Pharm Res (2015) 32:2928–2936
DOI 10.1007/s11095-015-1674-6

RESEARCH PAPER

# The Effect of Active Pharmaceutical Ingredients on Aerosol Electrostatic Charges from Pressurized Metered Dose Inhalers

Yang Chen • Paul M. Young • David F. Fletcher • Hak Kim Chan • Edward Long • David Lewis • Tanya Church • Daniela Traini

Received: 9 January 2015 / Accepted: 9 March 2015 / Published online: 19 March 2015


## ABSTRACT

***Purpose*** This study investigated the effect of different active pharmaceutical ingredients (API) on aerosol electrostatic charges and aerosol performances for pressurized metered dose inhalers (pMDIs), using both insulating and conducting actuators.

***Methods*** Five solution-based pMDIs containing different API ingredients including: beclomethasone dipropionate (BDP), budesonide (BUD), flunisolide (FS), salbutamol base (SB) and ipratropium bromide (IPBr) were prepared using pressure filling technique. Actuator blocks made from nylon, polytetrafluoroethylene (PTFE) and aluminium were manufactured with 0.3 mm nominal orifice diameter and cone nozzle shape. Aerosol electrostatics for each pMDI formulation and actuator were evaluated using the electrical low-pressure impactor (ELPI) and drug depositions were analysed using high performance liquid chromatography (HPLC).

***Results*** All three actuator materials showed the same net charge trend across the five active drug ingredients, with BDP, BUD and FS showing positive net charges for both nylon and PTFE actuators, respectively. While SB and IPBr had significantly negative net charges across the three different actuators, which correlates to the ionic functional groups present on the drug molecule structures.

***Conclusions*** The API present in a pMDI has a dominant effect on the electrostatic properties of the formulation, overcoming the charge effect arising from the actuator materials. Results have shown that the electrostatic charges for a solution-based pMDI could be related to the interactions of the chemical ingredients and change in the work function for the overall formulation.

**KEY WORDS** aerosols · APIs · electrostatics charges · metered dose inhalers

## ABBREVIATIONS

| | |
|---|---|
| ABS | Acrylonitrile butadiene styrene |
| API | Active pharmaceutical ingredient |
| APIs | Active pharmaceutical ingredients (Plural) |
| BDP | Beclomethasone dipropionate |
| BUD | Budesonide |
| ELPI | Electrical low-pressure impactor |
| FPF | Fine particle fraction |
| FS | Flunisolide |
| GSD | Geometric standard deviation |
| HFA | Hydrofluoroalkane |
| HFA 134a | 1,1,1,2-tetrafluoroethane |
| HPLC | High performance liquid chromatography |
| IPBr | Ipratropium bromide |
| MMAD | Mass median aerodynamic diameter |
| pMDI | Pressurized metered dose inhaler |
| PTFE | Polytetrafluoroethylene |

Y. Chen • P. M. Young • D. Traini (✉)
Respiratory Technology, Woolcock Institute of Medical Research and Discipline of Pharmacology, Sydney Medical School
The University of Sydney, Sydney, NSW 2037, Australia
e-mail: Daniela.traini@sydney.edu.au

D. F. Fletcher
School of Chemical and Biomolecular Engineering
The University of Sydney, Sydney, NSW 2006, Australia

H. K. Chan
Advanced Drug Delivery Group, Faculty of Pharmacy (A15)
University of Sydney, Sydney, NSW 2006, Australia

E. Long
Wolfson School of Mechanical and Manufacturing Engineering
Loughborough University, Loughborough, Leicestershire LE11 3TU, UK

D. Lewis • T. Church
Chiesi Ltd, Units T1 - T3, Bath Rd. Ind. Est.
Chippenham, Wiltshire SN14 0AB, UK

SB Salbutamol base
USP United States Pharmacopeia

## INTRODUCTION

Aerosolised medication is often prescribed for the treatment of respiratory illness such as asthma and chronic obstructive pulmonary disease (1,2). The pressurized metered dose inhaler (pMDI) is a system designed to generate an inhalable aerosol that accurately delivers the active pharmaceutical ingredients (APIs) to the respiratory tract (3). This occurs through the following five mechanisms: impaction, sedimentation, interception, diffusion and electrostatic deposition (4–6). Whilst the first four mechanisms have been extensively studied over the years (7–9) and are closely related to the aerosols physical characteristics, such as particle size and shape, it was not until recently that electrostatics forces became an area of interest in pulmonary drug delivery (10).

Most pharmaceutical ingredients are dielectric materials and highly susceptible to electrostatic charge generation and accumulation, through contact/friction charging between particles and material surfaces (11,12). Although it is well recognised that electrostatic charges can be a nuisance during manufacture and handling of pharmaceutical powders by promoting agglomeration, segregation and adhesion, especially when fine particles are involved (13,14), research studies using theoretical predictions (15–18), *in vitro* lung models (19,20), *in vivo* animal and human subjects (21–25) have all suggested that electrostatic force on charged particles can significantly influence the aerosol performance for pulmonary drug delivery. In addition, aerosol charges can also influence the sizing of *in vitro* studies with cascade impactor (26).

The deposition of charged particle in the respiratory tract is described by two general mechanisms: space and image charge. The former space charge refers to the natural repulsive force created by the electron cloud on the charged particles, especially when aerosol are condensed (27). Therefore, space charges play an important role during pMDI plume formation and consequently deposition on the pharyngeal tracheal region (28). The latter, image charge, predominantly influences the downstream aerosol deposition through induction of image charges with opposite polarity on nearby surfaces, for example the airway wall, hence promoting electrostatic deposition in the lung (10,27).

When a pMDI is actuated, the pressurized mixture of hydrofluoroalkane (HFA) propellant and drug (solubilised or suspended) with or without co-solvents/excipients is exposed to the atmospheric pressure. Consequently, the rapid transition of propellant into its gaseous state aerosolises the APIs carried by the HFA. Flash boiling, cavitation and evaporation during the atomisation process creates an interaction between the liquid, solid and gas components of the formulation, providing contact surfaces for triboelectrification. Therefore, factors that contribute to electrostatic charge generation for pMDI aerosols are often related to the physical and chemical properties of the device, including the material used for the actuator, the design of the orifice nozzles and chemical structure of the drug and excipients used in the formulation. In previous studies, different actuator materials and nozzle designs were selected from the triboelectric series and assessed for their influence on the resultant electrostatic properties (28,29). It was found that the net charge profiles obtained with a formulation containing no drug and low co-solvent (ethanol 1%) emitted from a cone nozzle design followed the triboelectric series (29). However, when an active pharmaceutical ingredient (API; beclomethasone dipropionate) was introduced into the formulation, no 'trend' was found and the net charge profiles changed between different actuator materials (29). These results suggested that the API in a pMDI formulation has a strong influence on the overall electrostatic properties of the generated aerosol plume.

In nature, the driving mechanism for triboelectrification is the materials' work function (30–32). It is an indication of the materials' surface property and refers to the energy required to remove electrons from a solid to an immediate point outside the solid (in a vacuum) (33). In metals, the valance band is filled with electrons up to the Fermi level, which overlap with the conduction band. Therefore, electron can move freely within a metal and the work function is the energy difference between the Fermi levels and the vacuum. For insulators, the Fermi level lies in the large band gap that exits between the valance and the conduction band, indicating that no electrons are present in the conduction band and it therefore has a much higher work function energy (34–36). During contact charging, two materials come in contact and electrons will transfer from lower to higher work function in attempt to reach thermodynamic equilibrium (37). After separation, the material that gains electrons will charge negatively and the material that loses electrons will charge positively. However, the work function is strongly influenced by the materials' surface conditions, including contamination of other atoms/molecule, surface reaction (oxidation, ionisation), surface structures, as well as environmental factors such as humidity, especially for dielectric materials used in pharmaceutical aerosols (38).

In pMDIs, drug particles are generated through complex phase transitions and chemical interactions between the propellant, co-solvent/excipients and the APIs.

Thus it is difficult to predict the electrostatic potential for pMDI aerosols and current studies can only rely on *in vitro* screening analysis for individual factors that could contribute to aerosol electrostatics. Therefore, this study focused on investigating five solution-based pMDIs with different APIs (beclomethasone dipropionate, budesonide, flunisonide, salbutamol base and

ipratropium bromide, respectively) to elucidate how active drugs can influence aerosol electrostatic charge, with both insulating and conducting actuator materials.

## MATERIALS AND METHODS

### Materials

Five active pharmaceutical ingredients (APIs), comprising beclomethasone dipropionate (BDP), budesonide (BUD), flunisolide (FS), salbutamol base (SB) and ipratropium bromide (IPBr) were chosen as model drugs (Fig. 1) and supplied by Chiesi Farmaceutici S.p.A (Parma, Italy). Standard aluminium pMDI canisters (C128P, Batch 1002043-3, 18 ml brim capacity) were obtained from Presspart Manufacturing Ltd (Lancashire, UK) and fitted with 50 µl metering valves (batch BK0313029, Bespak Europe Ltd, Norfolk, UK). The propellant 1,1,1,2-Tetrafluoroethane (HFA 134a) was provided by Solvay Chemicals (Brussels, Belgium), and all other analytical grade chemicals, used as received, were purchased from Sigma-Aldrich Pty Ltd (Castle Hill, Australia). Water used through out the study was purified by reverse osmosis (Milli-Q, Sydney, Australia).

### Sample Preparation

Five solution-based pMDIs containing different API ingredients were prepared using pressure filling technique according to Table I. The required quantity of individual drugs were accurately weighed and dissolved in co-solvent ethanol (14.9% *w*/*w*) into aluminum canisters. Each canister was immediately crimped with the metering valve and pressure filled with propellant HFA 134a using a Pamasol P2016 laboratory crimp and filling plant (Pamasol Willi Maäden AG, Pfaffikon, SZ). Solubility of the drug was confirmed visually using glass containers (Saint Gobain, France). All canisters were stored at ambient temperature for 24 h prior to testing.

**Table I** Formulation Details for the Solution Based pMDIs with Different APIs

| APIs | Target dose (µg) | Drug (% *w*/*w*) | Ethanol (% *w*/*w*) | HFA 134a (% *w*/*w*) |
|---|---|---|---|---|
| BDP | 50 | 0.1 | 14.9 | 85 |
| BUD | 50 | 0.1 | 14.9 | 85 |
| FS | 50 | 0.1 | 14.9 | 85 |
| SB | 50 | 0.1 | 14.9 | 85 |
| IPBr | 50 | 0.1 | 14.9 | 85 |

*BDP* Beclomethasone Dipropionate, *BUD* Budesonide, *FS* Flunisolide, *SB* Salbutamol Base, *IPBr* Ipratropium Bromide

### Actuators Manufacture

The pMDI actuator blocks were manufactured using three different materials including nylon, polytetrafluoroethylene (PTFE) (both from Ensinger GmbH, Nufringen, Germany) and aluminum (Aalco Metals Ltd, Cobham, UK); representing positive, negative and conducting triboelectric materials, respectively (39). The nozzle design with a nominal orifice diameter of 0.3 mm and cone outer shape was selected to represent the most commonly utilized geometry in commercial pMDI actuators and manufactured with *Siemens NX* software using high-speed-steel cutting tools. Orifice diameters were confirmed using microscope and *MediaCybernetics* Image-Pro software, with dimensional accuracy up to ±0.01 mm. All actuator blocks were washed and sonicated with purified water and ethanol prior to first use. Air-drying

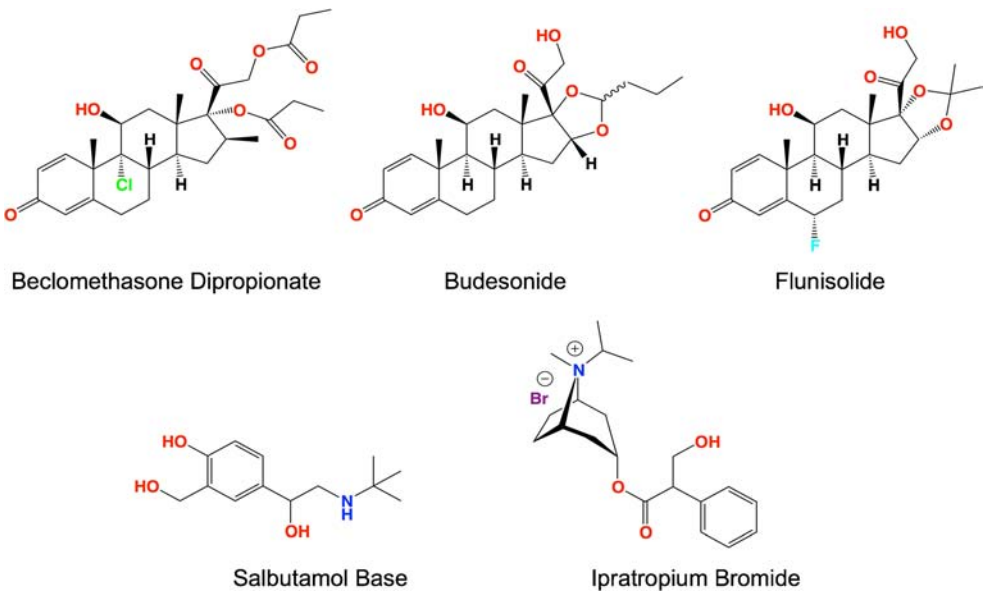


**Fig. 1** Molecule structure for the five selected active pharmaceutical ingredients.

was used instead of heat drying to prevent changes to the orifice diameter. Adaptors to house the actuator block of the pMDI were custom designed using computer aided design (ANSYS DesignModeler, release 13, ANSYS Inc, PA, USA) and built in acrylonitrile butadiene styrene (ABS) using a 3D printer (Dimension Elite, MN, USA).

### Measurements of Aerosols Electrostatic Charge

A modified 13 stage electrical low-pressure impactor (ELPI™, Dekati Ltd, Finland), without the corona charger, was used to measure the aerosol electrostatic charge distribution, as described previously (29,40). The pMDI was shaken for 10 s and primed to waste twice using a commercial actuator before being fitted to the actuator block with the custom built adaptor. The airflow through the ELPI was set at 30 L/min using Sogevac® model SV25 vacuum pump (Leybold, France) and a calibrated Copley® model 4000 flow meter (Nottingham, UK). The pMDI unit was connected to the ELPI *via* United States Pharmacopeia (USP) induction port and baseline zeroed after the electrometer readings were stabilized. Five single actuations from each pMDI formulation were dispersed into the ELPI cumulatively, with 30 s delay between each dose. The aerosol charges were measured and current recorded using the ELPI-VI 4.0 software (Dekati Ltd, Finland) as femto amps per second (fA/s) and then converted to charge data during analysis. All experiments were randomized and performed in triplicate under standard laboratory conditions (temperature ~25°C and relative humidity ~40–50%).

### High Performance Liquid Chromatography (HPLC)

The drug captured on the actuator block, adaptor, USP induction port and impactor stages was recovered using rinsing solution (Table II) specific for each API and quantified chemically using a Shimadzu prominence UFLC system equipped with a SPD-20A UV–vis detector, LC-20AT solvent delivery unit, SIL-20A HT autosampler (Shimadzu Corporation, Japan). Chromatographic conditions for each API formulation are summarized in Table II. Fresh drug standards were prepared in rinsing solution and all mobile phase solutions were filtered through 0.45 μm filters and degassed by ultra-sonication for 10 min. The HPLC method was validated for all APIs throughout the concentration range of 0.1–100 μg/mL.

### Data Analysis

Aerosol electrostatic charge data for each pMDI formulation were derived from electric current results obtained from the ELPI. The net charge was calculated as the total charge from the 13 stages of the impactor and shown as the mean for the three experiments. The mass recoveries of individual APIs were analyzed as the total mass of five cumulative actuations. Total ex-valve dose, throat USP deposition and fine particle fraction (<6.66 μm) were calculated and expressed as a percentage of the targeted dose (5 accumulative shot of 50 μg per shot, equivalent to 250 μg). Mass median aerodynamic diameter (MMAD) was calculated assuming linearity between 84% and 16% of the cumulative mass undersize lognormal distribution and the geometric standard deviation (GSD) was determined as $(d_{0.84}/d_{0.16})^{1/2}$. Charge to mass ratio was analysed as total charge and mass of three replicate experiments. Two sample Student t-test heteroscedastic (assuming unequal variances) and one-way ANOVA (unstacked) analysis was performed using STATPlus® statistics software package (AnalystSoft Inc, VA, USA). Significant difference was based $p<0.05$.

## RESULTS AND DISCUSSION

The influence of different active pharmaceutical ingredients, formulated as solution pMDIs, on the aerosol performance and electrostatic charge profiles have been investigated in this study and results are discussed below.

### The Effect of APIs on Overall Aerosol Net Charge Using Different Actuator Materials

The net charge of five different APIs and three different actuator materials were calculated as the total charge derived from the 13 stages of the ELPI. The mean of the three replicate experiments are shown in Fig. 2. Actuator material Nylon and PTFE were selected to represents the extreme of the triboelectric series, with Nylon being positive and PTFE as negative charged materials, respectively. Aluminium is ranked close to neutral and was selected as conducting material for comparison (39).

In general, all three actuator materials showed the same net charge trend across the five active drug ingredients, with BDP, BUD and FS showing positive net charges, while SB and IPBr having negative net charges. Statistical analyses using one-way ANOVA showed no significant differences between nylon, aluminium and PTFE actuators, when the same API was used, but significant difference across different APIs when the same actuators was used (one way ANOVA, $p<0.05$). This is consistent with a previous study where the addition of active drug ingredient in a pMDI formulation diminished the actuator materials' triboelectric effect on aerosol charges (29).

For both Nylon and PTFE actuators, which are insulating thermoplastics with distinctively different static charging trends, BDP, BUD and FS showed positive charges, ranging from 134.78±127.29 pC (BUD with Nylon actuator) to 332.74±86.74 pC (BUD with PTFE actuator), but no significant differences (Student t test, Fig. 2). These results suggest that the API may have a dominant effect on the measured aerosol electrostatic

**Table II** Chromatographic Conditions for the Chemical Assay

| Formulations | Rising solution | Mobile phase (*v/v*) | Column | Flow rate (ml/min) | Injection volume (μl) | UV detection |
|---|---|---|---|---|---|---|
| BDP | 80% Methanol<br>20% $H_2O$ | 68% Methanol<br>32% 0.05% *w/v* Ammonia Acetate aqueous solution | Waters Novapak® C18 | 1 | 100 | 240 nm |
| BUD | 80% Methanol<br>20% $H_2O$ | 60% Methanol<br>40% deionized water | Waters Novapak® C18 | 1 | 100 | 243 nm |
| FS | 80% Ethanol<br>20% $H_2O$ | 35% Acetonitrile<br>65% 1% *v/v* acetic acid solution | Waters Bondapak® C18 | 2 | 50 | 254 nm |
| SB | 80% Methanol<br>20% $H_2O$ | 60% Methanol<br>40% 0.1 *w/v* SDS aqueous solution | Waters Novapak® C18 | 1.5 | 100 | 276 nm |
| IPBr | 100% $H_2O$ | 20% Acetonitrile<br>80% Sodium phosphate Buffer pH4 | Waters Novapak® C18 | 1 | 100 | 210 nm |

All mobile phases were filtrated through a 0.45 μm filter prior to HPLC use

*BDP* Beclomethasone Dipropionate, *BUD* Budesonide, *FS* Flunisolide, *SB* Salbutamol Base, *IPBr* Ipratropium Bromide

charge (Fig. 2). BDP, BUD and FS are all corticosteroids with very similar molecular structures (Fig. 1). They all contain electronegative atoms, such as oxygen and fluorine, capable of dipole-dipole attraction and hydrogen bonding. The interaction between the corticosteroids, HFA 134a and co-solvent ethanol could result in a change of work function for the final aerosol particles, and similar functional groups on the BDP, BUD and FS molecules could produce comparable work functions for the three drugs, inducing similar contact charging profiles with the actuator material surfaces. Additionally, it is important to recognize that triboelectrification between insulators are complex. In theory, electrons would flow from a material with low work function to the one with higher work function. From the net charge results, BDP, BUD and FS all have dominantly positive charge polarity, indicating an electron transfer from the aerosol to the actuator material (Fig. 2, Nylon and PTFE). A possible explanation for such observation could be the presence in the formulation of 15% co-solvent ethanol. A previous study has shown that ethanol reduced the electronegativity of HFA 134 propellant and shifted the net charge for a pMDI aerosol toward positive/neutrality (29). At the same time, interaction between co-solvent, drug and propellant within the formulation could potentially reduce the dielectric properties of the aerosol, hence reducing the work function energy. Lower work function allows the material to lose electrons, which is reflected in the net charge results (Fig. 2).

When BDP, BUD and FS pMDI formulations were used with the conducting aluminum actuator, results showed almost neutral net charge profiles, with significantly lower magnitude compared with nylon and PTFE at an average less than 50 pC (Fig. 2, Aluminum). These results might be due to the fact that the work function of these corticosteroids formulations could be close to the work function of aluminum, hence electrons transfer between the aerosols and material surface is limited after reaching equilibrium. Meanwhile, the conducting property of aluminum allows free movement of electrons within the solid

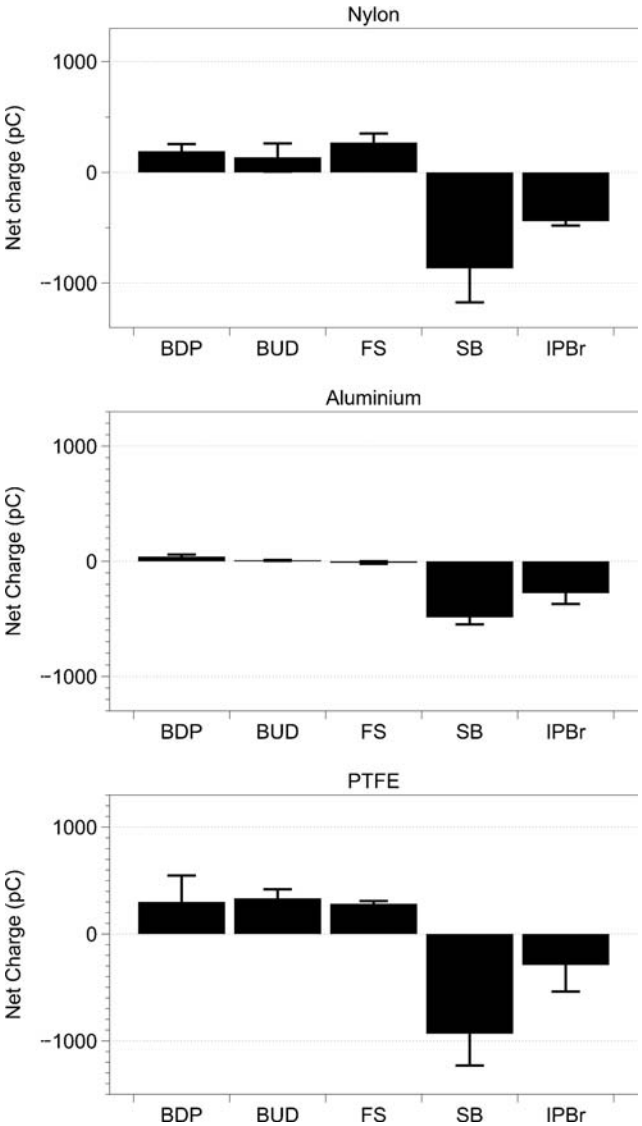


**Fig. 2** Net charge for all APIs with nylon, aluminium and PTFE actuators, ($n = 3 \pm SD$).

body, hence could form a negative electron cloud on the surface of the material and potentially neutralize the positive charges on the aerosol particles after contact charging.

In comparison, significant differences in net charges were observed between SB and IPBr (Fig. 2) with the same actuator material (Student t-test, $p<0.05$) for nylon and PTFE. SB showed a negative charge profile for all three actuators, with the highest magnitude shown with PTFE at $-930.32\pm300.25$ pC (Fig. 2). SB is a short acting $\beta_2$-adrenergic receptor agonist. Its molecular structure contains three hydroxyl groups. It is hypothesized that the strong electronegativity of the HFA 134a propellant may attract hydrogen ions forcing the hydroxyl groups to become hydroxide anions and carry negative charges. Therefore, the overall net charge for SB is negative (Fig. 2).

IPBr also demonstrated negative charge polarity with all actuator materials tested, but with a smaller magnitude, at an average of $-334.52\pm90.73$ pC. IPBr is an anticholinergic drug, with a permanently positively charged ammonium cation and negatively charged bromide ion. The bipolar nature of IPBr could cause potential neutralization of the electrostatic charges generated following triboelectrification of the aerosol droplets with the actuator materials, hence generating a reduced net charge magnitude (Fig. 2).

In is interesting to note that the conducting actuator aluminum did not show significant difference in net charges with SB and IPBr, compared with nylon and PTFE actuators. Probably, due to the functional groups and ions present, the conductivity of SB and IPBr increases and the work function can be reduced. This should cause electrons to flow from the aerosols to the material surfaces, in contrast with the observed results (Fig. 2). These results could be related to the presence of ionic groups within the formulation, depended on the pH of the HFA/ethanol solution. However, since PMDIs are pressurized systems, it is difficult to determine the actual physiochemical properties of the mixture inside the canisters and therefore hard to predict the possible downstream effects of molecular functional groups on aerosol electrostatics. Future studies will investigate this aspect of the project.

## The Effect of APIs on Aerosol Performance Using Different Actuator Materials

Aerosol electrostatic results have shown that the APIs have a dominant effect on pMDI aerosol charge profiles. Since aerosol performance can be influence by both drug formulations and device design, it is important to investigate the aerodynamic properties for the pMDIs and examine the correlation between particle characteristics and static charges.

Cumulative particle size distribution plots were calculated from the cumulative mass under-size for each individual API and are shown in Fig. 3. Statistical analyses using one-way ANOVA showed no significant differences between different drugs for the same material. At the same time, no significant difference was found for the same drug with different actuator materials, indicating different drug ingredients have no influence on particle size distribution for the pMDI formulations. However, significant differences in MMADs were observed across the different APIs for all three actuator materials (one way ANOVA); with values of BDP $0.76\pm0.01$ μm, BUD $0.91\pm0.07$ μm, FS $0.89\pm0.00$ μm, SB $0.70\pm0.02$ μm and IPBr $0.95\pm0.02$ μm, respectively. A general mean GSD value at $2.31\pm0.29$ indicated all pMDI formulations were polydispersed.

Furthermore, total ex-valve dose, throat USP deposition and fine particle fractions less than 6.66 μm were analyzed, based on the percentage of the designed target dose and shown in Figs. 4, 5 and 6. Statistical analyses indicated significant differences in total ex-valve dose between different APIs

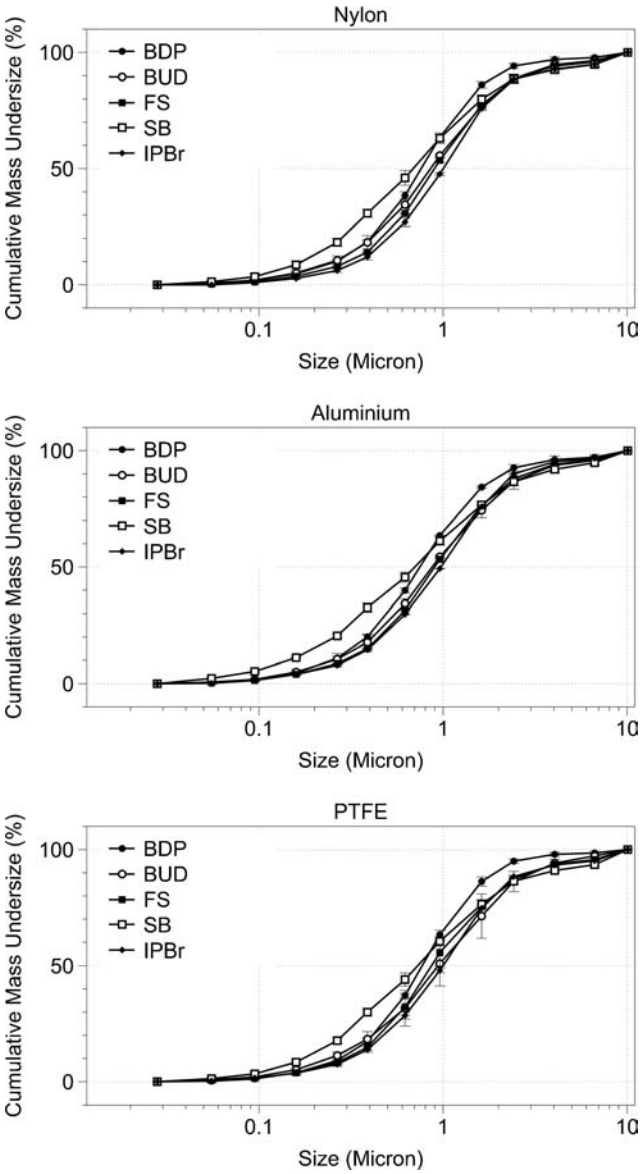


**Fig. 3** Cumulative mass undersize plots for all APIs with nylon, aluminium and PTFE actuators ($n=3$, % CMU ± SD).

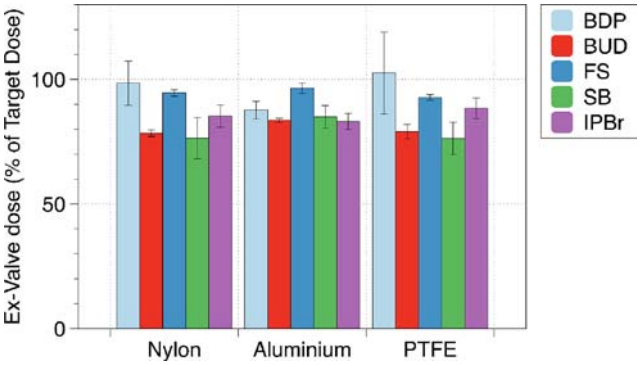


**Fig. 4** Total ex-valve dose for all APIs with nylon, aluminium and PTFE actuators, expressed as % of targeted dose: 5 accumulative shots of 50 $\mu$g per shot equivalent to 250 $\mu$g, ($n = 3 \pm$ SD).

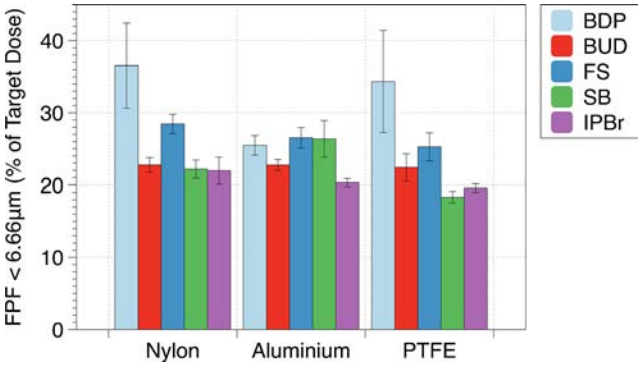


**Fig. 6** Fine particle fraction less than 6.66 $\mu$m for all APIs with nylon, aluminium and PTFE actuators, expressed as % of targeted dose: 5 accumulative shots of 50 $\mu$g per shot equivalent to 250 $\mu$g, ($n = 3 \pm$ SD).

using nylon, aluminum and PTFE actuators. Higher emitted dose were shown with BDP and FS for all three materials, compared with the other three APIs (Fig. 4), suggesting less drug retention in the device. However, the emitted dose for all drugs did not correlate with the static charge profiles, which could be due to reduced charge magnitude (Fig. 2).

Drugs collected in the USP throat for all API formulations are shown in Fig. 5. One-way ANOVA showed statistically significant difference across different APIs for the same actuator material; SB had the smallest USP deposition compared with the other drugs. This is an interesting observation, as SB had the most negative net charge profile. From the molecule structure of SB (Fig. 1), it is know that SB had the lowest density among the five APIs studied. This generates smaller particles after atomization, supported by the small MMAD of SB (0.70 ± 0.02 µm). Although small size particles tends to charge more negatively (41), it could also travel at a higher velocity, limiting the time for the plume expansion effects due to space charge, reducing throat deposition (Fig. 5).

The fine particle fraction (FPF) of particles less than 6.66 µm was calculated based on the drug mass recovered from the ELPI impactor stages and is shown as a percentage of the target dose in Fig. 6. This is a representation of the respiratory fraction of the pMDI formulation that is suitable for lung deposition. Generally, no significant differences were found in FPF for the same drug with different actuator materials; except significant higher fine particle fractions were found with BDP using nylon (36.55% ± 5.91) and PTFE (34.34% ± 7.09) actuators, respectively, compared with aluminum and other pMDI formulations.

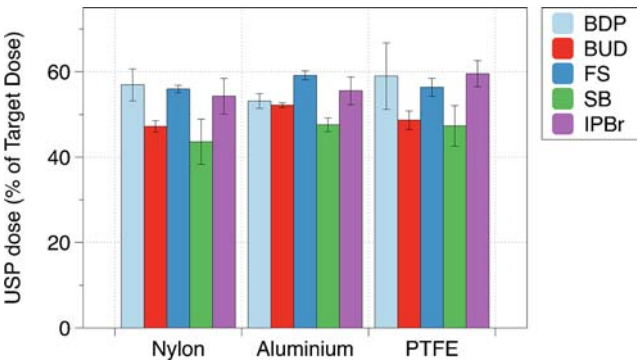


**Fig. 5** Throat USP deposition for all APIs with nylon, aluminium and PTFE actuators, expressed as % of targeted dose: 5 accumulative shots of 50 $\mu$g per shot equivalent to 250 $\mu$g, ($n = 3 \pm$ SD).

Although these results show that larger amount of positive charge particles could result in a higher fine particle fraction, the same results were not observed with other APIs and actuator materials (Fig. 6). In general, there was no clear relationship between the electrostatic charges and aerosol performance, using different APIs.

## The Effect of APIs on Charge to Mass Ratio Using the Aluminum Actuator Material

It is important to note that while there is no clear trend between aerosols charge and aerosol performance, the elementary charge of each particle can be important in understanding the involvement of charges in particle behaviours. To investigate this aspect, mass to charge ratios were calculated by dividing the net charge with the total mass recovery from the impactor. Results are shown in Table III.

Similar trends as the net charge have been observed with the charge to mass ratio. Corticosteroids BDP, BUD and FS had positive elementary charges, with small magnitudes, ranging from 0.65 ± 0.30 pC/µg (BUD with aluminium) to 29.21 ± 8.78 pC/µg (BUD with PTFE) (Table III), respectively. SB

**Table III** Total Charge Per Mass (pC/$\mu$g) of the APIs, ($n = 3$, ±SD)

| API | Nylon (pC/$\mu$g ± SD) | Aluminium (pC/$\mu$g ± SD) | PTFE (pC/$\mu$g ± SD) |
|---|---|---|---|
| BDP | 11.63 ± 3.37 | 3.05 ± 1.69 | 18.48 ± 17.09 |
| BUD | 11.10 ± 10.58 | 0.65 ± 0.30 | 29.21 ± 8.78 |
| FS | 18.19 ± 5.98 | 0.81 ± 0.83 | 21.55 ± 3.89 |
| SB | −73.63 ± 25.28 | −35.46 ± 7.54 | −94.57 ± 30.45 |
| IPBr | −38.23 ± 6.24 | −26.23 ± 6.20 | −28.38 ± 25.05 |

particles carried the most negative charges, especially with PTFE actuator (−94.57±30.45 pC/μg), which is equivalent to an elementary charge of −31.04±12.59 pC per particle. This amount of charge per particle is the highest among all five APIs studied, but is low compared with previous studies. Melandri *et al.* has shown that mono-dispersed particles could increase deposition when particles carried about 200 elementary charges per particle (21,42); where Yu and Chandra found a threshold of 50 elementary charge per particle was required to alter deposition of 1 μm particles (16). Both these studies have demonstrated deposition changes with unipolar charges and mono-dispersed particles. However, the dielectric properties of inhalation pharmaceutical powder show the aerosol will be dominated by bipolar charges, and the GSD value obtained from this study also shows particles are poly-dispersed. Therefore, no clear trends were observed between aerosol electrostatics and aerosol depositions for different APIs. However, it is significant that the use of drug ingredients in pMDI formulation is the determinant in aerosol charge polarity.

## CONCLUSIONS

The API present in a pMDI has a dominant effect on the electrostatic properties of the formulation, overcoming the charge effect arising from the actuator materials. The presence of ionic functional groups in a drug molecule structure significantly influences the polarity of the contact generated electrostatic charges. In this study, no specific trend was observed between the deposition patterns and aerosol electrostatic charge profiles for the five API pMDIs formulations. However, results have shown that the electrostatic charges for a solution-based pMDI could be related to the interactions of the chemical ingredients and change in the work function for the overall formulation.

## ACKNOWLEDGMENTS AND DISCLOSURES

This research was supported under Australian Research Council's Linkage Projects funding scheme (project number ARC-LP100200156) and Chiesi Ltd, Chippenham, Wiltshire, United Kingdom. A/Professor Traini is the recipient of an Australian Research Council Future Fellowship (project number FT12010063). Professor Young is the recipient of an Australian Research Council Future Fellowship (project number FT110100996).

## REFERENCES

1. Global Initiative for Asthma Report: Global Strategy for Asthma Management and Prevention. 2014. Available from http://www.ginasthma.org. Accessed 18 Nov 2014.
2. Global Initiative for Chronic Obstructive Lung Disease (GOLD): Global Strategy for the Diagnosis, Management and Prevention of COPD. 2014. Available from: http://www.goldcopd.org/. Accessed 17 Nov 2014.
3. Newman SP. Principles of metered-dose inhaler design. Respir Care. 2005;50(9):1177–90.
4. Suarez S, Hickey AJ. Drug properties affecting aerosol behavior. Respir Care. 2000;45(6):652–66.
5. O'Doherty M, Miller R. Aerosols for therapy and diagnosis. Eur J Nucl Med. 1993;20(12):1201–13.
6. Hinds WC. Aerosol technology: properties, behavior, and measurement of airborne particles. New York: Wiley-Interscience; 1982. 442 p. 1982;1.
7. Davies CN, Muir DC. Deposition of inhaled particles in human lungs. Nature. 1966;211(5044):90–1.
8. Heyder J. Particle transport onto human airway surfaces. Eur J Respir Dis Suppl. 1981;119:29–50.
9. Lourenco RV, Cotromanes E. Clinical aerosols: I. Characterization of aerosols and their diagnostic uses. Arch Intern Med. 1982;142(12):2163–72.
10. Kwok PCL, Chan HK. Electrostatics of pharmaceutical inhalation aerosols. J Pharm Pharmacol. 2009;61(12):1587–99.
11. Bailey AG. Charging of solids and powders. J Electrost. 1993;30:167–80.
12. Bailey A. Electrostatic phenomena during powder handling. Powder Technol. 1984;37(1):71–85.
13. Rowley G. Quantifying electrostatic interactions in pharmaceutical solid systems. Int J Pharm. 2001;227(1):47–55.
14. Pu Y, Mazumder M, Cooney C. Effects of electrostatic charging on pharmaceutical powder blending homogeneity. J Pharm Sci. 2009;98(7):2412–21.
15. Ingham DB. Precipitation of charged-particles in human airways. J Aerosol Sci. 1981;12(2):131–5.
16. Yu CP, Chandra K. Precipitation of submicron charged-particles in human lung airways. Bull Math Biol. 1977;39(4):471–8.
17. Diu CK, Yu CP. Deposition from charged aerosol flows through a pipe bend. J Aerosol Sci. 1980;11(4):397–402.
18. Thiagarajan V, Yu CP. Sedimentation from charged aerosol flows in parallel-plate and cylindrical channels. J Aerosol Sci. 1979;10(4):405–10.
19. Chan TL, Yu CP. Charge effects on particle deposition in the human tracheobronchial tree. Ann Occup Hyg. 1982;26(1–4):65–75.
20. Saini D, Gunamgari J, Zulaloglu C, Sims RA, Mazumder MK. Effect of electrostatic charge and size distributions on respirable aerosol deposition in lung model. IEEE Ind Appl Soc. 2004;2:948–52.
21. Melandri C, Tarroni G, Prodi V, Dezaiacomo T, Formignani M, Lombardi CC. Deposition of charged-particles in the human airways. J Aerosol Sci. 1983;14(5):657–69.
22. Tarroni G, Melandri C, Prodi V, Dezaiacomo T, Formignani M, Bassi P. An indication on the biological variability of aerosol total deposition in humans. Am Ind Hyg Assoc J. 1980;41(11):826–31.
23. Ferin J, Mercer TT, Leach LJ. The effect of aerosol charge on the deposition and clearance of Tio2 particles in rats. Environ Res. 1983;31(1):148–51.
24. Fraser DA. The deposition of unipolar charged particles in lungs of animals. Arch Environ Health. 1966;13(2):152–7.
25. Vincent JH, Johnston WB, Jones AD, Johnston AM. Static electrification of airborne asbestos—a study of its causes, assessment and effects on deposition in the lungs of rats. Am Ind Hyg Assoc J. 1981;42(10):711–21.
26. Vinchurkar S, Longest PW, Peart J. CFD simulations of the Andersen cascade impactor: model development and effects of aerosol charge. J Aerosol Sci. 2009;40(9):807–22.
27. Finlay WH. The mechanics of inhaled pharmaceutical aerosols: an introduction. London: Academic; 2001.

28. Chen Y, Young P, Fletcher D, Chan HK, Long E, Lewis D, *et al.* The effect of actuator nozzle designs on the electrostatic charge generated in pressurised metered dose inhaler aerosols. Pharm Res. 2015;32:1237–48.
29. Chen Y, Young PM, Fletcher DF, Chan HK, Long E, Lewis D, *et al.* The influence of actuator materials and nozzle designs on electrostatic charge of Pressurised Metered Dose Inhaler (pMDI) formulations. Pharm Res. 2014;31(5):1325–37.
30. Gallo C, Lama W. Classical electrostatic description of the work function and ionization energy of insulators. Ind Appl IEEE Trans. 1976;IA-12(1):7–11.
31. Vick F. Theory of contact electrification. Br J Appl Phys. 1953;4(S2):S1.
32. Skriver HL, Rosengaard N. Surface energy and work function of elemental metals. Phys Rev B. 1992;46(11):7157.
33. Kittel C, McEuen P, McEuen P. Introduction to solid state physics. New York: Wiley; 1976.
34. Singleton J. Band theory and electronic properties of solids. New York: Oxford Univ. Press; 2001.
35. Bailey AG. The charging of insulator surfaces. J Electrost. 2001;51:82–90.
36. Matsusaka S, Masuda H. Electrostatics of particles. Adv Powder Technol. 2003;14(2):143–66.
37. Schlaf R. Tutorial on work function. Tampa: USF Surface Science Laboratory, Dept of Electrical Engineering at University of South Florida; 2007.
38. Hoe S, Traini D, Chan H-K, Young PM. Measuring charge and mass distributions in dry powder inhalers using the electrical Next Generation Impactor (eNGI). Eur J Pharm Sci. 2009;38(2):88–94.
39. Diaz A, Felix-Navarro R. A semi-quantitative tribo-electric series for polymeric materials: the influence of chemical structure and properties. J Electrost. 2004;62(4):277–90.
40. Kwok PCL, Glover W, Chan HK. Electrostatic charge characteristics of aerosols produced from metered dose inhalers. J Pharm Sci. 2005;94(12):2789–99.
41. Lacks DJ, Levandovsky A. Effect of particle size distribution on the polarity of triboelectric charging in granular insulator systems. J Electrost. 2007;65(2):107–12.
42. Melandri C, Prodi V, Tarroni G, Formignani M, De Zaiacomo T, Bompane G, et al. On the deposition of unipolarly charged particles in the human respiratory tract. Inhaled Part. 1975;4:193–201.