CHARACTERISATION OF THE ELECTROSTATIC PROPERTIES OF PMDI FORMULATIONS VIA ELECTROSTATIC LOW PRESSURE IMPACTOR MEASUREMENTS (ELPI™)

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Aims and Objectives

The main aim of the study was to investigate the electrostatic properties of CFC and HFA formulated aerosols from placebo and commercial pMDIs, and to evaluate the use of a relatively new instrument, the Electrical Low Pressure Impactor (ELPI™), for particle size and aerosol electrostatic measurements.

Introduction

The reformulation of CFC driven MDIs with HFA-MDIs has provided the opportunity for technical improvements in the pharmaceutical performance characteristics of MDIs. However, with the unwanted problems associated with reformulation, such as insufficient solubility of surfactants and incompatibility of HFA propellants with valve gasket materials, several pertinent changes to the characteristics of HFA propelled formulations have been somewhat overlooked. One such area is aerosol electrostatics. Aerosol particles generated from pMDIs are ubiquitously charged, and have been found to play a critical role in the deposition characteristics within spacer devices and human airways. *In-vitro* studies have shown that drug loss inside a large polycarbonate spacer devices from a CFC driven salbutamol pMDI can be as high as 81% w/w of the metered dose[1]. Similarly, multiple actuations of a salbutamol CFC-pMDI into a large polycarbonate volume spacer prior to inhalation reduces the amount of drug available to the patient by 60%, when compared to a single actuation followed by inhalation, repeated the same number of times[2]. Interestingly, studies of drug delivery from a salbutamol HFA-pMDI via a large volume polycarbonate spacer was found to be twice that of a CFC formulation via the same spacer[3]. A theoretical computer model study of inhaled charged aerosols has predicted that inherent charges carried by aerosol particles have a significant effect on the deposition pattern within the respiratory tract[4]. The model, based on Weibel's symmetrical A model for the lung, demonstrated that by increasing the particle charge from 1 electronic (elementary) charge per particle to 1700 electronic (elementary) charge per particle led from an initial increase deposition efficiency in the lower respiratory tract, due to image charge forces, to the domination of space charge forces, and a corresponding shift in deposition to the upper respiratory airways. Thus, a knowledge of material and formulation factors, which influence inherent charge of particles upon aerosol generation, and the possibility for controlling charge to mass ratio of aerosol particles may play an important role in characterising and increasing the deposition efficiency in human airways of novel pMDI generated aerosols. In this study, we have utilised the use of a relatively novel instrument, the Electrical Low Pressure Impactor (ELPI™), for real time particle size and aerosol electrostatic measurements of the aerosol properties of placebo and commercial CFC and HFA driven suspension formulations of salbutamol sulphate.

Apparatus

The ELPI™(electrical low pressure Impactor) is based on the Berner type multijet low pressure Impactor. In its standard operational mode, the ELPI™ enables real time particle size distribution and concentration measurements in the size range of 0.03 – 10 µm, without the need of analysing the mass on each impactor stage by chemical methods[5]. Measurement is based on very sensitive electrometers, which measures the electrical current as corona charged aerosol particles impact on each of the electrically isolated impactor stages (Figure 1). The precisely known charge (ca. 5kV), induced on the particles by ion bombardment, allows the electrical current signals to be converted to aerodynamic size distributions (number, area, volume) using properties relating to the charger efficiency values and the effective cut-off diameters of each impactor stage. Currents are measured versus the cut-off size range (d_{50}) of each impaction stage. In conjunction with a 10.5µm pre-separator, the effective cut-off diameters for each impaction stage at 10 l/min is shown in Table 1. With the corona charger turned off, the ELPI can also be utilised as a 12 stage size classified electrometer. In the electrometer mode, measurement of electrical currents from each electrically isolated impactor stage allows direct characterisation of the electrostatic nature of the aerosol cloud generated from pMDI inhalers.

By measuring the properties of an aerosol in the two operating modes (charger on and off), the following parameters can be measured:

1. Real time aerodynamic size distribution (number, area, volume, mass) of an aerosol.
2. Mean charge distribution of an aerosol cloud as a function of particle size.
3. Total charge to mass ratio of the delivered dose (<10.5µm).
4. Mean (elementary) electrical charges of the active drug as a function of particle size.

Stage	1	2	3	4	5	6	7	8	9	10	11	12	13*
D50% (µm)	0.030	0.060	0.0108	0.170	0.260	0.400	0.650	1.000	1.600	2.500	4.400	6.800	10.000

Table 1: The effective cut-off aerodynamic diameters corresponding to 50% efficiency for each impactor stage at 10 l/min.

Materials and Methods

The ELPI™ was evaluated with commercial 100µg salbutamol sulphate chlorofluorocarbon (CFC) (Ventolin Inhaler®) and hydrofluoroalkane (HFA) (Ventolin Evohaler®) driven pMDI products (GlaxoSmithKline), and their associated drug free placebos. Aerosols from pMDI devices were introduced to the ELPI™ via a 10cm glass extension tube (ϕ_d = 30mm) to allow evaporation of the propellant and to minimise impaction of the high-velocity aerosol cloud released from the pMDI to the walls of the entry port of the ELPI™ and the corona charger. The nominal air flow through the system was maintained at 10l/min. For particle size distribution measurements (charger on), five actuations from a new device were shot to waste followed by six cumulative shots into the ELPI™. The electrical currents collected from different stages of the impactor are subsequently converted to a mass distribution by multiplying the current distribution by the conversion vector and by a vector formed from the masses of spheres having diameter equal to the cut off diameter of each stage. For purely electrostatic measurements (charger off), the five shots to waste were followed by 10 sequential shots into the ELPI™. By simply integrating the area under each curve, a mean charge distribution of the aerosol for each impactor stage could be determined.

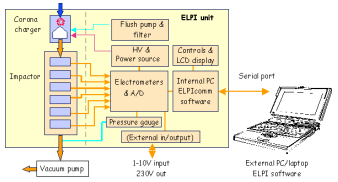


Figure 1: Schematic representation of the ELPI™ system

Results and Discussion

Representative current versus time responses from each impactor stage in the electrometer mode for a placebo HFA 134a formulation are shown in Figure 2. The sinusoidal type response at the upper stages is characteristic of an aerosol going through the upper stages without being collected. A negative image current peak is induced as the negatively charged particles enter the stage and a positive current peak is formed as the particles leave the stage, without being collected. The resultant current over these two peaks is zero. However, as the aerosol concentration changes, due to inertial impaction and propellant evaporation, the image current produced by leaving and entering particles may not be cancelled out and a representative current peak is formed.

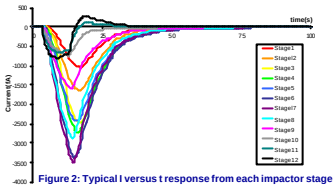
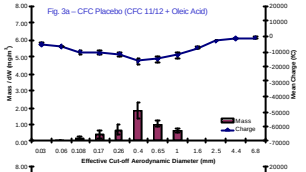
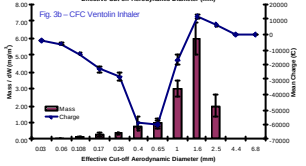


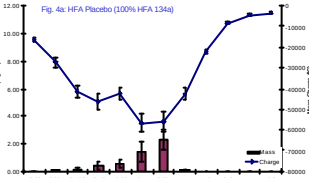
Figure 2: Typical I versus t response from each impactor stage

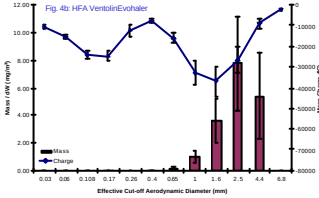
The mean charge and mass distribution for CFC and HFA propelled placebo and commercial pMDI devices are shown in Figures 3(a,b) and 4(a,b) respectively. For the placebo CFC system (CFC 11/12 + oleic acid), a small electronegative response was measured at each electrometer, with a maximum response centered at the 0.40 µm impaction stage. The presence of the oleic acid gives rise to the low aerosol concentration mass distribution. The addition of the salbutamol sulphate drug gave rise to a bipolar response in the electrometer mode. As for the placebo, negligible charges were measured on the 6.8µm and 4.4µm cut-off stages, purporting minimal inertial impaction. Such behaviour is indicated in the particle mass distribution. A electropositive response was subsequently measured at the 2.5µm and 1.6µm cut-off stages. The deviation from the electronegative response of the placebo suggests that the positive charge is induced by the presence of the salbutamol salt. By comparing mass distributions, for placebo and Ventolin inhaler, it is apparent that the electropositive signal relates to the inertial impaction of the suspended drug. As the aerosol cloud continues to travel through the inertial impactor the aerosol experiences a sharp change in polarity, to a highly electronegative signal. The sudden change in polarity is evident at the cut-off collection diameters around 1.0µm, with the maxima between 0.4µm and 0.65µm. The origin of the electronegative response remains somewhat unclear.





For HFA driven systems, electronegative signals were measured, in the electrometer mode, on all impaction stages. For the placebo (100% HFA 134a), a large electronegative current was measured with a corresponding maximum charge of -56pC centered at 0.4µm -0.65µm. The mass distribution of the propellant spray gave rise to a very low aerosol concentration, with negligible inertial impaction for aerodynamic diameters above 1µm. With the introduction of the salbutamol sulphate (Ventolin Evohaler), the mean electronegative charge on each impaction stage decreased quite significantly in comparison with the placebo system. Furthermore, although similar profiles were observed for the two systems, the shift in the maximum response to the upper impaction stages corresponded to the increased inertial impaction of the active drug at these stages (Figure 4b). The decrease in the electronegative nature of the aerosol cloud for the commercial HFA system may possibly be due to a complex contact electrification process during actuation from the inhalation device; whereby, the salbutamol sulphate drug charges electropositively, and to a lesser degree, than the electronegative charge of the hydrofluoroalkane propellant. As a result, the net response from the aerosol cloud is a concomitant decrease in the electronegative signal. Previous measurements of the triboelectric charging of micronised salbutamol sulphate particles, in air, with plastic and metal components were found to induce a net electropositive response[6].





By summating the individual charges for each impaction stage, the net electrostatic behaviour of an aerosol cloud can be elucidated for the aerosol particles (not only active drug) with aerodynamic diameters less than 10µm. The boxplot in Figure 5 shows the total mean charge of the commercial suspension pMDI formulations and their corresponding placebos. The red filled circles are the mean values for n=10 measurements. As expected, the CFC vehicle gives rise to a net increase in the electrostatic properties of an aerosol cloud. Furthermore, it is envisaged that augmented problems may exist for particles which triboelectrically charge electronegatively with the materials of a HFA pMDI device.

Conclusions

- HFA driven placebo and commercial Ventolin pMDI aerosols were omni-electronegative, whilst CFC Ventolin aerosols were bipolar.
- Placebo measurements indicate that HFA propellants have a higher propensity for triboelectric charging than CFCs.
- The ELPI allows real time measurement of particle size distributions and electrostatic properties of aerosols generated from pMDI inhalers.

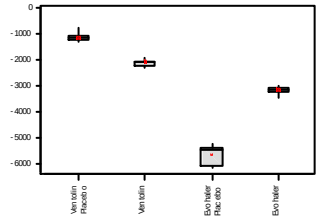


Figure 5: The total net charge for CFC and HFApMDIformulations

Acknowledgement

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