The electrical Next Generation Impactor

An improved methodology for characterizing electrostatic charge distribution across the entire particle size range of an aerosolized inhalation formulation

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Triboelectrification, the process by which particles pick up electrical charges as a result of friction, inevitably occurs during mixing, handling, and aerosolization of inhalation formulations. Charges on the particles of aerosol clouds can have significant effects on product performance, affecting the detachment of active pharmaceutical ingredient (API) from the carriers used in some DPI formulations, as well as deposition in delivery devices and in the lungs [1-4]. In some cases, such as when a patient generates a charge in an MDI spacer by rubbing it with a cloth instead of air drying, resulting in the deposition of the majority of the dose on the inside of the spacer, the consequences of electrostatic charging can be very serious.

In order to solve product performance problems that result from triboelectrification, formulators need to understand the nature of the charges generated within aerosolized formulations. Obtaining the necessary data, however, has proved difficult due to the extreme complexity and dynamic nature of the aerosol systems, in which particles of different sizes may acquire different charges; humidity and temperature may change during aerosolization; and charges on other components of the system may vary. For example, pMDIs generate a rapidly-cooling propellant aerosol, while DPIs often contain micron-sized particulates mixed with larger carrier materials that separate during the aerosolization process, complicating the measurement.

An ideal instrument for characterizing the charges on aerosol particles would provide data showing the distribution of charge across the particle size distribution at patient relevant flow rates (30-100 L/min). To meet this need, the University of Sydney has developed a system using a modified Next Generation Pharmaceutical Impactor (NGI). The electrostatic NGI (eNGI) represents a major advance in the ability of formulators to obtain information about charges generated in pharmaceutical aerosols.

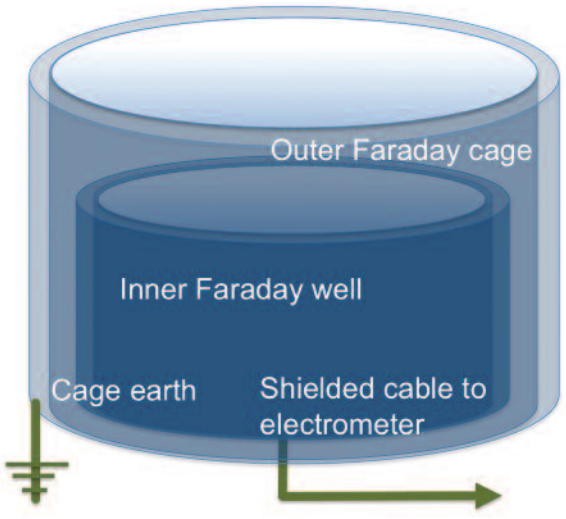
The need for a new instrument

Historically, scientists have used the Faraday cup (Fig. 1) to study charge in droplet or particle masses, a method limited to the bulk state [5-7]. The Faraday cup measures the charge induced in a particle mass as the particles pass into an electrically conducting chamber from a current known as an image charge in the surrounding walls. An outer Faraday cage surrounds a well, eliminating ambient induction of current flow in the well by external fields such as radio waves. The resultant current induced in the particle mass is transferred via an insulated wire to an electrometer, and integrating the current measured over time gives the bulk charge.

The standard Faraday cup measures only the charge of the entire formulation bulk and cannot measure

Figure 1

Basic schematic of the Faraday cup



the dynamic properties of aerosol clouds. Modified flow-through cups can measure the charges on aerosols as the clouds pass through [8]; however, these systems are still limited to bulk characterization. Although bulk aerosol characterization provides a significant amount of information, the dynamic nature of inhaler formulations and the non-linear nature of their size distributions make measuring their charges accurately extremely complex.

Measuring charge across a size distribution

Studying the aerosol cloud during particle size analysis provides an obvious solution to the problem of monitoring the dynamics of electrostatic charging during aerosolization. The two most common pharmacopoeial methods for measuring the aerodynamic particle size distribution of inhalation aerosols, the standard NGI and the Andersen cascade impactor (ACI), lack the ability to measure electrical charge; however, with some modification, a cascade impactor can reproduce the conditions inherent in a series of Faraday cups, leading to the possibility of characterizing electrostatic charge in conjunction with particle size.

Cascade impactors consist of a series of stages, each of which includes an arrangement of nozzles through which the particle-laden air passes and a collection plate. At each successive stage, the nozzle configuration results in an increased velocity so that smaller and smaller particles gain enough inertia to impact on the collection plate. Each stage has a particular cut-off diameter that describes the size of the particle that will impact the plate in that stage.

In the modified NGI, each whole stage assembly in the cascade impactor represents a "cage," and each collection plate serves as an isolated "cup" (Fig. 2). Particles with enough velocity to pass through a stage induce a zero net charge on the impactor plate, while particles with enough inertia to impact on the plate produce a net positive or negative charge. "Stacking" a series of these Faraday wells in the form of impactor stages with different cut-off diameters, as in a cascade impactor, allows for measurement of the charge distribution across the entire aerosol cloud.

The creation of the eNGI involved modifying a standard NGI by electrically isolating all 8 collection cups, the optional pre-separator, and the USP throat and connecting them to a multi-channel femto-electrometer (Fig. 3). This modification allows for the measurement of the simultaneous charge distribution of an aerosol cloud as it passes through the impactor and deposits on the various components. Researchers can then get a visual representation of the charge and particle size distributions on the same graph (Figs. 4 and 5).

Advantages of the eNGI

A cascade impactor called the Electrical Low Pressure Impactor (ELPI), manufactured by Dekati, has the ability to measure dynamic electrostatic charge and mass deposition [9]. In addition to pharmaceutical applications, the ELPI is used for environmental and industrial applications such as air quality measurement and characterization of automotive exhaust particle size distributions and operates at air flows of 10 or 30 L/min. While the ELPI, which is not a pharmacopoeial method, can provide information relevant to electrostatic charges in pharmaceutical aerosols, the eNGI offers a number of advantages for that specific application.

For one thing, the eNGI is based on an impactor that is a pharmacopoeial method and is designed specifically for inhalation medicines and capable of testing formulations at patient relevant flow rates up to 100 L/min [10]. The NGI also offers a pre-separator option for the removal of large particles such as a lactose carrier. The absence of a pre-separator on the

Figure 2

Schematic of simple cascade plate electrostatic apparatus

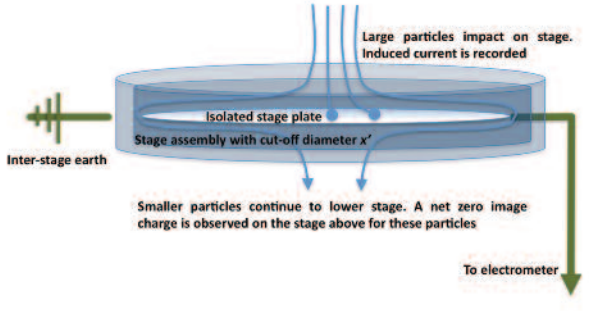


Figure 3

Schematic of the eNGI assembly

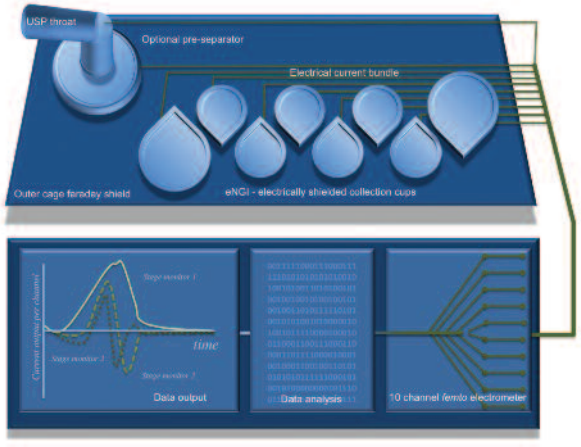


Figure 4

Deposition and charge distributions of Qvar using the eNGI

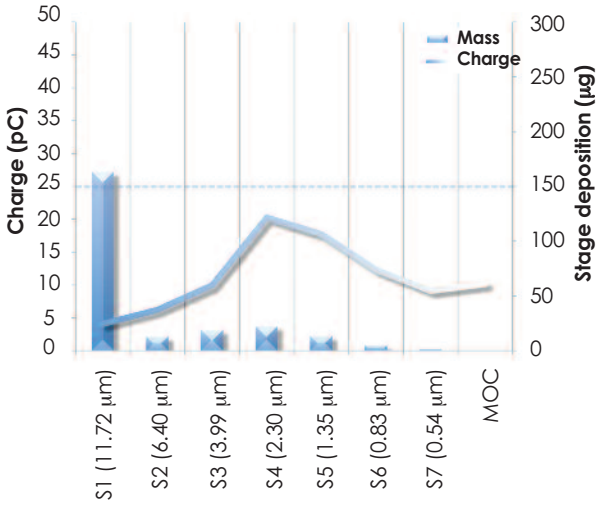
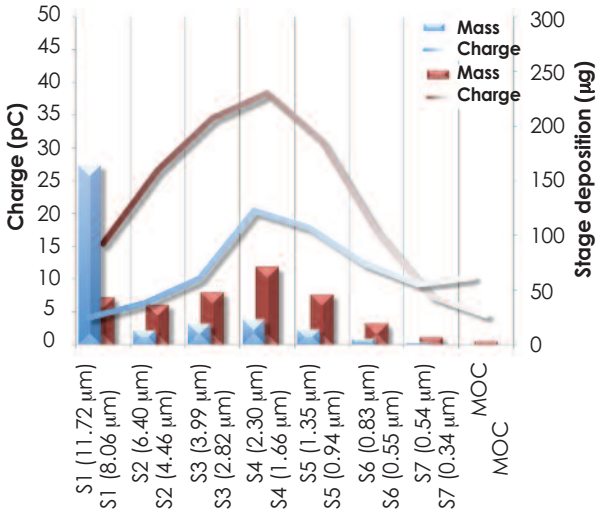


Figure 5

Deposition and charge distribution of Pulmicort Turbuhaler



ELPI prevents its use with carrier-based DPI formulations since it cannot remove the relatively large lactose particles and therefore cannot measure the charge on the carrier separately from the charges on the API.

In addition, the small size of the 25 mm collection plates in the ELPI may preclude testing of certain dosage levels. Given that the relationship between the electrostatic charges on the carrier and the API determines the force needed to detach the API to produce a fine particle fraction during inspiration, the eNGI's ability to measure the charge on the carrier represents a significant advantage.

There has been interest in making the eNGI commercially available within the next few years; for the time being, the prototype apparatus is providing researchers with concurrent measurements of particle size and electrostatic charge distributions.

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