Investigation of nozzle designs and material on the electrostatic charge of pressurised metered dose inhaler

Yang Chen[1], Daniela Traini[1], David F. Fletcher[2], Hak Kim Chan[3], David Lewis[4], Tanya Church[4], Paul M. Young[1]

[1]Respiratory Technology; Woolcock Institute of Medical Research and Discipline of Pharmacology; Sydney Medical School; The University of Sydney, NSW 2037, Australia
[2]School of Chemical and Biomolecular Engineering, The University of Sydney, NSW 2006, Australia
[3]Advanced Drug Delivery Group, Faculty of Pharmacy, The University of Sydney, NSW 2006, Australia
[4]Chiesi Ltd, Units T1 - T3, Bath Rd. Ind. Est., Chippenham, Wiltshire, SN14 0AB United Kingdom

SUMMARY

Background: Electrostatic charge plays an important role in particle deposition in pressurised metered dose inhaler (pMDI) and is influenced by factors, such as chemical/physical properties of the formulation and device materials. Charges can accumulate at the sharp edges of the pMDI actuator, leading to electrostatic discharge to the surrounding environment and causing changes in inhalation aerosol charge profile. In this study the influence of different nozzle designs, using conducting and insulating actuator materials, on pMDI aerosols performance was investigated.
Methods: Two actuator materials (aluminium and polyethylene terephthalate), each with four types of nozzle designs (flat, curved flat, cone and curved cone) were tested using the electrical low-pressure impactor (ELPI) for the determination of their electrostatic charge profiles. Beclomethasone (BDP) pMDI solution was chosen as model formulation and drug deposition was analyzed and assayed using high performance liquid chromatography (HPLC).
Results: Curved nozzle designs for the insulating PET actuator significantly influenced charge profiles (-ve polarity to +ve polarity) and drug deposition (ANOVA, $p<0.05$) compared with the metal aluminium actuator. These results are probably due to the change of plume geometry imparted by the curved edge nozzle design. Aluminium flat nozzle shown significantly higher electronegative charge (-249.45pC ± 77.22) and higher induction port deposition (66.78 % of total ex-valve dose), indicating particle deposition is influenced by the electrostatic charge magnitude.
Conclusion: The property of the actuator materials and nozzle designs could both influence aerosol electrostatic charges suggesting that, by choosing different nozzle design and actuator materials combination, drug deposition pattern for pMDI formulations could be altered.

INTRODUCTION

Aerosols emitted from a pMDI are known to be charged (1) and the attraction/repulsion forces generated from such electrostatic charges plays an important role in the deposition mechanisms of pulmonary drug (2). Although both theoretical and experimental studies have established that increased drug deposition is associated with charged particles under suitable conditions (3-6), the mechanisms behind this electrostatic charge generation in pMDI aerosols still remain unclear. This is largely due to the complexity of mechanisms involved during a pMDI actuation. These mechanisms includes: flash-boiling evaporation of the propellant and the solvents, liquid-gas-solid phase transition, material properties of the device/actuator, conductivity and electrostatic potentials of the different pMDI components, generation, accumulation and relaxation of the electrostatic charge on the actuator and aerosols. All these parameter can influence the triboelectric charge properties of the pMDI aerosols.

The mechanism by which a material acquires charges upon contact/friction with another material is called triboelectrification. Furthermore, there are three other ways to gain charges, including electron, ions and materials transfer (7). The electron transfer is the major mechanism for triboelectrification, especially for conductor material contact charging, such as metal. As electrons can move relatively free within the entire conductor body, the accumulated charges on the conductor material show a uniform polarity (8). This creates an electric field within the conductor material, mostly concentrated at the sharp edges of the material. The redistribution of the build up of electrons will then concentrate at those sharp edge regions and eventually leads to dielectric breakdown of the surrounding air, with consequent spark electrostatic discharge (9). Although electron transfer is believed to be the charging mechanism for insulators, such as polymers, there are new studies that have proposed transfer of ions that may already be present on the polymer's surface or acquired from the atmosphere water content as the main mechanism (9-12). The polarity of such acquired charges will largely depend on the acidity and basicity of the polymeric material. Unlike conductors, where build up charges is distributed throughout the material, insulators are unable to allow deep penetration or free movement of the electrostatic charge. Consequently, the accumulated charge would be localised on isolated spots on the insulator's surface with different polarity distribution (12). Electrostatic discharges also arise from insulating materials present at the surface with highest curvature. However, multiple accumulated charge spots on a single insulator surface could discharge simultaneously and lead to brush-like electrostatic discharge (13).

Although it is not well recognized in the pharmaceutical industry, electrostatic discharge has been well investigated in other industrial areas, including particle separation (e.g. recycling) and powder/fuel processing (e.g. mining) (14, 15). Many factors that could influence the nature of the electrostatic discharge include chemical/physical properties of the charged surface, surface geometry and the magnitude and polarity of the electrostatic charge. In a previous study, the pMDI actuator nozzle shape, flat and cone were shown to greatly influence the electrostatic charging dynamics of a BDP solution based pMDI aerosol (16). Also, it was shown that by changing the sharp edges of the flat and cone nozzle design with curved ones, the polarity of the charge profile for the pMDI aerosol with an insulator actuator material like PTFE was completely reversed (17). This study extends the previous investigation to include four actuator nozzle designs and two actuator materials selected from the triboelectric series to further assess their influence on pMDI aerosols triboelectrification.

MATERAILS AND METHODS

A pMDI formulation containing 50µg/dose BDP was prepared with 15% w/w ethanol co-solvent in 1,1,1,2-tetrafluroethane (HFA 134a) propellant using standard aluminium canisters (Presspart Manufacturing Ltd, Lancashire, UK) fitted with 50µl-metered valves (Bespak Europe Ltd, Norfolk, UK). Aluminium and Polyethylene terephthalate (PET) were selected from the triboelectric series and used to make the actuator, as no commercial options are available. Four types of nozzle designs were manufactured including: conventional flat and cone, and curved flat and curved cone, using a laser drill technique (Figure 1). All nozzles had a 0.3 mm aerodynamic atomisation orifice diameter and 1mm jet length. The actuator was fitted with the canister using an in-house designed adaptor constructed via a rapid- prototype printer (Dimension Elite, MN, USA) using acrylonitrile butadiene styrene (ABS) (the actuator/canister/adaptor unit is not earthed). Native charges generated from the pMDI aerosols with different actuator nozzle designs were measured using a modified 13-stage electrical low-pressure impactor (ELPI, Dekati Ltd, Finland), with the corona charger removed. At a flow rate of 30 l/min, 5 consecutive pMDI actuations at an interval of 30 seconds each, were delivered to the impactor and charge data were recorded by the electrometers connected to stage 1 to 12 as current versus time (fA/s). Drug depositions on each stage were recovered and chemical analysis of the BDP was conducted using a validated HPLC method. Three replicates were preformed for each experiment (5 shots per run × 3 runs). The net charge is based on the total charge of the 12-recorded stages of the electrostatic charge profile and mass deposition data is expressed as the mean of 3 repeats, with standard deviation. All experiments were randomised and preformed inside enclosed Perspex box under controlled humidity (~45% RH) using wet or dry air at 25°C.

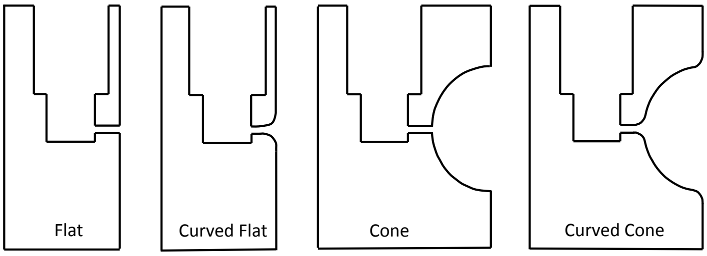

Figure 1: Four actuator nozzle design including flat, curved flat, cone and curved cone, all with an aerodynamic atomization orifice diameter of 0.3mm.

RESULTS AND DISCUSSION

The net charge profile for the pMDI aerosols generated from each nozzle designs and both materials are shown in Figure 2.

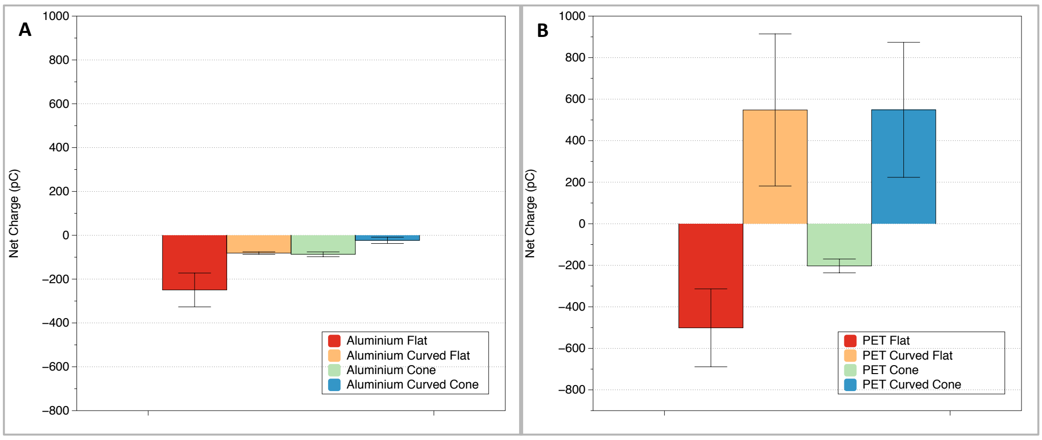

Figure 2: Net charge profiles for all actuator nozzle designs with materials: A- aluminium and B- PET (*n=3;* ±SD).

Generally, the aluminium actuator produced net electronegative charge profiles with magnitude significant lower than the PET actuator. This is consistent with the triboelectric charging behavior of aluminium, classified into the positively charged group and consequently resulting in a negative charged aerosol cloud (Figure 2A). Also, the aluminium conducting property may allow backflow of electrons from the charged aerosols to the actuator material body, resulting in a lesser charge magnitude compared with the PET.

For the PET actuator, the polarity of the charge profiles varied between different nozzle designs and large errors were present throughout the net charge data (Figure 2B). One possible reason is that PET is classified in the negative group of the triboelectric series, but relatively close to the neutral region (18). This would make the material able to charge both negatively and positively, depending on the properties of the other material that come in contact with it. The pMDI formulation used in the study containing HFA 134a, which is fairly non-conducting propellant. However, the addition of the 15% ethanol co-solvent increased the conductivity of the aerosols. This favors the transfer of electrons/ions from the PET surface to the semiconducting droplet during contact charging process, hence resulting in a higher magnitude of net charge profiles (Figure 2).

Statistically significant differences (ANOVA $p<0.05$) in net charge were observed when the curved nozzle designs were compared with conventional nozzles, for both materials. For aluminium, curved flat and curved cone nozzles demonstrated reduced negative charges, compared with the conventional geometries. The negative charge droplets arising from the aluminium actuator are evaporating and the charges carried by such shrinking droplets will eventually reach the Raleigh limit (the amount of charges that can be carried by a droplet with certain size) and bursting into smaller droplets due to the repulsive forces of the same charges present on the surface. Smaller droplets with unipolar charges will repel each other and cause plume expansion, hence increasing the chance of electron exchange with the curved nozzle surface and reduces the charge magnitude in the aluminium actuators. For the PET, the curved designs completely reversed the charge polarity for the flat and cone nozzle. This result is similar to previous findings where Teflon was used as actuator material (17). It was hypothesized that curved nozzle designs changed the plume geometry to have a wider angle due to the lack of defining edges. Therefore, the electron exchange between the outer edges of the aerosol plume with actuator nozzle surface is significantly increased. This results in net electronegative-charged aerosols on the outside region of the plume to have higher chance to deposit on the induction port area. In consequence, the impacted aerosol will be the core aerosols within the plume that has high density of counter charge polarity, which reflected by the net charge results (Figure 2B).

As described before, electrons/ions generated from triboelectrification have a tendency of concentrating at the sharp edge of the actuator nozzle. The possibility of accumulated electrons/ions to discharge to the surrounding environment could alter the electrostatic charge profiles of the pMDI aerosols. However, for both PET and aluminium actuators, there is no sudden reduction or escalation in charge magnitude for the curved nozzle designs compared with the conventional ones. A possible explanation could be related to the fact that electric discharges are normally carried by electrons and both aluminium and PET are positively charged, due to high electronegativity of the HFA 134 propellant resulted from the fluorine elements. Therefore, electrons are concentrated on the evaporating propellant contain droplets, whether discharge of excessive electrons occurs from the aerosols droplets still remains unclear.

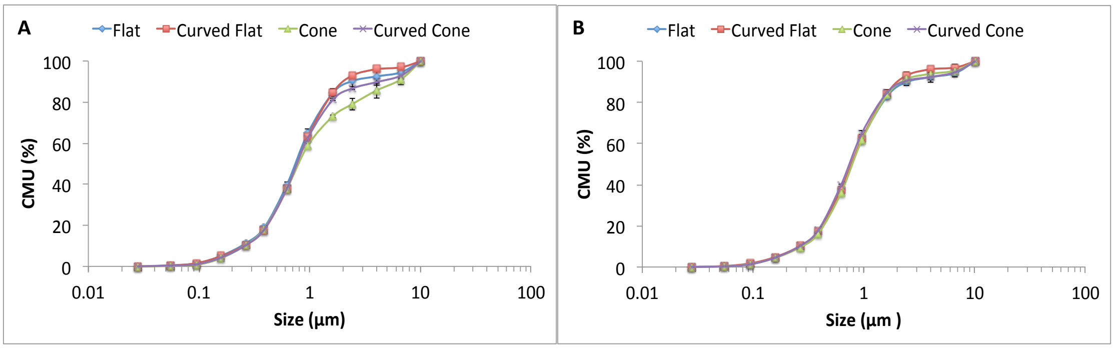

Figure 3: Cumulative mass undersize distribution for all actuator nozzle designs with material A: aluminium and B: PET, (*n=3;* ±SD).

To further understand the relationship between the aerosol charge profiles and the actuator nozzle designs, aerosol performance parameters were analyzed. Particle size distributions are shown as percentage of cumulative mass undersize in Figure 3. No significant differences were observed for all nozzle designs and actuator materials, except for aluminium cone at particle size range from 1.62 to 4.02 µm (one way ANOVA, $p<0.005$) (Figure 3A). These results show actuator nozzle geometry and material have no significant influence on the aerodynamic particle size distribution of pMDI aerosols.

Further analysis of emitted dose (ED), drug deposition in the USP throat region (USP), fine particle fraction (% FPF < 6.66µm) and mass median aerodynamic diameter (MMAD) for all nozzle designs and both materials are shown in Figure 4. No significant differences were observed for MMAD with all four types of nozzle design and both materials, except for aluminium with cone geometry (one way ANOVA, $P<0.5$). This is associated with a lower emitted dose from the pMDI. The aluminum flat nozzle was shown to have the highest USP deposition (Figure 4A), compared with other nozzle designs with the most electronegative charge profile (Figure 2A). This could be the result of plume expansion due to the repulsive force of highly unipolar charged aerosols, indicating that the higher charge magnitude is capable of modifying particle deposition for pMDI. For PET, significantly less emitted dose for cone and curved cone nozzle were observed (one way ANOVA, $p<0.005$), compared with flat and curved flat, possible due to the larger contact surface area present in the cone outer shape (Figure 4B). Although no significant differences were found in the emitted dose for the flat and curved flat PET nozzle, the drug deposition in the USP induction port for the curved flat design was significantly higher than flat nozzle (student t-test, $p<0.05$). This is then reflected again in the USP drug deposition of the curved cone nozzle that was found to be higher than the cone nozzle (student t-test, $p<0.05$). Interestingly, high USP depositions for both curved nozzles are associated with the reversed net charge polarity for the pMDI aerosol with actuator PET (Figure 2B). This supports our hypothesis that curved nozzle designs can have an effect on plume geometry hence increase induction deposition with more negative charged particles.

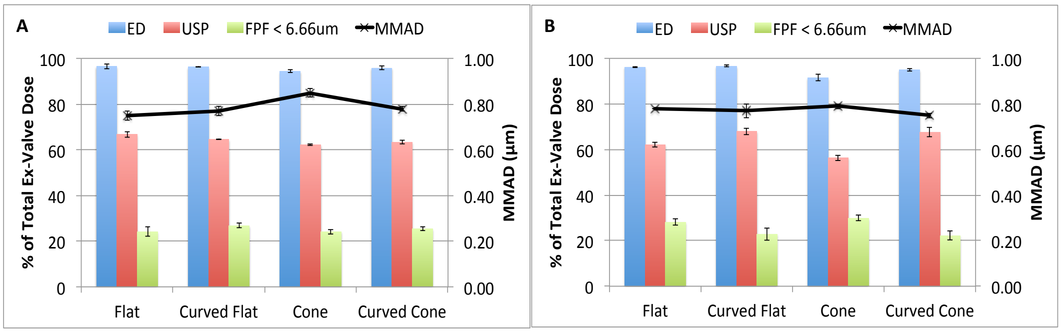

Figure 4: Emitted dose (ED), USP deposition (USP), Fine particle fraction (% FPF < 6.66um) and mass median aerodynamic diameter (MMAD) for the pMDI formulation with all nozzle designs for both material A: Aluminium and B: PET (*n=3;* ±SD).

CONCLUSIONS

In summary, four different pMDI actuator nozzle designs built with two different materials, aluminium and PET were investigated for their effect on aerosol electrostatic charges using a BDP solution based pMDI formulation. It was found that curved nozzle designs built with an insulating polymer, like PET, could influence the electrostatic charge and particle deposition patterns of pMDI aerosols. Aluminium did not show the same trend, but showed high induction port deposition associated with high electrostatic charge magnitude, which could result from plume expansion by the repulsion force from unipolar charged aerosols. However, due to the different contact charging mechanism of conductor and insulator, it cannot be definitely concluded that electrostatic discharge is influencing triboelectrification of the pMDI aerosols. Future studies using high speed imaging of the plume pattern and droplet size distribution are underway and have the potential to corroborate our hypothesis.

REFERENCES

1. Kwok PCL, Glover W, Chan HK. Electrostatic charge characteristics of aerosols produced from metered dose inhalers. J Pharm Sci-Us. 2005 Dec;94(12):2789-99. PubMed PMID: ISI:000233733300018. English.
2. Kwok PCL, Chan HK. Electrostatics of pharmaceutical inhalation aerosols. J Pharm Pharmacol. 2009 Dec;61(12):1587-99. PubMed PMID: ISI:000281136700002. English.
3. Ingham DB. Precipitation of Charged-Particles in Human Airways. J Aerosol Sci. 1981;12(2):131-5. PubMed PMID: ISI:A1981LN21400005. English.
4. Diu CK, Yu CP. Deposition from Charged Aerosol Flows through a Pipe Bend. J Aerosol Sci. 1980;11(4):397-402. PubMed PMID: ISI:A1980KM94500007. English.
5. Chan TL, Yu CP. Charge Effects on Particle Deposition in the Human Tracheobronchial Tree. Ann Occup Hyg. 1982;26(1-4):65-75. PubMed PMID: ISI:A1982PT13100006. English.
6. Melandri C, Prodi V, Tarroni G, Formignani M, Bompane GF, Dezaiacomo T, et al. Deposition of Unipolarly Charged-Particles in Human Respiratory-Tract. Health Phys. 1977;33(3):273-. PubMed PMID: ISI:A1977EA33600022. English.
7. Lowell J, Rose-Innes A. Contact electrification. Advances in Physics. 1980;29(6):947-1023.
8. McCarty LS, Whitesides GM. Electrostatic charging due to separation of ions at interfaces: contact electrification of ionic electrets. Angewandte Chemie International Edition. 2008;47(12):2188-207.
9. Thomas SW, Vella SJ, Kaufman GK, Whitesides GM. Patterns of electrostatic charge and discharge in contact electrification. Angewandte Chemie. 2008;120(35):6756-8.
10. Castle G. Contact charging between insulators. J Electrostat. 1997;40:13-20.
11. Lewis T. Charge transport, charge injection and breakdown in polymeric insulators. Journal of Physics D: Applied Physics. 1990;23(12):1469.
12. Williams MW. Triboelectric charging of insulating polymers–some new perspectives. AIP Advances. 2012;2(1):010701-9.
13. Fredholm O, Lovstrand K. On the discharge of static electricity from an insulator surface. Journal of Physics E: Scientific Instruments. 1972;5(11):1058.
14. Miller HC. Flashover of insulators in vacuum: review of the phenomena and techniques to improved holdoff voltage. Electrical Insulation, IEEE Transactions on. 1993;28(4):512-27.
15. Oda T, Ito Y. Studies on electrostatic surface discharges on corona-charged polymer surfaces. Industry Applications, IEEE Transactions on. 1990;26(4):656-61.
16. Chen Y, Wong WHW, Lewis DA, Church T, Traini D, Young PM. Triboelectrification Study of a Pressurized Metered Dose Inhaler (pMDI) Formulation Using Different Actuator Materials and Orifice Designs. Respiratory Drug Delivery 2012. 2012;Vol 3:845-50.
17. Chen Y, Traini D, Fletcher DF, Chan HK, Lewis DA, Church T, et al. The Effect of Pressurized Metered Dose Inhaler (pMDI) Actuator Nozzle Design on Triboelectrification and Aerosol Deposition. RDD Europe 2013 (2013). 2013;2:439-44.
18. Diaz AF, Felix-Navarro RM. A semi-quantitative tribo-electric series for polymeric materials: the influence of chemical structure and properties. J Electrostat. 2004 Nov;62(4):277-90. PubMed PMID: ISI:000224503900003. English.