively charged. This might be the basis for the preferred charge polarity of the propellants. The anion attracting ability of fluorine atoms was also alluded to by Yatsuzuka et al²⁹ in the discussion on the negative charging of Teflon after contact with water droplets (Section 1.3).

Due to the asymmetrical spatial arrangement of fluorine atoms on the carbon backbone, both HFA-134a and 227 are polar molecules. HFA-134a is the more polar one because of the higher imbalance of electronegativity within the molecule. This is

reflected in the higher dipole moment (2.058 vs. 0.93 debye)²⁰ and higher dielectric constant of HFA-134a over those of HFA-227 (9.5 vs. 4.1)¹⁹. The more polar a molecule, the stronger are its electrostatic forces, thus it should become charged easier. This supports the higher charges measured on HFA-134a droplets.

The transfer of electrons during charging may be viewed as a competition of electronegativities between the propellant and the valve/actuator materials with which it contacts. These components are made of organic polymers. Hostaform is a polyoxymethylene polymer (also known as polyacetal), PBT a polyester, and EPDM is polymerised ethylene propylene diene. The actuators were moulded with polypropylene. These materials commonly consist of hydrogen, carbon, and oxygen atoms, all of which are less electronegative than fluorine. Thus both HFAs charged negatively against them at low water contents.

Propellant charges shifted towards neutrality with increasing water contents (Figures 5.3 to 5.8). HFA-134a even charged positively at high water contents. There may be a number of possible reasons for the trend. Firstly, the added water may increase the electrical conductivity of the propellant, which would suppress charging. This inverse relationship between conductivity and charging has been reported for organic³⁰ and aqueous^{29,31-33} liquids. Secondly, the spiked water may decrease the bulk electronegativity of the propellant through the introduction of oxygen atoms. This would decrease electron capture by HFA, so the aerosols become less negatively charged. A further increase in the water content may reduce the propellant electronegativity to a level below that of the MDI component materials, in which case the HFA would lose electrons to the polymers and become positively charged.

Gallo and Lama hypothesised that ‘insulators with higher dielectric constants tended to acquire excess positive charge when placed in contact with other materials having lower dielectric constants’³⁴. Charge results from the present MDI study do not fully agree with this prediction. Dielectric constants of organic polymers are generally between 2 and 4³⁵ while those for pure HFA-134a and 227 are higher, 9.5 and 4.1²⁰, respectively, yet both aerosols charged negatively. Furthermore, HFA-134a has a higher dielectric constant than HFA-227, but it charged more negatively than HFA-227 against the same valve material. The results thus contradict Gallo and Lama’s theory. However, the situation is different when water content is considered. Since water has a dielectric constant of 79.55 at 295 K and 0.1 MPa³⁶, its addition to the propellant should increase the bulk dielectric constant. Therefore the charges generated would progressively shift towards the positive polarity, as observed. The contradicting results suggest that the dielectric constant hypothesis does not seem to be sufficient in explaining the charging process. Besides the polymers, the liquefied propellant also contacts with metal MDI components, such as the aluminium canister and stainless steel spring in the metering chamber, which may contribute to charge generation.

Kulphaisal et al¹⁶ also found that the fine particle dose charge of HFA-134a MDIs changed from negative to positive when the water ingress > 300 ppm through storage. The water contents of the HFA-227 inhalers remained low after storage due to their lower hygroscopicity so their fine particle dose charges were negative¹⁶. Fifty µL valves with EPDM or nitrile elastomers were used but the material for the core components was not stated. Although the effect of water content on charge polarity

agreed with that observed in the present study, the magnitudes measured by Kulphaisal et al were lower. The lower metering volume (50 vs. 65 μL) of the valves used by Kulphaisal et al may decrease the amount of charges produced. However, the 1.3-fold increase in the metering volumes does not totally explain the 3-fold difference in the charge magnitudes between the two studies. Differences in the valve core materials employed may also play a role. As discussed above, PBT valves generated lower charges than Hostaform ones. Valves of various elastomer, body, and stem compositions were also found to generate different magnitudes and polarity of charges on albuterol sulfate and levalbuterol sulfate particles by Peart et al¹⁷.

The particle charge and size of the aerosols were not appreciably affected by the moisture on the actuators (Figure 5.4 and 5.5). On the other hand, the charge and mass distributions were dramatically altered in humidified air (Figures 5.5 and 5.6). Particle size growth at high RH has been documented on solution and suspension MDIs³⁷. As the propellant evaporations from a droplet it cools the non-volatile constituents in the formulation. This promotes the condensation of water from the humidified air on the particles, thereby increasing their sizes³⁷. In the present study, the relatively non-volatile water in the MDIs is believed to precipitate from the evaporating HFA droplets and become small ice crystals depositing on the ELPI stages.

HFA-227 produced larger droplets than HFA-134a when the aerosols were measured immediately after actuation by laser diffraction (Figure 5.10), as expected from its lower vapour pressure (3.90 vs. 5.72 bar at 20°C)²⁰. However, all particle sizes measured by the ELPI at 5% and 50% RH were largely similar, regardless of the propellant, valve type, and water content. This indicates that propellant and

evaporation was complete by the air suction through the ELPI and that the water contents tested were too low to significantly increase particle size.

Chemical assay of a marker was the only feasible method to determine the propellant droplet size distribution in the ELPI. Some assumptions were involved in the derivation of the propellant droplet size distribution from that of the chemical marker. It was assumed that propellant droplets only deposited on the stages with detectable crystal violet. As discussed below, deposition did occur on stages with undetectable marker. However, the percentage of these deposits would be small by mass compare to those detected so their negligibility was reasonable. The concentration of crystal violet in a droplet was also assumed to be the same for all droplet sizes. In reality, the solute concentration will increase as the solvent evaporates. Furthermore, droplets of different sizes have different evaporation rates due to the Kelvin effect³⁸. Thus the crystal violet concentration changes with time and droplet size. As an approximation, this variable was taken to be constant in the calculations for this study. Ideally, the dynamics of solute concentration in an evaporating droplet travelling through the jet paths in the ELPI should be computed but such modelling is very complex and is beyond the scope of this thesis.

Generally, the net and FPD charges were not affected by actuator moisture and RH, except for Hostaform valves (Figures 5.7 and 5.8). This implies that the amount of charges produced from an inhaler was constant regardless of external conditions. The reason for the exceptional behaviour of Hostaform valves is unclear. It is improbable that the internal valve components inside the canister would be susceptible to the high RH in such brief exposures to high humidity. Perhaps the electrostatic properties of

the external Hostaform valve stem changed very rapidly immediately after contacting with humidified air. More investigation is needed to clarify this point.

The specific charges (Tables 5.3 to 5.6) of the propellant droplets in the present study are three orders of magnitude lower than those on drug particles actuated from MDIs (Table 3.2). These are very low charges thus the number of elementary charges per droplet for most size fractions at 5% and 50% RH were near zero (Tables 5.7 to 5.9). It should be noted that the calculated numbers of elementary charge were rounded to the nearest unit figure, thus a decimal value less than one was rounded to zero. Since an elementary charge (i.e. charge of an electron) is the lowest physically possible charge, a decimal value implies that the droplets have unequal share of the net charge of a given size fraction amongst its population, with some droplets neutral in charge. The value for the upper size fractions could not be calculated because no crystal violet could be detected. However, there should be deposits on those stages because non-background charges were detected there (Figures 5.3 to 5.6). The amount of crystal violet in the upper size fractions was therefore below the limit of detection. Since these are very low in mass, the specific charges of these particles should be especially high. Thus the specific charge and the number of elementary charges per droplet increase with increasing droplet size. This trend is confirmed in the data for MDIs tested in humidified air where crystal violet could be assayed in the upper size fractions (Table 5.10).

As a charged droplet evaporates the charges remain on the droplet until the electrostatic repulsive force overcomes the surface tension that maintains droplet integrity^{3,39}. When this point is reached, the droplet ruptures to generate smaller, more

stable ones that carry away parts of the original charges. This evaporation-fission cycle is repeated on the successive generations of daughter droplets. The maximum amount of charge a droplet of a given size can carry before it becomes unstable is called the Raleigh limit. It may be calculated with the following equation:

$$q^2 = 64\pi^2 \epsilon_0 \gamma a^3 \quad (\text{Equation 5.1})^{39}$$

where q is the Rayleigh limit, ϵ_0 the permittivity constant (8.854×10^{-12} F/m), γ the liquid surface tension, and a the radius of the droplet. Using this equation, the theoretical Rayleigh limits of the various ELPI size fractions were calculated for HFA-134a and 227 (Table 5.11).

Table 5.11. Theoretical Raleigh limits of HFA-134a and 227 droplets at the ELPI cutoff diameters calculated by Equation 5.1. Surface tension of HFA-134a and 227 at 20°C are 8.69 and 6.96 mN/m, respectively²⁰.

Stage	Cutoff diameter (μm)	HFA-134a	HFA-227
1	0.0280	72	65
2	0.0552	200	179
3	0.0948	449	402
4	0.159	975	873
5	0.266	2111	1889
6	0.388	3718	3327
7	0.621	7528	6738
8	0.960	14470	12950
9	1.62	31721	28388
10	2.42	57915	51831
11	4.04	124922	111798
12	6.66	264411	236633

Comparing against Table 5.11, the numbers of elementary charges per droplet estimated in the present study of both HFAs are below the theoretical Raleigh limits for all size fractions. Thus the estimation was reasonable.

The initial polydisperse droplets after exiting the MDI (Figure 5.10) will decrease in size through propellant evaporation until the non-volatile particles remain. During this size reduction, it is probable that the droplets would undergo successive electrostatic fissions when the Raleigh limits are reached. This essentially divides the original charges generated upon actuation amongst progressively smaller droplets. This may explain the observed trend of decreasing numbers of elementary charges per droplet with decreasing droplet sizes. Droplets in a particular size fraction therefore could

consist of three types, those that originated from the initial droplet population, those that resulted from evaporation, and others from electrostatic fissions. Collectively all these droplets carry the charges generated upon inhaler actuation.

5.6 Conclusion

The charge profiles of both HFA-134a and 227 had high intra- and inter-inhaler variation but on average the puffs contained negative charge. The electronegative fluorine atoms in the HFA molecules were thought to be responsible for this preferred polarity. HFA-134a produced higher charges than HFA-227 because its molecule is more polar. The charges of both HFAs shifted towards neutrality or positive polarity with increasing water content. HFA-134a charged positively when the water content exceeded 300 ppm. This effect was explained by: 1) an increase in electrical conductivity; and/or 2) a decrease in the bulk electronegativity. Moisture on the actuator did not affect aerosol charging or particle size. The HFA droplets were submicron in size at 5% and 50% RH, but increased ten-fold at 92% RH. This was attributable to condensed water on the propellant-cooled particles in humidified air, causing particle growth. The HFA aerosols (without drug) carried low specific charges. The number of elementary charges per droplet decreased with decreasing droplet size. This was explained by the fission of charged droplets upon reaching the Raleigh limit and subsequent distribution of the original charge by the daughter droplets.

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Chapter 6

Conclusion

6.1 Summary

In this thesis electrostatic charges generated from MDIs and DPIs were successfully quantified using a modified ELPI. The aerosol charges were often bipolar and were formulation- and size-dependent. Charge levels on the particles were in the range that may potentially affect the particle deposition in the lungs. Such detailed data could not be obtained from simpler instruments such as the Faraday pail or aerosol electrometer apparatus.

The electrostatic characteristics of aerosols produced from a number of commercial MDIs were examined in **Chapter 2**. The aerosol charge profile were MDI-dependent because of differences in the drug, formulation, and the valve stem material of the inhalers. The calculated number of elementary charges per particle of size $\leq 6.66 \mu\text{m}$ ranged from zero to several ten thousands.

Using an electrostatic voltmeter, high surface potentials were found in **Chapter 3** on the internal walls of new AeroChamber[®] Plus spacers. The surface charges were successfully removed by coating the spacers with household detergent. Both the new and detergent-coated spacers reduced the aerosol charges, throat deposition, FPD, and MMAD. Detergent-coated spacer had less spacer drug retention than the new ones

because the low surface charges minimised electrostatic particle deposition. Consequently, drug output through these spacers was enhanced. Particles delivered from spacers carried lower inherent charges than those directly from MDIs. Those with higher charges might be susceptible to electrostatic forces inside the spacers and were thus retained.

Pulmicort[®] and Bricanyl[®] Turbuhalers[®] were dispersed at 60 L/min in **Chapter 4** by the addition of a Y-tube and a second vacuum pump to the ELPI setup. The DPIs showed drug-specific responses to particle charging at different RHs. Bricanyl[®] was more susceptible to RH, showing decreased charges with increasing RH. In contrast, particle charges from Pulmicort[®] decreased at 40% RH but increased at higher RHs. The difference in hygroscopicity of the drugs may be a major factor. A dual mechanistic charging model was proposed to explain the charging behaviours.

The charge profiles of both drug-free HFA-134a and 227 MDIs were measured in **Chapter 5**. There were high intra- and inter-inhaler variations but on average the droplets contained negative charge. The electronegative fluorine atoms in the HFA molecules were thought to be responsible for this preferred polarity. The more polar HFA-134a produced higher charges than HFA-227. The charges of both HFAs shifted towards neutrality or positive polarity with increasing water content, with HFA-134a charging positively when the water content exceeded 300 ppm. This effect was explained by: 1) an increase in electrical conductivity; and/or 2) a decrease in the bulk electronegativity by the spiked water. Moisture on the actuator did not affect aerosol charging or particle size. The submicron HFA droplets at 5% and 50% RH increased ten-fold in size at 92% RH. The size growth was attributable to condensed water on

the propellant-cooled particles in humidified air. The drug-free HFA aerosols carried low specific charges. The number of elementary charges per droplet decreased with decreasing droplet size. It was postulated that charged droplets may undergo electrostatic fission when the Raleigh limit was reached, with the original charge subsequently distributed amongst the daughter droplets.

6.2 Future work

The findings in this thesis provided some insights into the relationship between the formulation (drug, excipients, and device component materials), environmental factors such as RH, and aerosol charging. The results also generated hypotheses that require further exploration. Electrification is a complex process and complementary research on various physicochemical properties (e.g. hygroscopicity, crystallinity, mapping of surface energy sites on particle surfaces, and dielectric behaviours) of the drug and other formulation components would supply useful information to assist the interpretation of aerosol charge data. The properties named above were found to be relevant in this thesis but the list is not complete. Future research may uncover other pertinent factors associated with charging.

The effects of charge on lung deposition should also be investigated *in vivo* in order to verify the computer simulation models. An understanding of the fundamentals of aerosol charging *in vitro* allows the manipulation of the formulation to control the charges and, in turn, drug delivery *in vivo* if the models are correct. Applications of

this knowledge would be of interest to the pharmaceutical industry in the design of inhalation products.

Appendix A

The ELPI Fine Particle Correction Algorithm

Aerosol particles are charged electropositively by the corona charger when the ELPI is used in its original sizing mode (Section 1.11.3). These high charges create an electrostatically repulsive force, known as space-charge force, which pushes the particles towards the walls inside the impactor¹. Thus the particles tend to deposit on higher stages than they should. This would oversize the particles. To compensate for this a correction algorithm was incorporated into the computer data collection software for the ELPI. The correction function can be set to be on or off. Essentially, some of the current signals detected in the upper stages are shifted to the lower stages if the algorithm is set on. More details of this algorithm are discussed by Moisio².

The corona charger was not used in most of the work described in this thesis. However, the correction algorithm was inadvertently set on in the experiments in Chapters 2, 3, and 4. It was set off in the experiments in Chapter 5. Since the inhaler aerosols carried significantly less charge than those charged by the corona charger, the correction function should not be needed. However, the raw current signals had already been modified by the algorithm before the data were saved. Therefore the effect of fine particle loss correction on the MDI charges was tested. Flixotide[®] MDI was used for this purpose because it produces reproducible charge profiles.

Six actuations from a Flixotide[®] inhaler were actuated into the ELPI under four conditions.

- 1) Correction function OFF; six puffs sampled collectively in one run
- 2) Correction function ON; six puffs sampled collectively in one run
- 3) Correction function OFF; six puffs sampled individually in separate runs
- 4) Correction function ON; six puffs sampled individually in separate runs

Charge profiles of the six puffs under each condition were averaged (Figure A.1). The correction algorithm did not significantly alter the measured charges. This may be due to the relatively low magnitudes of the natural aerosol charges compared to the charges derived from corona charging. Thus the data collected in Chapters 2, 3, and 4 were acceptable for use in the discussions.

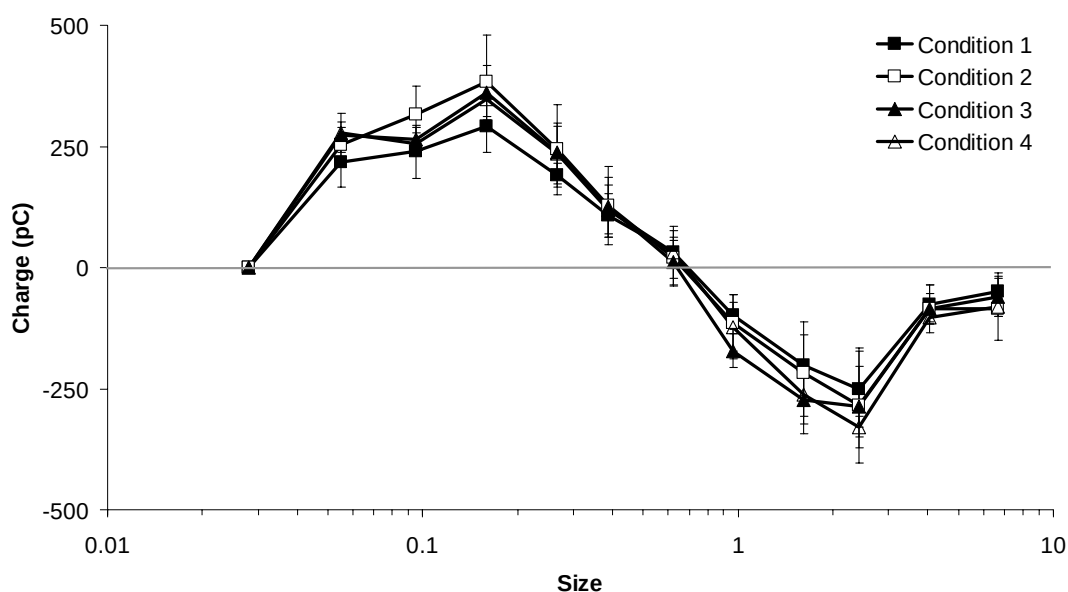


Figure A.1. Mean charge profiles for Flixotide[®] measured with and without the correction algorithm, sampled collectively or individually ($n = 6$).

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Appendix B

Mean Charge and Mean Mass Profiles of Multiple Puffs from MDIs

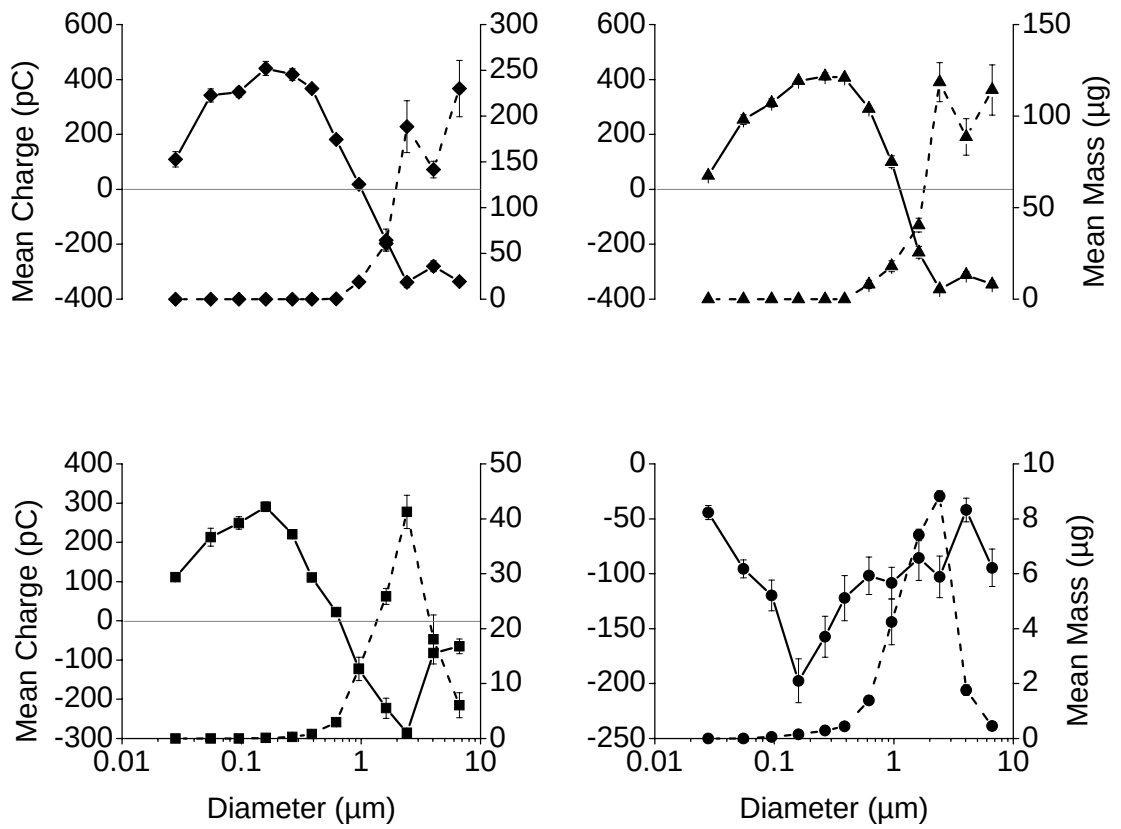


Figure B.1. Mean charge and mean mass profiles of the MDIs measured on multiple puffs. Solid lines represent the charge and dotted line the mass (♦ Intal® Forte, ▲ Tilade®, ■ Flixotide®, ● Ventolin®; n = 18 for Intal® Forte, n = 30 for Tilade®, Flixotide®, and Ventolin®).

Appendix C

Measurement of Electrostatic Charge of Nebulised Aqueous Droplets with the ELPI

Most of the material in this appendix was published as an abstract in *Respiratory Drug Delivery IX*¹.

Introduction

Deposition of aerosol particles or droplets may be influenced by their electrostatic charges²⁻⁴. It is also known that liquids may be charged by spraying^{5,6}. This study examines the electrostatic characteristics of aqueous droplets using a modified electrical low pressure impactor (ELPI). In this study, the corona charger inside the ELPI was removed so that inherent charges on the droplets could be measured.

Materials and Methods

A Sidestream[®] durable jet nebuliser was coupled to a Porta-Neb[®] air compressor (both by Medic-Aid, West Sussex, UK). To control the duration of nebulisation, a solid-state timer switch (Omron[®] model H3CR-A8) was installed in the power cord of the air compressor. The ELPI (Dekati Ltd., Tampere, Finland) with the corona charger removed was used in the electrostatic measurements. A Sogevac[®] model SV25 vacuum pump (Leybold S.A.S., Bourg-lès-Valence, France) provided air suction

through the ELPI. Aerosol samples were introduced into the instrument via a USP metal induction port. Details of the instrumental setup and method may be found in the study by Glover and Chan⁷.

The air flow through the ELPI was controlled at 30 L/minute. The initial 1-second samples, instead of the subsequent samples, were measured due to a decline in charge over time. The initial samples were found to be more reproducible than later samples. Initially 2.5 mL of deionised water was nebulised. Subsequently the starting volume was varied from 1 mL to 5 mL to examine its effect on the charge profile.

Results and Discussion

The electric current data collected by the ELPI is shown in Figure C.1. Charges of the various size fractions were derived from the current data by calculating the area under the corresponding curves. The aerodynamic diameter of the droplets is measured by the ELPI. Higher charges were measured on higher stages (Figure C.2) and the total charge detected per 1-second aerosol sample varied with different starting volumes of water in the nebuliser (Figure C.3).

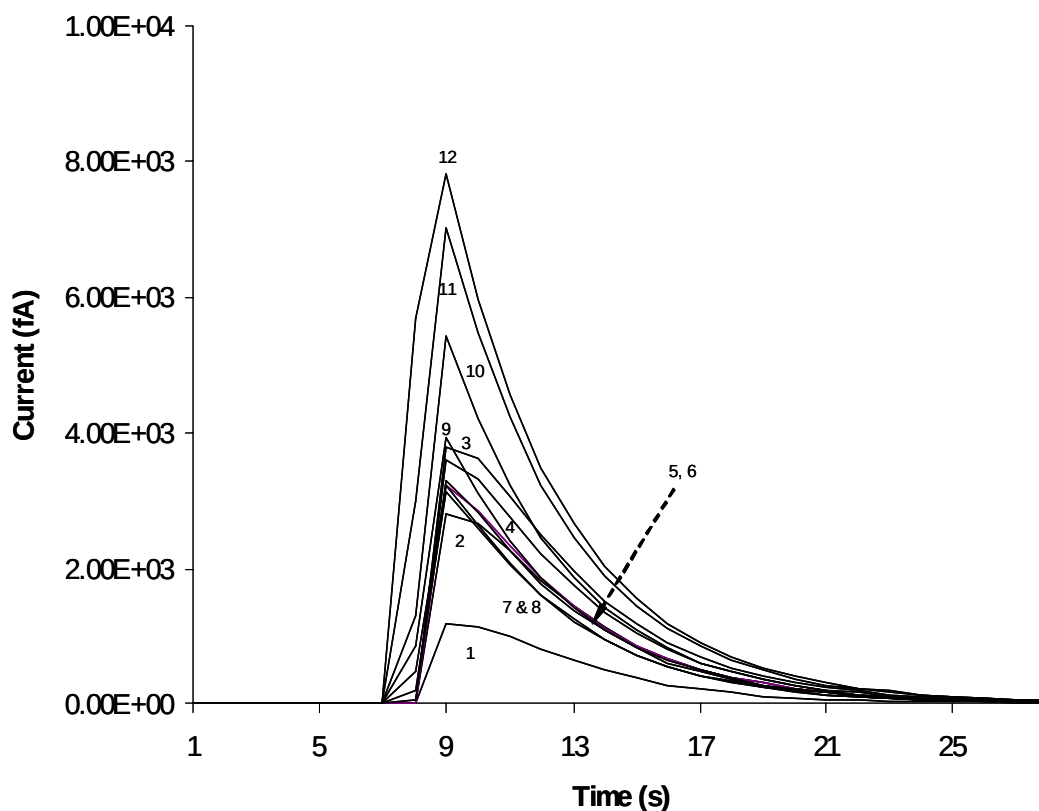


Figure C.1. Electric current data of an aerosol sample at a starting volume of 2.5 mL of water. Numerals next to the plot indicate the respective ELPI stages.

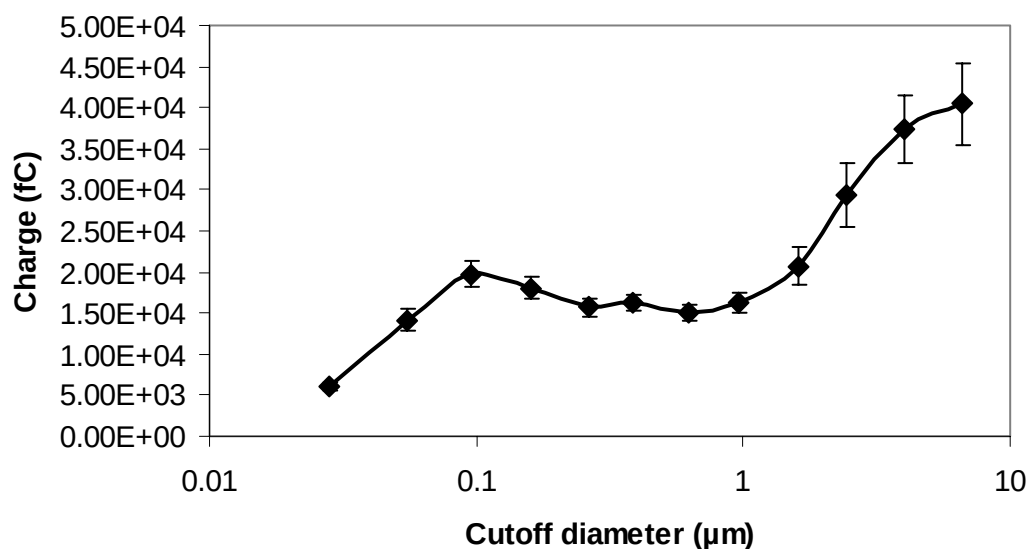


Figure C.2. Charge profile derived from six aerosol samples at a starting volume of 2.5 mL of water ($n = 6$).

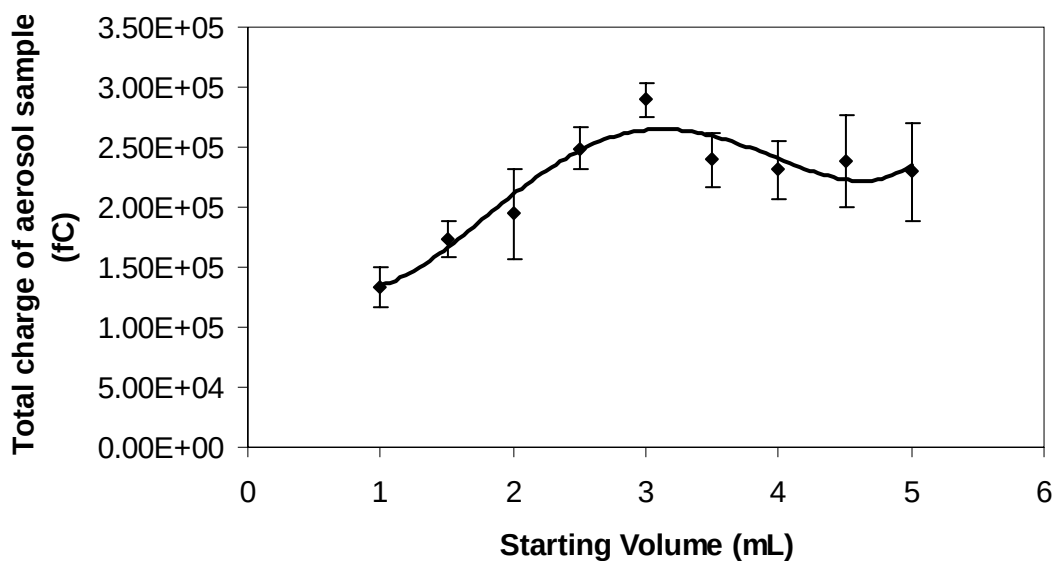


Figure C.3. Effect of the starting volume on the total charge of aerosol (n = 6).

All nebulised droplets carried positive charges and different size fractions possessed different levels of charge. The charges detected in a given stage may be due to one or both of two factors, namely, the innate charges on the water droplets and the number of charged droplets in that particular size fraction. To differentiate these two factors the size distribution of the nebulised aerosol would need to be known. The total charge of the aerosol was found to depend on the volume of liquid being nebulised. This may be due to other factors such as the reduction in temperature of the liquid and possible changes in conductivity and pH during nebulisation.

The use of ELPI in the measurement of inherent charges on liquid droplets is a novel application of the instrument. The electrostatic characteristics of nebulised droplets have not been extensively studied. The comprehensive charge profile of nebulised droplets derived from the ELPI would facilitate the understanding on liquid charging and the role of electrostatic charge on deposition of aerosol particles or droplets in the airways.

References

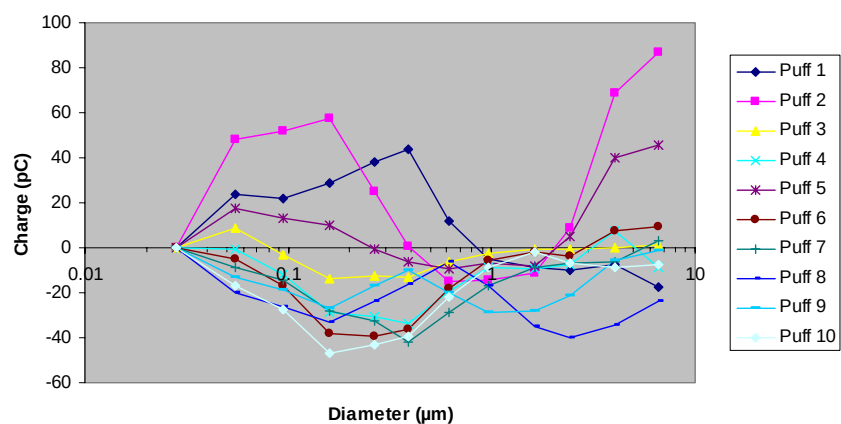
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Appendix D

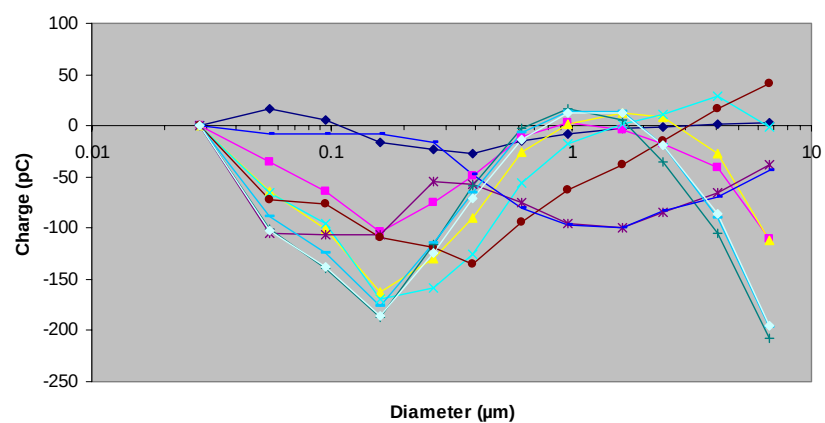
Charge Profiles of Individual Puffs from Drug-Free HFA- 134a and 227 MDIs

The charge profiles of the individual puffs generated from drug-free HFA-134a and 227 MDIs are included in this appendix. The legend is given in the first plot only as it applies to all the other profiles.

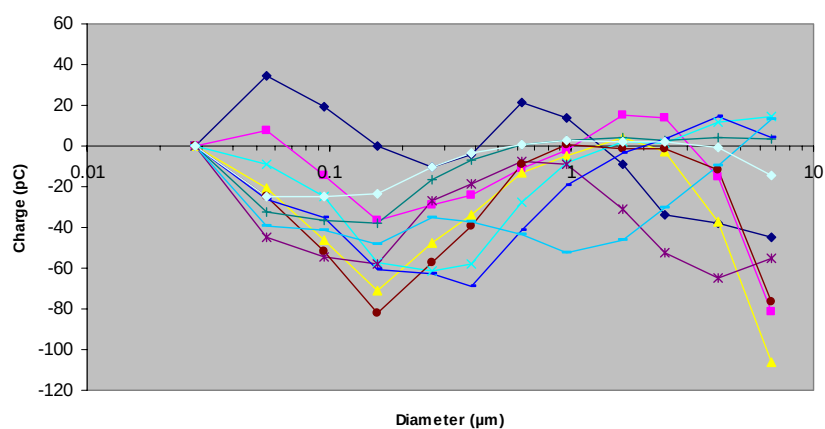
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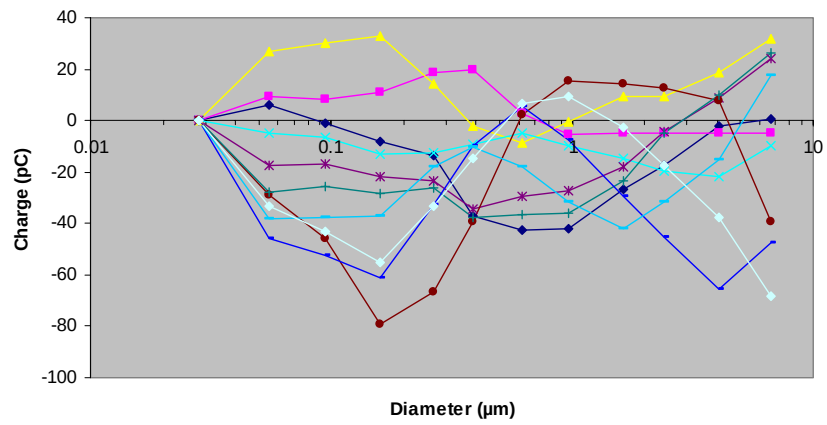
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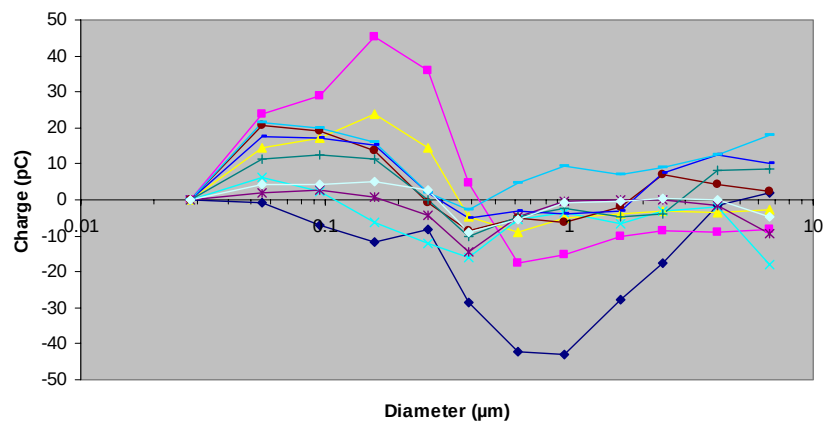
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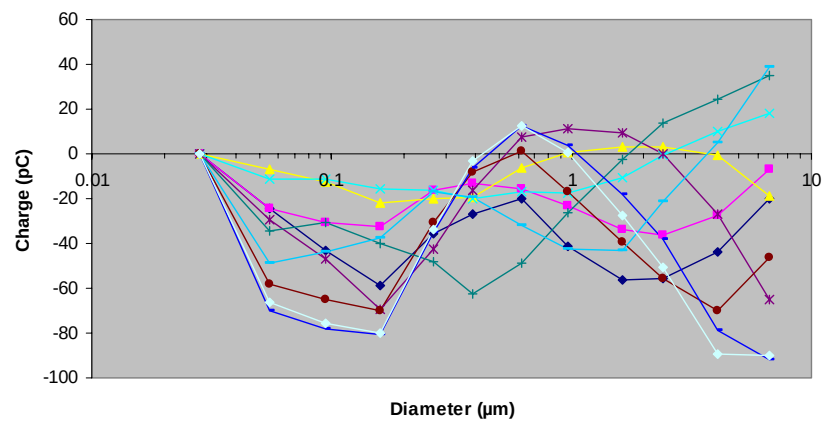
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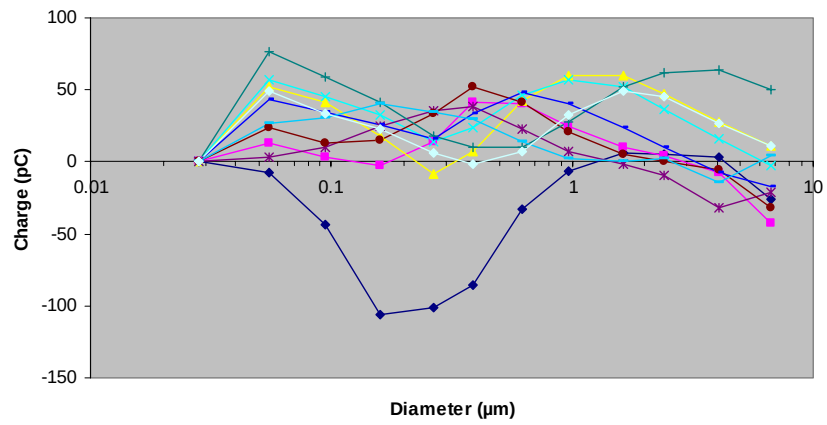
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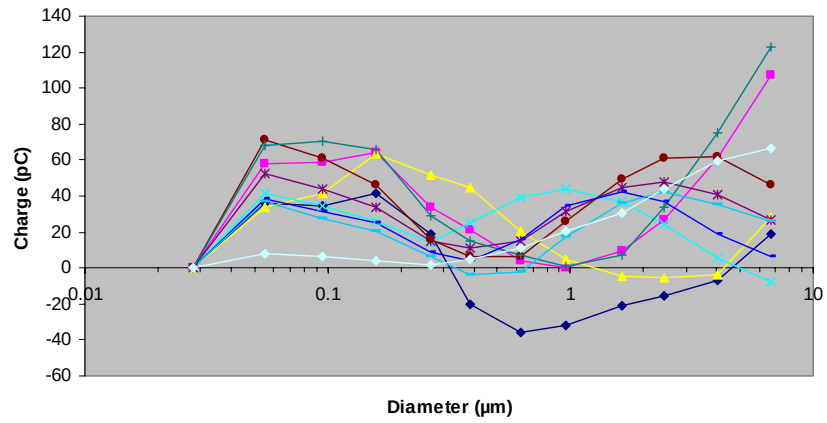
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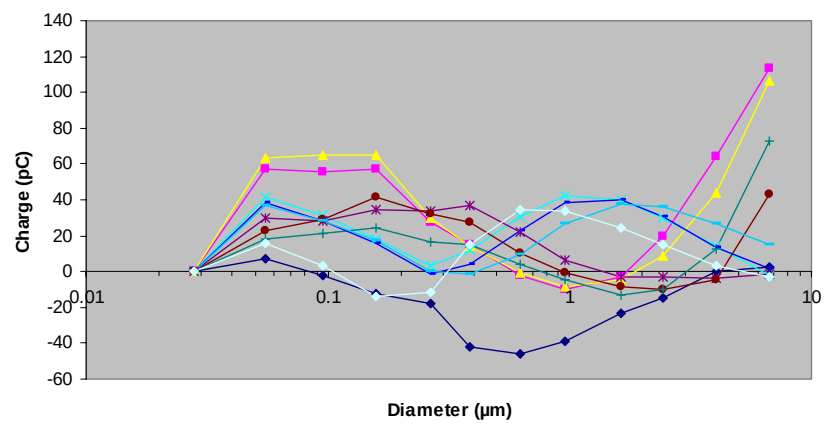
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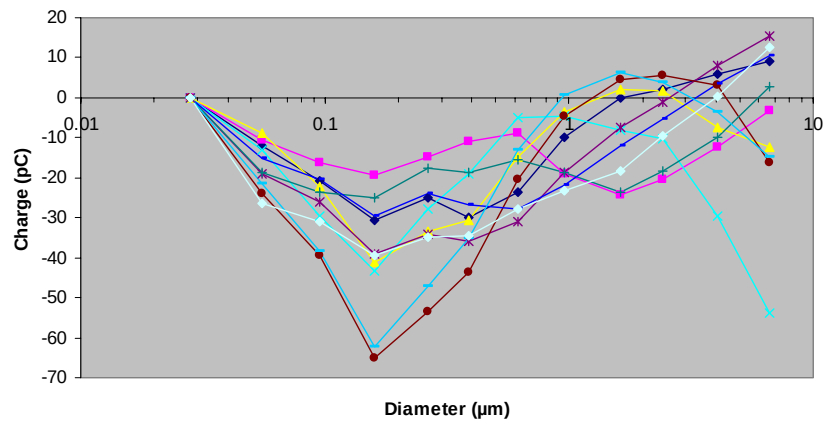
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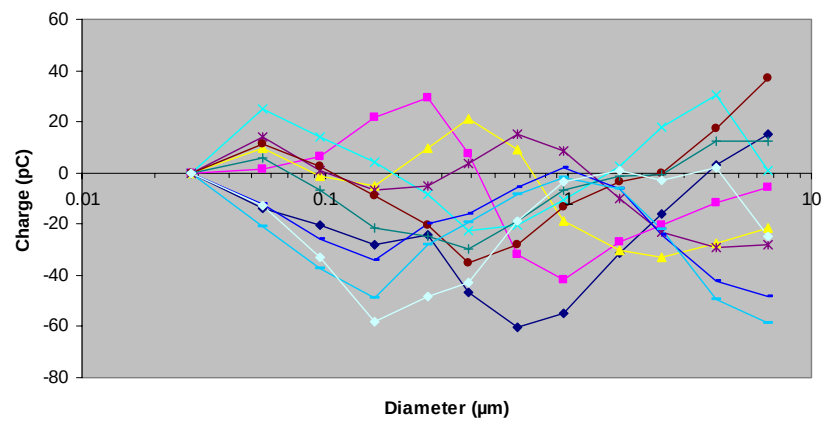
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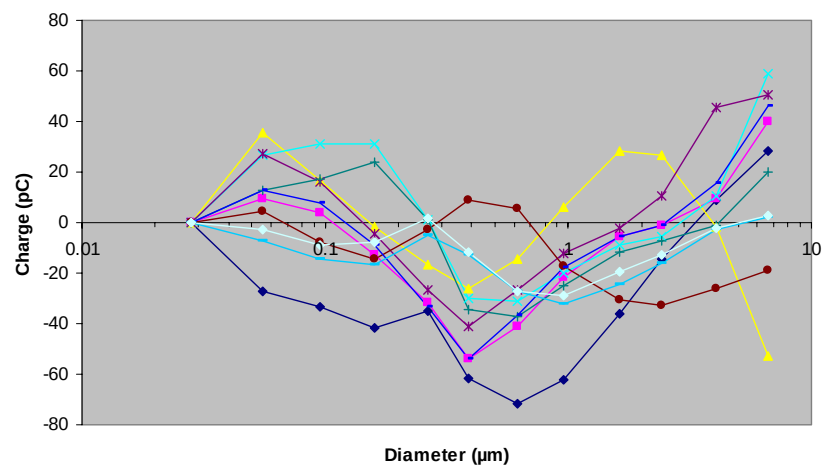
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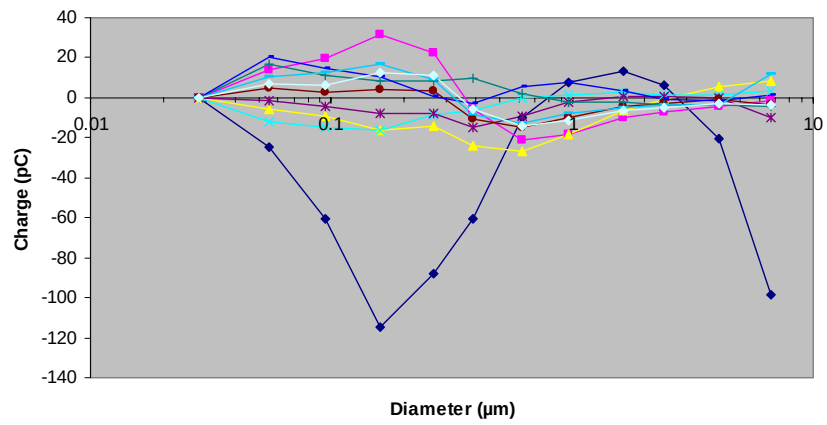
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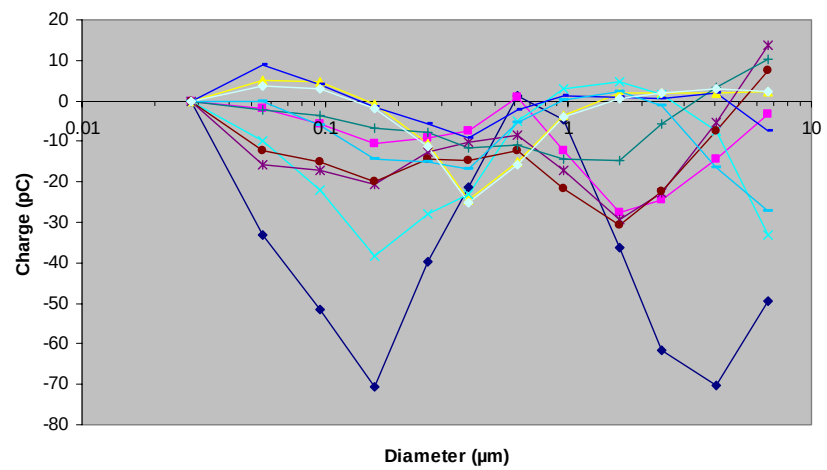
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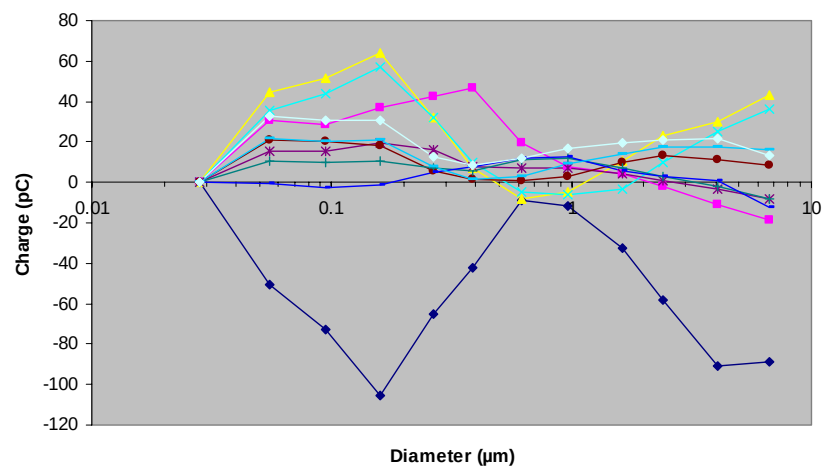
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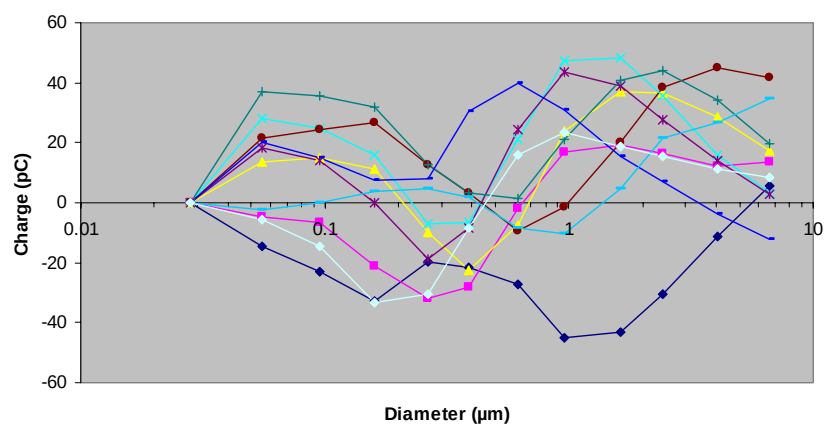
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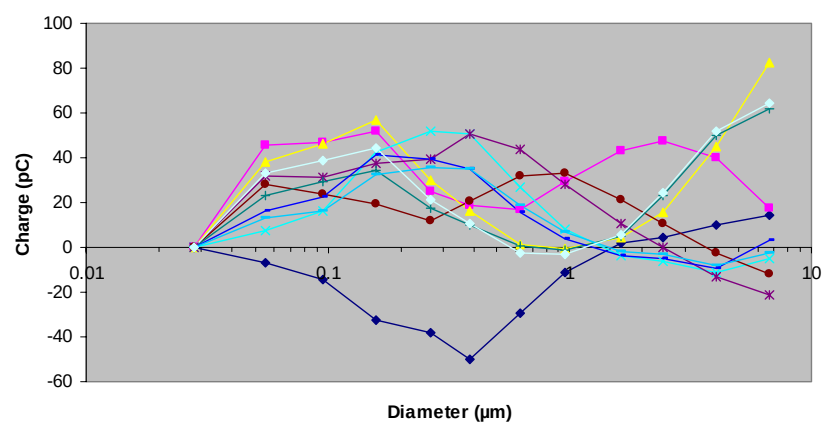
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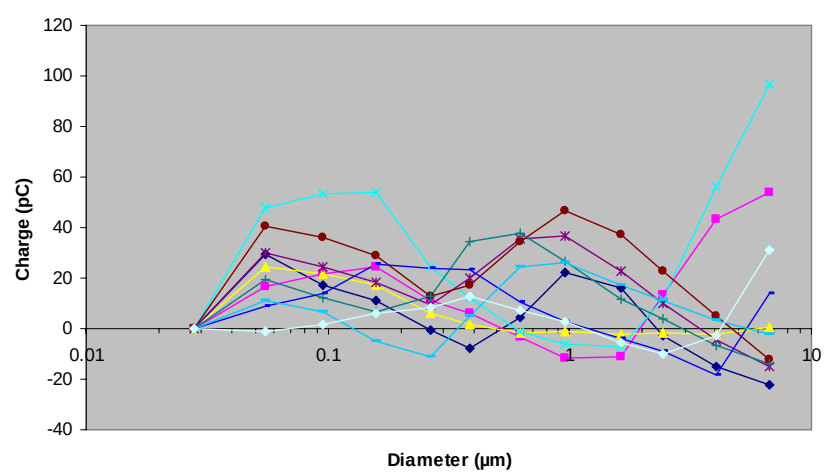
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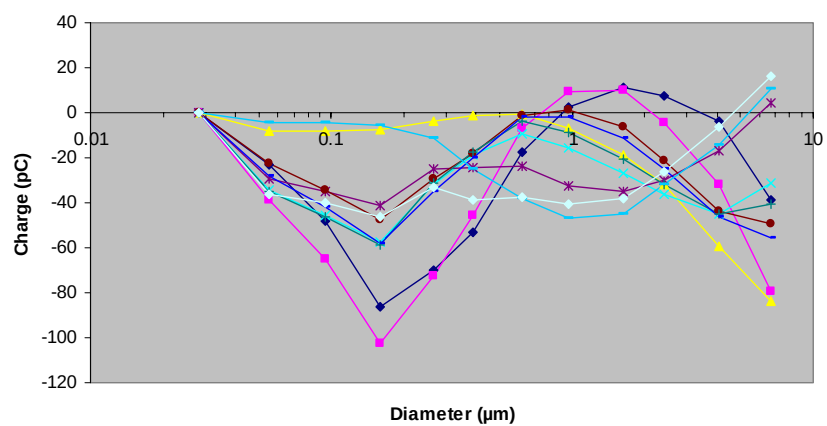
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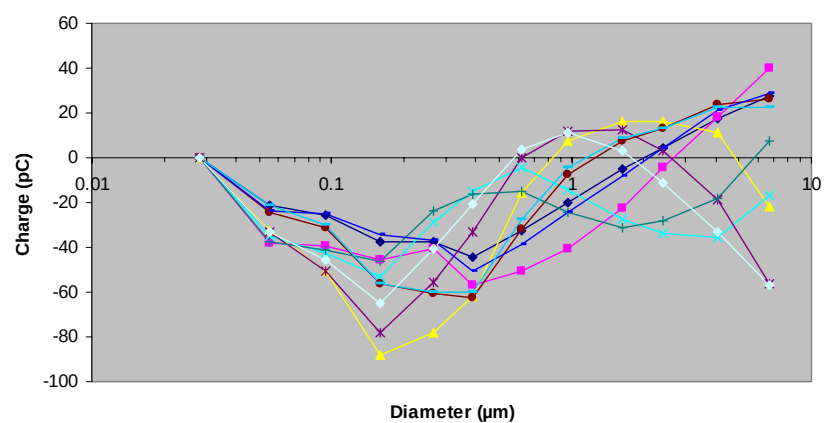
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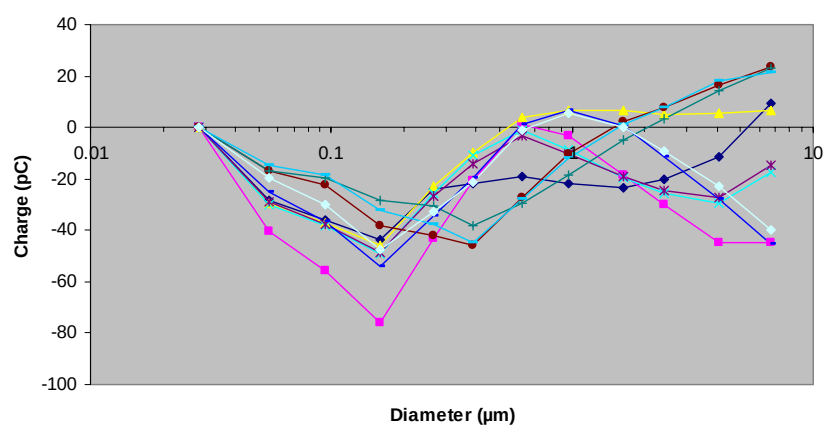
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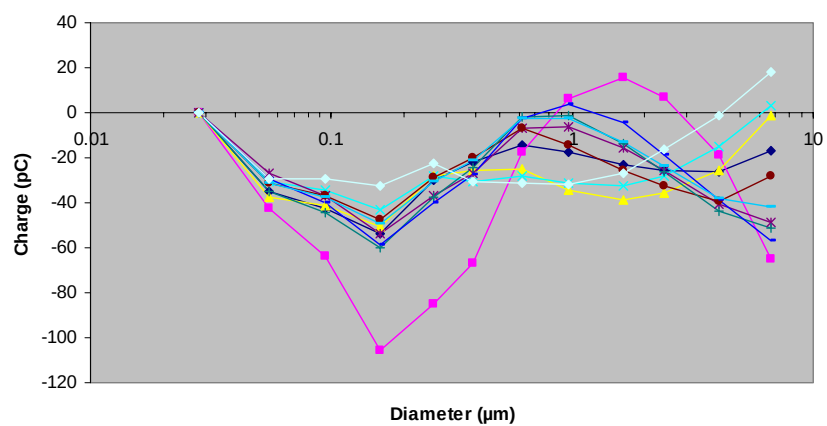
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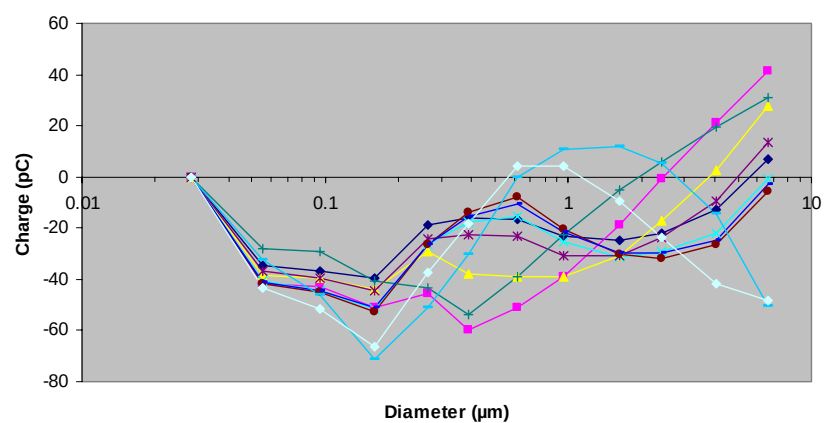
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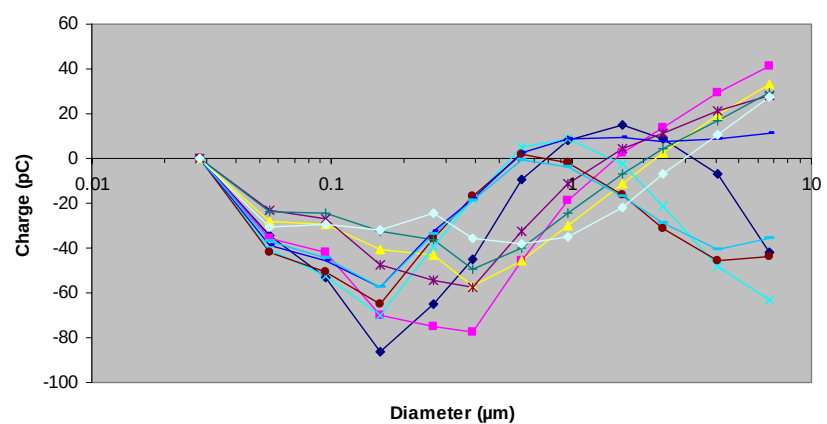
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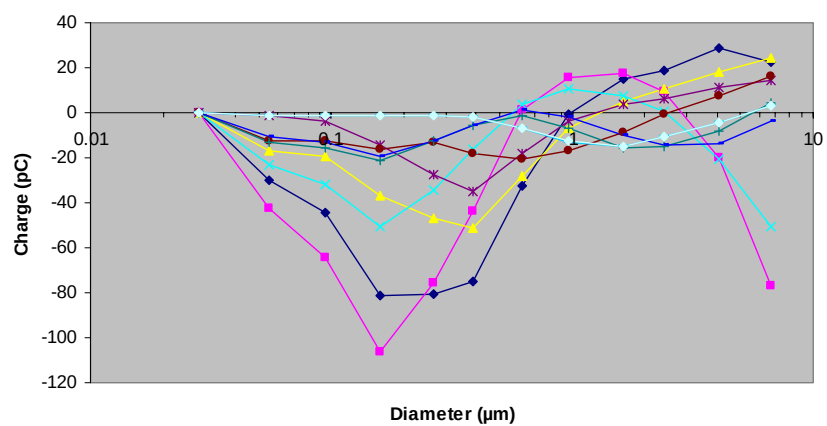
HFA-227 / Hostaform / Medium water content canister #2
Dry actuator / Dry air



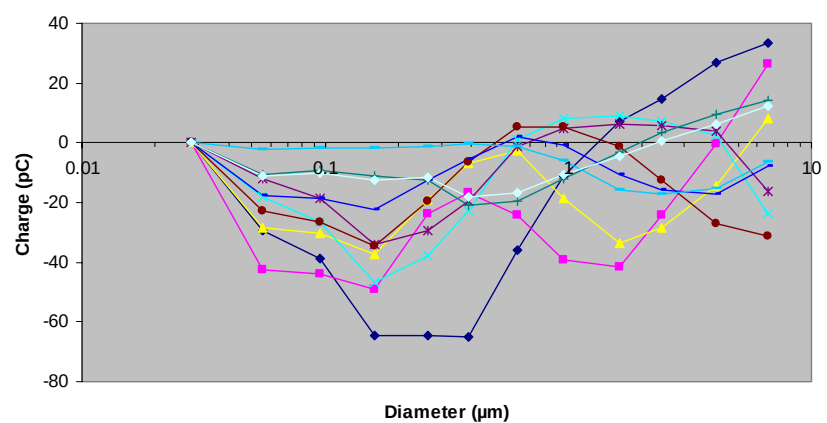
HFA-227 / Hostaform / Medium water content canister #3
Dry actuator / Dry air



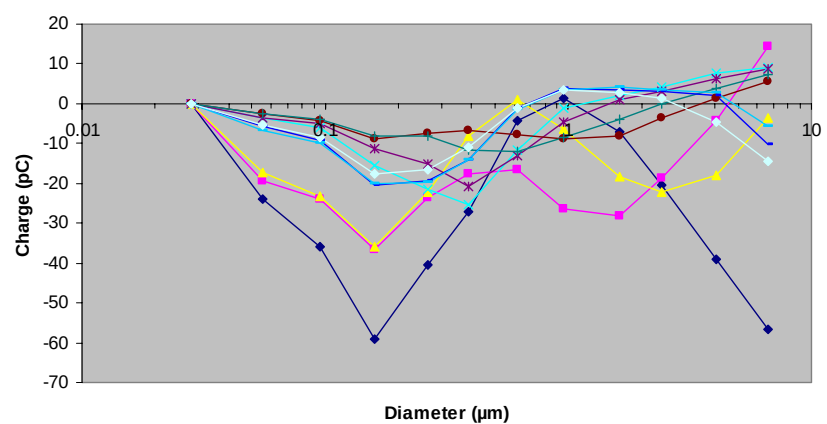
HFA-227 / Hostaform / High water content canister #1
Dry actuator / Dry air



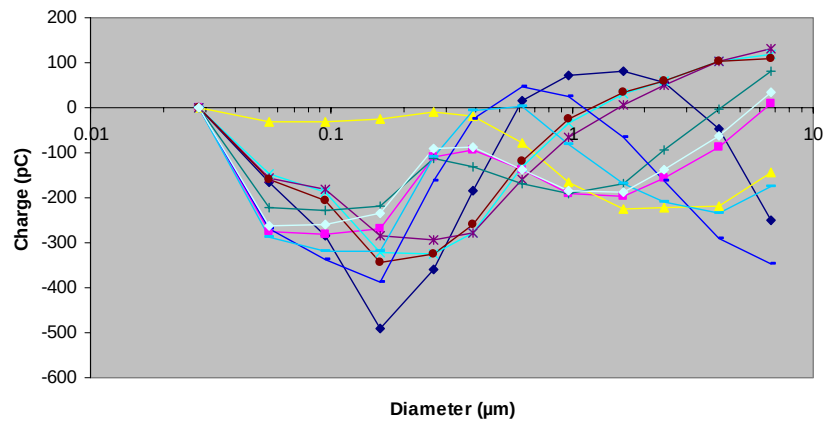
HFA-227 / Hostaform / High water content canister #2
Dry actuator / Dry air



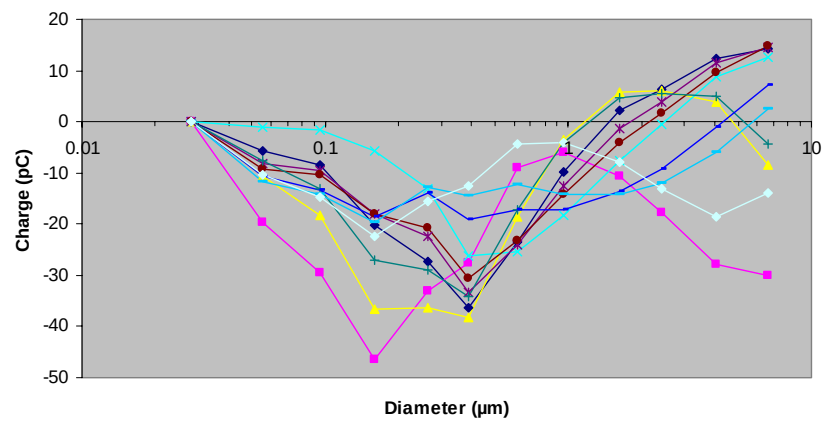
HFA-227 / Hostaform / High water content canister #3
Dry actuator / Dry air



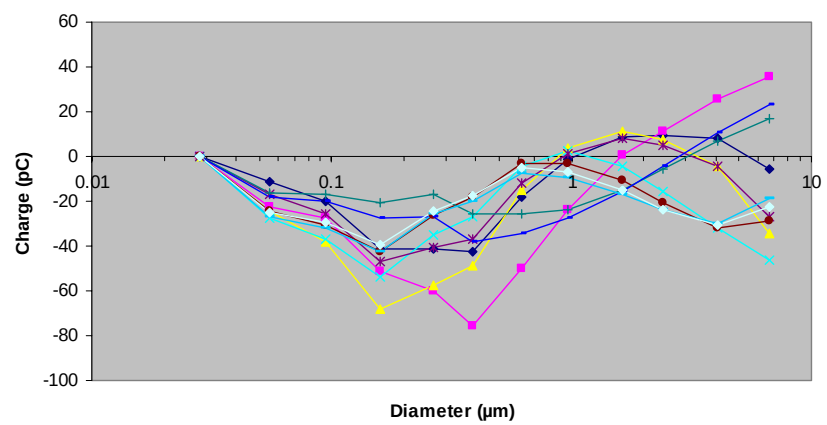
HFA-227 / PBT / Low water content canister #1
Dry actuator / Dry air



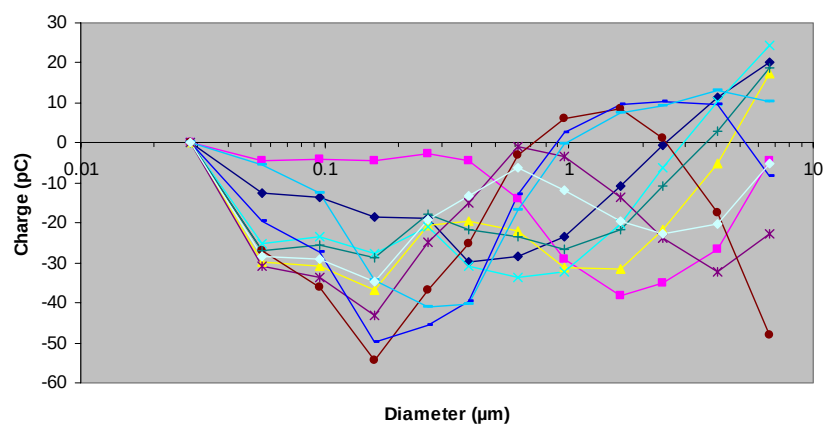
HFA-227 / PBT / Low water content canister #2
Dry actuator / Dry air



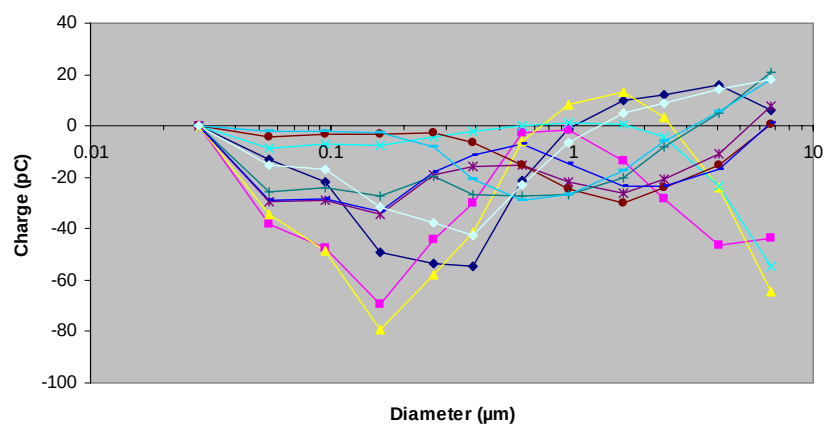
HFA-227 / PBT / Low water content canister #3
Dry actuator / Dry air



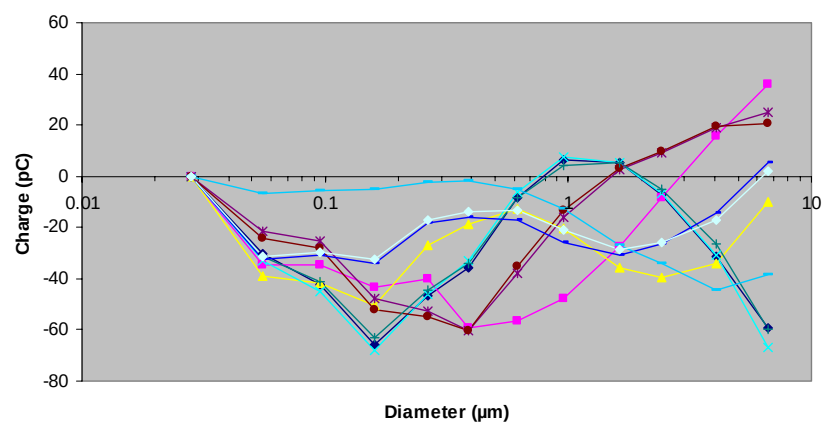
HFA-227 / PBT / Medium water content canister #1
Dry actuator / Dry air



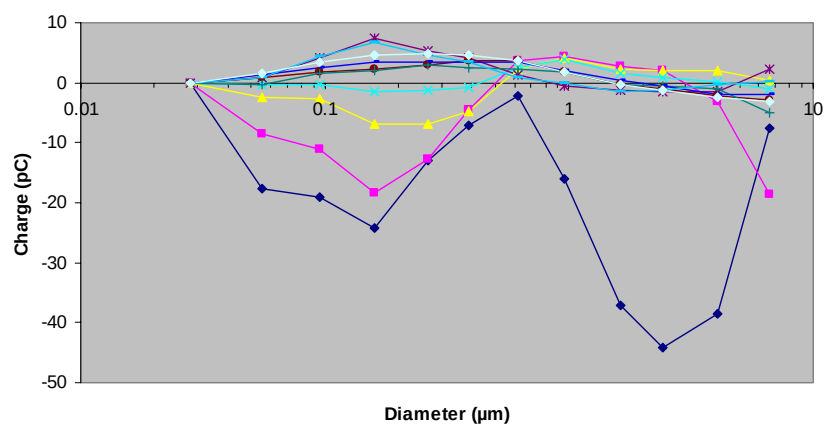
HFA-227 / PBT / Medium water content canister #2
Dry actuator / Dry air



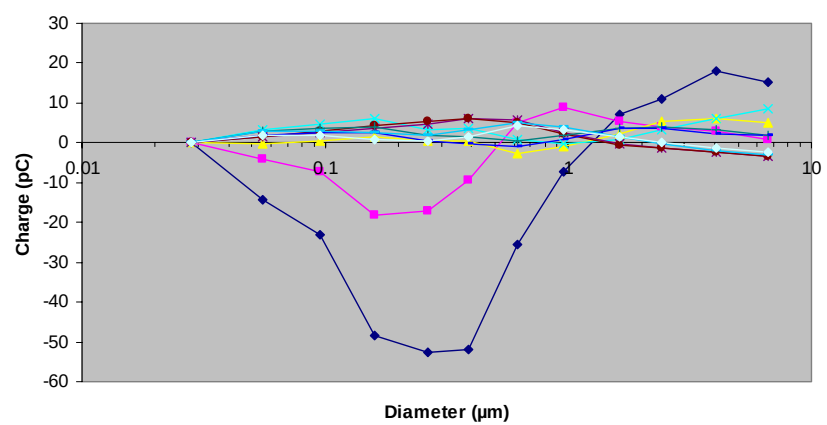
HFA-227 / PBT / Medium water content canister #3
Dry actuator / Dry air



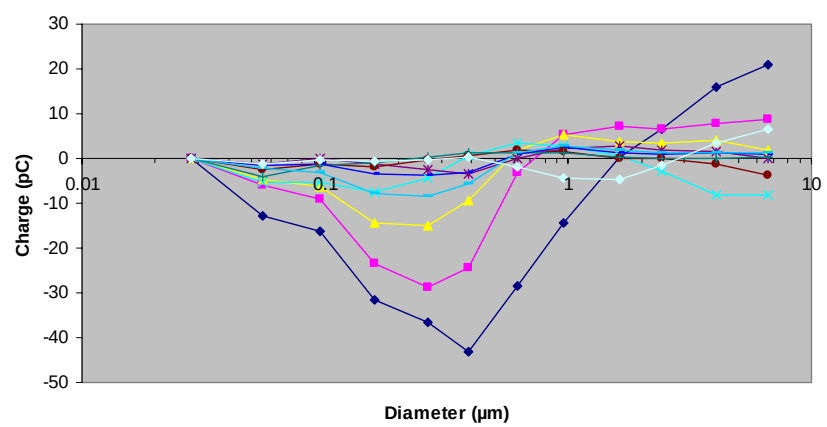
HFA-227 / PBT / High water content canister #1
Dry actuator / Dry air



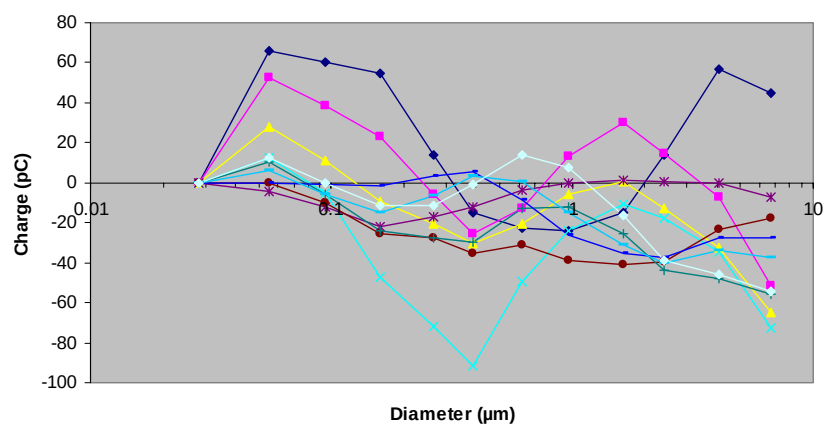
HFA-227 / PBT / High water content canister #2
Dry actuator / Dry air



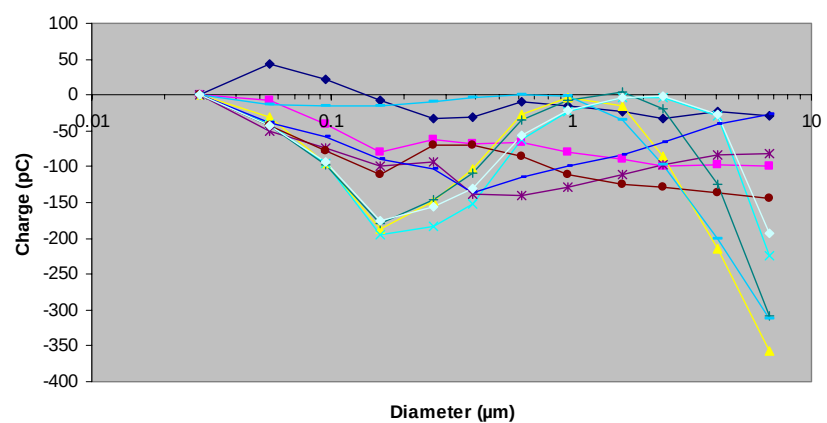
HFA-227 / PBT / High water content canister #3
Dry actuator / Dry air



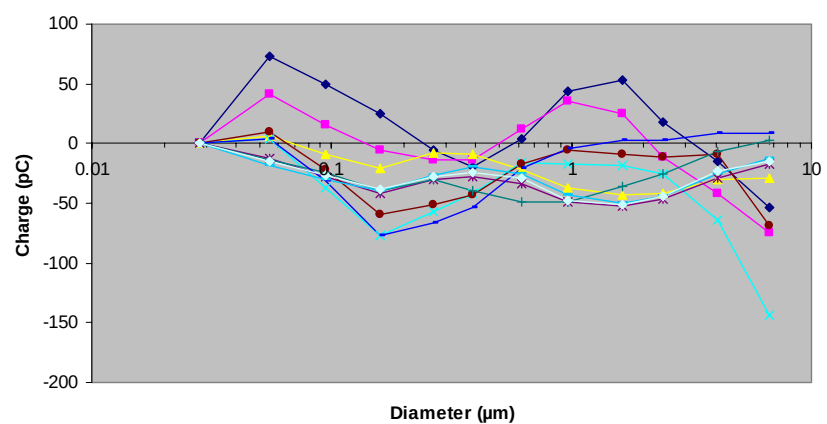
HFA-134a / Hostaform / Low water content canister #1
Dry actuator / 50% RH



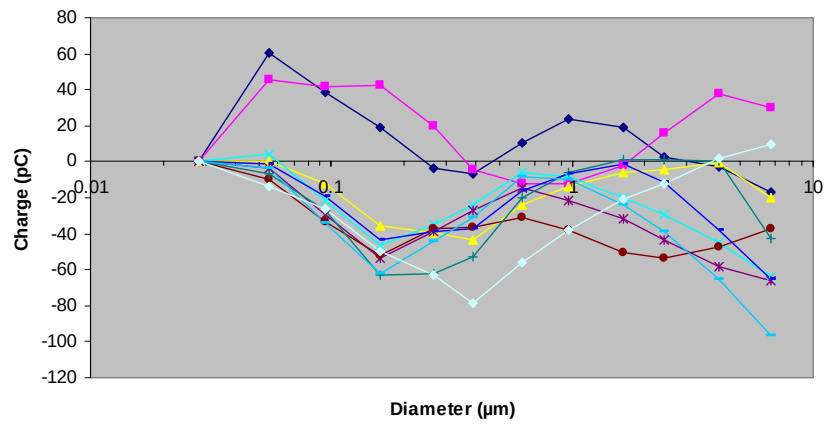
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Dry actuator / 50% RH



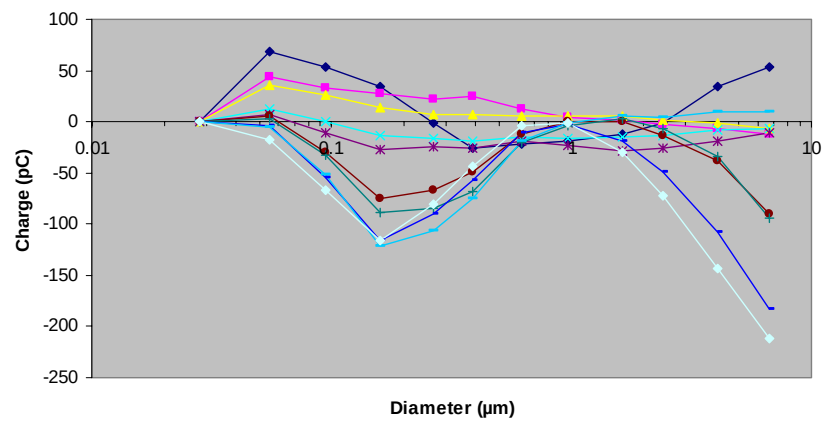
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Dry actuator / 50% RH



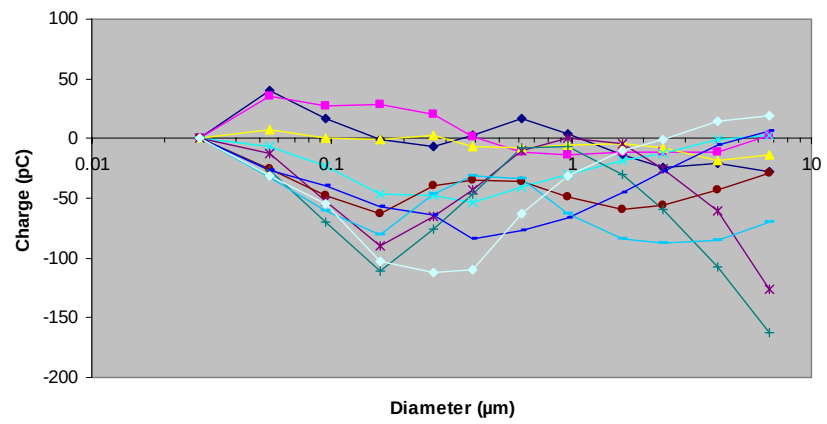
HFA-134a / Hostaform / Medium water content canister #1
Dry actuator / 50% RH



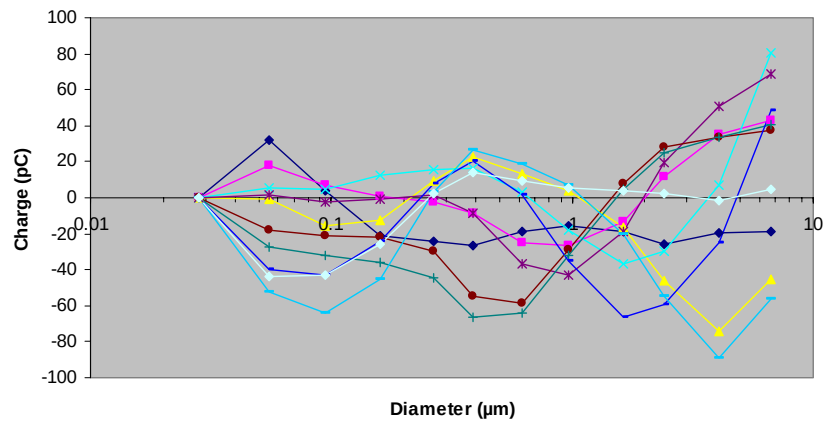
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Dry actuator / 50% RH



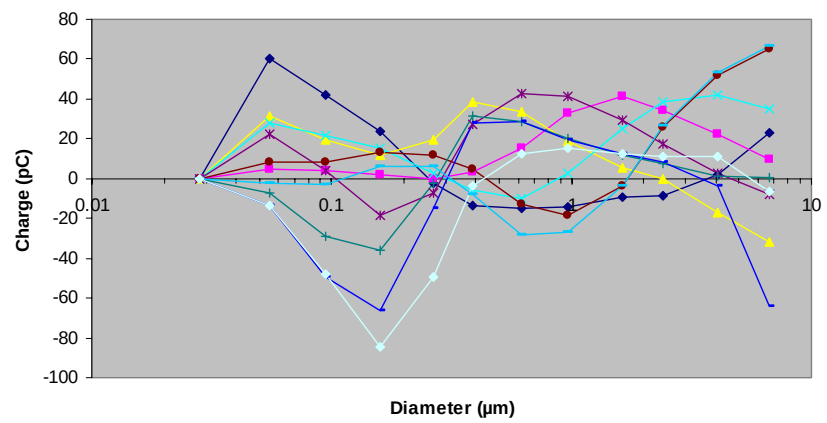
HFA-134a / Hostaform / Medium water content canister #3
Dry actuator / 50% RH



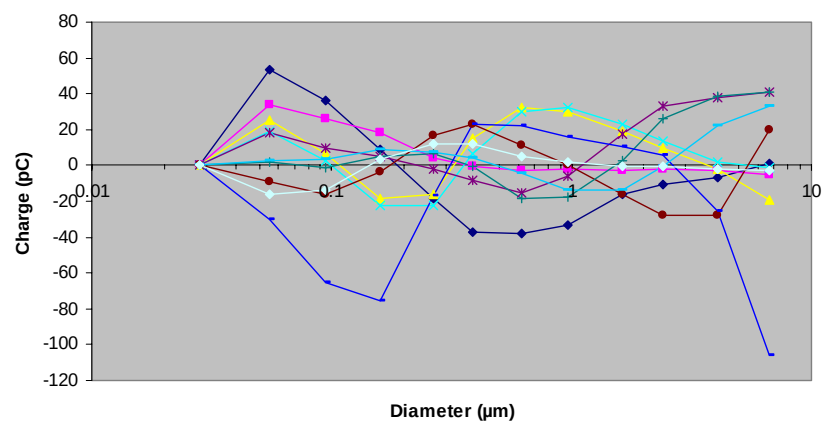
HFA-134a / Hostaform / High water content canister #1
Dry actuator / 50% RH



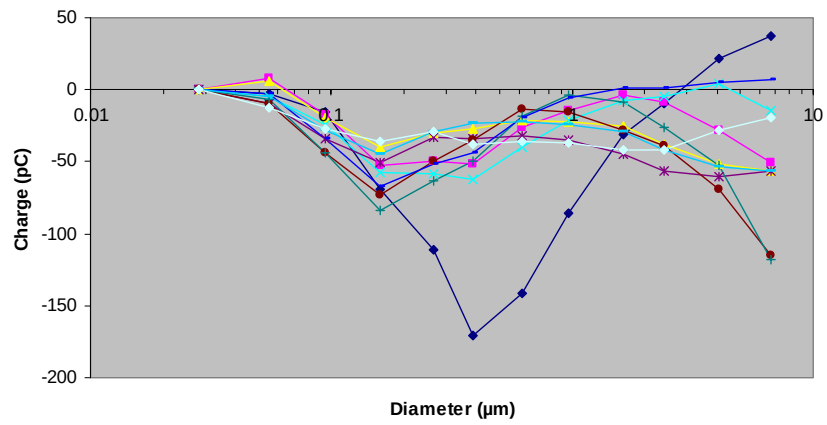
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Dry actuator / 50% RH



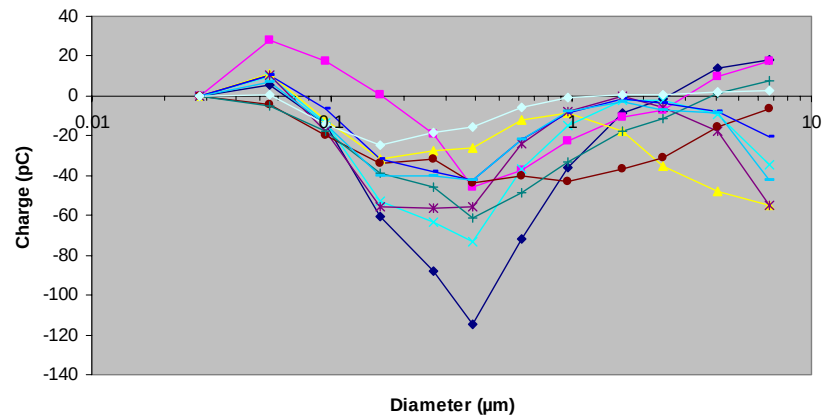
HFA-134a / Hostaform / High water content canister #3
Dry actuator / 50% RH



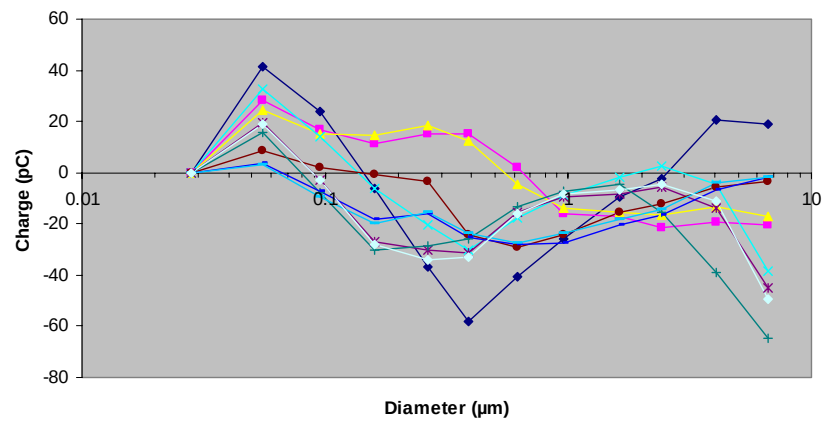
HFA-134a / PBT / Low water content canister #1
Dry actuator / 50% RH



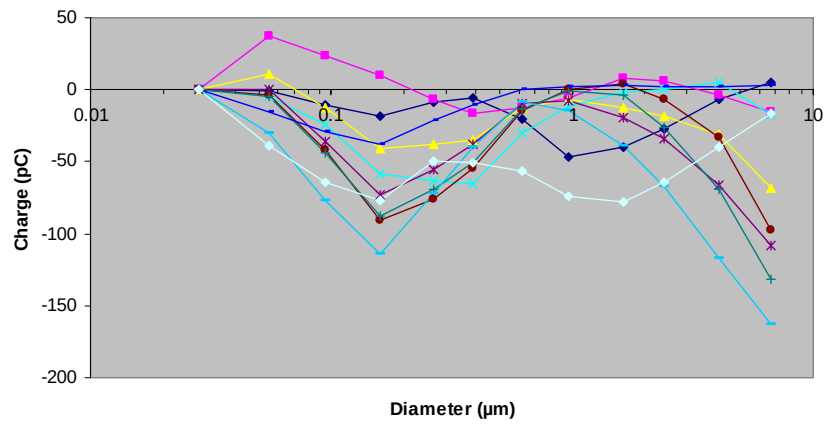
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Dry actuator / 50% RH



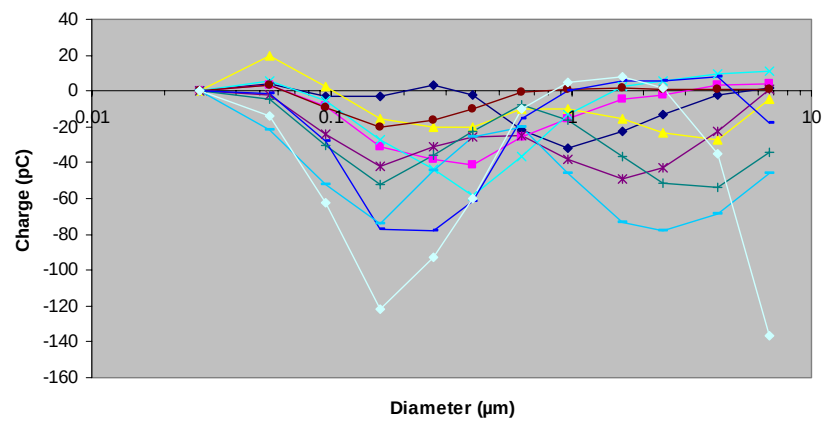
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Dry actuator / 50% RH



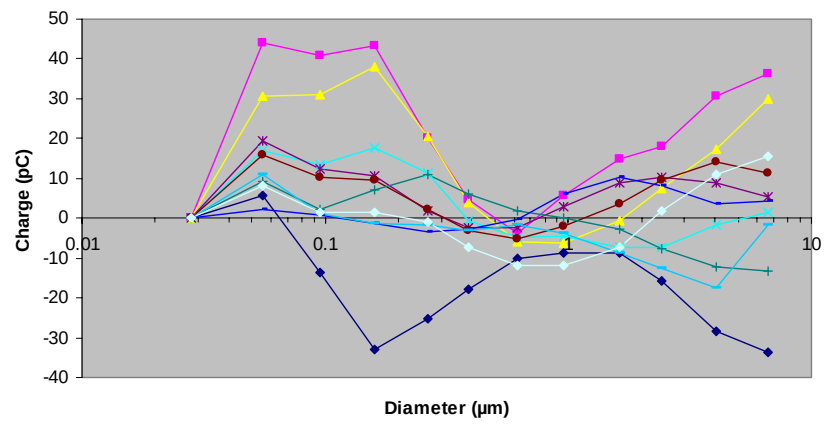
HFA-134a / PBT / Medium water content canister #1
Dry actuator / 50% RH



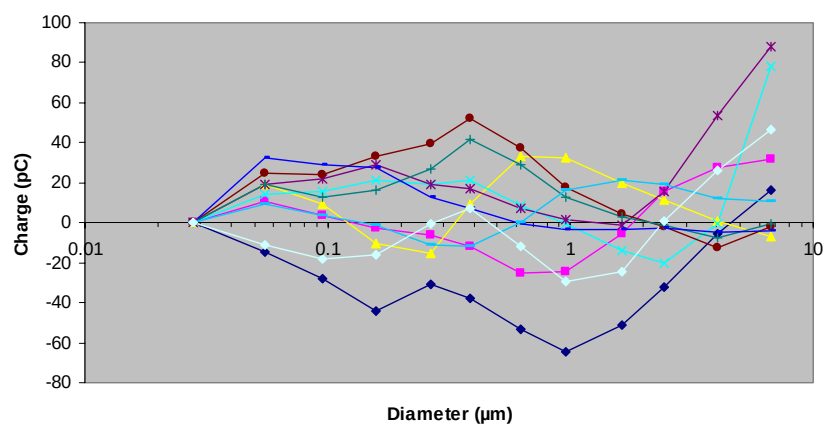
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Dry actuator / 50% RH



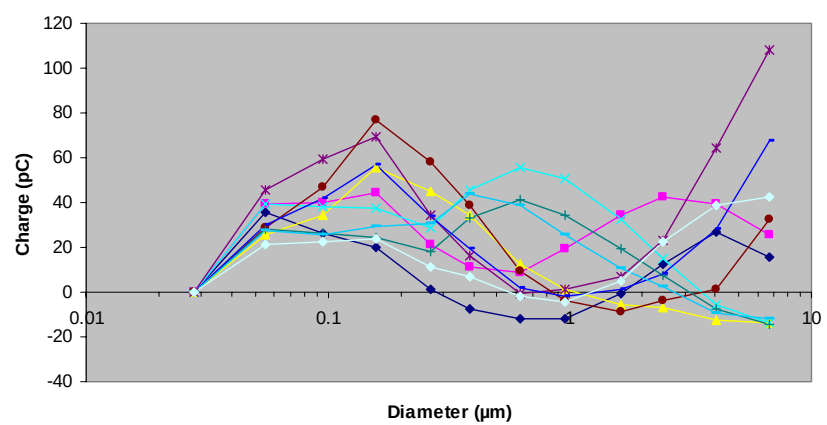
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Dry actuator / 50% RH



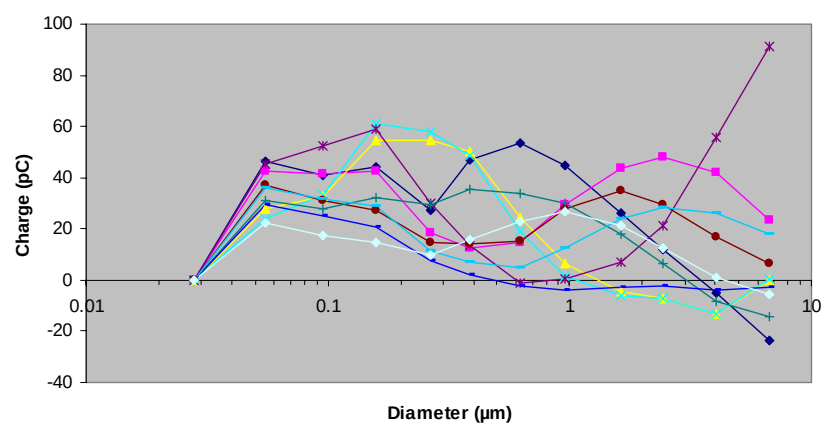
HFA-134a / PBT / High water content canister #1
Dry actuator / 50% RH



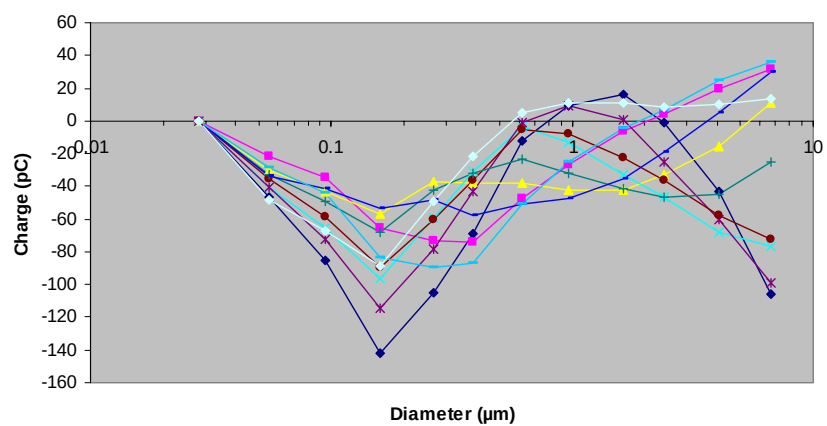
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Dry actuator / 50% RH



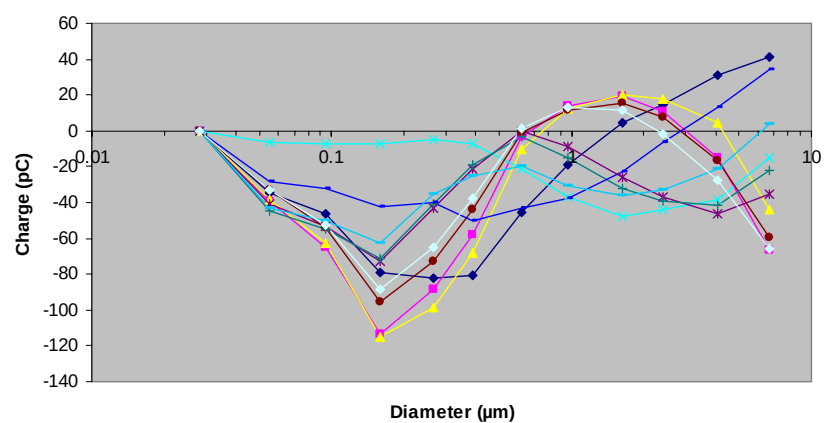
HFA-134a / PBT / High water content canister #3
Dry actuator / 50% RH



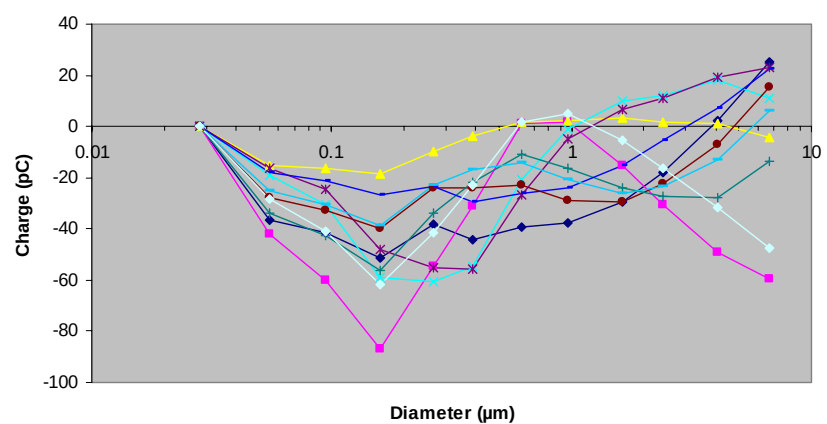
HFA-227 / Hostaform / Low water content canister #1
Dry actuator / 50% RH



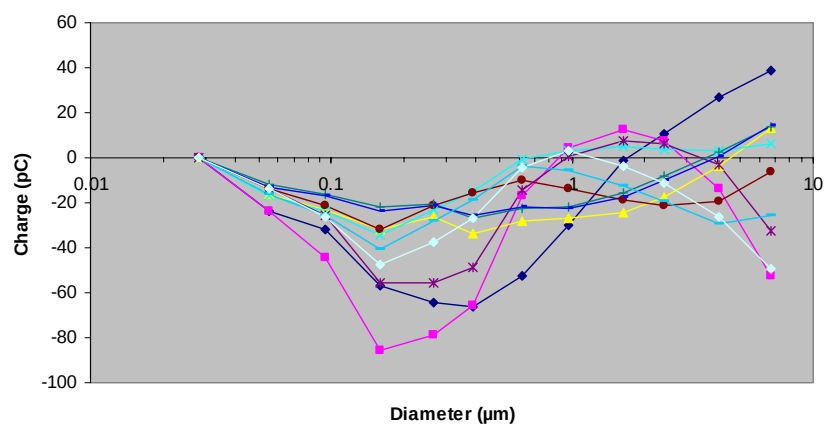
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Dry actuator / 50% RH



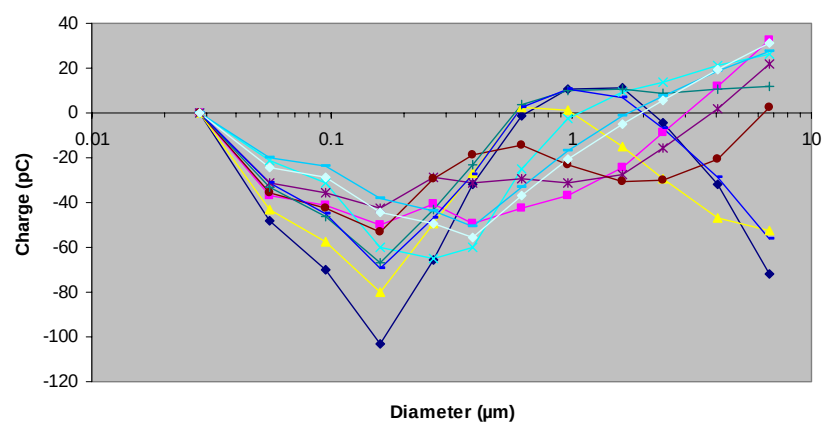
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Dry actuator / 50% RH



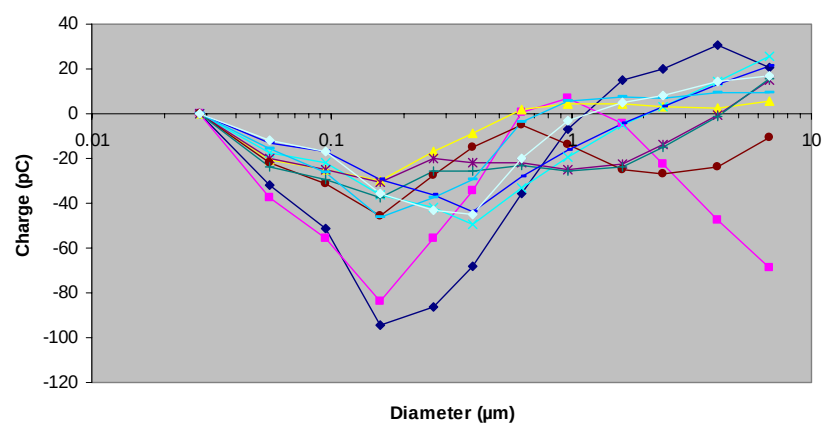
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Dry actuator / 50% RH



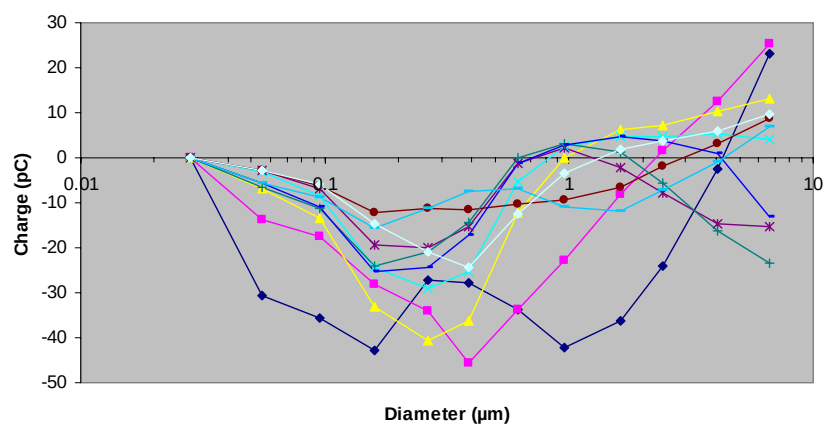
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Dry actuator / 50% RH



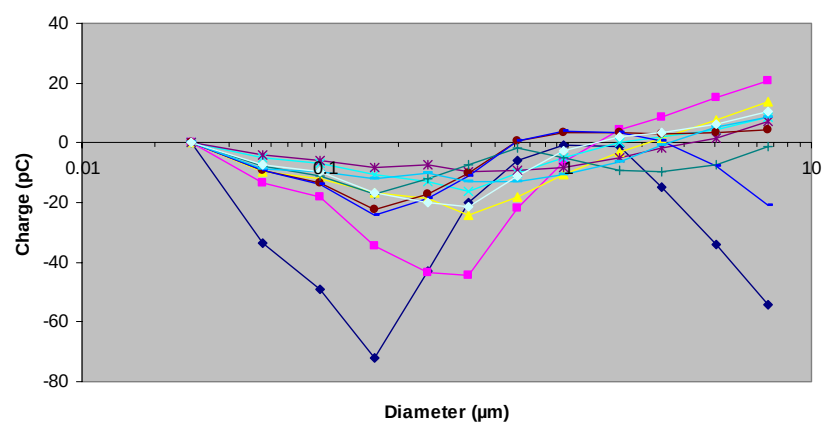
HFA-227 / Hostaform / Medium water content canister #3
Dry actuator / 50% RH



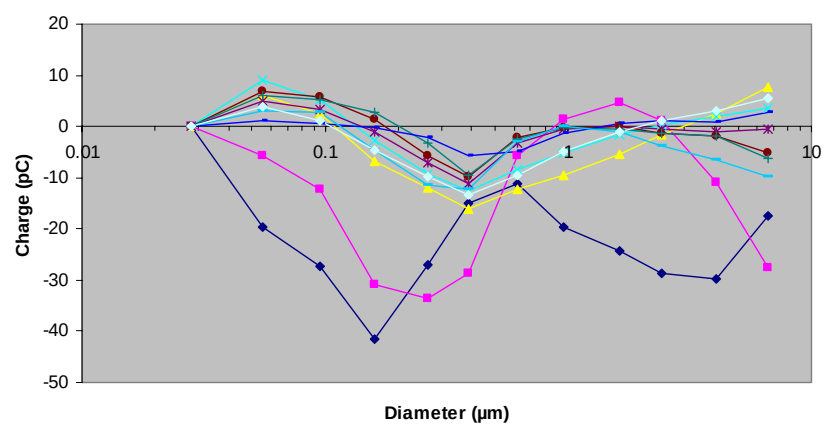
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Dry actuator / 50% RH



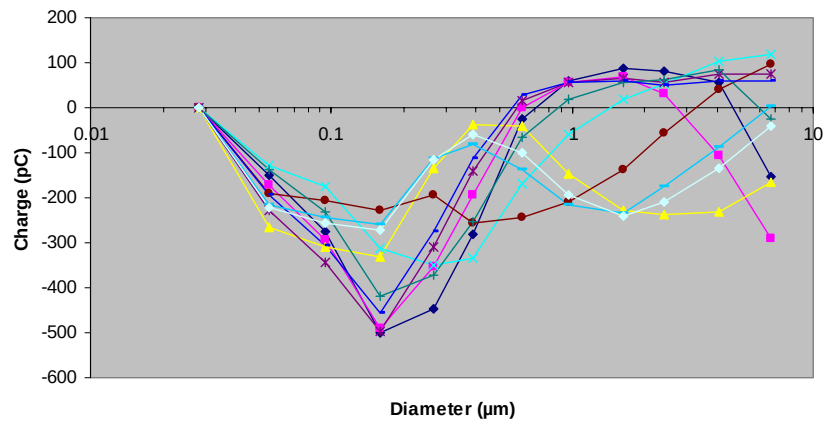
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Dry actuator / 50% RH



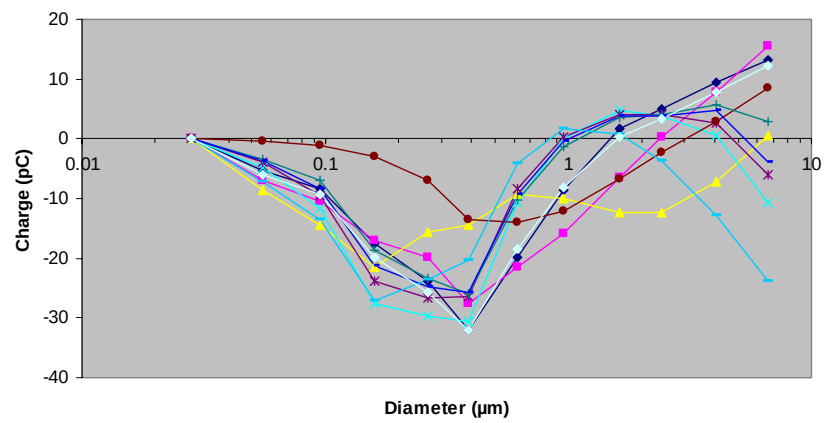
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Dry actuator / 50% RH



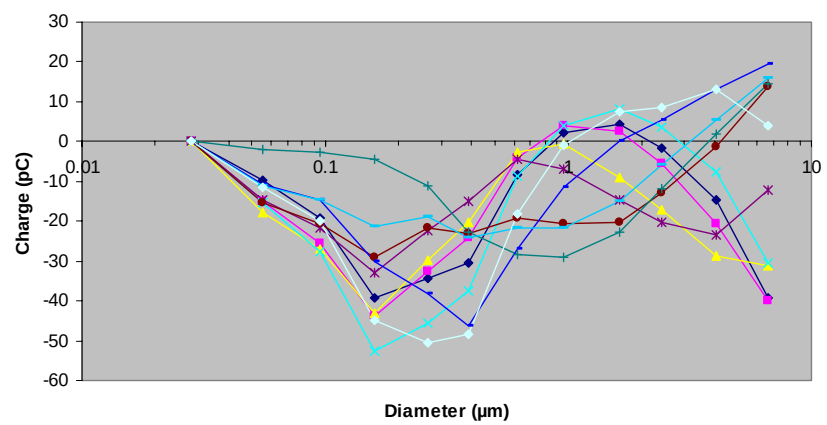
HFA-227 / PBT / Low water content canister #1
Dry actuator / 50% RH



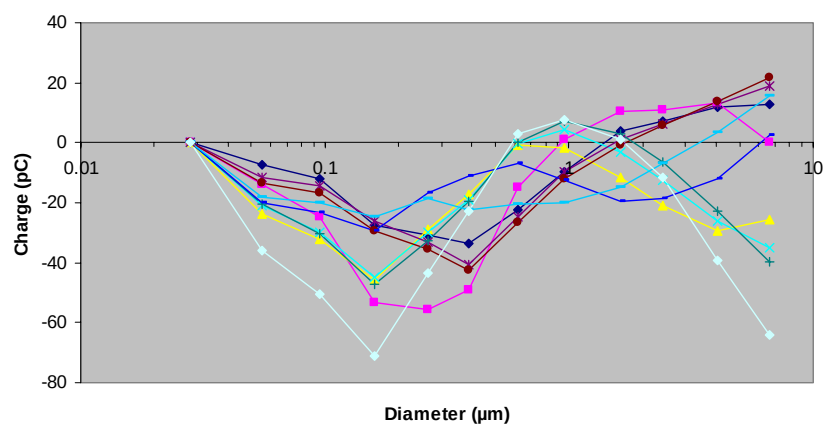
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Dry actuator / 50% RH



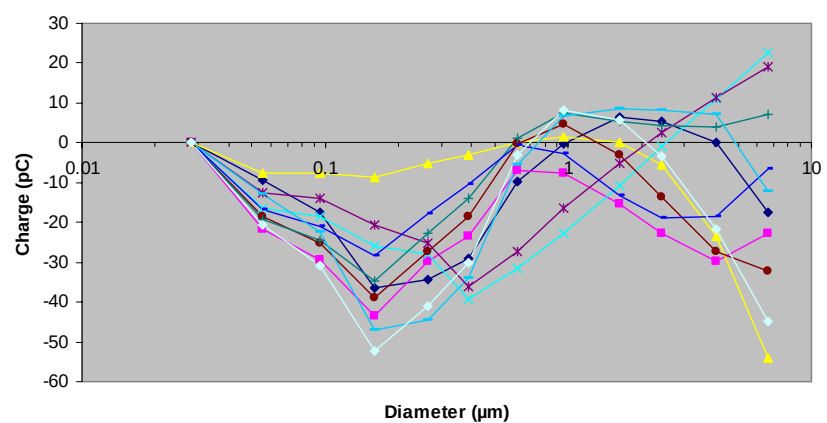
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Dry actuator / 50% RH



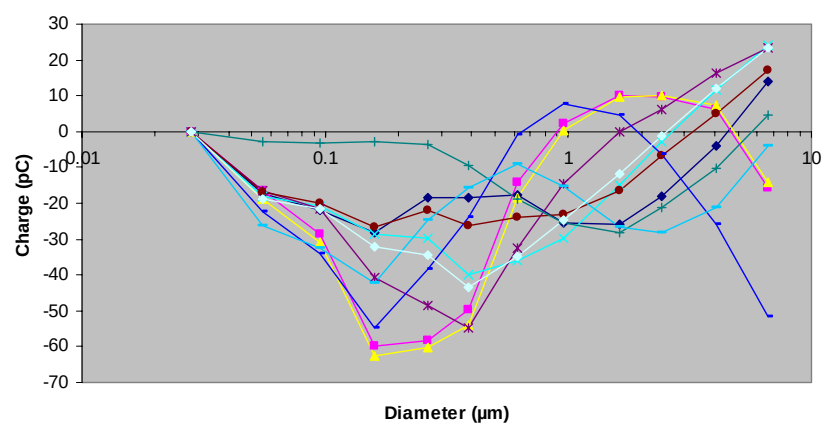
HFA-227 / PBT / Medium water content canister #1
Dry actuator / 50% RH



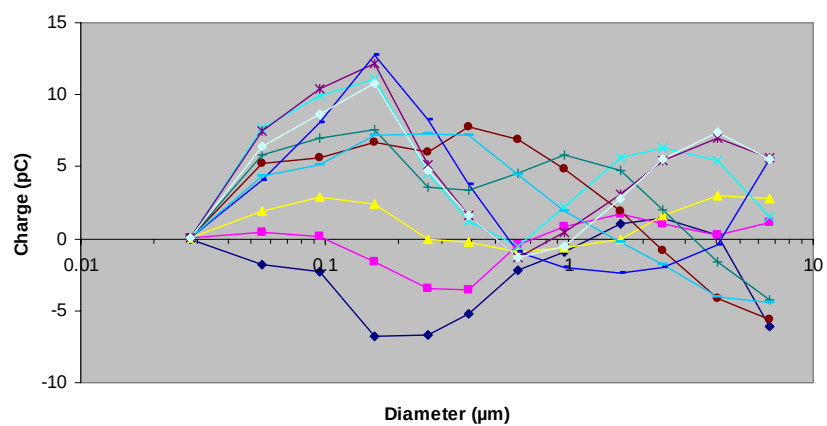
HFA-227 / PBT / Medium water content canister #2
Dry actuator / 50% RH



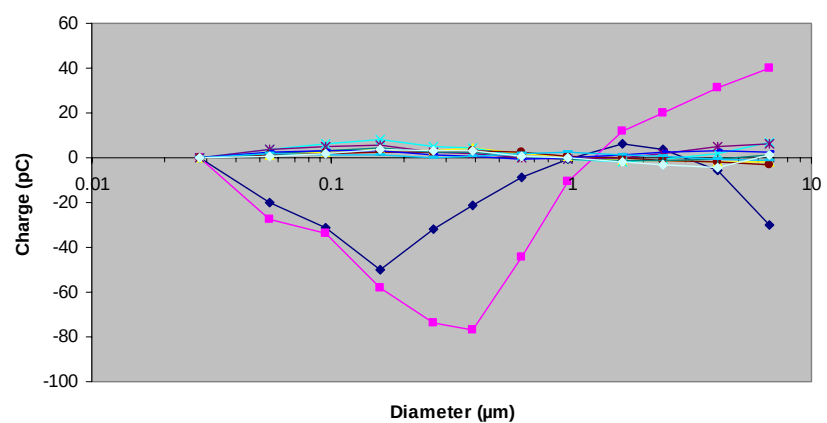
HFA-227 / PBT / Medium water content canister #3
Dry actuator / 50% RH



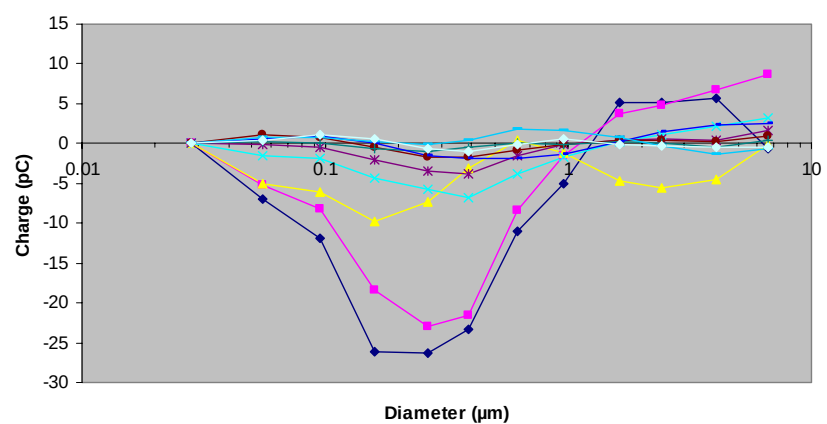
HFA-227 / PBT / High water content canister #1
Dry actuator / 50% RH



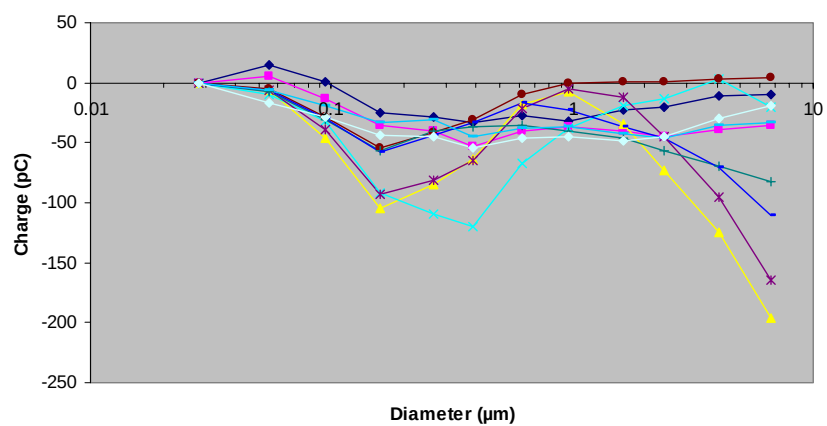
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Dry actuator / 50% RH



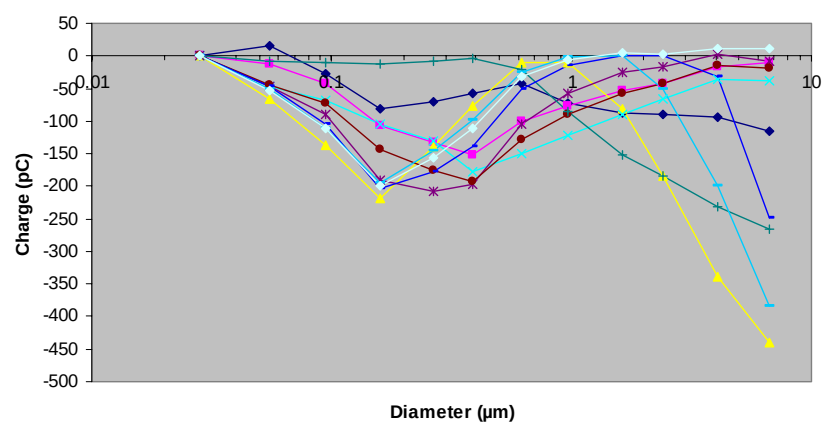
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Dry actuator / 50% RH



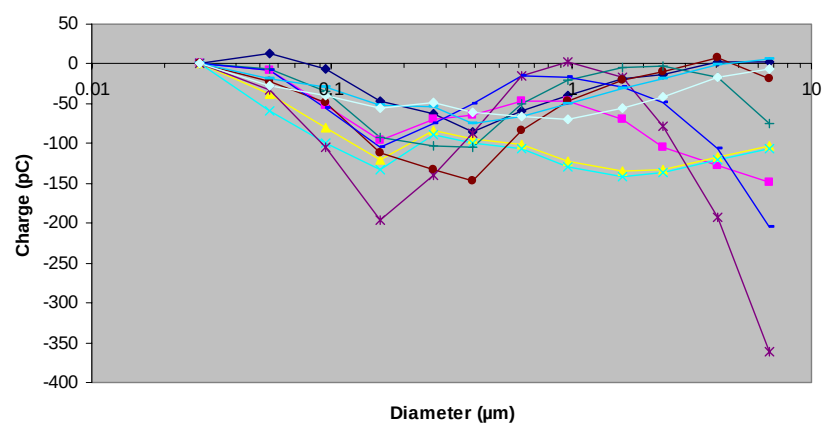
HFA-134a / Hostaform / Low water content canister #1
Wet actuator / 50% RH



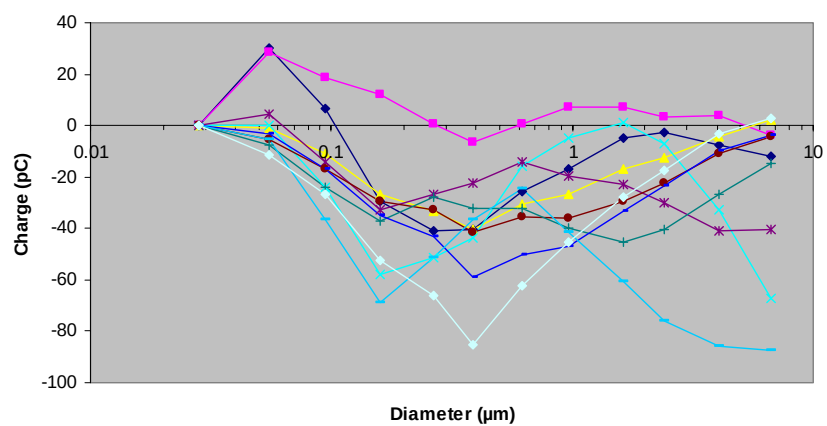
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Wet actuator / 50% RH



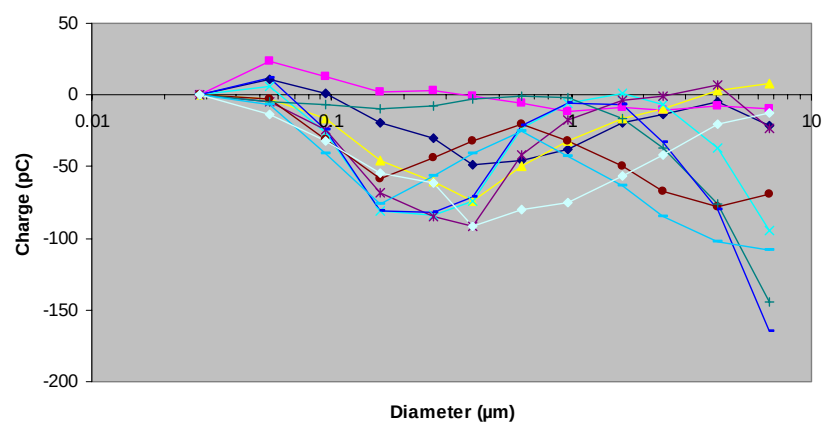
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Wet actuator / 50% RH



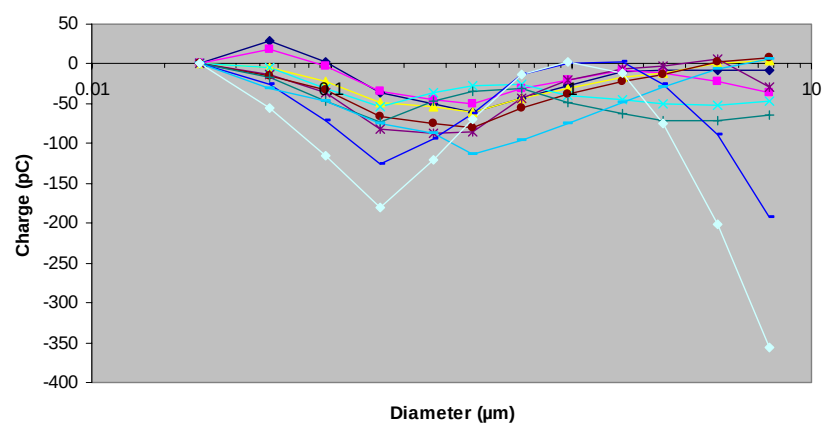
HFA-134a / Hostaform / Medium water content canister #1
Wet actuator / 50% RH



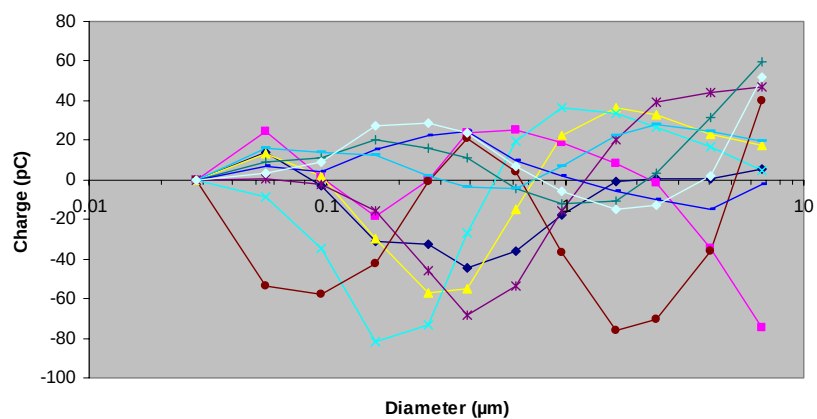
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Wet actuator / 50% RH



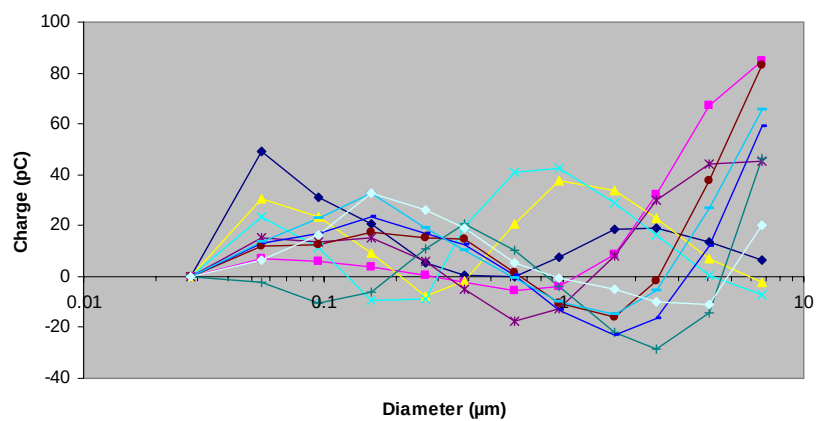
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Wet actuator / 50% RH



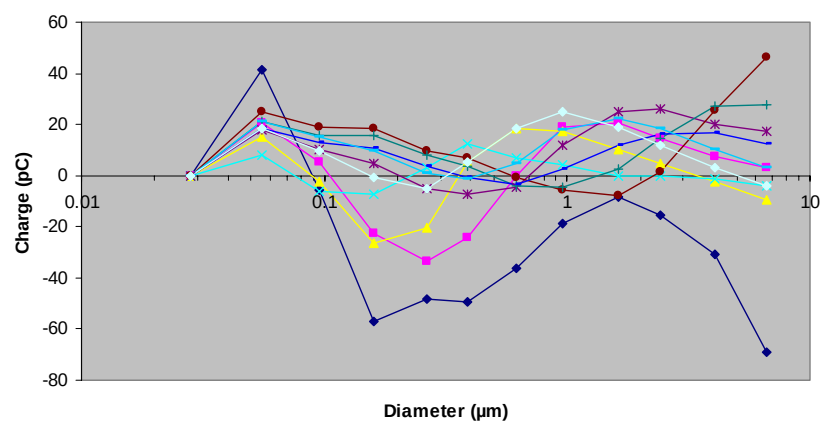
HFA-134a / Hostaform / High water content canister #1
Wet actuator / 50% RH



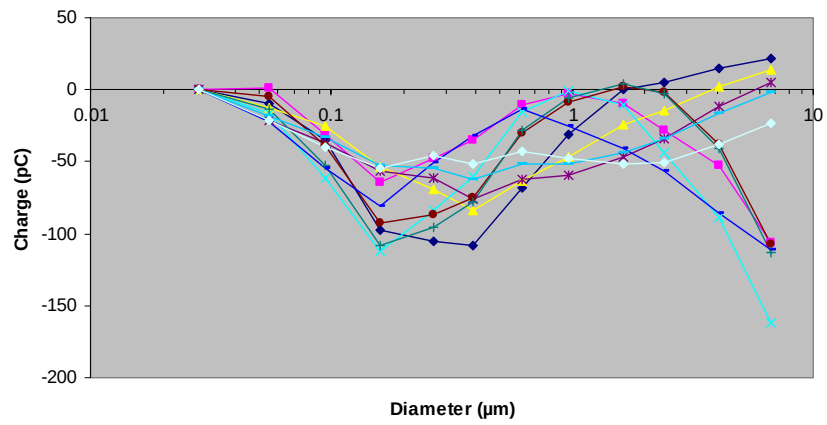
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Wet actuator / 50% RH



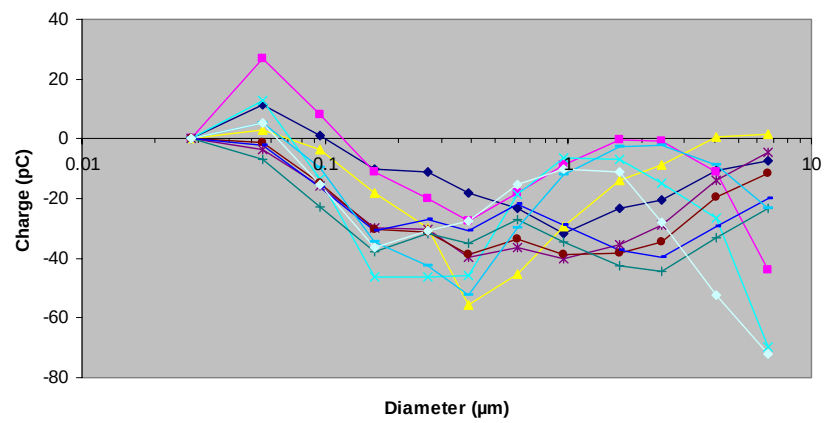
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Wet actuator / 50% RH



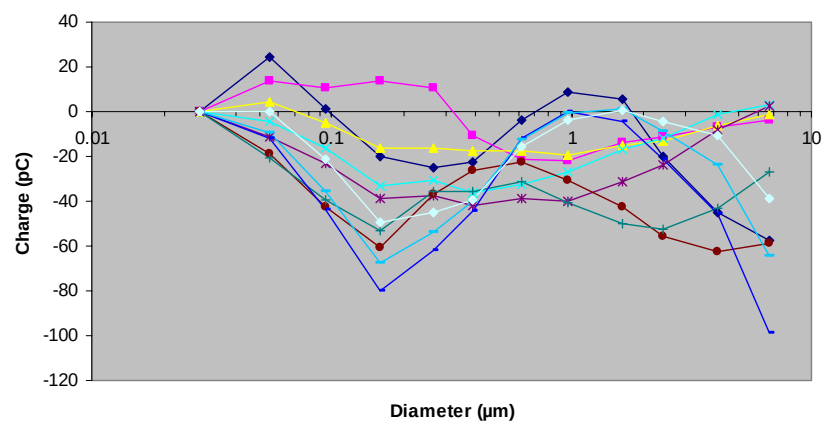
HFA-134a / PBT / Low water content canister #1
Wet actuator / 50% RH



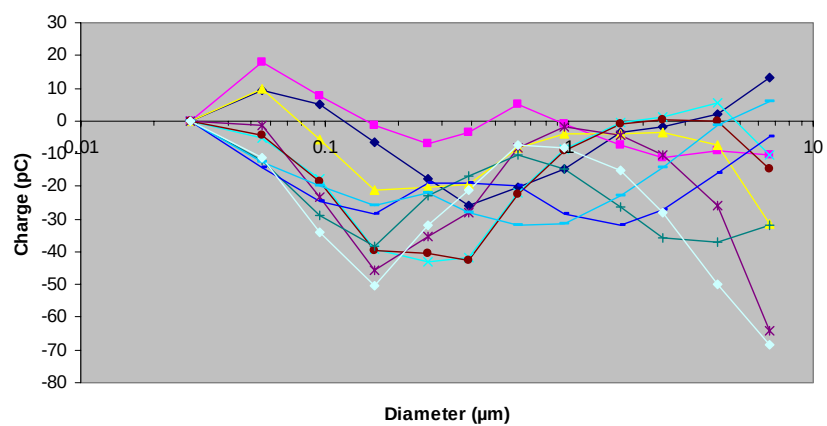
HFA-134a / PBT / Low water content canister #2
Wet actuator / 50% RH



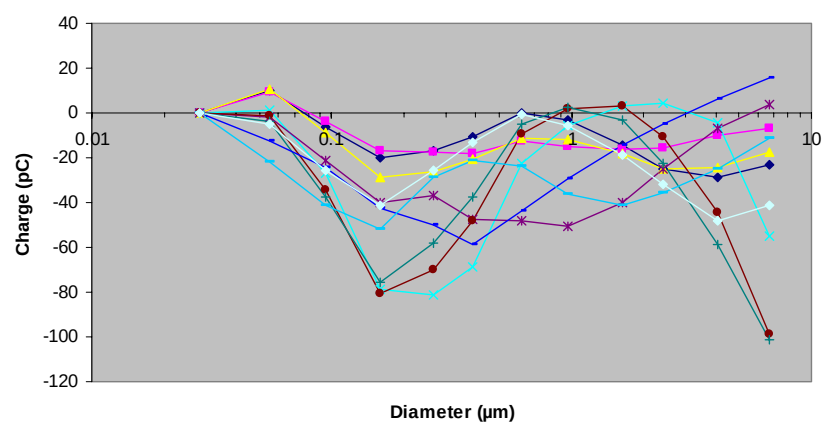
HFA-134a / PBT / Low water content canister #3
Wet actuator / 50% RH



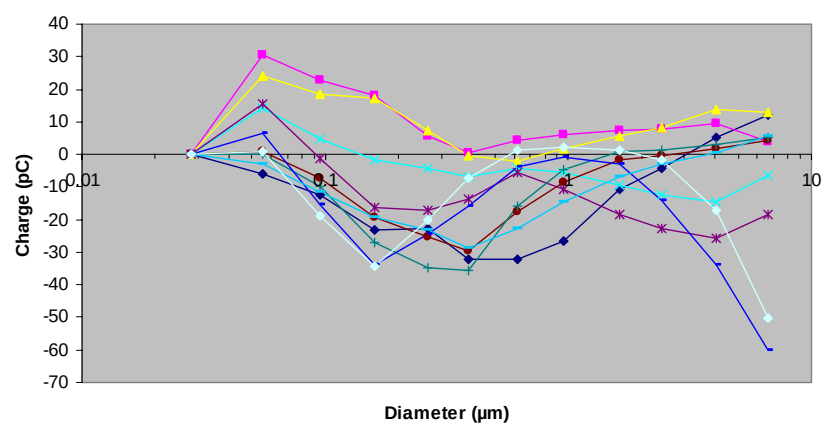
HFA-134a / PBT / Medium water content canister #1
Wet actuator / 50% RH



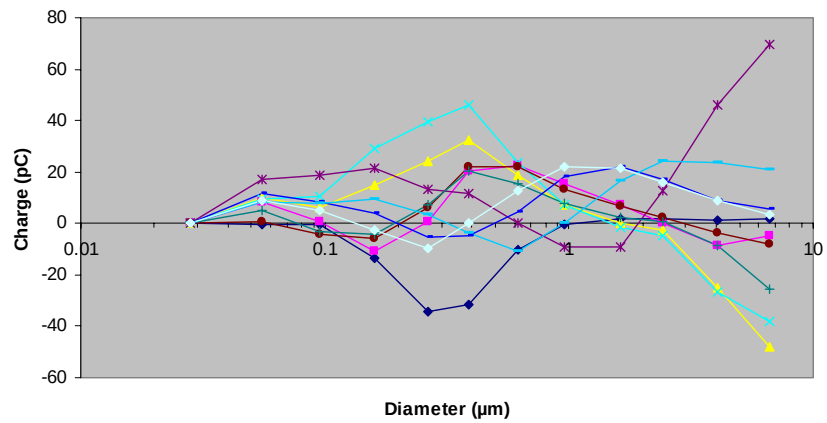
HFA-134a / PBT / Medium water content canister #2
Wet actuator / 50% RH



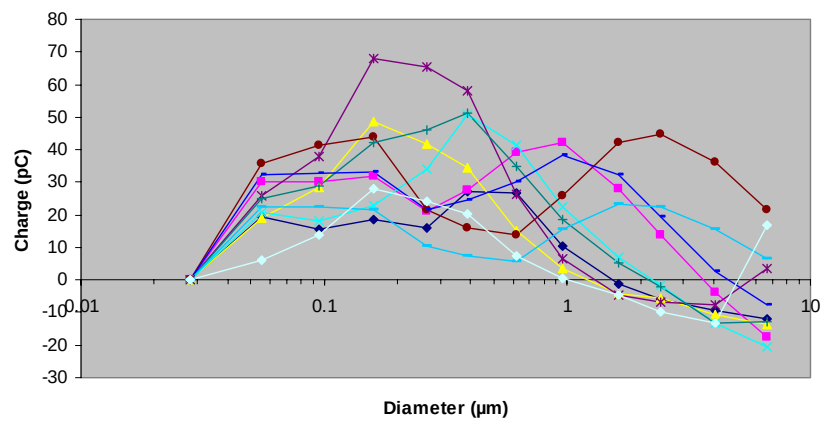
HFA-134a / PBT / Medium water content canister #3
Wet actuator / 50% RH



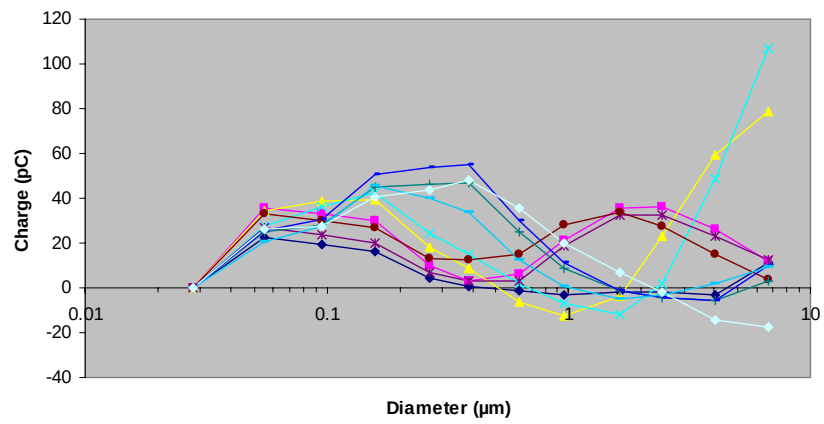
HFA-134a / PBT / High water content canister #1
Wet actuator / 50% RH



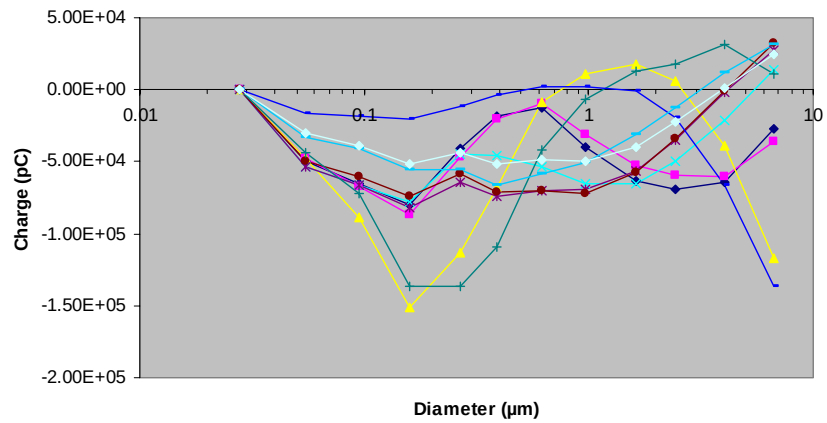
HFA-134a / PBT / High water content canister #2
Wet actuator / 50% RH



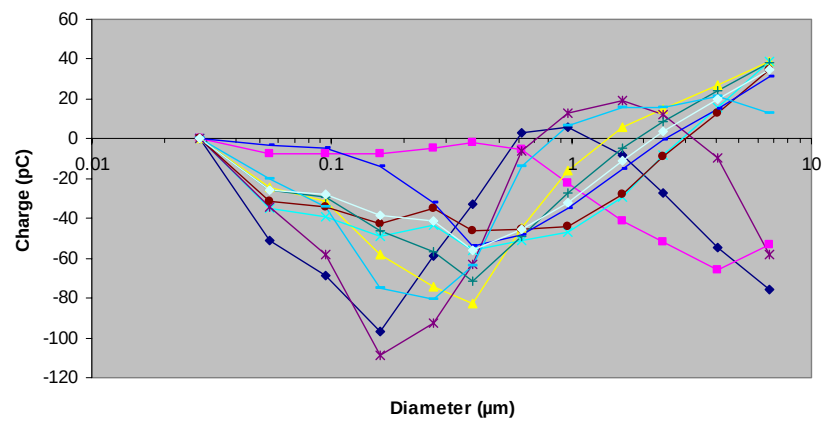
HFA-134a / PBT / High water content canister #3
Wet actuator / 50% RH



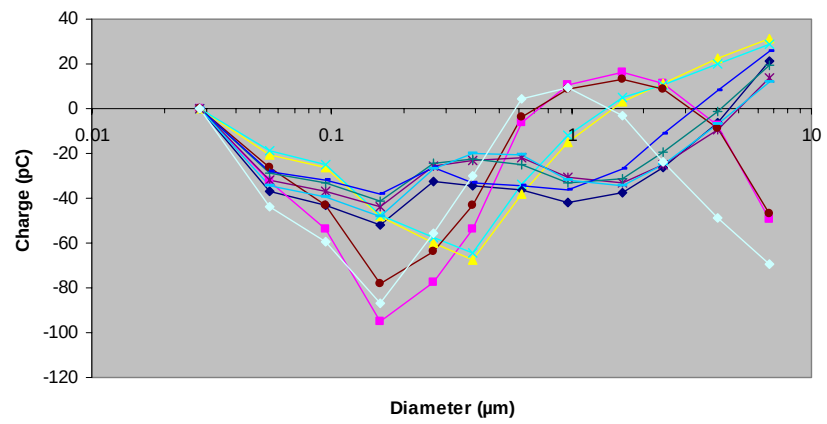
HFA-227 / Hostaform / Low water content canister #1
Wet actuator / 50% RH



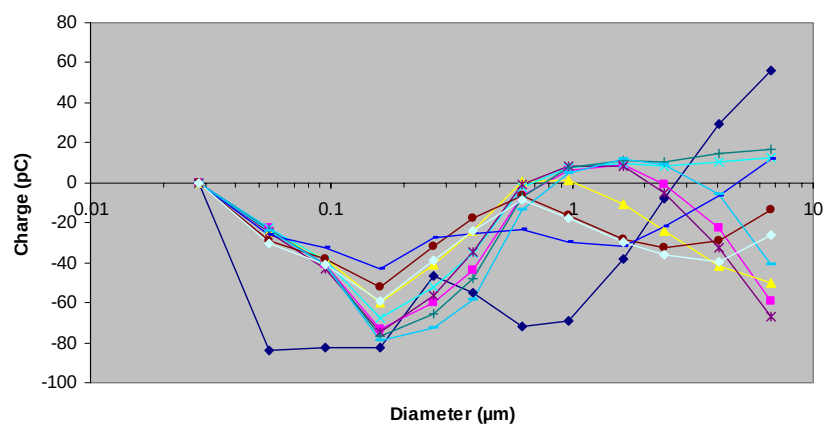
HFA-227 / Hostaform / Low water content canister #2
Wet actuator / 50% RH



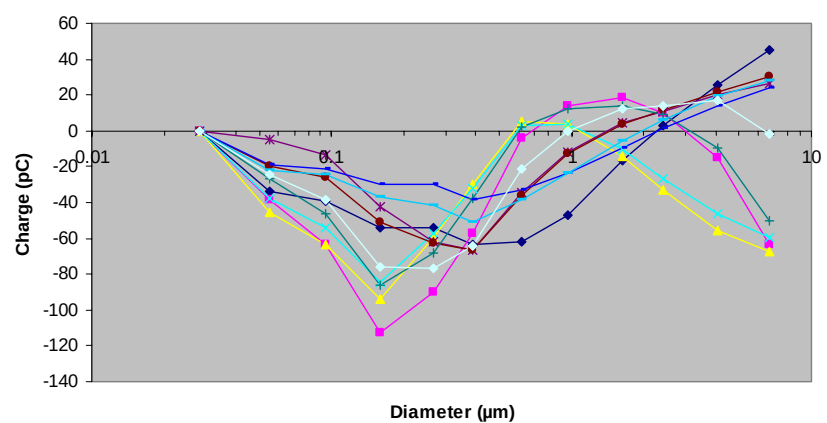
HFA-227 / Hostaform / Low water content canister #3
Wet actuator / 50% RH



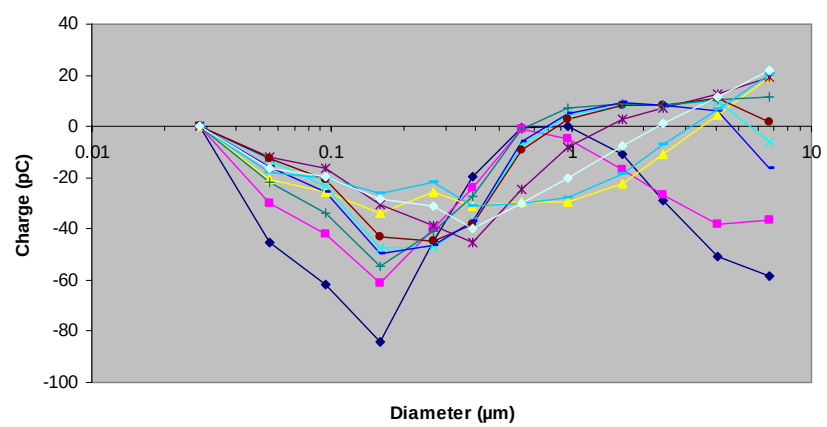
HFA-227 / Hostaform / Medium water content canister #1
Wet actuator / 50% RH



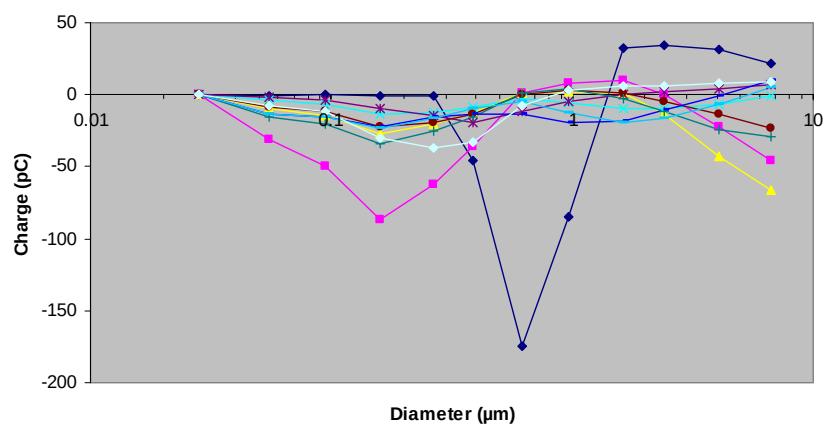
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Wet actuator / 50% RH



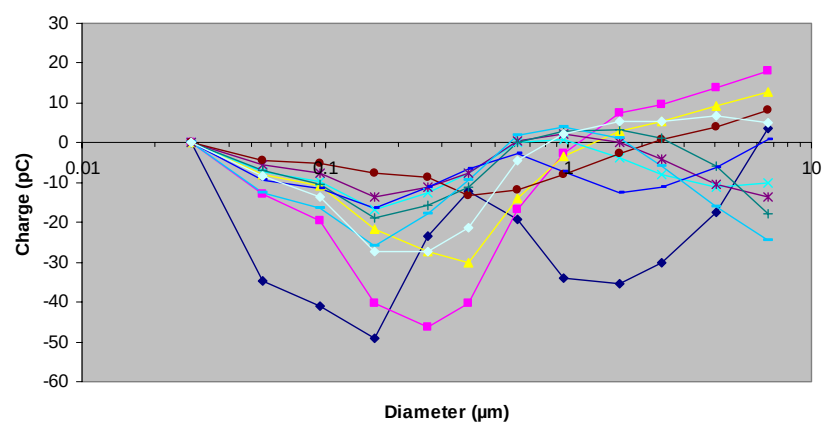
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Wet actuator / 50% RH



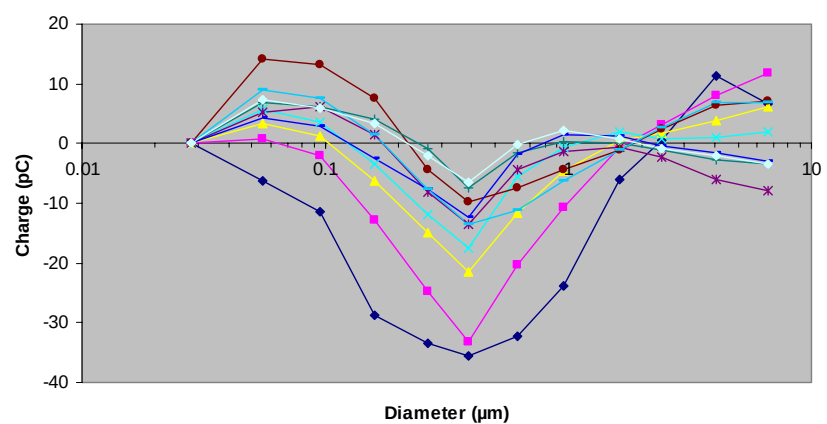
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Wet actuator / 50% RH



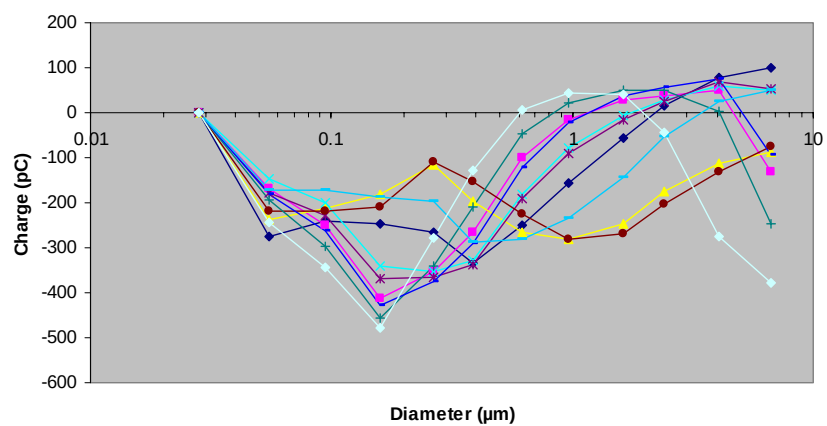
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Wet actuator / 50% RH



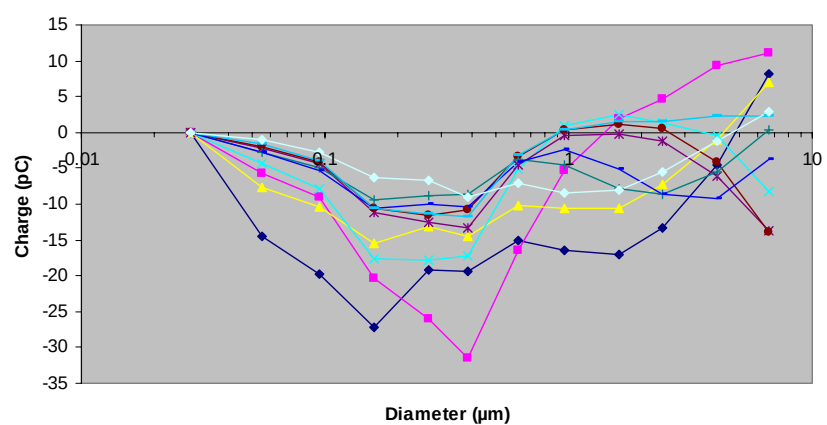
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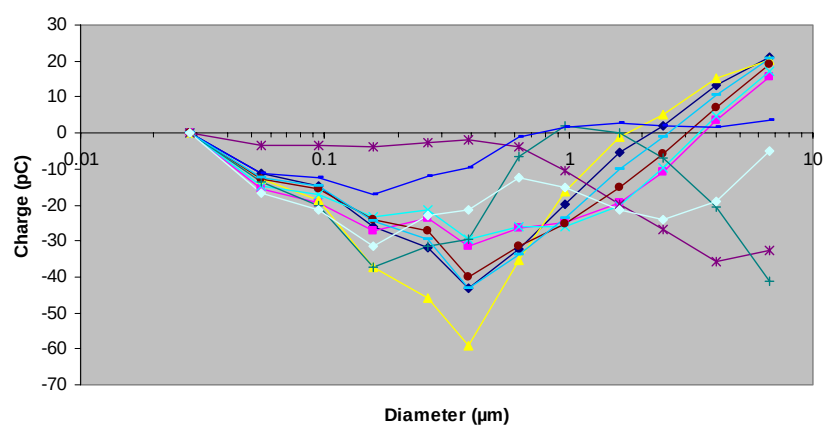
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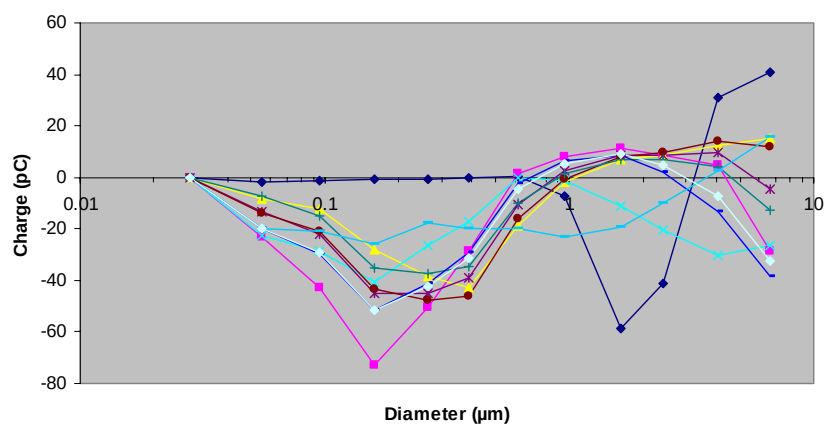
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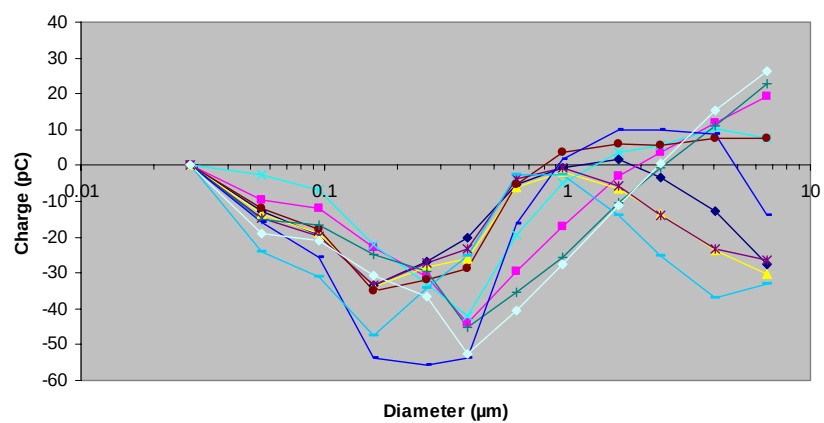
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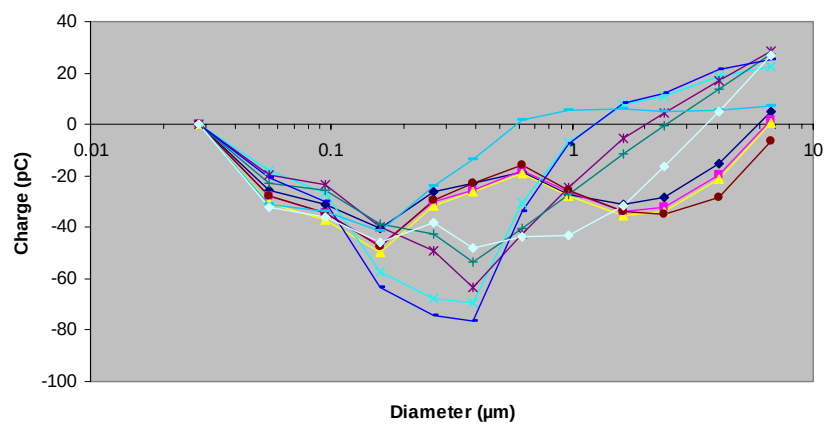
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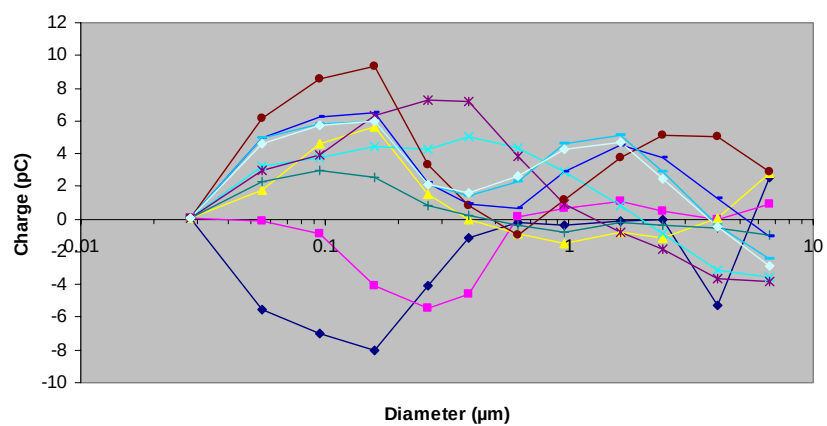
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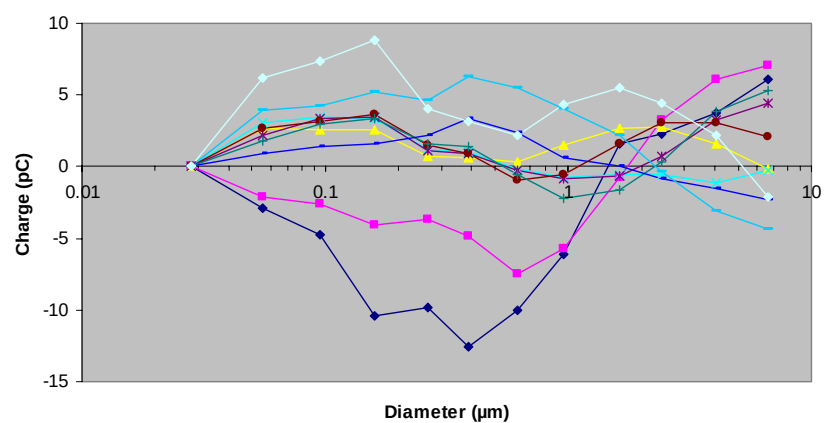
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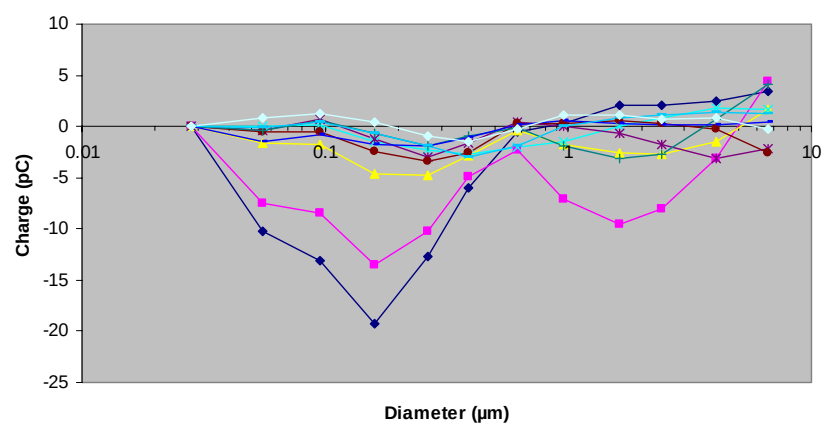
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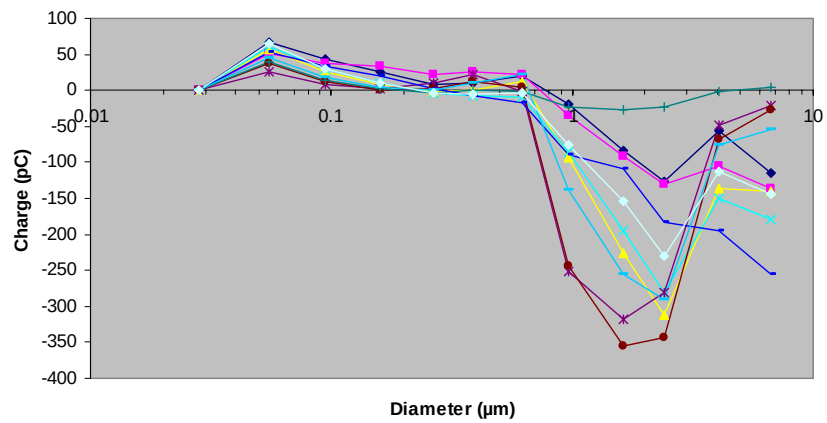
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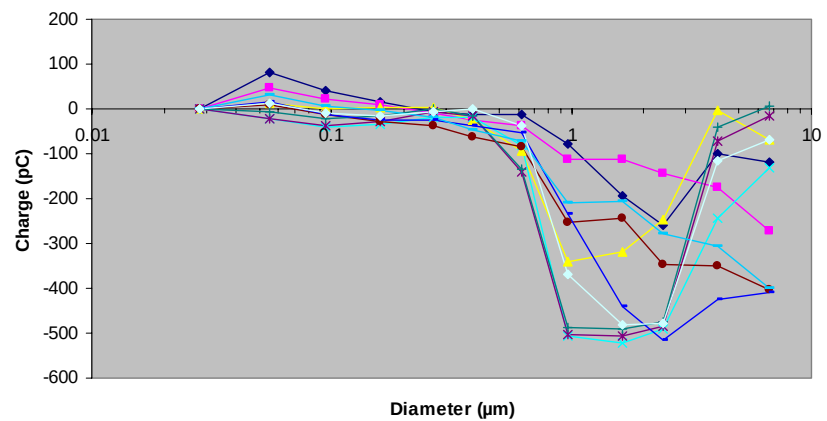
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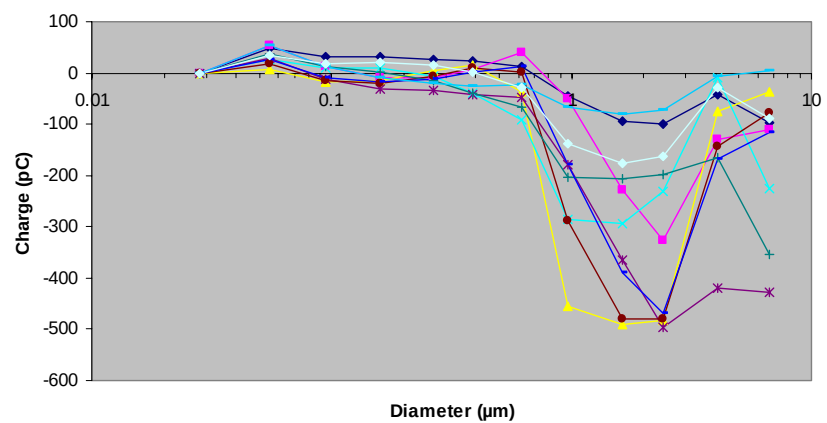
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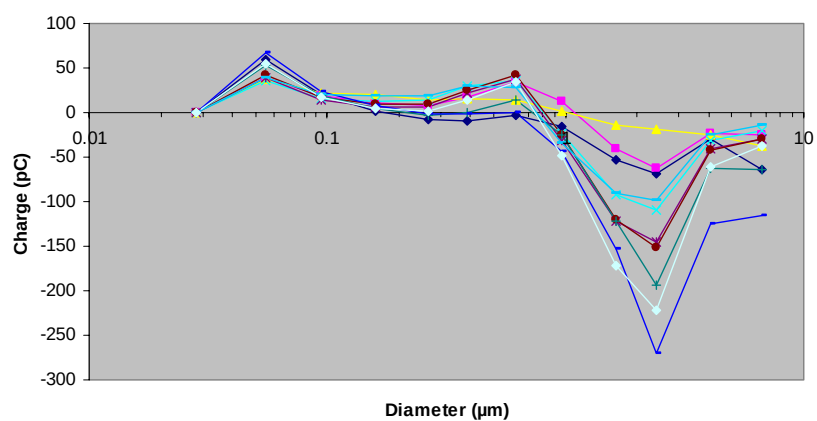
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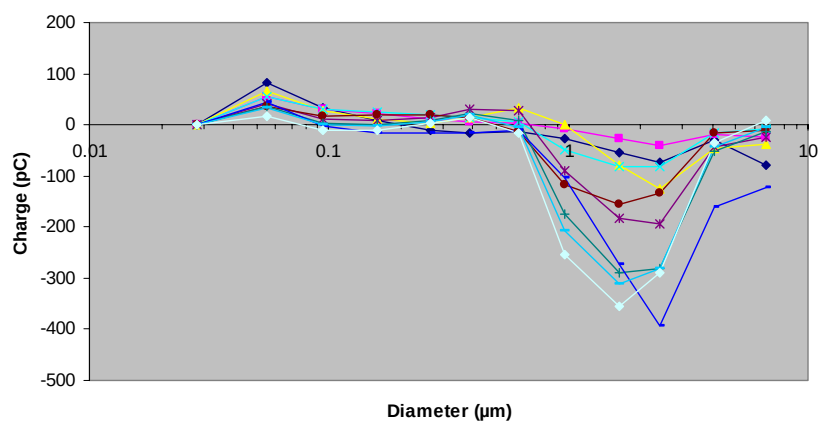
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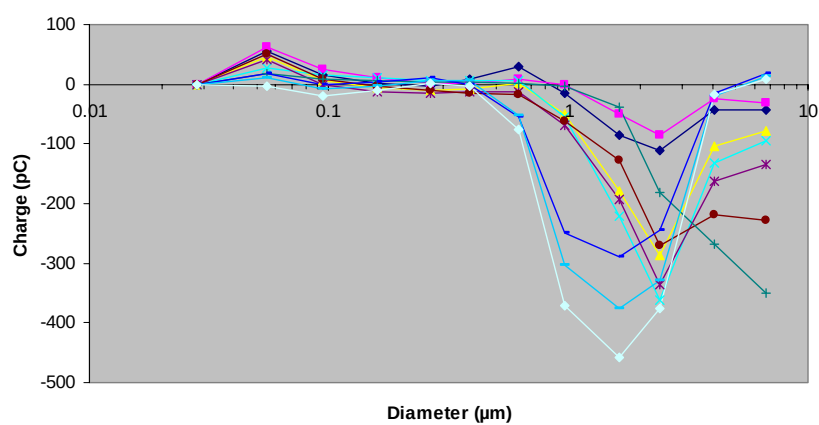
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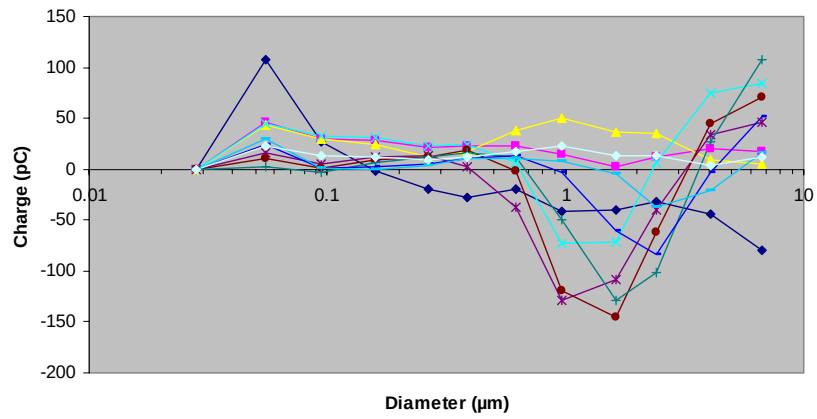
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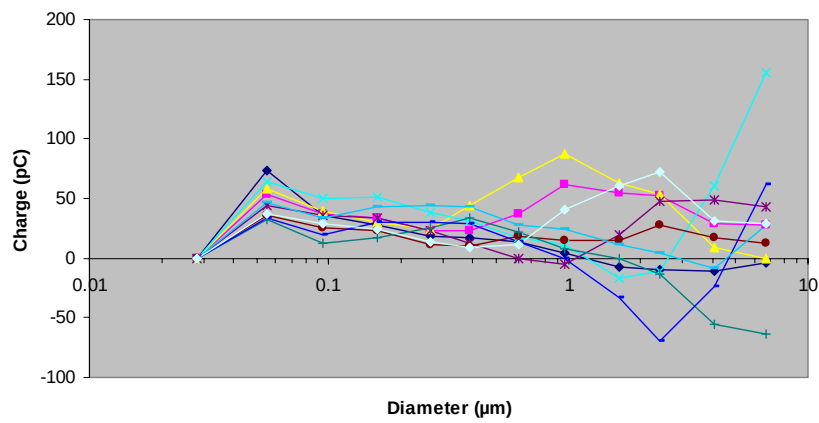
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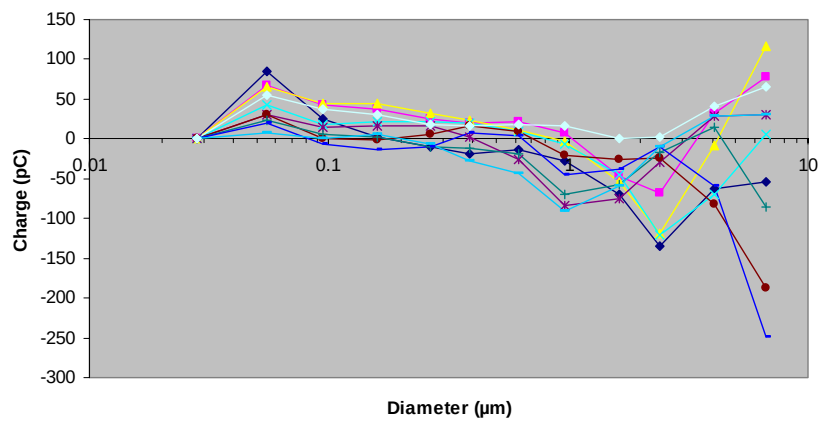
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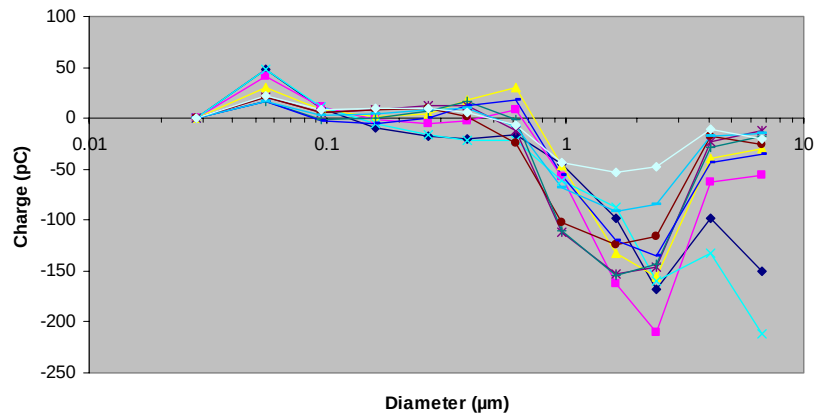
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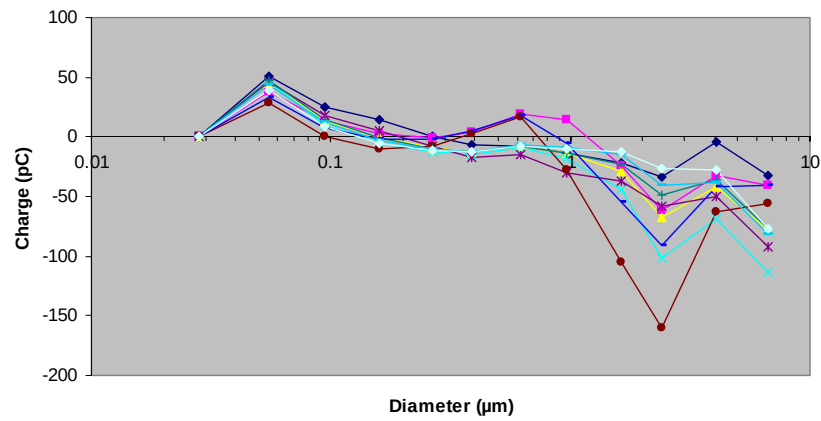
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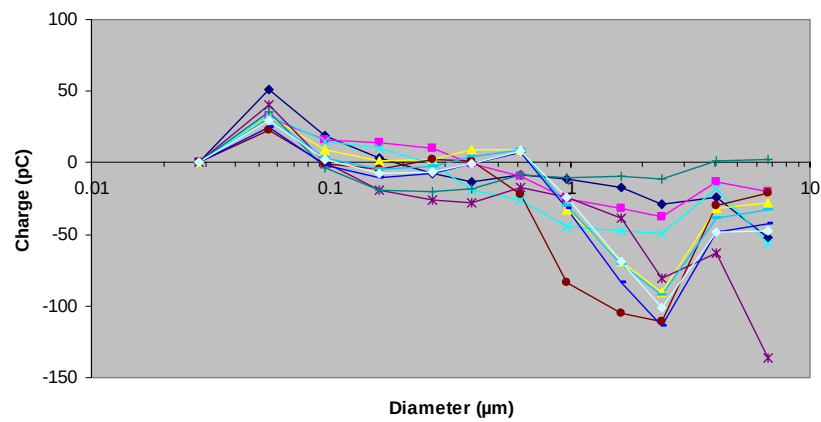
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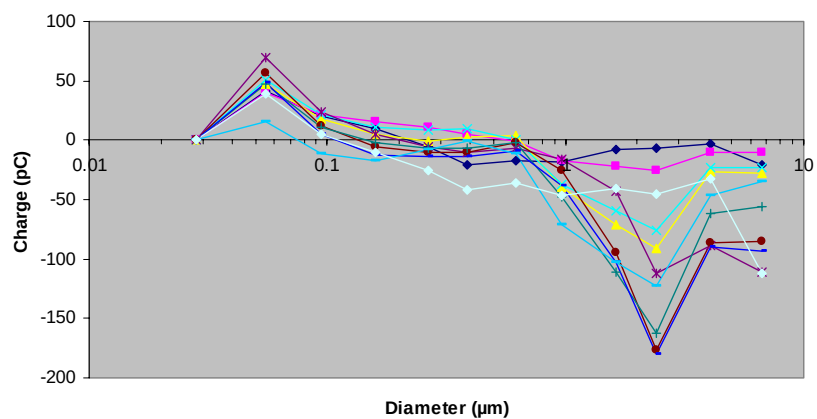
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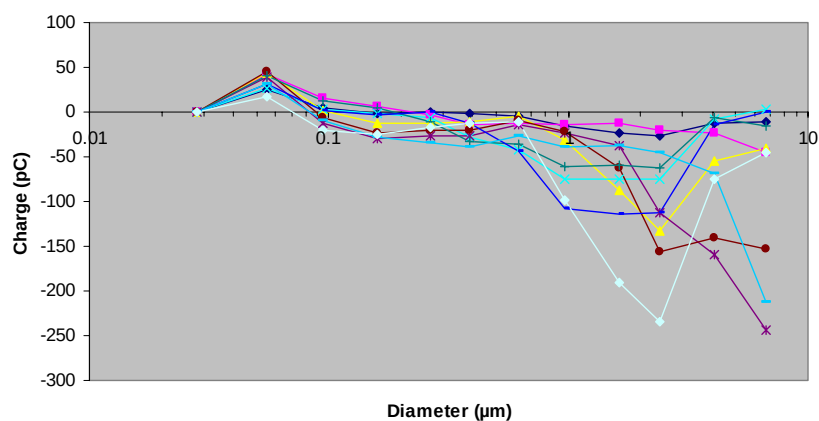
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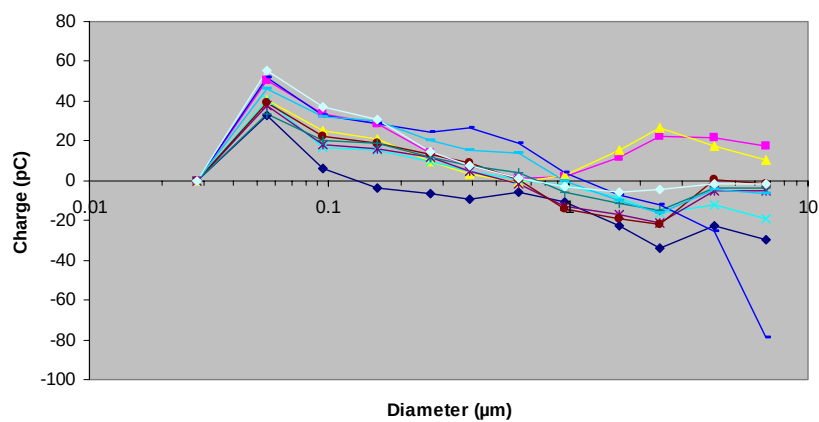
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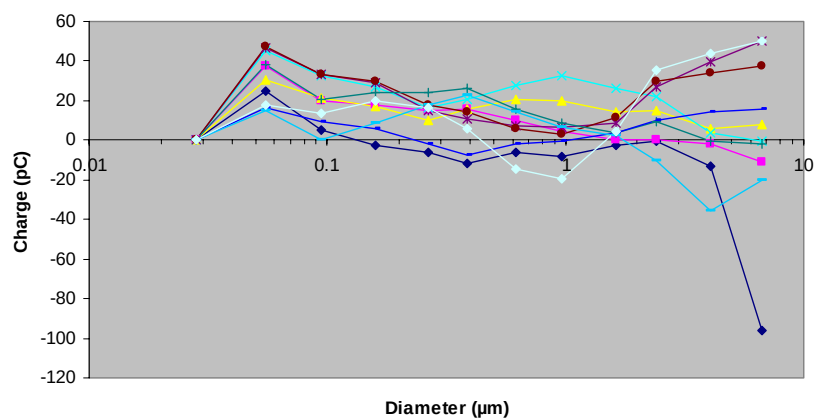
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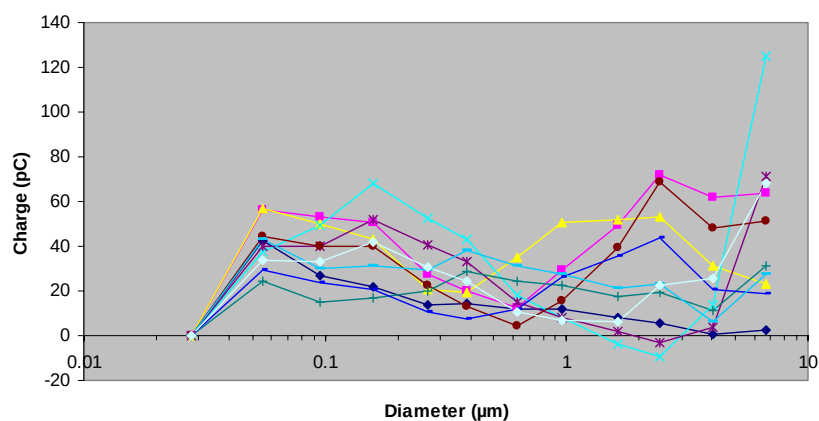
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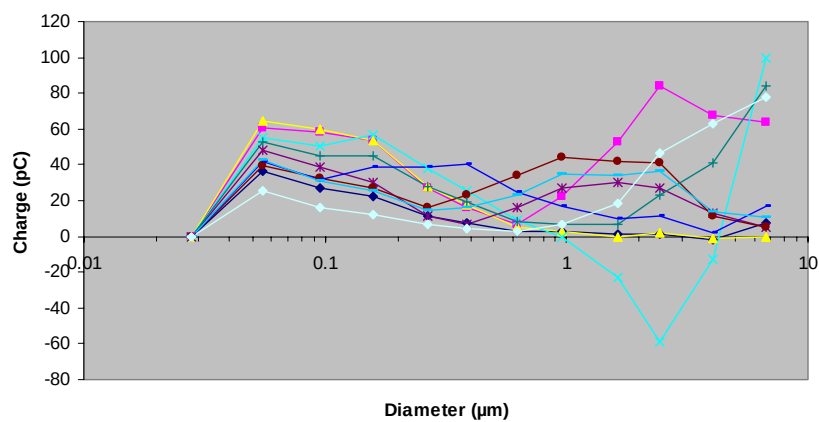
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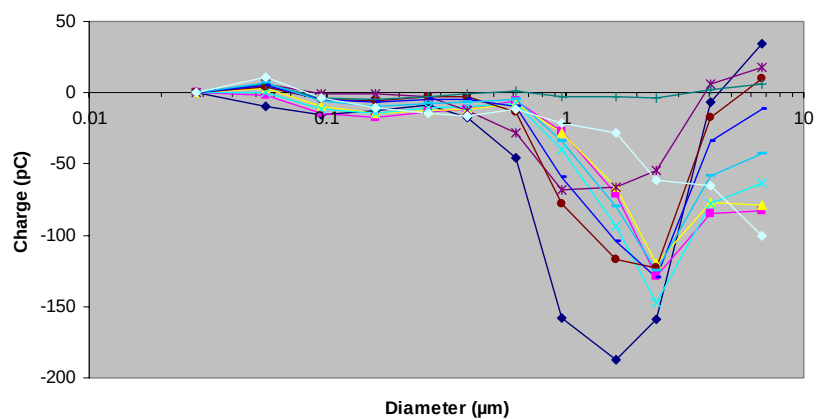
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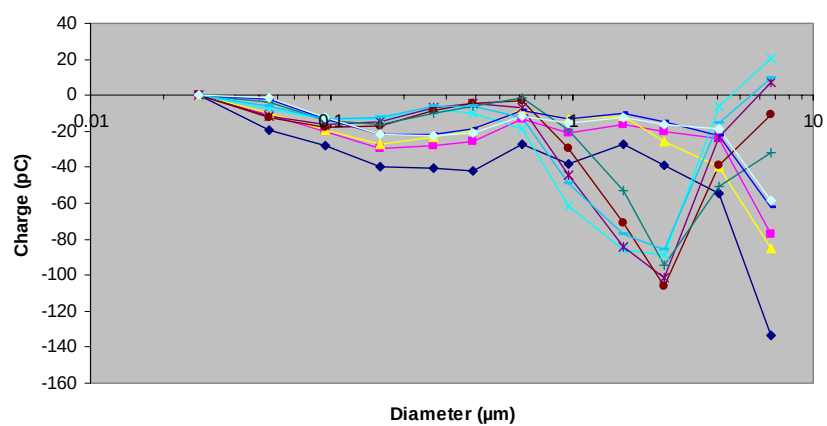
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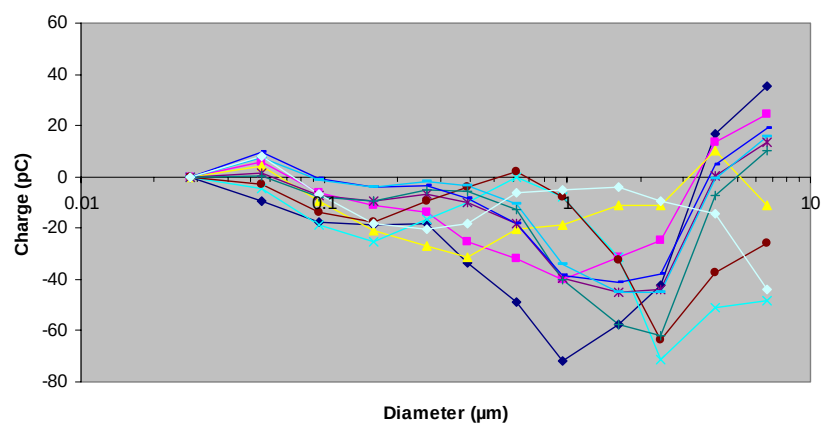
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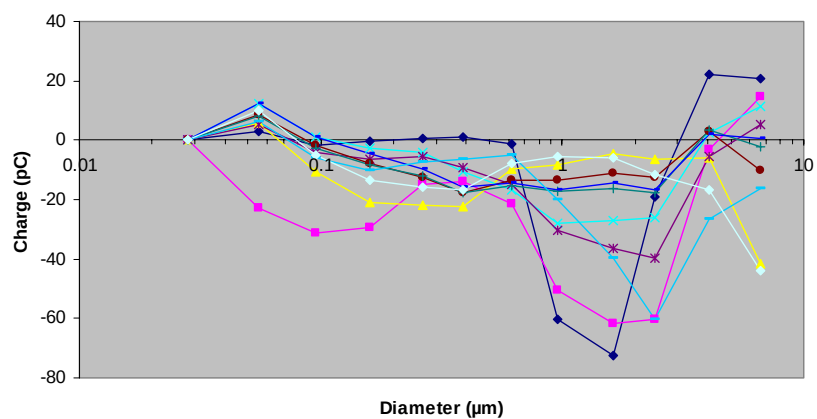
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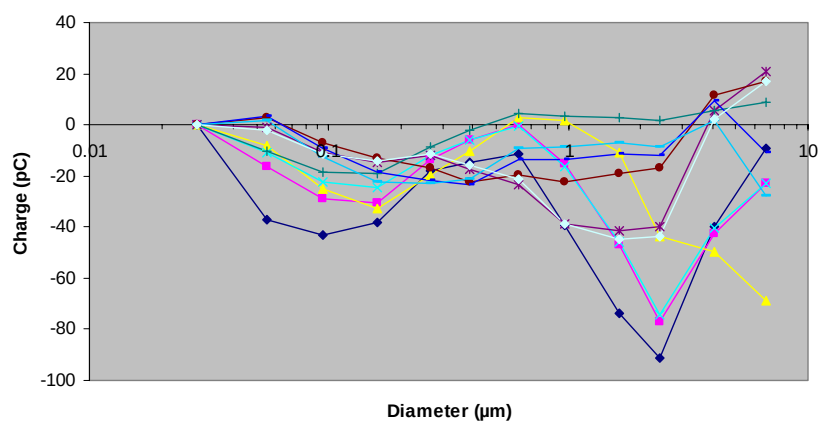
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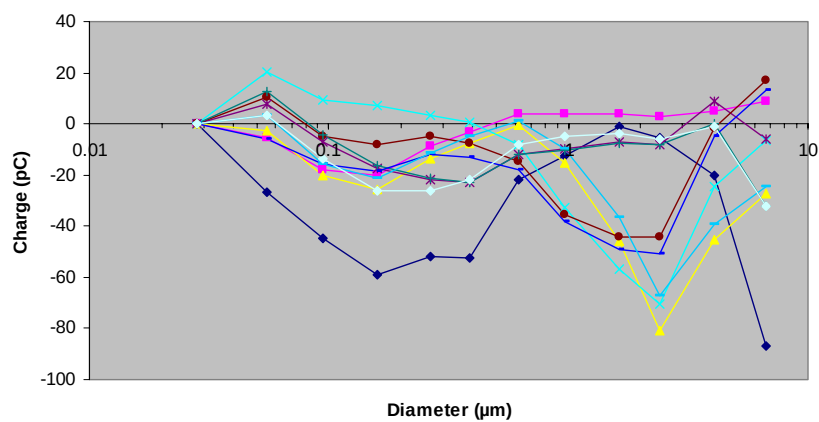
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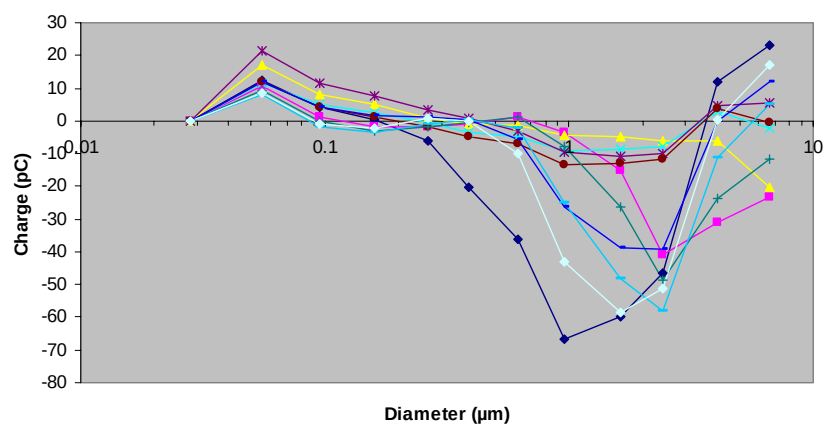
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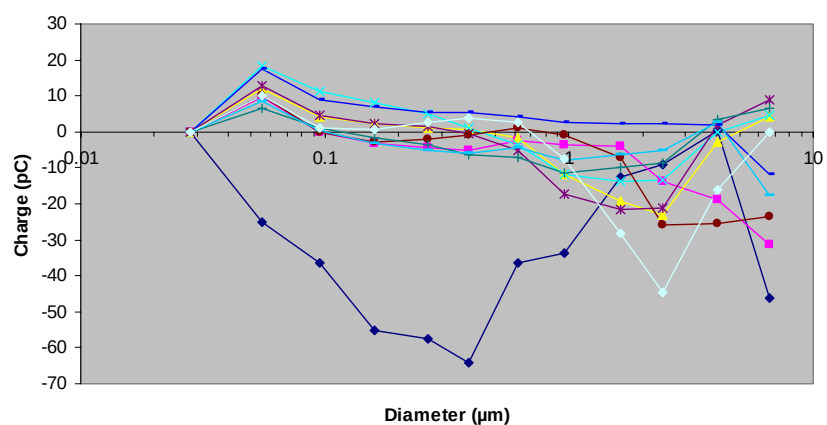
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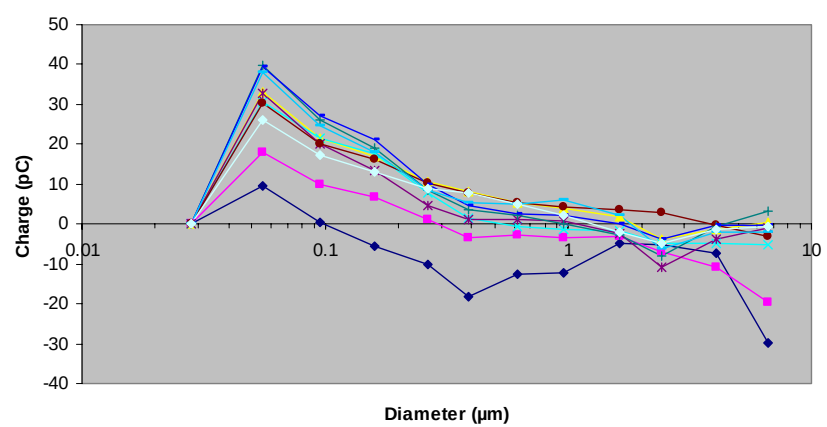
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Wet actuator / Humidified air



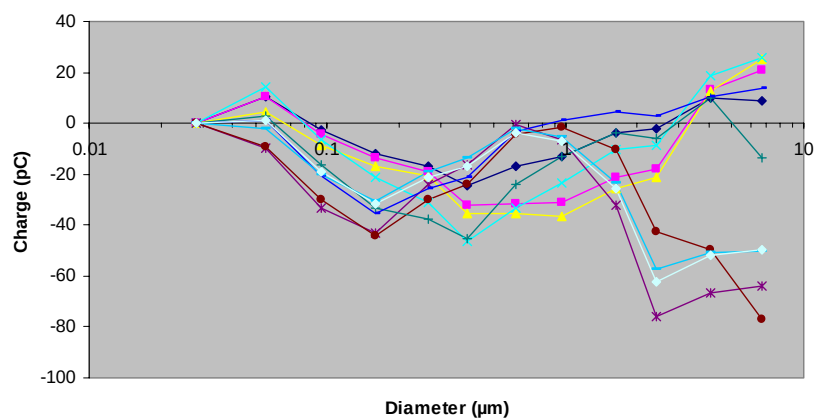
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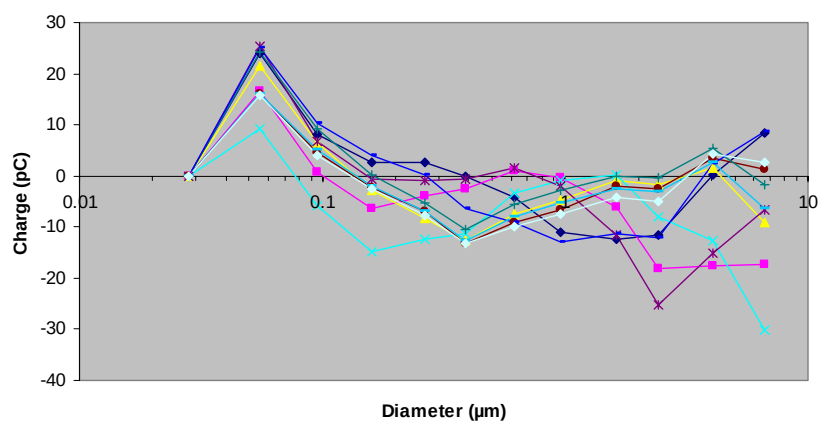
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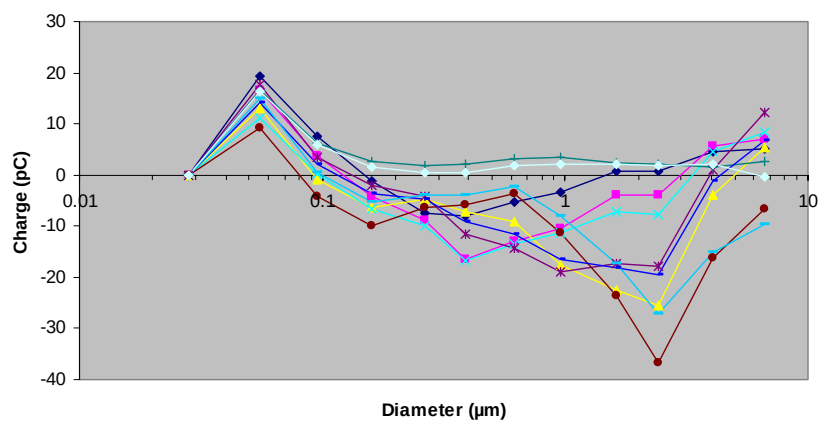
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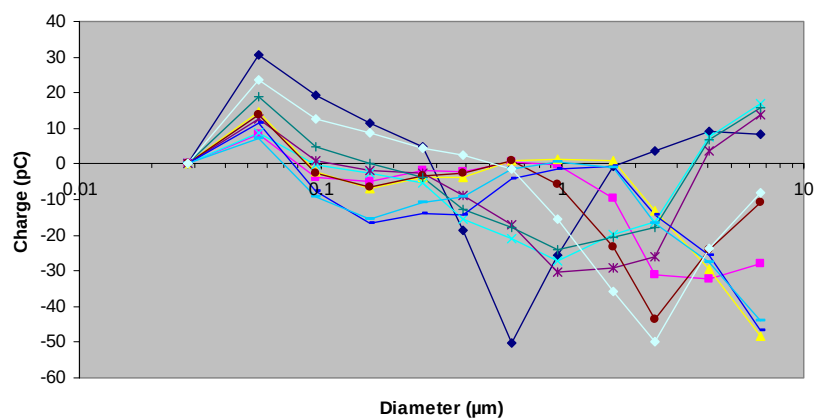
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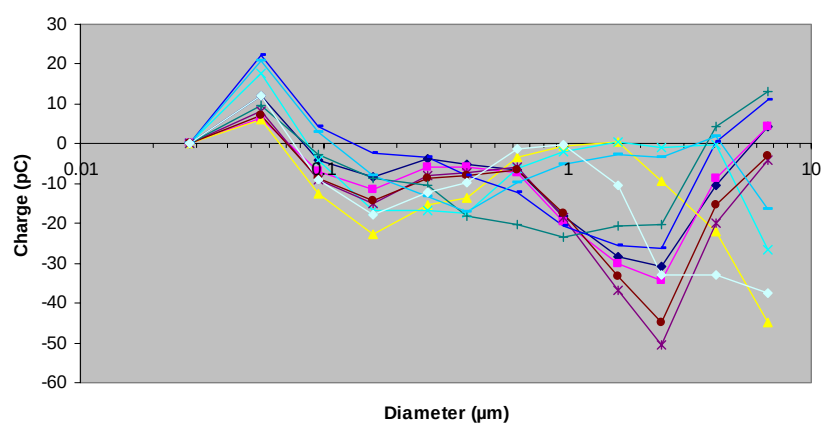
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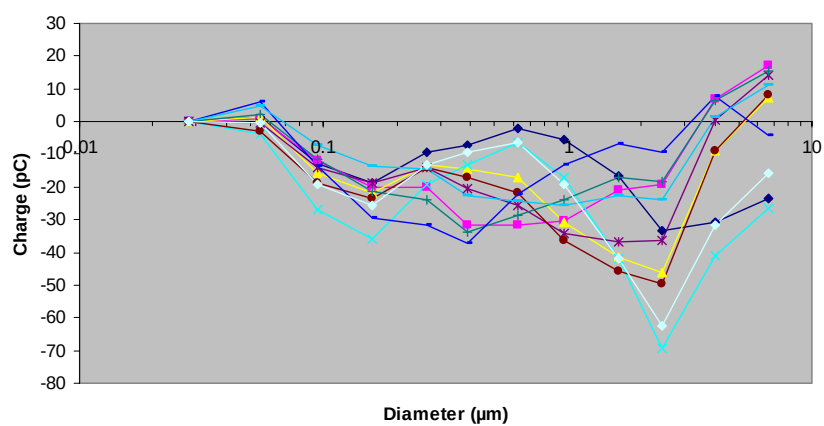
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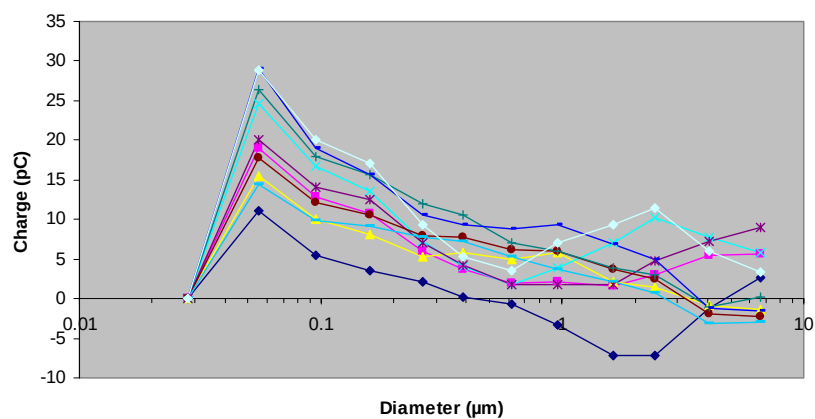
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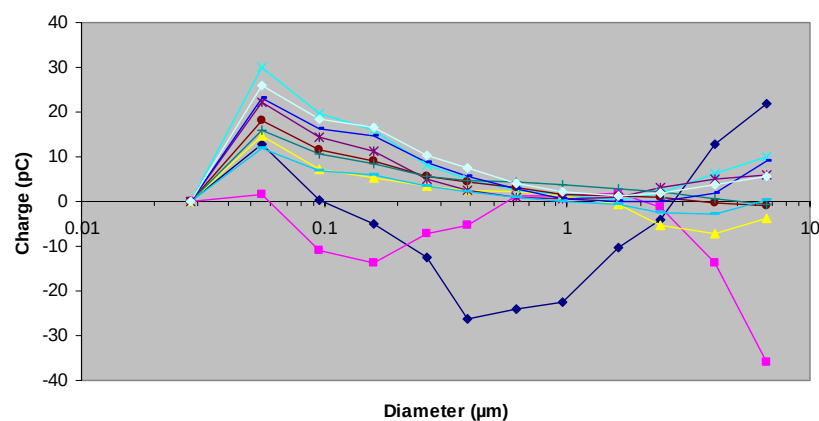
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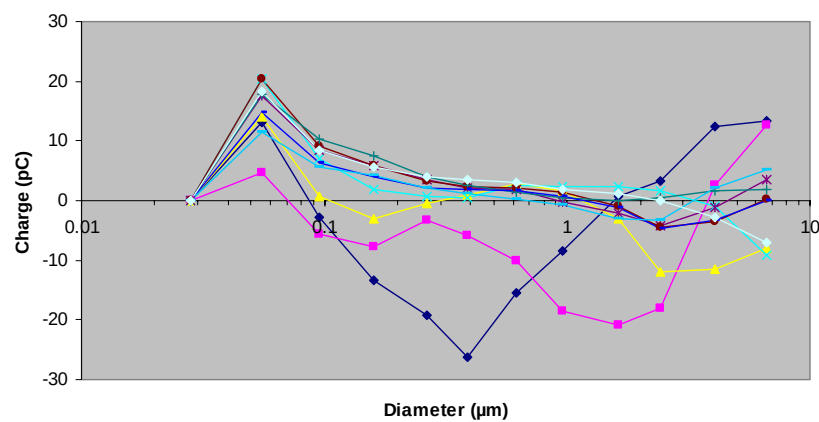
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Wet actuator / Humidified air



HFA-227 / PBT / High water content canister #3
Wet actuator / Humidified air



Appendix E

Published Experimental Papers and Book Chapter

Electrostatic Charge Characteristics of Aerosols Produced from Metered Dose Inhalers

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ABSTRACT: The electrostatic charge properties of aerosols produced by commercial metered dose inhalers (MDIs), including Ventolin[®], QVAR[®], Flixotide[®], Intal[®] Forte, and Tilade[®] were studied using a modified 13-stage electrical low pressure impactor (ELPI) with aerodynamic diameter cutoff ranging from 0.028 to 10.07 μm . All the stages are electrically insulated from each other with the last 12 stages connected individually to electrometers with sensitivity at femtoampere levels. Aerosol particles deposited on the impactor stages according to their aerodynamic diameters and their charges were measured by the electrometers. The deposited drug mass was assayed chemically using HPLC. The results show that particles of bipolar charge distribution were produced reproducibly from Intal[®] Forte, Tilade[®], and Flixotide[®]. In contrast, those from Ventolin[®] and QVAR[®] displayed charge variation, depending on the time lapse between actuations. This suggests that charge relaxation may influence the charging of these two MDIs. Mass distributions were reproducible for all MDIs except for Ventolin[®], the first puff from which was always the highest in dose. The different charge characteristics of the MDIs could be attributed to differences in the drug and formulation as well as valve materials. In general, submicron particles showed a larger variation in the charge-to-mass ratio (q/m). This indicated charge contribution by propellant/excipients (which produce submicron particles) rather than the drug itself. The calculated number of elementary charges per drug particle of size $\leq 6.06 \mu\text{m}$ ranged from zero to several ten thousands. The charge level is sufficiently high to have a potential effect on the deposition of the inhaled particles in the respiratory tract. In conclusion, the ELPI provided more detailed charge information about the MDI aerosol particles. Different aerosol charge profiles were shown by commercial MDIs, and the results can be explained by variation in the drug, formulation and the MDI materials. The results may have practical significance on lung deposition of MDI aerosols and regulatory aspects of generic aerosol products.

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Keywords: electrostatic charge; metered dose inhalers (MDIs); propellants; aerosol formulation; ELPI

INTRODUCTION

Since its first development in the mid-1950s,¹ metered dose inhaler (MDI) has been the most popular drug delivery device for the treatment

of respiratory diseases. MDIs are portable and relatively easy to operate by the patient for self-administration. Although the aerosol characteristics such as particle size and output of MDIs have been measured extensively over the years, the electrostatic properties of these particles are poorly studied. It is well known that electrostatic deposition is one of the five major mechanisms of aerosol deposition in the lungs.² Computer modeling and limited *in vivo* inhalation studies

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conducted on human subjects indicate that electrostatic charges may affect total and regional deposition in the lung.^{3–8}

Electrostatic charge distribution studies of MDIs were previously conducted using an aerosol electrometer apparatus that was built in-house.^{9–12} The instrument is essentially a two-stage impactor with a Faraday pail as the second stage for collecting fine particles ($<5\ \mu\text{m}^{10}$). The net charge on the fine particle mass was measured with an electrometer. The limitation of this setup is that while the net charge of the fine particles was measured the charges among different size fractions could not be discerned. Thus if an aerosol carries bipolar charges, the two polarities would be masked by each other as only the overall charge is detected. The drawback has been overcome with a modified setup of the electrical low pressure impactor (ELPI) described by Glover and Chan.¹³ The instrument is conventionally used for near real-time size measurements of airborne particles.^{14–17} The ELPI consists of a 13-stage impactor with a corona charger situated directly above the top stage. In its conventional operation, the corona charger is charged to +5 kV,¹⁸ and the resulting electric field imparts a known amount of charges to the particles introduced into the impactor by vacuum suction. All the impactor stages are electrically insulated from each other with the last 12 stages connected individually to 12 electrometers with sensitivity at femtoampere levels. The particles subsequently deposit onto the stages according to their aerodynamic sizes with their charges measured by the respective electrometers. Particle size distribution is then derived from the electric current measurements. Further details on the theoretical background and electronics of the ELPI were given by Keskinen et al.¹⁶ Instead of charges imparted by the corona charger, inherent charges on aerosol particles produced from MDIs

were measured in the present study. The corona charger was thus unnecessary and was removed since its presence may potentially cause artefact in the measurement due to contact charging of the particles. The deposited mass on each stage was assayed using HPLC. The electrometer reading from each stage represented the net charge (sum of both positive and negative charges) contributed by all particles collected on the individual stages. The ELPI provides a high resolution of size classification and can detect variation of net charge within the different particle size fractions.

The aim of the present study was to employ this novel technique to investigate charge profiles of aerosols generated from commonly used MDIs.

MATERIALS AND METHODS

Metered Dose Inhalers and Sampling Protocol

Five types of widely available MDIs were examined in the study, including Ventolin[®] (100 μg salbutamol sulphate; Allen & Hansburys, Australia), QVAR[®] (100 μg beclomethasone dipropionate, 3M Health Care, UK), Flixotide[®] (250 μg fluticasone propionate; Allen & Hansburys, Australia), Intal[®] Forte (5 mg sodium cromoglycate; Aventis Pharma, UK), and Tilade[®] (2 mg nedocromil sodium; Aventis Pharma, UK). All of these MDIs are hydrofluoroalkane (HFA) products. QVAR[®] is a solution MDI, whereas the other four are suspensions (Table 1). Three inhalers of each type were measured for measuring both charge and mass characteristics. All inhalers were used before the expiry date and were primed to waste by actuation according to the instructions specified on the consumer medicine information leaflets. After priming, five single puffs (#1–5) from each inhaler were individually determined for the

Table 1. MDI Formulations Evaluated²⁶

Inhaler	Drug (Dose/Actuation)	MDI Type	Propellant	Formulation Excipients	Valve Stem Material ^a
Ventolin [®]	Salbutamol sulphate (100 μg)	Suspension	HFA-134a	None	Plastic
Intal [®] Forte	Sodium cromoglycate (5 mg)	Suspension	HFA-227	Povidone, Macrogol 600,	Plastic
Tilade [®]	Nedocromil sodium (2 mg)	Suspension	HFA-227	Povidone, Macrogol 600, Menthol	Plastic
QVAR [®]	Beclomethasone dipropionate (100 μg)	Solution	HFA-134a	Ethanol	Metal
Flixotide [®]	Fluticasone propionate (250 μg)	Suspension	HFA-134a	None	Plastic

^aSpecific details are not available as they are proprietary information of the manufacturers.

charge and mass profiles. There was a lapse of an hour or longer between actuations to allow mass assay procedure to follow. These aerosol samples are referred to as 'discrete puffs.' The next ten puffs (#6–15) were actuated continuously (about 30 s apart) into the ELPI and their charge profiles measured sequentially. No mass was assayed for these ten puffs. The ELPI was cleaned and reassembled. Immediately after actuating the MDI twice to waste, a single puff (#18) was collected in the ELPI for charge and mass determinations. This puff is referred to as a 'continuous puff.'

Measurement of Electrostatic Charge

A modified ELPI (Dekati, Finland) was used in the electrostatic measurements. The corona charger was removed from the instrument so that innate charges on the particles could be measured. The performance of the ELPI was not found to be altered significantly by this modification.¹³ Aerosol samples were introduced via a USP throat. Tight-fitting adaptors flush with the MDI mouthpieces were used to ensure complete aerosol

sampling. The presence of the adaptors was not found to affect the electrostatic charge profile of the MDI aerosols. Ninety microlitres of a 1 g/15 mL solution of silicone fluid (200 Fluid/60000 cSt; Dow Corning, Australia) in cyclohexane (Ajax Finechem, Australia) was applied to each ELPI impactor stage to minimize particle bounce and re-entrainment during sampling. The cyclohexane was allowed to fully evaporate before the stages were assembled. A Sogevac[®] model SV25 vacuum pump (Leybold, France) provided air flow at 30 L/min through the ELPI. The electric currents induced on the impactor stages were measured and recorded by the ELPIVI 3.1 software from Dekati. The current range setting for charge measurement was 40,000 fA. The experimental setup is shown schematically in Figure 1.

Mass Quantification of Deposited Drug Particles

Throughout the study, the actuators and valve stems were not washed (hence the drug deposited on these parts not assayed) to avoid possible effects of cleaning on charge generation and to

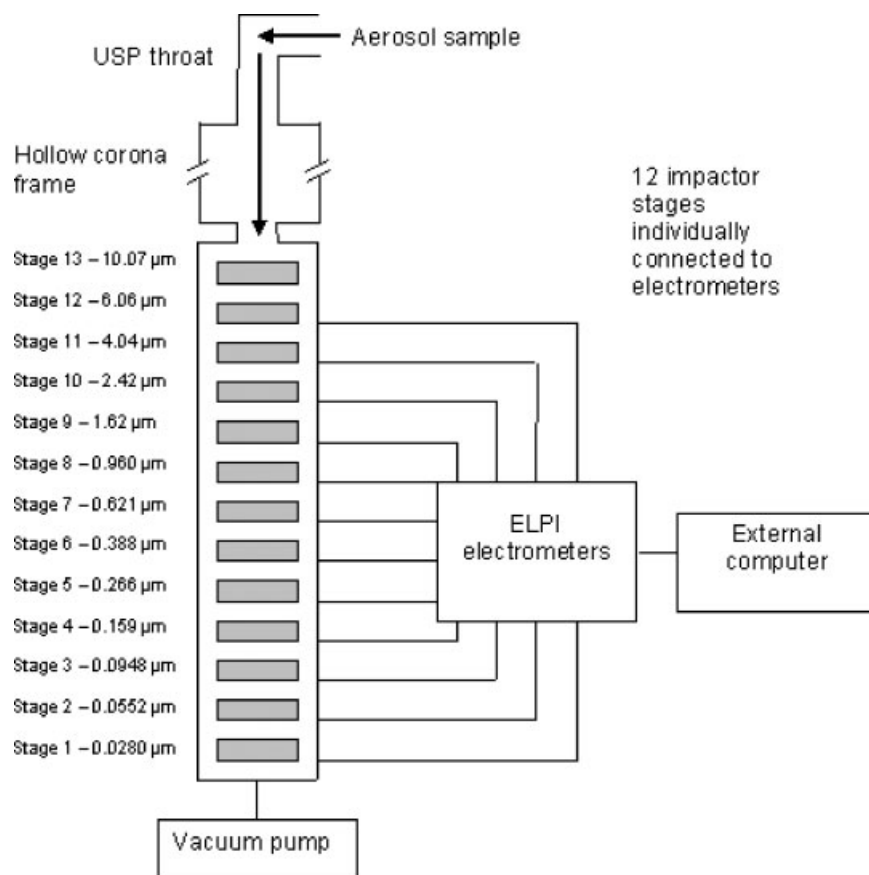


Figure 1. Schematic of the ELPI instrument setup. Diagram not drawn to scale.

partly resemble patient use. Drug particles deposited on the adaptor, USP throat, hollow corona frame, and ELPI stages were assayed chemically using high performance liquid chromatography (HPLC).

Sample Preparation for HPLC

Chromatographic conditions for the assays are summarized in Table 2. Fresh standard solutions were prepared to generate standard curves before each HPLC run.

Ventolin[®]

The adaptor, throat, and corona frame were each washed exhaustively with 5 mL of water. The impactor stages were sonicated for 10 min in beakers containing 5 mL of the mobile phase and 5 mL of cyclohexane, which was used to dissolve the silicon fluid to allow the extraction of the drug into the mobile phase. The liquid mixtures were centrifuged at 3080g for 15 min to separate the two phases. Samples were taken from the aqueous phase for assay.

Intal Forte[®] and Tilade[®]

The drug extraction method was similar to the one for Ventolin[®], except the water used was 10 mL instead of 5 mL.

QVAR[®] and Flixotide[®]

Drug extraction by sonication was carried out in 5 mL of the respective mobile phase (Table 2). For QVAR[®], 10 µg/mL triclosan was also present in the mobile phase as an internal standard. The samples were not centrifuged as no cyclohexane was used, hence no phase separation required.

Data Analysis

The charge on each impactor stage was derived from the electric current data by calculating the area under the curve in the current versus time plot for that particular stage. The net charge was calculated from the sum of charges on all stages. The fine particle dose charge was taken as the sum of charges on all particles of size ≤6.06 µm, corresponding to those on Stage 11 and below. Likewise, the ex-actuator dose was the total drug mass recovered without the actuator and the fine particle dose (FPD) was the sum of drug mass deposits on Stage 11 and below. The *specific*

Table 2. Chromatographic Conditions for the Chemical Assays

Inhaler	Mobile Phase ^a	Column ^b	Mobile Phase Flow Rate (mL/min)	UV Detection (nm)	Injection Volume (µL)	Limit of Quantitation (LOQ; µg/mL)	Accuracy at LOQ (%)	Concentration Range for Standards (µg/mL) ^c
Ventolin [®]	300 mL methanol 200 mL deionised water	C18	1.5	276	100	0.05	95–105	0.04–10 ($r^2 = 0.9996$)
Intal [®] Forte	0.5 g sodium lauryl sulphate 260 mL acetonitrile 140 mL phosphate buffer	Amino-propyl	2.0	320	20	0.5	97–103	0.06–500 ($r^2 = 0.9998$)
Tilade [®]	Same conditions as those for Intal [®] Forte					0.1	99–100	0.06–500 ($r^2 = 0.9994$)
QVAR [®]	350 mL methanol 150 mL deionised water	C18	1.0	240	100	0.1	98–112	0.02–20 ($r^2 = 0.9996$)
Flixotide [®]	250 mL methanol 190 mL deionised water 50 mL acetonitrile 8.5 mL acetic acid	C18	1.0	242	50	1	104–105	0.02–200 ($r^2 = 0.9992$)

^aAll mobile phases were filtered through a 0.45 µm filter by vacuum prior to the HPLC runs.

^bColumn temperature was 30°C.

^cStandard curves for all HPLC runs were linear in the concentration range measured. Coefficients of determination are in parentheses. Precision for all assays were <1% relative standard deviation between 10 and 50 µg/mL.

charge, or charge-to-mass ratio (q/m), for a given size fraction was calculated by dividing the charge by the mass in that size fraction. The number of elementary charges (n) per drug particle in a particular size fraction was estimated by the following equation:

$$n = \frac{C\rho V}{e} \quad (1)$$

where C is the specific charge, ρ the true density of the particles, V the volume of a particle, and e the elementary charge (1.602×10^{-19} C). The particles were assumed to be spherical and have an average true density of 1.5 g/cm^3 . For a given ELPI stage, V was calculated from the cutoff diameter.

Faraday Pail Charge Measurement for Ventolin® MDIs

The Faraday pail method was also employed to measure the net charge of the Ventolin® aerosol for comparison (see later Discussion). Single puffs were discharged through an USP throat into the inner well of a Faraday pail (Model 284/22B, Monroe Electronics, Lyndonville, NY) connected to a NanoCoulomb Meter (Model 284, Monroe Electronics). The net charge of particles that exited the throat was thus measured. Six puffs

from each of the three Ventolin® inhalers were sampled.

RESULTS AND DISCUSSION

The charge profiles of aerosols show substantial differences among the five types of inhalers (Figures 2–4). Bipolar charges were produced from Intal® Forte, Tilade®, and Flixotide®, irrespective of discrete or continuous puffs. Ventolin® produced bipolar charges in the discrete puffs, but the continuous puffs were unipolar negative (Figure 3). However, after lapsing for an hour or longer the Ventolin® inhalers produced bipolar aerosols again. In contrast, discrete puffs from QVAR® were unipolar positive while continuous puffs were only very lightly charged. Thus, aerosols produced from the MDIs carry charge and the charge is MDI-dependent. The charge levels measured for the various particle size fractions may depend on: (i) the level of innate charges on the particles and/or (ii) the amount of charged particles in a specific size fraction. The mass of deposited drug measured by HPLC will help to differentiate these two factors (see later Discussion). The charge profile and net charge produced per actuation was reproducible for Intal® Forte, Tilade®, and Flixotide® (Figure 2 and Table 3), while those from QVAR® showed a large

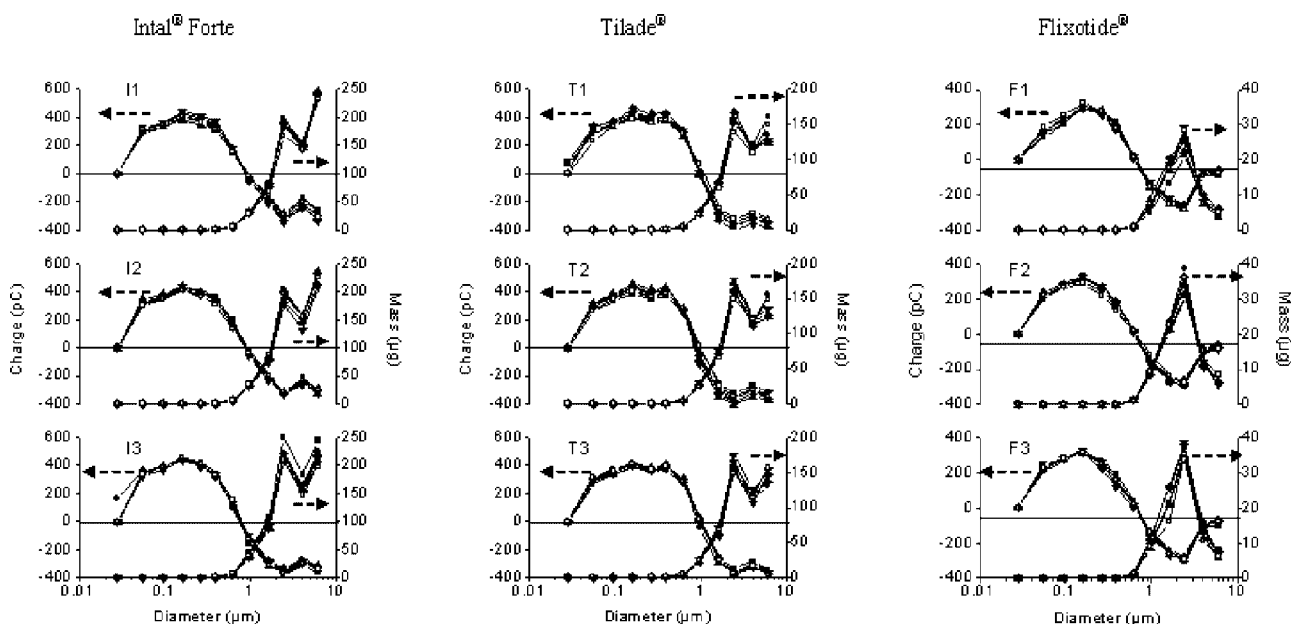


Figure 2. Charge and mass profiles of Intal® Forte (I1–I3), Tilade® (T1–T3), and Flixotide® (F1–F3) inhalers. Actuations #1 to #5, and #18 are shown for each MDI (■ #1, ● #2, ▲ #3, ▼ #4, ◇ #5, □ #18).

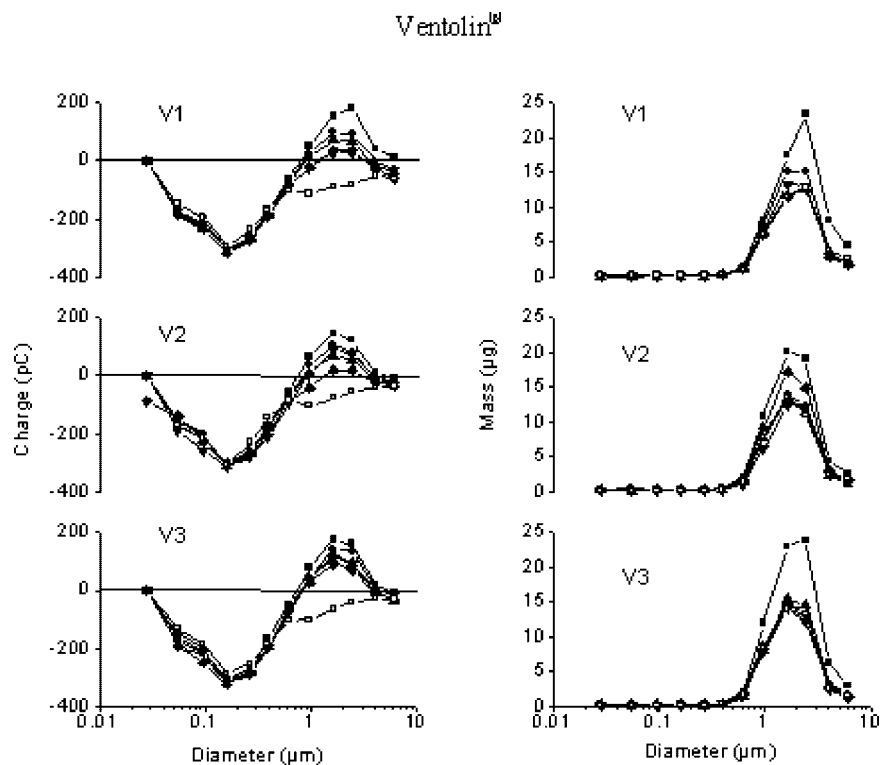


Figure 3. Charge and mass profiles of Ventolin[®] (V1–V3) inhalers. Actuations #1 to #5, and #18 are shown for each MDI (■#1, ●#2, ▲#3, ▼#4, ◇#5, □#18).

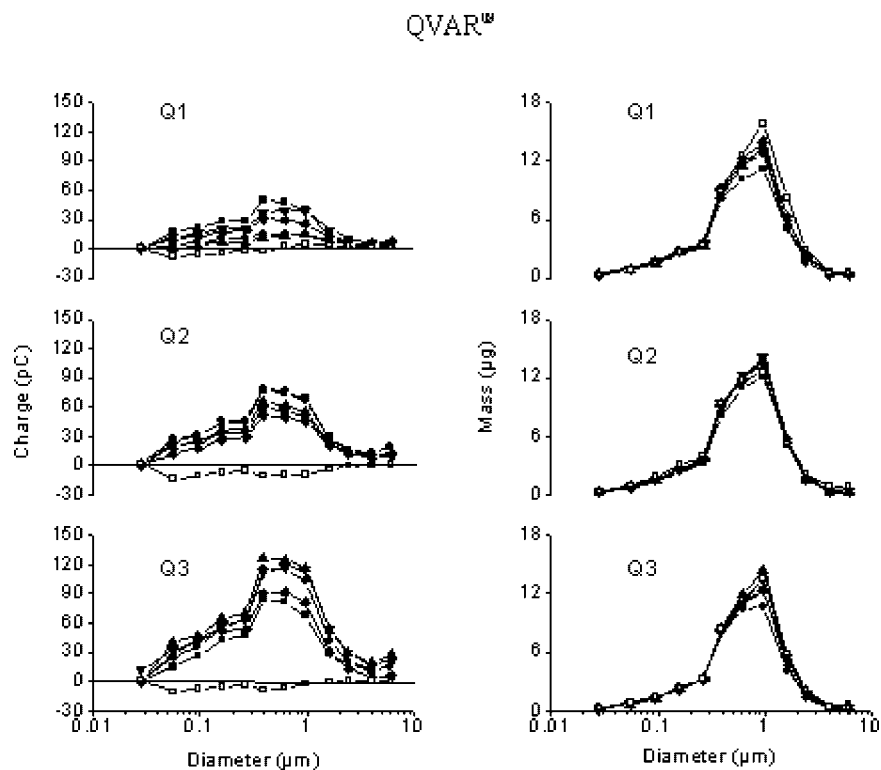


Figure 4. Charge and mass profiles of QVAR[®] (Q1–Q3) inhalers. Actuations #1 to #5, and #18 are shown for each MDI (■#1, ●#2, ▲#3, ▼#4, ◇#5, □#18).

Table 3. Mean Ex-Actuator and Fine Particle Doses; Mean Net and Fine Particle Dose Charges ($n = 18$)^a

Inaler	Ex-Actuator Dose (μg)	Fine Particle Dose (μg)	Net Charge (nC)	Fine Particle Dose Charge (nC)
Ventolin [®]	97.22 (18.70)	43.13 (9.38)	-1.13 (0.23)	-1.10 (0.22)
Intal [®] Forte	4332.62 (161.86)	480.25 (42.53)	+0.80 (0.13)	+1.12 (0.12)
Tilade [®]	1844.18 (112.61)	373.22 (19.40)	+0.79 (0.07)	+1.15 (0.08)
QVAR [®]	74.26 (13.94)	49.60 (3.21)	+0.30 (0.24)	+0.29 (0.23)
Flixotide [®]	198.47 (19.98)	72.74 (11.62)	+0.38 (0.03)	+0.45 (0.03)

^aSix actuations from each of 3 MDIs. Standard deviations are in parentheses.

inter- and intra-inhaler variation (Figure 4 and Table 3). Although the charge profile obtained over six actuations from three QVAR[®] inhalers were similar in trend they differed in magnitude over the entire particle size range. However, the size distributions showed little change (Figure 4). Ventolin[®] displayed some mass and charge variation (Figure 3). Most noticeably are: (i) the first puff being always the highest in dose, and (ii) the continuous puffs being negatively charged in the size range 0.960–4.04 μm as opposed to the positive charge of the discrete puffs. Since the mass distributions of the continuous and discrete puffs were similar, the variations in their charge profiles were not due to dose non-uniformity, but other MDI aspects. Flixotide[®], Ventolin[®], and QVAR[®] use 1,1,1,2-tetrafluoroethane (HFA-134a or norflurane) as the propellant but QVAR[®] also contains ethanol (Table 1). In addition, QVAR[®] is the only MDI used in this study that has a metal valve stem, while all the others have plastic ones. These differences are most likely the source of variation in QVAR[®] as ethanol may interact with the rest of the formulation system, including the valve stem material. Furthermore, water ingress into MDI formulation is well documented.¹⁹ It is likely that water may also be present as an impurity in the formulation and affect the charging.⁹ The results also indicate that it is the propellant–drug combination rather than the propellant itself that determines the charge in the aerosol, since both Flixotide[®] and Ventolin[®] contain norflurane without excipients, yet the former produces bipolar charges reproducibly and the latter bipolar or unipolar negative charges (depending on discrete or continuous puffs). The puff-dependent charging of Ventolin[®] indicates that charge relaxation may influence the charging of salbutamol sulphate from this formulation. Upon actuation, as electrostatic charges are produced on the emitted particles, counter-charges must reside in the actuator, valve components, and/or drug deposits

in these locations. These residual charges take time to decay and their presence may affect charging of the particles in the subsequent actuation. A similar mechanism may apply to QVAR[®] between the discrete or continuous puffs. The lack of this effect in Intal[®] Forte, Tilade[®], and Flixotide[®] suggests different electrostatic characteristics of these drugs and formulations. Future investigation is necessary to understand these charging mechanisms.

The charge profiles of Intal[®] Forte, Tilade[®], and Flixotide[®] share a similar trend, with positive charges measured below 0.6 μm and negative charges above that size (Figure 2). The charge polarity of Intal[®] Forte and Tilade[®] changes over between Stages 8 and 9, corresponding to particle cutoff diameters of 0.960 and 1.62 μm , respectively. The FPDs of Intal[®] Forte (480 μg) and Tilade[®] (373 μg) are comparable which can account for their similar fine particle dose charges (Table 3). However, a difference in the FPD did not yield a proportional difference in the fine particle dose charge for the other three MDIs. Any dose dependency of charging between different types of MDIs should be apparent from the specific charges (charge-to-mass ratios). The specific charges and estimated number of elementary charges per particle in the upper size fractions of Intal[®] Forte and Tilade[®] were comparable, but differed for the other MDIs (Tables 4 and 5). This suggests that the similar charging of Intal Forte[®] and Tilade[®] aerosols is due to their similar formulations. Both MDIs contain povidone, and macrogol 600 in the propellant 1,1,1,2,3,3,3-heptafluoropropane (HFA-227) (Table 1). These results support earlier reports that the charge of an MDI aerosol may be controlled by its formulation.^{11,12}

The average FPDs obtained from Ventolin[®] and Tilade[®] (Table 3) agreed with those reported in other studies.^{21,22} There are no data in the literature on HFA Flixotide[®] and QVAR[®] for direct comparison with the present results. However, the

Table 4. Mean Specific Charges of the MDIs (μC/g) (n = 15 Unless Otherwise Noted)^a

Stage	1	2	3	4	5	6	7	8	9	10	11	12
Size (μm)	0.0280	0.0552	0.0948	0.159	0.266	0.388	0.621	0.960	1.62	2.42	4.04	6.06
Ventolin [®]	-30.39 ^b (105.45)	-1454.42 ^b (931.04)	-1675.81 (707.77)	-2775.76 (1819.23)	-2489.88 (1710.98)	-713.77 (265.67)	-53.87 (19.71)	+2.48 (3.90)	+6.33 (2.46)	+5.68 (2.17)	-2.53 (4.67)	-16.25 (10.13)
Intal [®] Forte	+174.31 ^c (513.93)	+4389.60 ^c (6406.17)	+3581.58 ^c (4773.74)	+1843.72 ^c (479.38)	+5053.33 ^c (7742.24)	+697.41 (460.07)	+28.31 (7.47)	-2.00 (1.11)	-2.73 (0.42)	-1.65 (0.13)	-1.61 (0.23)	-1.40 (0.16)
Tilade [®]	+4004.58 ^c (13856.24)	+33313.76 ^c (109991.13)	+11559.19 ^c (21075.90)	+8998.53 ^b (11681.46)	+7105.29 ^c (7208.67)	+575.87 (143.59)	+67.88 (9.06)	-0.61 (1.61)	-4.37 (0.34)	-2.28 (0.15)	-2.71 (0.23)	-2.57 (0.32)
QVAR [®]	+4.12 (15.70)	+25.41 (15.52)	+18.1 (10.38)	+14.73 (7.98)	+11.44 (6.03)	+7.90 (4.45)	+5.81 (3.22)	+4.71 (2.66)	+4.88 (2.84)	+8.38 (4.77)	+28.56 (19.12)	+40.82 (31.47)
Flixotide [®]	N/A ^e	N/A	N/A	N/A	N/A	N/A	+14.43 (10.19)	-18.19 (3.46)	-12.27 (1.91)	-8.96 (1.67)	-8.40 (1.41)	-12.51 (2.98)

^aFive discrete actuations from each of the three MDIs. Standard deviations are in parentheses.

^bn = 14 due to negligible mass detected on certain runs.

^cn = 12 due to negligible mass detected on certain runs.

^dn = 9 due to negligible mass detected on certain runs.

^en = 8 due to negligible mass detected on certain runs.

^fn = 7 due to negligible mass detected on certain runs.

^gN/A—no estimation was conducted due to negligible mass.

Table 5. Estimated Number of Elementary Charges Per Drug Particle for the MDIs Calculated by Equation 1 (n = 15 Unless Otherwise Noted)^a

Stage	1	2	3	4	5	6	7	8	9	10	11	12
Size (μm)	0.0280	0.0552	0.0948	0.159	0.266	0.388	0.621	0.960	1.62	2.42	4.04	6.06
Ventolin [®]	0 ^b (0)	-1 ^b (1)	-7 (3)	-55 (26)	-230 (158)	-204 (76)	-63 (23)	+11 (17)	+132 (51)	+395 (151)	-818 (1509)	-17730 (11052)
Intal [®] Forte	0 ^d (0)	+4 ^e (5)	+15 ^f (20)	+36 ^f (9)	+466 ^d (714)	+200 (132)	+33 (9)	-9 (5)	-57 (9)	-115 (9)	-520 (76)	-1524 (170)
Tilade [®]	0 ^c (1)	+27 ^b (91)	+48 ^c (88)	+177 ^b (230)	+656 ^c (665)	+165 (41)	+80 (11)	-3 (7)	-91 (7)	-158 (10)	-875 (76)	-2802 (348)
QVAR [®]	0 (0)	0 (0)	0 (0)	0 (0)	+1 (1)	+2 (1)	+7 (4)	+20 (12)	+102 (59)	+582 (332)	+8233 (6182)	+44535 (34338)
Flixotide [®]	N/A ^e	N/A	N/A	N/A	N/A	N/A	+17 (12)	-79 (15)	-256 (40)	-623 (116)	-2714 (454)	-13646 (3246)

^aFive discrete actuations from each of the three MDIs. Standard deviations are in parentheses. Calculations based on an average true density of 1.5 g/cm³, pharmaceutical powders generally have true densities between 1.0 and 2.0 g/cm³.³²

^bn = 14 due to negligible mass detected on certain runs.

^cn = 12 due to negligible mass detected on certain runs.

^dn = 9 due to negligible mass detected on certain runs.

^en = 8 due to negligible mass detected on certain runs.

^fn = 7 due to negligible mass detected on certain runs.

^gN/A—no estimation was conducted due to negligible mass.

fine particle fractions from HFA Flixotide[®] inhalers in the present study were consistent with those from chlorofluorocarbon (CFC) Flixotide[®] inhalers,²³ both of which are suspension formulations. The same applied to those from QVAR[®] 100 µg MDIs in the present study and QVAR[®] 50 µg MDIs used by Leach et al.²⁴ The results of mass measurements in the present study show a large proportion of drugs deposited in the inhaler mouthpiece and USP throat. The mass profiles of Intal[®] Forte, Tilade[®], Flixotide[®], and Ventolin[®] show similar trends, with progressively less drugs deposited down successive ELPI stages and negligible amounts past Stage 7, corresponding to a cutoff diameter of 0.621 µm (Figures 2 and 3). This is consistent with the fact that micronised particles used in suspension-type MDIs generally range from 1 to 5 µm.²⁵ However, the QVAR[®] mass profile shows more particles in the lower size fractions, which is due to QVAR[®] being a solution formulation.^{24,26} A comparison of the charge and mass profiles of Intal[®] Forte, Tilade[®], and Flixotide[®] shows that while an increased level of charge (+ve or -ve polarity) follows a higher amount of deposited drug, an increased charge is also found in the lower stages where only very little drug was detected (Figures 2 and 3). These MDIs show high levels of positive charges measured without much drug particles below 0.6 µm, and negative charges were detected for drug particles above 1.0 µm. In contrast, Ventolin[®] reveals significant negative charges below 0.6 µm, and the charge level is diminishing above 0.6 µm where more drug particles are present. This has led to a very high specific charge, i.e., charge to mass ratio, in the submicron size fractions (Table 4). There may be two possible explanations. First, this may be due to the increased specific surface area (surface area per unit mass) of the submicron particles. Since the mechanical charging, or triboelectrification, of powders is due to contact and friction with solid surfaces,²⁷ an increase in the specific surface area of the solids would increase the extent of charging, and hence the higher specific charges. However, since the absolute amount of drug measured was little, the total surface area and thus the charge level would also be low. Second, as discussed above, the high charges measured on the lower stages may be mainly contributed by propellant/excipients (and water as an impurity), rather than the drug itself. Thus the charge to mass ratios derived for the submicron fractions may be confounded by the excipient charge and may not truly reflect the specific charges of the

drug particles, which may also contribute to the large errors in the values (Table 4). It is well known that for the suspension-type formulations the smaller droplets may not contain any solid drug particles²⁸. Thus the droplets that deposit on the lower stages may contain only excipients contributing to the charge measured. The contribution of excipients to the charge of MDI aerosols had been alluded to by Glover and Chan (2004) and earlier by Peart et al.¹¹ on reformulated MDIs. The small droplets may also be produced from the evaporation and/or bursting of larger droplets. Charges are known to remain on a droplet during evaporation, hence the repulsive forces between the charges increase as the droplet size decreases.²⁹ The droplet explodes to generate smaller charged droplets when a critical size is reached at which the repulsive electrostatic forces overcome the surface tension of the droplet.³⁰ Evaporation and bursting may continue to occur on the daughter droplets. For suspension MDIs, droplets originally containing drug particles may burst asymmetrically to yield droplets with and without particles. For those containing drug particles, charges from the propellant remain on the particles after evaporation. Thus the resultant charges on these particles are net charges contributed by both the excipients and the drug. On the other hand, the empty droplets would only carry charges from the excipients. This may account for the different charging between the upper and lower size fractions of the aerosols.

Unlike the four suspension-type inhalers, QVAR[®] shows a different trend with charge following the mass closely (Figure 4). QVAR[®] is a solution MDI containing ethanol and norflurane, both being volatile. Droplets actuated from the inhaler would contain the dissolved drug, with an amount directly proportional to the size of the droplet. Also, the mass ratio of drug to excipients is constant for droplets of all sizes, including those undergoing or produced from evaporation and explosion. Thus the charge contribution by the excipients is likely to follow the drug mass according to the droplet size, resulting in the resemblance in the trend of the charge and mass profiles.

The specific charge of the size fractions containing a significant drug mass shows a value between -60 and +70 µC/g, mostly in the range of -30 to +30 µC/g (Table 4). Besides the physicochemical properties of the drug and formulation, interactions of the drug and formulation with materials composing the metering valve and stem of the inhaler may be responsible for the charging, as had

been investigated by Peart et al.¹² on reformulated MDIs. Since charging of particles originates from their interactions with surfaces, the valve stem being the exit of MDI aerosols would be the site of significant charging of particles as they are blasted out of the canister with the propellant. Hence the material and design of valve components may play a crucial role.

In the present study, the number of elementary charges per drug particle was estimated from the specific charge (Table 5). For all of the MDIs, larger drug particles carry more charge, presumably due to more surface area per particle for charging through triboelectrification and other physico-chemical interactions. It is worthy to note that based on computer simulation results by Bailey et al.,⁸ these magnitudes of charge on the particles are high enough to affect particle deposition in the airways. Thus, the electrostatic properties of the aerosol may need to be examined in addition to other quality control routines (such as dose output and particle size) for MDIs. The findings may also have regulatory implications for generic aerosol products. For example, aerosols produced from MDI generic products using formulation and/or components non-identical to the innovator product may have different charge profiles. Since aerosol particles from MDIs carrying high enough charges may affect deposition in the airways, different charges from generic products may potentially generate different lung deposition patterns. Clinical studies involving both therapeutic effect and lung deposition are necessary to fully address the potential effects of aerosol charge.

The fine particle dose charge of the HFA formulation of Ventolin[®] measured earlier by Peart et al.¹⁰ was -230 pC compared with -1.10 nC from the present study (Table 3). The difference in the definitions of the fine particle fraction (5 vs. $6.06\text{ }\mu\text{m}$) does not account for this fivefold difference. This prompted the charge measurements of Ventolin[®] aerosols using the USP throat/Faraday pail setup. The charge results obtained from this procedure (mean $\pm$ standard deviation; $n = 6$) were -2.57 ± 0.31 , -2.99 ± 0.26 , -2.55 ± 0.70 nC for inhalers V1, V2, and V3, respectively. (The higher magnitude of these results is partly because ELPI does not measure the large particles deposited in the corona frame and stage 13 but the Faraday pail measurements include these particles.) Hence, the ELPI and Faraday pail results from the present study are comparable, both being consistently higher than the earlier value by Peart et al. The difference in instrumental design

may account for the discrepancy between results from the present study and those by Peart et al.¹⁰. The aerosol electrometer apparatus³¹ is simpler in design, more akin to a two-stage impactor with an electrometer connected to a Faraday pail that serves as the fine particle stage. In contrast, the ELPI has a more intricate design with sensitive electrometers connected to each impactor stage. Furthermore, the aerodynamic environments within the two instruments may vary and not be completely congruent. In those studies^{11,12} only the net charge of the fine aerosol particle dose was measured. Thus, the charge profiles derived did not show specific charges on the particles within the various size fractions. More detailed profiles are desirable since charges of opposite polarities as functions of particle size may mask each other and detailed information on the specific charge versus the aerodynamic diameter cannot be discerned from an impactor with a low size resolution. This shortfall is overcome with ELPI, which provides more details illustrating relationships between the size and charge of aerosol particles.

In conclusion, the electrostatic characteristics of aerosols produced from a number of commercial MDIs were successfully examined using a modified ELPI. The aerosol charge profile was found to be MDI-dependent. The results are ascribable to differences in the drug, formulation and the valve stem material of the MDI. The calculated number of elementary charges per particle of size $\leq 6.06\text{ }\mu\text{m}$ ranged from zero to several ten thousands. The high charge levels on particles may have a potential effect on the deposition of the aerosol particles in the lung when inhaled.

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Effect of spacers on the electrostatic charge properties of metered dose inhaler aerosols

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Abstract

The electrostatic charge properties of commercial metered dose inhaler (MDI) aerosols, including Ventolin[®], Flixotide[®], Tilade[®] and QVAR[®], sampled through new and detergent-coated AeroChamber[®] Plus spacers were studied using a modified 13-stage electrical low pressure impactor (ELPI) with aerodynamic cutoff diameters ranging from 0.028 to 10.07 μm . Aerosol particles deposited on the impactor stages according to their aerodynamic diameters and their charges were simultaneously measured by the electrometers. The deposited drug mass was assayed chemically using HPLC. The surface potential on the inner spacer wall was measured with an electrostatic probe before and after aerosol actuation. High surface potentials were found on the new spacers whereas the detergent-coated spacers had minimal charges due to the conductive coating. MDI aerosol charges were decreased when spacers were used but the charge profiles of the aerosols were not altered qualitatively. New spacers had the lowest throat deposition, fine particle dose, and net aerosol and fine particle charges as a result of high spacer retention. These trends were partially reversed by the detergent-coated spacers. In general, the charge per mass of drug (charge-to-mass ratio) for particles from detergent-coated spacers was higher than those from new spacers. This was thought to be due to the reduction of electrostatic deposition inside the spacer thus leading to particles carrying higher charges being sampled. The calculated number of elementary charges per drug particle ranged from zero to several hundred, which is sufficiently high to potentially affect lung deposition. The ELPI provided high resolution charge profiles on MDI aerosols delivered through spacers.

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1. Introduction

Spacer devices are used with metered dose inhalers (MDIs) to overcome problems in coordinating inhalation with actuation, especially in children, and reduce throat deposition of drug particles (Newman, 2004). These devices may be broadly classified into three groups according to their design, namely, tube spacers, holding chambers, and reverse-flow devices (Newman, 2004). The general term ‘spacers’ is used to describe these devices collectively in this paper. A spacer serves as a reservoir to hold the aerosol cloud for the patient to inhale through a one-way valve at a natural pace. It also provides a chamber in which MDI droplets may decelerate and evaporate to a smaller size before inhalation to reduce throat deposition and enhance penetration into the lungs (Barry & O’Callaghan, 1996).

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Most spacers are constructed with lightweight plastic materials for portability and durability. Plastics are electrical insulators, thus electrostatic charges may be generated and accumulated on spacer surfaces through contact and friction, or triboelectrification (Hendricks, 1973), during handling. Many studies have shown that spacer charges adversely affect drug output and consequently lung deposition due to particle retention inside the spacer (Barry & O'Callaghan, 1994, 1995; Dewsbury, Kenyon, & Newman, 1996; Piérart, Wildhaber, Vrancken, Devadason, & Le Souëf, 1999; Wildhaber, Devadason, Eber, Hayden, Everard, Summers et al., 1996). Conversely, a reduction in spacer surface charges counteracts this effect. This suggests that spacer drug retention is due to electrostatic particle deposition on the internal walls. Methods of varying degrees of effectiveness have been reported for the reduction or elimination of surface charges on plastic spacers (Barry & O'Callaghan, 1995; Kenyon, Thorsson, Borgstrom, & Newman, 1998; O'Callaghan, 1997; O'Callaghan, Lynch, Cant, & Robertson, 1993; Wildhaber, Devadason, Eber, Hayden, Everard, Summers et al., 1996; Wildhaber, Devadason, Hayden, James, Dufty, Fox, et al., 1996). The most popular method for charge reduction is coating the spacers with dilute surfactant solutions (Piérart et al., 1999; Wildhaber, Devadason, Hayden, James, Dufty, Fox, et al., 1996). Ionic surfactants were found to perform better than nonionic ones (Wildhaber, Devadason, Hayden, James, Dufty, Fox, et al., 1996). This supports the hypothesis that a conductive surfactant coating on the spacer surface is effective in dissipating charges (Kenyon et al., 1998). The optimal treatment was to immerse the spacer in a detergent solution followed by drip-drying without rinsing with water (Piérart et al., 1999). The use of commercial detergents is simple, economical, and relevant to patient use in the community setting, and thus this procedure was adopted in the present study.

Particles emitted from MDIs are known to be charged (Kwok, Glover, & Chan, 2005; Peart, Kulphaisal, & Orban, 2003). Electrostatic interactions between charges on these particles and those on spacer surfaces may contribute to spacer deposition (Dewsbury et al., 1996; O'Callaghan et al., 1993; Piérart et al., 1999; Wildhaber, Devadason, Eber, Hayden, Everard, Summers et al., 1996; Wildhaber, Devadason, Hayden, James, Dufty, Fox, et al., 1996). However, the electrostatic properties of MDI aerosols delivered via spacers have not been studied hitherto. An aerosol electrometer apparatus has been used by Peart et al. (Kulphaisal, Peart, & Byron, 2002; Peart et al., 2003; Peart, Magyar, & Byron, 1998; Peart et al., 2002) to measure charges sampled directly from MDIs. It is essentially a two-stage impactor with a Faraday pail as the second stage for collecting and measuring the net charge on fine particles $< 5 \mu\text{m}$ (Peart et al., 2003). The limitation of this setup is that the charges and polarities among different size fractions could not be discerned as only one net charge was measured. Recently, a modified setup of the electrical low pressure impactor (ELPI) was used by Glover and Chan (2004) and Kwok et al. (2005) that provided more detailed charge and mass profiles on MDI aerosols. Discussion on the general instrumental setup and data treatment may be found in the above references. Although many studies had been conducted on the effect of spacer charges on MDI aerosol drug output by cascade impaction (Barry & O'Callaghan, 1995; O'Callaghan et al., 1993; Piérart et al., 1999; Wildhaber, Devadason, Eber, Hayden, Everard, Summers et al., 1996; Wildhaber, Devadason, Hayden, James, Dufty, Fox, et al., 1996), only the mass profiles were measured. The aerosol charge profiles were a major aspect missing from these studies because charge data cannot be obtained using conventional impactors. The ELPI overcomes this drawback and was employed in the present study to acquire a more complete understanding of the effects of spacers on aerosol charges.

The aim of the present study was to employ the modified ELPI to investigate charge and mass profiles of aerosols from commercial MDIs sampled through new and detergent-coated plastic spacers. This paper focuses on the AeroChamber[®] Plus spacer because it has a soft adaptor universal for the MDIs to provide a common sampling system.

2. Materials and methods

2.1. Metered dose inhalers, spacers, and sampling protocol

The four types of MDIs examined in the study were Ventolin[®] (100 μg salbutamol sulphate; Allen & Hanburys, Australia), Flixotide[®] (250 μg fluticasone propionate; Allen & Hanburys, Australia), Tilade[®] (2 mg nedocromil sodium; Aventis Pharma, UK), and QVAR[®] (100 μg beclomethasone dipropionate, 3M Health Care, UK). All are hydrofluoroalkane (HFA) products, with QVAR[®] being a solution formulation and the other three being suspensions. Nine new inhalers of each type were used before expiry, three without a spacer, three with new spacers and three with detergent-coated spacers. All MDIs were primed to waste prior to use according to the consumer medicine information leaflets.

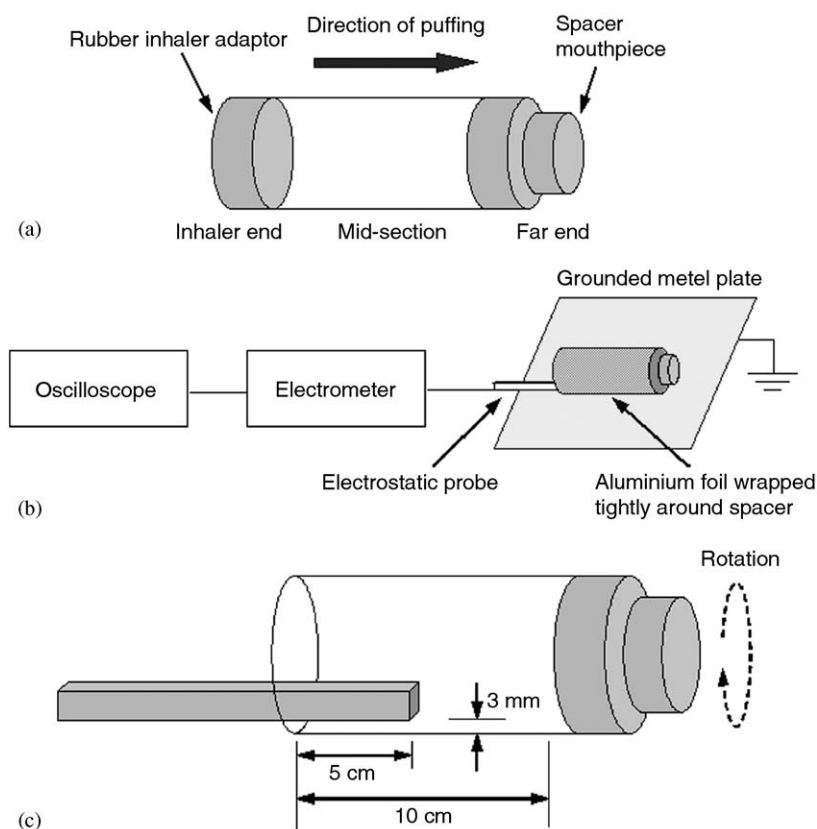


Fig. 1. (a) Nomenclature of the spacer parts. (b) Schematic of the spacer surface potential measurement setup. (c) Probe-to-surface distances inside the spacer. Diagrams not drawn to scale.

In the case of MDIs without spacer coupling, three single puffs from each inhaler after priming were individually sampled for the charge and mass profiles, whereas only the first puff after priming was sampled in the spacer experiments.

New AeroChamber[®] Plus Valved Holding Chambers with Mouthpiece (Trudell Medical International, Canada) were used as new spacers upon removal from their packaging. After the first aerosol sampling and drug assay, these spacers were thoroughly cleaned and coated with detergent by soaking in a 1:5000 aqueous solution of Palmolive[®] (Colgate-Palmolive, Australia) for 5 min, followed by drip-drying under room conditions for 12–24 h.

2.2. Measurement of spacer wall surface potential

The surface potential on the internal spacer wall was measured with a side-view probe (Model 1017AS, Monroe Electronics, USA) connected to an Isoprobe[®] electrostatic voltmeter (Model 244A, Monroe Electronics, USA). The voltmeter was zeroed and the probe-to-surface spacing insensitivity was adjusted as specified in the manual. All new spacers were kept in the original packaging until the measurement. Charges were measured on all spacers immediately before and after aerosol sampling. The rubber inhaler adaptor (Fig. 1a) was removed from the spacer before measurement to allow close positioning of the electrostatic probe to the internal wall. A sheet of aluminium foil was wrapped tightly around the external surface and placed onto a grounded metal plate (Fig. 1b). The aluminium wrapping that contacted the metal plate was thus also grounded. The detection aperture of the probe was positioned inside the spacer, approximately 5 cm from the inhaler end and 3 mm above the internal surface (Fig. 1c). This is the mid-section of the spacer. The spacer was rotated about its longitudinal axis for one revolution. The surface potential along the inner circumference was measured by the electrometer and recorded by an oscilloscope (Model 54621A, Agilent Technologies, USA). The measurement was repeated at another position 10 cm from the inhaler end (Fig. 1c). This is in the far end of the spacer

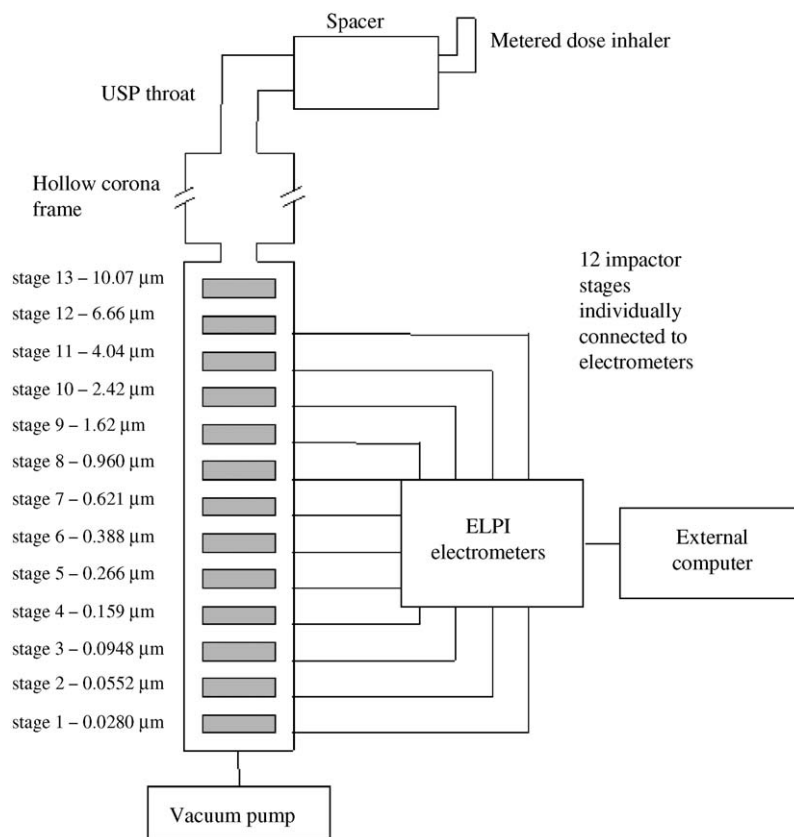


Fig. 2. Schematic of the ELPI setup the MDI/spacer measurement. For the MDI-alone experiments the inhaler was connected directly to the throat. Diagram not drawn to scale.

close to the mouthpiece. The same procedure was applied to the detergent-coated spacers. The surface potential at the inhaler end was not measured because the action of removing the rubber adaptor from the spacer would generate surface charges and thus confound the readings in this region. The adaptor was replaced onto the spacer after each surface potential measurement and before aerosol sampling.

2.3. Measurement of aerosol electrostatic charge

A modified ELPI (Dekati, Finland) with the corona charger removed and a USP throat attached was used to measure the inherent aerosol charges (Glover & Chan, 2004). Tight-fitting adaptors for the MDI and spacer mouthpieces were employed for complete aerosol sampling. Particle bounce and re-entrainment were minimised by the application of 90 μL of a 1 g/15 mL solution of silicone fluid (200 Fluid/60,000 cSt; Dow Corning, Australia) in cyclohexane (Mallinckrodt, USA). The solvent was allowed to evaporate before the assembly of the impactor stages. The air flow through the ELPI was 30 L/min, generated with a Sogevac[®] model SV25 vacuum pump (Leybold, France). The aerosol charges were measured and recorded using the Dekati ELPIVI 4.0 software with the current range set at 400,000 fA. The experimental setup is shown in Fig. 2.

All MDIs were shaken by hand for a few seconds before aerosol sampling. In the experiments without spacers, the vacuum pump was switched on to establish the air flow and the electric current signals zeroed before inhaler actuation into the ELPI. In the spacer experiments, the spacer was first connected to the USP throat with the vacuum pump switched off. The air flow was then started immediately after MDI actuation into the spacer. This was done to ensure that tight connection and alignment of the spacer to the throat was in place. The difference in the experimental protocols was found to have no effect on the drug mass recovered for the MDI aerosols. This is because a steady flow (which takes

400 ms) is already established before the aerosol entered the impactor stages (which takes > 900 ms). It was observed that the background electrical signals were always temporarily disturbed upon the commencement and termination of air flow through the impactor. These disturbances were low in magnitude relative to the sample signals and lasted only for a few seconds, after which a stable zero baseline was obtained. Before each spacer experiment the vacuum pump was switched on and off three times to generate the blank signals, the mean of which was calculated and subtracted from the aerosol measurements to account for these noises.

2.4. Mass assays of drug deposits

The drug deposits on the MDI actuators and valve stems were not assayed since the priming shot(s) also contributed to the deposits in these components. Furthermore, this allows the comparison of mass recoveries obtained with those from a previous study using similar assaying procedures (Kwok et al., 2005). Deposits inside the spacer, on the adaptor, USP throat, hollow corona frame, and ELPI stages were quantified chemically using high performance liquid chromatography (HPLC).

2.5. Sample preparation for HPLC

The drug extraction methods and chromatographic conditions were identical to those used previously (Kwok et al., 2005) except that in the present study no internal standard was used in the QVAR[®] assays and 5 mL of a 20:80 v/v water in methanol mixture was used for drug extraction in the QVAR[®] and Flixotide[®] assays.

2.6. Data analysis

The charge on each impactor stage was derived from the electric current data by calculating the area under the curve in the current versus time plot for that particular stage. The *net charge* was calculated from the sum of charges on all stages. The *fine particle dose charge* was taken as the sum of charges on all particles of size $\leq 6.66 \mu\text{m}$, corresponding to those on Stage 11 and below. Likewise the *fine particle dose (FPD)* was the sum of the drug mass deposits on Stage 11 and below. The *ex-actuator dose* is the total drug mass recovered from all the components assayed. The *spacer* and *throat deposits* are the masses of drug deposited in these parts. The *mass median aerodynamic diameter (MMAD)* was calculated from the ELPI drug assay data. The *charge per mass of drug*, or *charge-to-mass ratio* (q/m), for a given size fraction was calculated by dividing the charge by the drug mass in that size fraction. This was only derived for the size fractions containing detectable amounts of drug, corresponding to Stages 8–10 for suspension MDIs and Stages 4–9 for QVAR[®] solution MDIs. The number of elementary charges (n) per drug particle in a particular size fraction was estimated by the following equation:

$$n = \frac{q}{m} \cdot \frac{\rho V}{e}, \quad (1)$$

where ρ is the true density of the particles, V the volume of a particle, and e the elementary charge ($1.602 \times 10^{-19} \text{C}$). The particles were assumed to be spherical and have an average true density of 1.5 g/cm^3 because pharmaceutical powders generally have true densities between 1.0 and 2.0 g/cm^3 (Rowe, Sheskey, & Weller, 2003). For a given ELPI stage, V was calculated from the cutoff diameter. The ex-actuator dose, spacer deposition, throat deposition, FPD, MMAD, net charge, and the fine particle charge were analysed statistically using one-way analysis of variance (ANOVA), followed by the Tukey multiple comparisons post hoc test ($\alpha = 0.05$) to determine differences between the means. All statistical procedures were performed with Minitab[™] Statistical Software 13.31.

3. Results

Fig. 3 shows examples of surface potentials at the two measurement regions inside new and detergent-coated spacers. Before aerosol firing and sampling, high surface potentials were measured on the new spacers, the magnitude and distribution of which were non-uniform within and between spacers. Detergent-coated spacers showed minimal surface potentials that were fairly close to zero. The surface potentials on the new spacers were slightly altered after aerosol actuation and sampling. While the readings at some locations decreased in magnitude, those at other sites increased

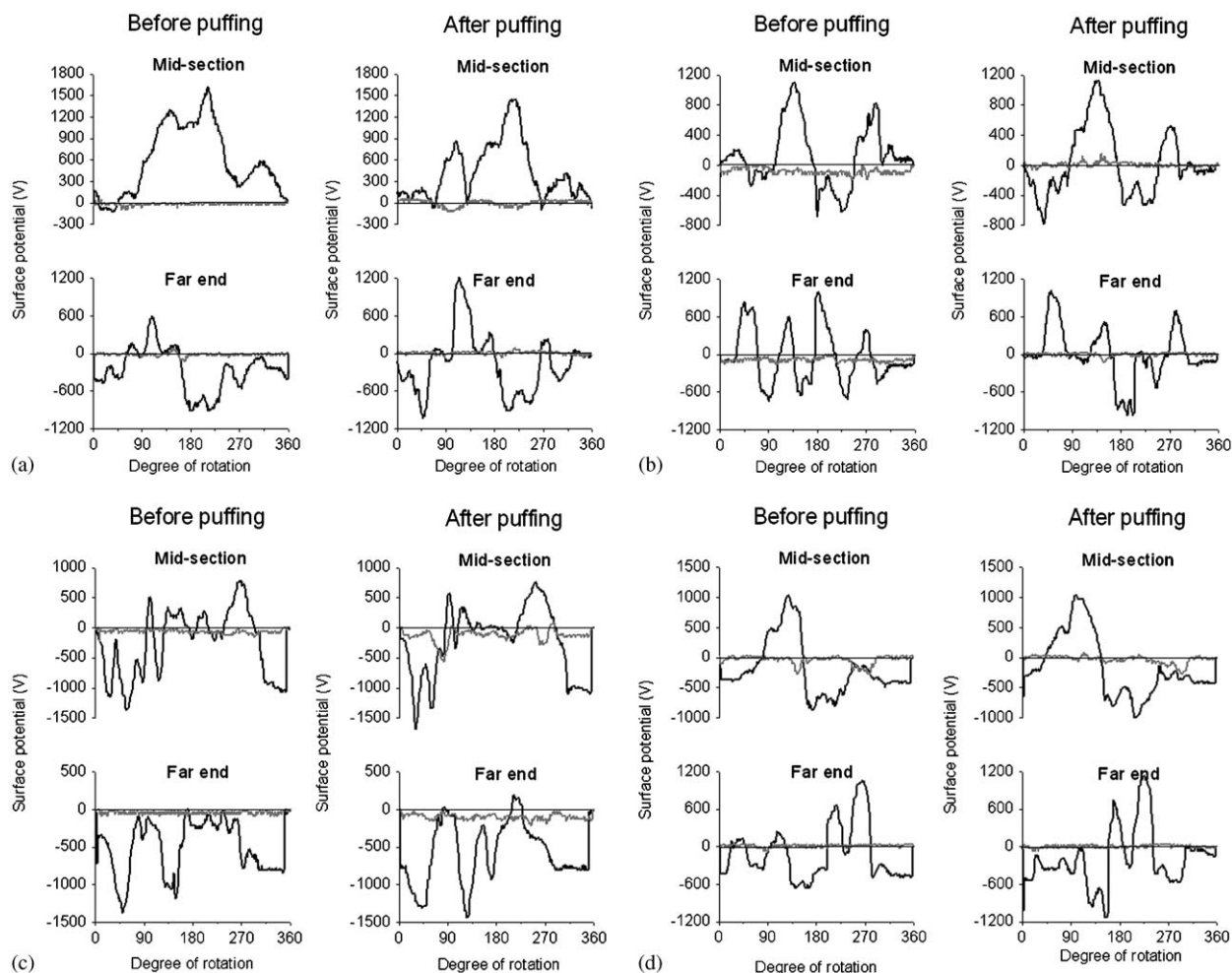


Fig. 3. Surface potentials on the internal wall at two locations inside a new (black line) and a detergent-coated (grey line) AeroChamber Plus® spacer before and after aerosol firing and sampling from (a) Ventolin®, (b) Flixotide®, (c) Tilade®, and (d) QVAR®.

both in the positive and negative polarities. The extent of change was also unequal. On the other hand, the surface potentials on detergent-coated spacers remained low after aerosol actuation.

The charge and mass profiles of the four types of MDIs with and without spacers are shown in Fig. 4. For MDIs used alone, the first puff after priming was not characteristically different in charge and mass to the two subsequent puffs, except for Ventolin®, the first puff (after priming) from which was higher in mass, as was also observed in the previous study (Kwok et al., 2005). Most drug deposits were on Stages 8–10 (0.960–2.42 μm) for the three suspension-type MDIs. On the other hand, QVAR®, being a solution formulation, produced smaller particles that deposited mainly on Stages 4–9 (0.159–1.62 μm). For the suspension MDIs, high charges were measured on the lower stages where only very little drug was detected. As discussed in the previous study, these charges are believed to originate from propellant/excipient droplets containing no drug particles (Kwok et al., 2005). Since patients are instructed by consumer medicine information leaflets to prime new MDIs before initial use, only the results from the first puff in the MDI-alone experiments were compared with those with spacers, from which only the first puff of an inhaler was sampled. Fig. 4 shows that both charge and mass outputs were decreased when a spacer was used. Of the two types of spacers, the new spacer gave the lowest charge and mass levels. However, the charge profiles were not qualitatively altered by the presence of a new or detergent-coated spacer. The charges were merely decreased in magnitude compared to those directly from a MDI.

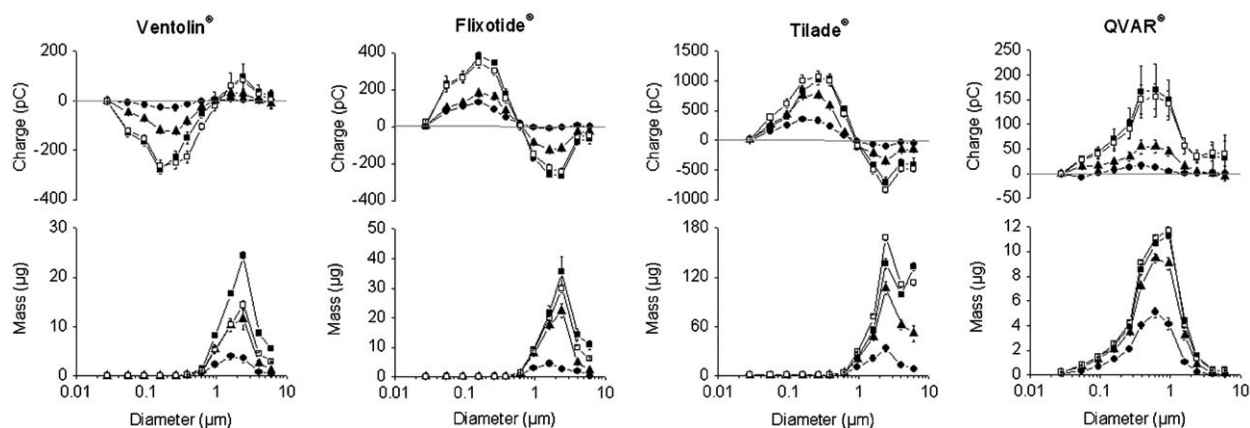


Fig. 4. Charge and mass profiles of Ventolin[®], Flixotide[®], Tilade[®], and QVAR[®] (■ MDI-alone, Puff #1; □ MDI-alone, Puffs #2 and #3; ● with new spacer, Puff #1; ▲ with detergent-coated spacer, Puff #1). Error bars represent standard errors ($n = 3$ for ■, ●, ▲; $n = 6$ for □).

The ex-actuator dose and various particle size and charge parameters are summarised in Table 1. Spacer retention was generally the highest when a new spacer was used. This in turn led to lower throat deposition, FPD, and net aerosol and FPD charges comparing to MDI-alone (Table 1) as fewer particles were available for sampling by the ELPI. These trends were counteracted by the detergent-coated spacer, with result values being intermediate in magnitude between those with MDI-alone and with a new spacer.

Tables 2 and 3 show the charges per mass of drug and estimated number of elementary particles per drug particle in the entire ELPI size range, respectively. In the size fractions containing major drug deposits (described above), both the charge per mass of drug and number of elementary charges per drug particle generally follow the order of “new spacer”, “detergent-coated spacer”, and “MDI-alone” in increasing magnitude. This is the same trend as that indicated in Table 1. In the size fractions with minimal drug deposition, the charges per mass of drug are high in both magnitude and variability. This is due to the low drug mass in the q/m ratio, along with the high charges being mainly contributed by the propellant and/or excipients.

4. Discussion

The charge profiles from the MDI-alone experiments are comparable to those obtained previously (Kwok et al., 2005) except for those of Tilade[®]. A range of 400,000 fA was used on the ELPI in the present study instead of the 40,000 fA setting used before. This increase in the electrometer range enabled the detection of higher charges present in the Tilade[®] aerosol that were missed in the earlier study. Ventolin[®], Flixotide[®], and QVAR[®] have lower charges so the 40,000 fA range used before was sufficient and no extra charges were detected on these aerosols at the higher range. The difference in the charge levels may be due to the high dose of Tilade[®], which is one order of magnitude higher in mass per actuation than the other three MDIs. The electrometers might be overloaded as the dense aerosol cloud of charged particles deposited on the ELPI stages. Indeed, even with the range set to the highest at 400,000 fA in the present study, the electric currents on certain stages still appeared to be over the range. Thus the charges measured for Tilade[®] in this study may not be complete, but the charge profiles are still valid in showing semi-quantitative trends with respect to particle size. However, in view of the limitations of the ELPI electrometers, dense aerosols of such kind may need to be diluted before measurement in the future.

The AeroChamber Plus[®] is a commonly used small volume (149 mL) (Asmus, Coonwanitwong, Kwon, Khorsand, & Hochhaus, 2003; Nagel, Wiersema, Bates, & Mitchell, 2002) cylindrical spacer with a rubber universal adaptor that may be fitted snugly with a variety of MDI actuator mouthpieces. Some other spacers are designed by MDI manufacturers to be specific for their own inhaler products. Since the volume and dimensions of a spacer are known to affect drug output characteristics (Barry & O’Callaghan, 1996, 2000), all MDIs in this study were used with the same type of spacer to avoid such variables.

Table 1
Ex-actuator dose, deposition, particle size, and charge parameters for the aerosols emitted from MDIs with and without a spacer

	Ex-actuator dose (μg)	Spacer deposition (μg)	Throat deposition (μg)	Fine particle dose (μg)	MMAD (μm)	Net charge (pC)	Fine particle dose charge (pC)
Ventolin [®]	MDI-alone	150.80 (9.03)	N/A	70.20 (6.11) ^{ab}	1.82 (0.01) ^{ab}	-792.23 (150.34) ^a	-815.81 (135.73) ^{ab}
	New spacer	127.84 (26.01)	113.62 (23.70)	0.65 (0.11) ^a	1.42 (0.04) ^a	-81.08 (32.18) ^a	-81.50 (33.32) ^a
	Detergent-coated spacer	104.43 (15.25)	66.04 (13.62)	2.07 (0.55) ^b	1.56 (0.05) ^b	-417.27 (50.43)	-406.15 (34.23) ^b
Flixotide [®]	MDI-alone	280.19 (41.46)	N/A	160.21 (28.78) ^{ab}	1.95 (0.02) ^{ab}	+567.61 (83.92)	+632.44 (61.83) ^a
	New spacer	250.41 (17.17)	233.72 (16.50) ^a	0.84 (0.20) ^a	1.34 (0.06) ^{ac}	+472.74 (87.77)	+473.01 (81.14)
	Detergent-coated spacer	223.88 (19.93)	156.46 (13.92) ^a	5.86 (0.37) ^b	1.65 (0.02) ^{bc}	+297.52 (20.77)	+321.60 (22.77) ^a
Tilade [®]	MDI-alone	1920.60 (52.98)	N/A	1215.23 (53.28) ^{ab}	3.75 (0.17) ^{ab}	+2070.24 (92.36) ^a	+2491.10 (171.46) ^a
	New spacer	2014.53 (93.77)	1893.50 (103.79) ^a	14.17 (1.28) ^a	1.78 (0.03) ^a	+1105.13 (51.83) ^{ab}	+1160.53 (58.78) ^{ab}
	Detergent-coated spacer	1800.60 (38.92)	1379.97 (9.40) ^a	74.08 (1.47) ^b	2.23 (0.07) ^b	+1917.59 (69.94) ^b	+2068.94 (83.50) ^b
QVAR [®]	MDI-alone	77.45 (2.05)	N/A	28.28 (2.85) ^{ab}	0.50 (0.01) ^a	+888.22 (257.20) ^a	+855.47 (225.75) ^a
	New spacer	66.86 (4.45)	45.77 (3.80) ^a	0.98 (0.15) ^a	0.43 (0.01) ^a	+50.90 (50.68) ^a	+29.78 (30.65) ^a
	Detergent-coated spacer	63.95 (4.57)	22.23 (3.36) ^a	1.83 (0.26) ^b	0.47 (0.01)	+261.08 (61.06)	+267.66 (64.07)

Data are presented as mean with standard error in parenthesis ($n = 3$). Results for MDI-alone experiments were derived from Puff #1 of each of the three inhalers. Means within a MDI type labelled with common letter(s) in the superscript are statistically different for a given parameter ($p \leq 0.05$). MMAD: mass median aerodynamic diameter; N/A: not applicable for MDI-alone experiments.

Table 2
Charges per mass of drug for the MDIs ($\mu\text{C/g}$)

	Stage	4	5	6	7	8	9	10
	Size (μm)	0.159	0.266	0.388	0.621	0.960	1.62	2.42
Ventolin [®]	MDI-alone	N/A	N/A	N/A	N/A	−0.50 (4.69)	+3.50 (3.03)	+3.83 (2.01)
	New spacer	N/A	N/A	N/A	N/A	+2.42 (1.03)	+1.72 (0.71)	+1.29 (0.63)
	Detergent-coated spacer	N/A	N/A	N/A	N/A	+0.85 (1.61)	+3.13 (1.37)	+2.37 (1.15)
Flixotide [®]	MDI-Alone	N/A	N/A	N/A	N/A	−19.01 (2.03) ^a	−12.05 (1.29) ^a	−7.80 (1.15)
	New spacer	N/A	N/A	N/A	N/A	−2.13 (2.46) ^a	−1.68 (1.26) ^{ab}	−3.18 (3.89)
	Detergent-coated spacer	N/A	N/A	N/A	N/A	−10.72 (2.25)	−7.42 (0.83) ^b	−5.23 (0.41)
Tilade [®]	MDI-alone	N/A	N/A	N/A	N/A	−2.33 (1.48)	−7.56 (0.71) ^a	−5.21 (0.64) ^a
	New spacer	N/A	N/A	N/A	N/A	−1.92 (0.91)	−3.33(0.76) ^a	−2.82 (0.50) ^a
	Detergent-coated spacer	N/A	N/A	N/A	N/A	−5.20 (1.33)	−4.57 (0.82)	−3.33 (0.18)
QVAR [®]	MDI-alone	+30.10 (7.89) ^a	+26.39 (7.63)	+19.92 (6.54)	+16.00 (5.16) ^a	+13.50 (3.83) ^a	+12.93 (1.87) ^{ab}	N/A
	New spacer	+6.12 (4.39) ^a	+6.12 (2.82)	+3.86 (1.63)	+2.27 (0.81) ^a	+0.99 (0.16) ^a	+0.94 (0.31) ^a	N/A
	Detergent-coated spacer	+11.48 (2.79)	+9.98 (2.53)	+7.49 (1.95)	+5.84 (1.30)	+4.98 (0.96)	+4.86 (1.02) ^b	N/A

Data are presented as mean with standard error in parenthesis ($n = 3$). Results for MDI-alone experiments were derived from Puff #1 of each of the three inhalers. Means within a MDI type labelled with common letter(s) in the superscript are statistically different for a given parameter ($p \leq 0.05$). N/A: not applicable for derivation of charge per mass of drug.

Table 3
Estimated number of elementary charges per drug particle for the MDIs calculated by Eq. (1)

	Stage	4	5	6	7	8	9	10
	Size (μm)	0.159	0.266	0.388	0.621	0.960	1.62	2.42
Ventolin [®]	MDI-alone	N/A	N/A	N/A	N/A	−2 (20)	+73 (63)	+266 (140)
	New spacer	N/A	N/A	N/A	N/A	+10 (4)	+36 (15)	+90 (44)
	Detergent-coated spacer	N/A	N/A	N/A	N/A	+4 (7)	+65 (29)	+164 (80)
Flixotide [®]	MDI-alone	N/A	N/A	N/A	N/A	−82 (9)	−251 (27) ^a	−542 (80)
	New spacer	N/A	N/A	N/A	N/A	−9 (11)	−35 (26) ^{ab}	−221 (270)
	Detergent-coated spacer	N/A	N/A	N/A	N/A	−47 (10)	−155 (17) ^b	−364 (29)
Tilade [®]	MDI-alone	N/A	N/A	N/A	N/A	−10 (6)	−158 (15) ^a	−362 (44) ^a
	New spacer	N/A	N/A	N/A	N/A	−8 (4)	−70 (16) ^a	−196 (35) ^a
	Detergent-coated spacer	N/A	N/A	N/A	N/A	−23 (6)	−95 (17)	−231 (12)
QVAR [®]	MDI-alone	+1(0)	+2 (1)	+6 (2) ^a	+19 (6) ^a	+59 (17) ^{ab}	+270 (39) ^{ab}	N/A
	New spacer	0 (0)	0 (0)	0 (0) ^a	+1 (1) ^a	+3 (2) ^a	+11 (8) ^a	N/A
	Detergent-coated spacer	0 (0)	0 (0)	+1 (1)	+4 (2)	+12 (6) ^b	+55(29) ^b	N/A

Data are presented as mean with standard error in parenthesis ($n = 3$). Results for MDI-alone experiments were derived from Puff #1 of each of the three inhalers. Means within a MDI type labelled with common letter(s) in the superscript are statistically different for a given parameter ($p \leq 0.05$). N/A: not applicable for derivation of number of elementary charges per drug particle.

The main body of AeroChamber Plus[®] is made of clear copolyester (Asmus et al., 2003), which is a non-conducting plastic. Thus charges are expected to be generated and retained on the surfaces (Barry & O'Callaghan, 1994; Piérart et al., 1999; Wildhaber, Devadason, Hayden, James, Dufty, Fox, et al., 1996), as shown in the high, non-uniformly distributed surface potentials of the new spacers (Fig. 3). The lowering of surface potentials by detergent-coating

signified a reduction of electrostatic charges on spacer surfaces. The changes in surface potential after aerosol sampling must be due to the deposition of charged drug particles and propellant droplets inside the spacer (Fig. 3).

The performance of the AeroChamber[®] Plus and the effect of detergent-coating on spacer retention and drug mass output in this study (Table 1) agreed with those reported in the literature (Barry & O'Callaghan, 1995, 1996; Berg, 1995; Newman, 2004; O'Callaghan, 1997; Piérart et al., 1999; Wildhaber, Waterer, Hall, & Summers, 2000). The shift in the FPD between MDI-alone, new spacers, and detergent spacers was also paralleled by a corresponding change in the net and FPD charges (Table 1). One apparent exception was Flixotide[®], which gave lower net and FPD charges from detergent-coated spacers than those from new ones. This is due to the bipolar nature of the aerosol cloud (Fig. 4). The negative portion of the charge profile was contributed by the drug particles whereas the positive portion by empty propellant droplets. Since the net charges for Flixotide[®] were positive, this implies that there were more charges from propellant droplets in the aerosol. Although both the positive and negative portions in the charge profile were dampened when spacers were used, the reduction of one polarity did not yield a proportional decline in the other. This resulted in more positive charges obtained from the new spacer and/or more negative charges from the detergent-coated one, as shown in the apparent anomaly in the order of net and FPD charges.

The decrease in charge levels from the spacers seen in Fig. 4 may be due to: (i) the lowering of inherent charges on the particles and/or (ii) the reduction in the amount or mass of charged particles in a specific size fraction. For further analyses the charge per mass of drug and the number of elementary charges per drug particle need to be considered. From Table 2, the charge per mass of drug is generally the lowest for the new spacers in size fractions having the most drug deposits (Stages 4–9 for QVAR[®], 8–11 for the suspension MDIs), followed by detergent-coated spacers and MDI-alone. Likewise, the estimated number of elementary charges per drug particle displayed the same trend (Table 3). This implies that the particles that exited from a new spacer, hence sampled by the ELPI, possessed lower inherent charges. Furthermore, particles carrying higher charges became available by reducing the spacer surface potential with detergent and even more so without a spacer. Thus the spacer acts like an electrostatic filter and particles carrying a higher charge (i.e. more elementary charges) appeared to be more susceptible to the effects of spacer surface charges and become retained. This phenomenon may be interpreted using Coulomb's Law:

$$F \propto \frac{q_1 q_2}{r^2}, \quad (2)$$

where F is the electrostatic force between two charged bodies, q_1 and q_2 their charges, and r the distance between them. If q_1 represents the charge of a particle and q_2 the charge on a small section of the spacer surface, then at a given q_2 on a new spacer and a set r , the electrostatic force exerted on the particle would simply be directly proportional to q_1 . Hence particles carrying a higher charge would have a higher tendency for electrostatic deposition inside the spacer. Conversely, if q_2 is greatly reduced or eliminated by detergent-coating, then for a given q_1 , the particle would experience a low electrostatic force and would be more likely to be delivered from the spacer. However, Coulomb's Law has its limitations in providing a full explanation on the data obtained. The equation describes both electrostatic attractive and repulsive forces, depending on the polarities of the charged bodies. Same polarities attract whereas opposites repel. From the ELPI charge profiles, it appears that all drug particles from a specific inhaler are charged to the same polarity. For instance, those from Flixotide[®] and Tilade[®] were all negatively charged (with positive charges from the propellant/excipients), and those from QVAR[®] were all positively charged (Fig. 4). From such data, it may be surmised that particular types of MDIs should experience more attraction or repulsion from the spacer wall than others if the surface potentials were predominantly of one polarity.

The calculation of the actual deflection of a charge in the presence of the electric field caused by a charged cylinder is very complex. In this paper, no attempt is made to determine precisely how the moving charges will be deflected due to a fixed charge on the spacer. However, some qualitative conclusions about the nature of charge transmission through the spacer can be drawn from simple arguments. Consider, for example, the situation if the spacer surface is charged with a uniform distribution of negative charges. Although by symmetry the electric field within a very long uniformly charged cylindrical spacer will be zero at points distant from the ends, the spacers considered here are not very long relative to their diameter. There will thus be a significant non-zero radial component of the electric field at all off-axis points near the entrance and exit of the spacer. The effect of this fringing electric field at the entrance to the spacer will be to repel negatively charged drug particles, deflecting their trajectories towards the axis of the spacer, and thus enhancing the output of these particles, such as those from Flixotide[®] and Tilade[®]. Conversely, the fringing electric field near the entrance of the spacer will attract positively charged particles, such as those from Ventolin[®] and QVAR[®], deflecting

them away from the axis of the system towards the internal surface of the spacer, and particles of this polarity will tend to be retained within the spacer, thus decreasing their emission. The reverse would be expected to occur if the surface of the spacer was positively charged. The extent of particle repulsion and attraction would be directly related to the magnitude of surface charges. The internal spacer wall could accidentally or artificially be charged in a clinical setting by wiping the surface with a fabric, such as a towel for drying or cleaning. Electrons would be transferred between the spacer wall and the fabric by triboelectrification. The polarity of charging depends on the relative positions of the spacer and fabric materials in the triboelectric series (Hendricks, 1973). A fundamental relationship between aerosol and spacer wall charges may be examined in a similar manner by wiping the spacer interior with a tissue (wetted with a slightly conductive volatile liquid such as ethanol) connected to an electrode of a variable DC voltage source. The magnitude and polarity of charging could subsequently be controlled by selecting the voltage and charging electrode, respectively, to obtain a uniform surface charge distribution.

In the present study with non-uniform surface charge potentials, all MDI aerosols tested were prone to spacer retention, which could be alleviated by a reduction in surface potentials regardless of the polarity of charges on the drug particles, so the situation is more complex than it seems. Although it is certain that fundamentally Coulomb's Law is obeyed on the microscopic level, macroscopically many factors may confound the observation. Firstly, the ELPI measures the net charge in each specific size fraction (Kwok et al., 2005). The charge on individual particles could not be distinguished, thus the heterogeneity in charge polarity might be masked. Secondly, the surface potentials on new spacers were non-uniformly distributed and were different within and between the spacers. This makes generalisation on surface charges and particulate behaviour inside the spacers difficult. Thirdly, aerosols are emitted from MDIs at very high velocities (30–50 m/s) (Berg, 1995). Inertial impaction inside the spacer may overcome electrostatic deposition, especially for the larger particles. This effect is expected to be compounded in small volume spacers such as the AeroChamber® Plus.

It is interesting to note the action of the spacer as an electrostatic filter and the particles it delivers carry lower charges than those directly from an MDI (Table 3). This may affect particle deposition in the lungs. Computational modelling on charged particle deposition in the airways showed that the deposition of 0.5 μm particles was increased in the lower airways when the number of elementary particle was increased from 0 to 200 (Bailey, Hashish, & Williams, 1998). The trend is similar for larger particles but progressively more charge is required for the effect. Since the magnitude of particle charges delivered from spacers fall within this range (Table 3), lung deposition may be affected by charge alteration, in addition to the already well-established effect of particle size reduction. Particle deposition by electrostatic forces becomes a significant mechanism in the lower airways owing to the small dimensions in these pulmonary areas (Bailey et al., 1998; Balachandran, Machowski, Gaura, & Hudson, 1997), in which r in Eq. (2) becomes small. Thus a change in the aerosol charges may have an impact on the deposition pattern. The elimination of spacer charges in the present study increased not only the FPD, but also the FPD charge (Table 1). The higher charges suggest that the deposition in the lower airways may be increased. It is well known that particle deposition from non-static spacers is improved in vivo (Kenyon et al., 1998; Piérart et al., 1999). Although this observation has been generally attributed to the increase in the FPD available, the contribution of electrostatic forces to the resultant deposition may also play a role. The findings from the present study are relevant to the design and use of spacers, which have an influence on particle charges and possibly deposition. Clinical studies investigating the influence of charges on therapeutic effect and lung deposition are necessary to fully address these potential issues.

5. Conclusion

A modified ELPI was successfully used to determine the charge profiles of MDI aerosols sampled from spacers. High surface charges were found on the internal walls of new AeroChamber® Plus spacers. Coating the spacer with detergent removed the surface charge leading to lower electrostatic retention of drugs in, and higher drug output from, the spacer. Most notably, particles delivered from spacers carried lower inherent charges than those directly from MDIs. The altered charge levels on drug particles administered via a spacer may have a potential effect on lung deposition when inhaled.

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