The Bipolar Next Generation Impactor (bp-NGI) as a Tool for the Simultaneous Measurement of the Bipolar Charge Distribution and Mass Quantification of Aerosols for Inhalation

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Summary

Interest in the nature of electrostatic charge build up on aerosol particles for inhalation has grown as pharmaceutical scientists seek to fully understand this complex phenomena and its influence on both pMDI and DPI performance. The net charge to mass ratios of aerosol particles have been measured with systems such as the ELPI [1] and the eNGI [2]. Bipolar charge measuring systems (BCMS) such as those developed by O'Leary et al. [3] and Kulon et al. [4] are capable of measuring the bipolar charge distribution of aerosols particles but are not ideally suitable for simultaneous mass determination. To overcome these limitations, the authors present a novel system for the simultaneous bipolar charge and mass quantification of inhalation aerosol particles using a specially designed Bipolar Next Generation Impactor (bp-NGI). The system utilises an electrostatic precipitation system consisting of both negative and positive electrodes and precipitation tubes which can be connected to any stage of an NGI, to a preseparator or USP throat. Negative and positive high voltages are applied to each electrode allowing electrostatic precipitation of the correspondingly charged aerosol particles onto the inner surfaces of the tubes. The tubes are connected to an electrometer, providing charge measurements of the aerosol particles deposited. The system can subsequently be dismantled and washed down with solvent so that quantification of the aerosol particles via reverse phase HPLC may be performed. The system was successfully employed to quantify the bipolar charge to mass ratios of Flixotide™ 250 pMDI.

Introduction

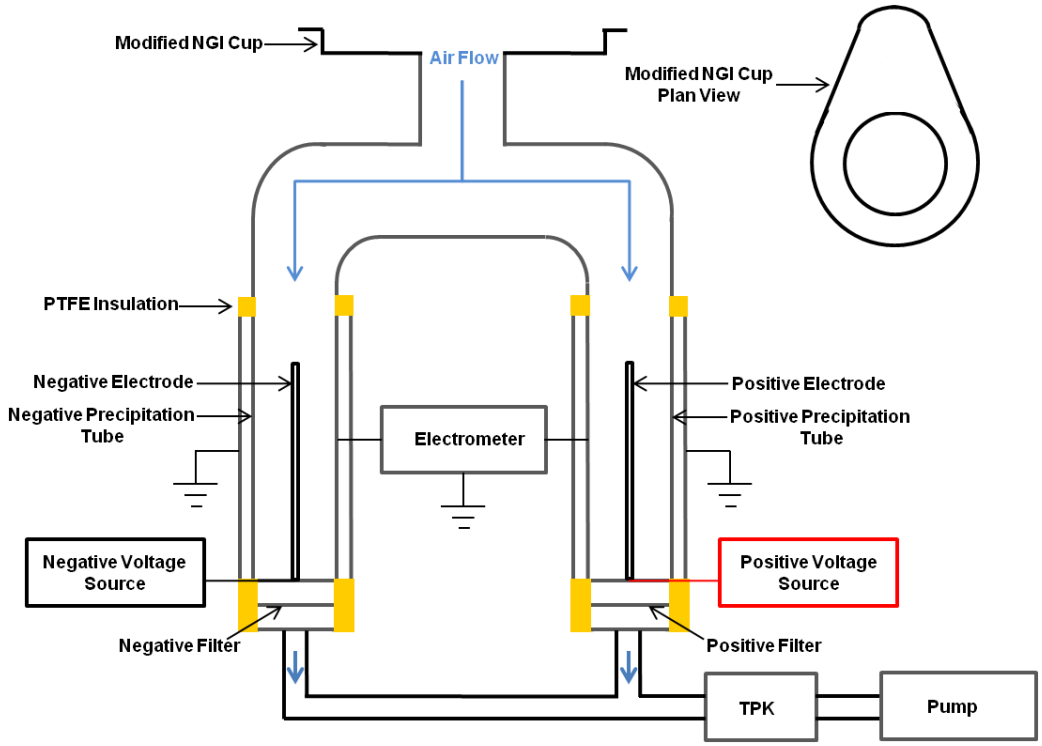
It is well known that upon aerosolisation of either a DPI or pMDI both carrier and drug particles present in the formulation are highly susceptible to becoming electrostatically charged via the mechanism of triboelectrification [5, 6]. Upon aerosolisation particles may enter a highly energetic state and may undergo numerous collisions with each other and with the inhaler during which, electron transfer may occur causing the creation of highly charged species. The precise mechanisms remain relatively poorly understood and so to rectify this various attempts have been made to accurately quantify the charge build up on aerosol particles in proportion to their mass and surface area. The first widely available commercial method developed was the ELPI (electrical low pressure impactor) in which an Andersen cascade type impactor was modified such that the impaction plates are electrically isolated and connected to electrometers allowing for simultaneous net charge measurements and mass quantifications to be performed [1]. The idea was taken further with the development of the Electrical Next Generation Impactor (eNGI) [2] in which the impaction cups of a conventional NGI are connected to an electrometer in a similar way as the ELPI and the net charge to mass ratios of aerosol particles are determined. These two systems also allow the mass of the aerosol particles to be quantified but both do not take into account the bipolar nature of the aerosol particles and only provide a measurement of the net of the negative and positive charges. Alternatively, by using the principals of electrostatic precipitation, systems such as those developed by O'Leary et al. and Kulon et al. [3, 4] allow the bipolar charge ratios of aerosol particles to be measured. However, these systems are not ideally suitable for performing accurate quantification of the deposited aerosol particles and as such do not provide the complete picture in terms of measurement of bipolar charge to mass ratios. To further the understanding of inhalation aerosol electrostatics, the authors present a novel apparatus for performing bipolar charge measurements and quantifications of aerosol particles – the Bipolar Next Generation Impactor (bp-NGI) which has been successfully used to characterise the bipolar charge to mass distributions of Flixotide™ pMDI.

Materials and Methods

Reverse phase high performance liquid chromatography (RP-HPLC) was performed using a PU-980 pump, AS-950 autosampler, a UV-975 UV detector and CO-965 column oven (Jasco Ltd. Essex, UK). Quantification of fluticasone in Flixotide™ was performed with a flow rate of 1.5mL/min, wavelength of 235nm, injection volume of 100µL, column temperature 40ºC. The mobile phase was 45:35:20 MeOH:ACN:deionised water (v/v). The column was an ODS hypersil, 200x4.6mm, 5µm. The retention time for fluticasone propionate was 2.43 minutes. Charge Measurements were performed using a 6517B electrometer, 6521 scanner card and KUSB-488B USB connector (Keithley Instruments Inc., Berkshire, UK) connected to a PC with Testpoint Version 6 software for data acquisition. The NGI, TPK and flow meter were purchased from Copley Scientific (Nottingham, UK).

A schematic representation of the bp-NGI is shown in Figure 1. The apparatus employs two electrostatic precipitators which efficiently collect both negatively and positively charged aerosol particles. Aerosol particles travel through the particular NGI stage and the flow is bifurcated into the two precipitators with one electrode being held at a high negative voltage and the other at the same but opposite polarity voltage with high voltage sources (Spellman, CZE1000R, West Sussex, UK). Negatively charged particles are repelled by the negative electrode and are deposited onto the negative precipitation tube and positive electrode. Positively charge particles are similarly deposited onto the negative electrode and are repelled by the positive electrode onto the positive precipitation tube. Aerosol particles with a very low electrical mobility, which are not precipitated onto either the electrodes or the precipitation tubes are collected on 0.45µm filters (Whatman, Fisher Scientific, UK) housed at the base of each precipitation tube.

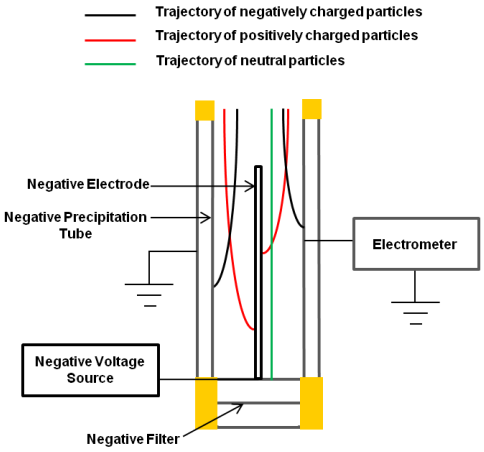
Figure 1. Electrostatic precipitation section of bp-NGI



An example of the particle trajectories within the negative precipitation section is shown in Figure 2. The flow rate is controlled by a TPK attached to a vacuum pump and is set with the flow meter. The dimensions of the bp-NGI were designed to ensure laminar flow is maintained with a Reynold's number of 424 at 30L/min. The precipitation tubes are connected via BNC (Bayonet Neill-Concelman) adapters and coaxial cables to a Keithley Instruments 6521 multi input scanner card which is connected to the electrometer for charge measurements. The system is modular in nature so that each part may be separately washed down for drug quantification via RP-HPLC. The operator is connected to earth at all times via a wrist band and the outer tubes surrounding the precipitation tubes are also connected to earth to create a Faraday shield from external electric fields and stray charges to further ensure the accuracy of the measurements.

The bp-NGI was set up to collect drug deposited on stages two and below via a conventional NGI. Five shots of Flixotide™ 250 (Allen and Hanbury's Ltd. Middlesex, UK) were fired through the bp-NGI and measurements of the electrostatic charge of the positively and negatively charged particles were performed for each shot. The mass of the negatively, positively and neutrally charged particles was quantified via RP-HPLC to calculate the bipolar charge to mass distribution within the bp-NGI. The experiments were performed in triplicate for statistical robustness. The voltage applied to the negative electrode was -3000V and the positive electrode was +3000V. The temperature range for all experiments was 20ºC ± 1 and the humidity range was 40% ± 2. The flow rate of the NGI was set to 30 L/min with 15 L/min pulled through each precipitator as a result of the bifurcation.

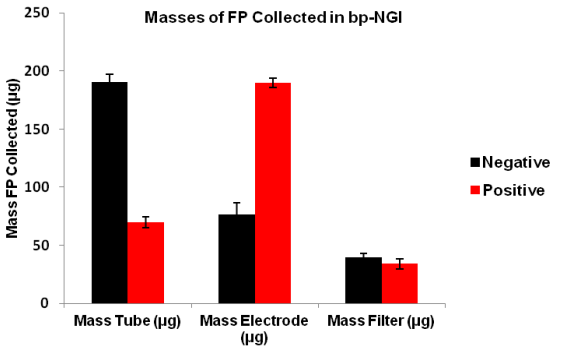
Figure 2. Example of particle trajectories within the negative precipitation section

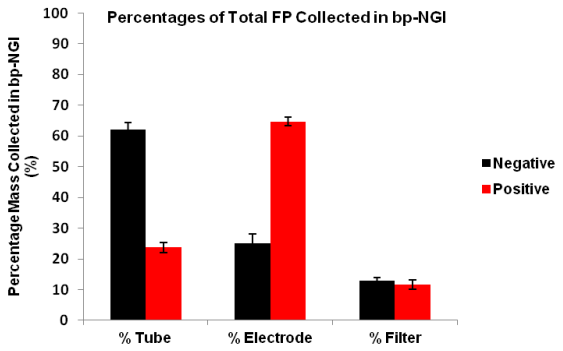


Results and Discussion

The mass deposition profile within the bp-NGI of fluticasone propionate (FP) from a commercial Flixotide™ 250 pMDI is shown in Figure 3. These data are expressed in terms of the mean quantity of drug deposited on each of the precipitation tubes, electrodes and filters and the percentage of the total amount of drug entering each precipitation section.

Figure 3. Mass and percentage mass of negative, positive and neutral particles of fluticasone propionate from 5 shots of Flixotide™ 250µg (n=3, mean ± SD).





Mass FP (µg) Collected in Precipitator Sections (n=3)				
	Precipitation Section			
	Negative	SD	Positive	SD
Mass Tube (µg)	190.27	7.05	69.86	4.94
Mass Electrode (µg)	76.78	9.74	190.08	3.98
Mass Filter (µg)	39.83	3.23	34.01	4.57
Total (µg)	306.88	20.03	293.94	13.49

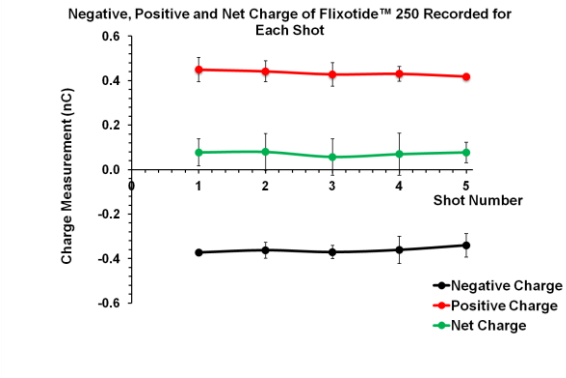
Percentages FP (%) Collected in Precipitator Sections (n=3)				
	Precipitation Section			
	Negative	SD	Positive	SD
Percentage Tube (%)	62.00	2.30	23.77	1.68
Percentage Electrode (%)	25.02	3.17	64.67	1.36
Percentage Filter (%)	12.98	1.16	11.57	1.55
Total (%)	100.00		100.00	

The results show that similar quantities of FP enter each precipitation section of the bp-NGI (306.88 ± 20.03µg in the negative section and 293.94 ± 13.49µg in the positive section) indicating an efficient bifurcation of the aerosolised particles as expected. The percentage of uncharged particles in each section is low with 12.98 ± 1.16% and 11.57 ± 1.55% captured on the negative and positive filters respectively. The mass ratio of negatively to positively charged particles on the precipitation tubes is in the region of 2.5:1.

The charge measurements for the negatively and positively charged FP particles per shot are illustrated in Figure 4. These data show both the individual negative and positive charge recorded per shot as well as the calculated

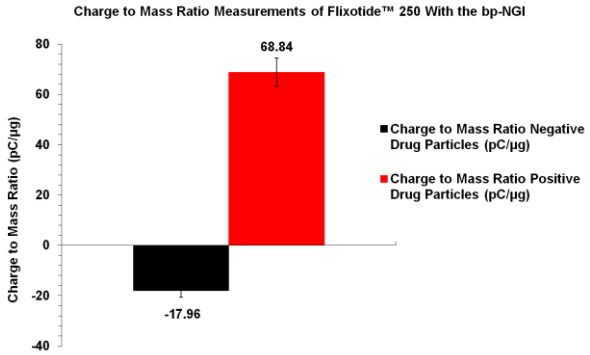
net charge of the particles. The average negative charge measured per shot was -0.335 ± 0.026nC while the average positive charge recorded was +0.459 ± 0.029nC.

Figure 4. Graph of Negative, positive and net charge of fluticasone propionate particles for each shot of Flixotide™ 250 (n=3, mean ± SD).



The corresponding charge to mass ratios of the negatively and positively charged particles of FP are shown in Figure 5 and are calculated by dividing the sum of the charge of each set of 5 shots measured on each of the negative and positive precipitation sections with the total mass of drug collected on each of the precipitation sections. The results show that even though there are 2.5 times the number of negatively to positively charged particles, the charge to mass ratio of the positively charged particles (+68.84 ± 5.58pC/µg) is significantly higher than for the negatively charged (-17.96 ± 2.76pC/µg).

Figure 5. Charge to mass ratios (pC/µg) of negatively and positively charged fluticasone propionate particles from Flixotide™ 250 (n=3, mean ± SD).



Conclusions

The authors present a novel system for measuring the bipolar charge to mass ratios of pharmaceutical inhalation aerosols using a modified Bipolar NGI (bp-NGI). The apparatus has been successfully employed to measure the electrostatic properties of Flixotide™ 250 pMDI. Further work will investigate dose strength, flow rate, and relative humidity to determine the effect on the bipolar charging characteristics of pMDI and DPI formulations.

References

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