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Review

Electrostatics of pharmaceutical inhalation aerosols

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Abstract

Objectives This review focuses on the key findings and developments in the rapidly expanding research area of pharmaceutical aerosol electrostatics.

Key findings Data from limited in-vivo and computational studies suggest that charges may potentially affect particle deposition in the airways. Charging occurs naturally in the absence of electric fields through triboelectrification, that is contact or friction for solids and flowing or spraying for liquids. Thus, particles and droplets emitted from pulmonary drug delivery devices (dry powder inhalers, metered dose inhalers with or without spacers, and nebulisers) are inherently charged. Apparatus with various operation principles have been employed in the measurement of pharmaceutical charges. Aerosol charges are dependent on many physicochemical parameters, such as formulation composition, device construction, relative humidity and solid-state properties. In some devices, electrification has been purposefully applied to facilitate powder dispersion and liquid atomisation.

Summary Currently, there are no regulatory requirements on characterising electrostatic properties of inhalation aerosols. As research in this area progresses, the new knowledge gained may become valuable for the development and regulation of inhalation aerosol products.

Keywords dry powder inhaler; electrostatic charge; meter dose inhaler; nebuliser; pharmaceutical aerosol; spacer

Introduction

Active pharmaceutical ingredients can be delivered to the lungs in the form of aerosols for local and systemic treatments. The most common pharmaceutical aerosol devices are dry powder inhalers (DPIs), metered dose inhalers (MDIs) and nebulisers. During formulation development of these products, the properties studied include particle size distribution, particle shape, powder flow, dose content uniformity, hygroscopicity, compatibility with the chosen excipients and/or propellants, and other physicochemical parameters related to stability.[1] To date, there are neither regulatory stipulations on the electrostatic properties of pharmaceutical aerosols nor pharmacopoeial methods for charge characterisation. Over the last few years, interest in the electrostatic charges of pharmaceutical aerosols has been growing, which is partly due to the availability of instruments capable of measuring pharmaceutical aerosol charge. Solid particles acquire charges from physical contacts between each other and between particles and inhaler components during dispersion.[2] On the other hand, disruption of the electrical double layer in liquid surfaces during atomisation generates spontaneously charged droplets.[2] Aerosols generated from inhalers are usually charged due to these processes. This paper provides a review of the research and innovation conducted in the field of pharmaceutical aerosol electrostatics.

Clinical significance of aerosol charges

Five mechanisms govern particle deposition in lung airways, namely, inertial impaction, gravitational sedimentation, diffusion, interception and electrostatic attraction.[3] Electrostatic charges enhance deposition by increasing attractive forces to airway surfaces. Since electrostatic force is inversely proportional to the square of the distance between charged objects (Coulomb's law), this mechanism is especially relevant for small airways and alveoli due to their confined internal spaces. The potential clinical significance has been investigated in limited in-vivo and in-vitro studies. Melandri *et al*.[4,5] found that the deposition of monodisperse 0.3–1.1-μm carnauba wax particles in human subjects

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increased with the amount of charges carried, up to about 200 elementary charges per particle. However, since only the net deposition was measured in these experiments, the specific location of deposition was unclear. It was assumed that the enhancements in deposition occurred in the alveoli.[4] In-vitro deposition of monodisperse 15–125-nm salt particles carrying one positive elementary charge per particle was higher than that of neutral particles in a tubular tracheal model[6] and a hollow airway cast.[7]

Computational models of the deposition of charged particles in the lungs have been developed using a dichotomous airway model.[8–10] Bailey *et al*. examined the complete respiratory cycle, including inhalation, pause and exhalation.[8,9,11,12] It was also applied to the administration of aerosol boli. Thus, the breathing pattern and delivery conditions could be more precisely defined. On the contrary, the deposition model of Balachandran *et al*. only considered the inhalation phase.[10] Electrostatic charges affected deposition in two ways, via the space charge force and the image charge force. Space charge force is the repulsion between charged particles in an aerosol cloud, whereas image charge force is the attraction between a charged particle and its image charge on a surface.[13] Although human airways are normally neutral, image charges with equal magnitude and opposite polarity to charged particles may be induced on the surfaces, especially inside small airways in the peripheral lung.[8,10] Balachandran *et al*. found that the deposition of 2.2-μm particles was increased in all airway generations when the number of elementary charges per particle was increased from 1 to 200.[10] Space charge forces were predominant in the upper airways and image charge forces in the lower airways. As the amount of charge was increased to half of Gauss' limit (the maximum charge a particle could hold), space charge forces overwhelmed and most particles deposited in the upper airways.[10] Similar effects of electrostatic forces on deposition were obtained by Bailey *et al*. for 0.5-μm and 5-μm particles, but contributions from the space charge force were not considered as it was deemed unimportant.[8] Human scintigraphic results of inhaled radiolabelled droplets from a nebuliser agreed with the simulation data regarding the total deposition and deposition in the 'head', while in-vivo alveolar deposition was higher than the model prediction.[9] The charges carried by the nebulised droplets were not reported in the study. Particle deposition in mid-airways was enhanced by increasing the particle charge and size of up to 2.5 μm.[11,12] It should be noted that these results were reported largely empirically without getting into the detail on deposition of the charged particles. Part of the reason could be due to a lack of knowledge of the charge distribution among different particle size fractions when these simulations were performed.

Electrostatics of pharmaceutical inhalation aerosols

Dry powder inhalers

DPIs deliver pharmaceutical particles into the respiratory tract by dispersing them in the airstream as the patient inhales through the device. Many drugs are organic materials having high electrical resistivities (>10^{13} Ωm),[14,15] with charge relaxation times of minutes to hours.[16] As the rates of charge decay from particle surfaces depend on the relaxation time,[16,17] these solids will have high tendencies to accumulate charges. Particles inevitably undergo triboelectrification from contacting each other and internal surfaces of the inhaler during dispersion, resulting in charged aerosols. Electrification is a complex phenomenon that is affected by many physicochemical factors. Usually, the higher the energy involved, the greater is the charging.[17]

Electrostatic profiles of drugs before and after aerosolisation from commercial Turbohalers and prototype Dryhalers were characterised by Byron *et al*.[18] Fine particle (<5.8 μm) charges of budesonide (Pulmicort) aerosols from Turbohalers were reproducibly positive and charges measured on the mouthpieces were negative after dispersion. On the other hand, terbutaline sulfate (Bricanyl) aerosols from devices of the same design showed inter- and intra-inhaler variations in charge polarity. In addition, time-dependent polarity was observed on one particular Bricanyl inhaler from which positive and negative charges were produced separately in time. However, both of these DPIs produced fine particle charges in the order of 100 pC. The specific charge, expressed as the net charge per unit mass of powder, was lowest in the drug reservoir, rose slightly after dose metering, and increased 10- and 300-fold in the fine particle aerosol for Bricanyl and Pulmicort, respectively. The electrostatic charges measured on powder samples in the inhaler reservoir may originate from micronisation during formulation processing before packaging. More charges were developed as a portion of powder was dispensed from the reservoir into the metering cavity. Triboelectrification during dispersion generated the highest amount of charges on the particles. A 2.5-μm particle from Pulmicort was estimated to carry 200 elementary charges,[18] which is high enough to affect deposition in the lung, according to computational models.[8]

Various compounds aerosolised from prototype Dryhalers showed drug-dependent charging, with differing polarities and magnitudes of specific charges.[18] However, all charges produced were significantly lower than those from Turbohalers. This suggests that deaggregation using turbulent airstreams in the Turbohaler produced more extensive triboelectrification than that provided by the high-speed rotor in the Dryhaler. In addition, terbutaline sulfate charged negatively and budesonide displayed time-dependent polarity from the Dryhaler. The different profiles of these two drugs obtained from the Turbohaler and Dryhaler indicate that charging is influenced by interactions between the formulation and the inhaler.[18]

The charges on the fine particles (<5 μm) of most drugs from the Dryhaler followed in magnitude, but are of opposite polarity, to those on particles retained in the inhaler, indicating that charges were separated from powder aggregates upon dispersion.[18] Since the Dryhaler experimental conditions were identical for the various drugs tested, a triboelectric series was constructed by ranking the magnitudes of the fine particle dose charges from positive to negative, as follows:[18] budesonide > lactose > salbutamol sulfate > terbutaline sulfate $\geq$ salbutamol base $\geq$ beclomethasone dipropionate.

Theoretically, each compound within the series should be charged negatively with respect to those preceding it when the powders are aerosolised as a blend from the Dryhaler. This was supported by the negatively charged salbutamol sulfate fine particles obtained from the dispersion of Ventolin Rotacaps, which contain a mixture of the drug with a lactose carrier.[18]

Palonen and Murtomaa[19] investigated a lactose carrier system containing beclomethasone dipropionate aerosolised from Easyhalers. The lactose particles were found to be positively charged whereas the drug particles were mostly negatively charged. Although the magnitude of charges did not balance between the carrier and the drug, the opposing polarities suggest charge separation resulted from the dislodgement of the beclomethasone dipropionate from large lactose particles during dispersion.

The influence of various formulation and inhaler parameters on the charging of salbutamol sulfate–lactose blends was studied by Telko *et al*.[20] These included the type of lactose carrier (milled *vs* sieved), drug load (0.50 *vs* 1.0% w/w), capsule fill weight (15 *vs* 30 mg), capsule material (gelatin *vs* carrageenan), and inhaler type (Inhalator vs Rotahaler). Although the charge profiles measured were variable, certain relationships could be gleaned. All parameters, except the capsule fill weight, affected the net charge. The absolute polarity of the aerosol was independent of drug load and capsule fill weight. The use of milled lactose, carrageenan capsules and/or Inhalator increased the tendency of positive charging. Conversely, sieved lactose, gelatin capsules and/or Rotahaler promoted negative charging. The absolute charge magnitude was increased by the use of milled lactose, 1.0% drug load, 30 mg fill weight, carrageenan capsules and/or Inhalator. The higher drug load and fill weight were expected to increase the amount of charged particles, thus increasing the absolute charge magnitude. The effect of milled lactose may be due to its higher proportion of charged fine particles and morphological differences compared with sieved lactose.[20] Higher charging by the Inhalator was attributed to its higher resistance, resulting in higher shearing and triboelectrification of the particles. Although not mentioned by Telko *et al*.,[20] possible differences in the constructing materials of the Inhalator and Rotahaler may also contribute to the differences in charging, similar to the effect observed on the capsule materials. Since neither charge-to-mass ratios nor charges-per-particle were reported in the study, this is a limitation to data interpretation because charge magnitude is affected by both the amount of charges carried by the particles and the amount of charged particles present. To eliminate this ambiguity, the measured charges should be normalised by dividing by the mass or number of particles. Trends of triboelectrification would be better analysed if normalised charges were used instead of raw charges.

Triboelectrification is highly dependent on relative humidity (RH). There are two aspects to consider in this regard, namely, the storage RH and the RH of the dispersion air. As expected, the fine particle dose charge-to-mass ratio decreased with increasing storage RH for a salbutamol sulfate/lactose binary dry powder blend.[21] On the other hand, the effect of RH of the dispersion air on DPI particle charging is more complex and drug-dependent. Aerosols from Pulmicort and Bricanyl Turbohalers showed distinctly different charging behaviour when the dispersion air RH varied from 15 to 90% RH.[22] The products were stored tightly capped and kept dry by internal desiccants. The fine particle dose from Pulmicort carried the highest absolute specific charge at 15 and 90% RH, but lowest at 40% RH. In contrast, the Bricanyl fine particle dose absolute specific charge decreased monotonically with increasing RH. It is well known that moisture adsorption on particle surfaces increases with increasing RH. This would lead to two concomitant consequences, namely, enhanced charge dissipation and particle cohesion. The charging behaviour of budesonide particles from Pulmicort resulted from the interplay of these two processes. The charge was high at 15% RH because of the low charge dissipation rate. At 40% RH, the higher moisture adsorption, hence higher charge dissipation, reduced the specific charge. The increased cohesion at and beyond 65% RH rendered the agglomerates more difficult to be dispersed. Thus, the particles that could be separated from the agglomerates to become the fine particle dose would be those carrying higher charges to counteract the cohesive forces, especially at 90% RH. The same scenario would also apply to terbutaline sulfate particles from Bricanyl. However, due to its ionic nature and higher hygroscopicity, charges generated on the fine particles would dissipate more rapidly than those on budesonide particles. Therefore the specific charges measured at 65 and 90% RH were low.[22]

Besides hygroscopicity, amorphous content may also be a factor in aerosol charging. Since amorphous and crystalline surfaces have different surface energies,[23] their charge transfer behaviours may also differ. However, it is generally difficult to vary the amorphicity of particles without changing their morphology because crystallisation necessitates the arrangement of molecules into orderly lattices. Nevertheless, the triboelectrification of amorphous and crystalline particles had been examined in some studies, despite their different morphologies. Upon aerosolisation, spray-dried salbutamol sulfate particles (amorphous, spherical) were found to be more electropositive than jet-milled ones (crystalline, plate-like).[24] The particle size profiles of the two solid forms were comparable, thus the difference in charging may be due to differences in crystallinity and/or morphology. Earlier, Murtomaa *et al*.[25] studied the effect of crystallinity and morphology on the charging of lactose particles. However, the data reported were inconclusive because not only the degree of crystallinity and morphology varied between samples, the particle size distributions also differed. Thus the roles that crystallinity and morphology play in triboelectrification is still open for exploration and more controlled studies are needed in the future.

The energy of powder dispersion from most DPIs is derived solely from the air flow generated by inhalation through the device.[26] However, it may be difficult for respiratory disease patients to inhale with sufficient effort to generate high enough air flow for efficient aerosolisation.[27] In view of this, electrostatic technologies have been applied to enhance powder dispersion in novel battery-operated DPIs. In an inhaler designed by Sun *et al*.,[27] metered

powder deposits are stored on a substrate composed of an insulative material, such as polyimide. Two electrodes, one in the form of a mesh overhanging the powder and the other as a backing underneath the substrate, are connected by an electrical power source. A short voltage pulse of 0.5–2 kV across the electrodes lasting for 0.3–1 ms is triggered by inhalation. The brief, but intense, electric field created thus releases the powder from the substrate, disperses it through the top mesh, and it is subsequently inhaled by the patient.

High electric fields are also employed in another novel DPI with a more elaborate setup.[28] Two compartments are separated by a rotatable drum. The inner chamber serves as a powder depot that also holds an electrode, which charges to a high voltage of approximately 10 kV when triggered by inhalation. The powder becomes charged by induction from the resultant electric field and deposits onto the neutral drum. The drum rotates and carries the powder into the outer compartment, which contains another highly charged electrode of opposite polarity to the first one. The electric field here is thus inverted and the particles are released from the drum. The aerosolised particles subsequently pass through an electric dosage regulator grid and mix with an inhaled airstream inside the inhaler. A deionising element located near the mouthpiece neutralises the particles before they enter the patient. The electronic and dosage regulatory functions of the inhaler are controlled by an in-built microprocessor.

Instead of inducing charges on particles with electric fields, Noakes *et al*.[29] proposed the direct application of a high voltage to the powder bulk. A multi-dose blister strip containing discrete amounts of powder is mounted on a roller system inside an inhaler with an upright opening for nasal or oral administration. The lower backing of the strip is composed of a conductive material. A blister is fed into place at the opening when a dose is needed and is then opened by a conductive plunger pushed from below. The plunger simultaneously charges from an electric power source and applies a high voltage (3–25 kV) directly to the exposed powder mass. This leads to the repulsion amongst, and hence the dispersion of, the charged particles. The whole sequence of operation may be breath-actuated.

Metered dose inhalers

MDIs have been popularly used for treating respiratory diseases due to their portability and simple operation. Since the MDI possesses multiple components of differing compositions and the fact that the formulation must travel through and contact these parts in the process of atomisation, generation of electrostatic charges in the aerosol particles would be expected. Both the chlorofluorocarbon (CFC) based Ventolin and the hydrofluoroalkane (HFA) based Airomir produced net charges of approximately 160 pC per puff, which was estimated to be equivalent to 300 and 490 elementary charges per respirable particle from each of the respective inhalers.[30,31] According to computer simulated results, these charge levels may be high enough to affect particle deposition in lung airways.[8]

It has been reported that the charging of MDI aerosols may be dependent on interactions between the formulation and the materials of various inhaler components. This was observed in the product-dependent charge profiles of commercial MDI aerosols.[32] Both the drug particles and propellant/excipient droplets carried electrostatic charges.[32,33] The charge profile of a HFA-134a formulation was altered by a sequential addition of absolute ethanol and dissolved beclomethasone dipropionate to the propellant.[34] Similarly, the low positive charges of HFA-134a droplets became highly negative after the addition of salbutamol sulfate particles to the MDI.[35] Therefore, each ingredient in the formulation contributes to the charging of the final product. The presence of water as an impurity in MDIs may also influence the electrostatic properties of the aerosol by inverting the polarity of the net charge.[36] The charge profiles of both HFA-134a and 227ea had high intra- and inter-inhaler variation but, on average, the puffs carried negative charges.[37] The electronegative fluorine atoms in the HFA molecules were thought to be responsible for this preferred polarity. Being more polar, HFA-134a produced higher charges than HFA-227ea. The charges of both HFAs shifted towards neutrality or positive polarity with increasing water content. In fact, HFA-134a charged positively when the water content exceeded 300 ppm. This effect was explained by an increase in electrical conductivity and/or a decrease in the bulk electronegativity with increasing moisture content.[37] Moisture on the actuator did not affect aerosol charging or particle size.

Repackaging of propellant blends, and salbutamol sulfate and levalbuterol sulfate MDI suspensions, with various combinations of valve components showed that elastomer and valve stem materials may affect aerosol charging.[38] CFC-11/12 propellant blends generated charge profiles of differing magnitudes and polarities when packaged in various combinations of valve body and stem materials.[38] CFC albuterol sulfate aerosols were charged more electronegatively with stainless steel valve stems than with acetal ones.[38] On the other hand, the levalbuterol sulfate counterparts produced net negative charges with nitrile (BK 356) elastomers and net positive charges with nitrile RB 190NT (BK 357) elastomers. Composition of MDI actuators may also play a role in aerosol charging. By charging polymeric substances used in actuators with a corona charger and monitoring the charge decay with a Faraday pail, Carter *et al*.[39] observed that the materials have varying degrees of electrostatic charge accumulation and decay properties.

The charging of MDI aerosols clearly has a physicochemical basis. It is related to interactions between the contents of the formulation (propellant, actives and other excipients) and the compositions of the inhaler components (metering valve, valve stem and actuator). Research in this area is progressing and a clearer understanding on MDI aerosol charging may enhance the design and use of these products, especially when coupled to spacers.

Spacer devices

A spacer device is a holding chamber for MDI aerosol clouds as the patient inhales through a one-way valve at a natural pace. Most spacers are made of plastics,[40] which are insulative. Thus electrostatic charges are easily generated and accumulated on the surfaces through handling. Interactions between these charges and the charged particles from

a MDI (see above) may decrease the drug output from a spacer. Conversely, reduction or elimination of electrostatic charges on spacer surfaces improved drug delivery.[40,41] Spacer charges may be significantly decreased by various types of treatments, such as coating the walls with a commercial antistatic lining[42,43] or priming the spacer before use.[44,45] The most popular method is coating with surfactants. Ionic surfactants are more effective than non-ionic ones,[46] suggesting that the antistatic effect of surfactants is due to enhanced conductivity of the spacer surface. The optimal procedure was to soak the spacer in dilute commercial detergent solution followed by drip-drying, without rinsing with water or wiping with towel.[47] Detergent treatment increased the aerosol residence time in the spacer[48] and in-vitro fine particle dose[46] by reducing deposition inside the spacer. It also decreased drug retention in spacers and increased lung deposition *in vivo*,[47] along with significantly improved bronchodilator response.[49]

In the studies referred to above, the in-vitro variables investigated mainly focused on the aerodynamic particle size distribution, fine particle dose, drug retention in the spacer and aerosol residence time or half-life in the spacer. In most cases, the spacer wall charges were not recorded, probably because the outcome concerned was on the improvement of drug delivery. When spacer charges were measured in one study, it was the 'static voltage on the outside surface of the spacer'[41] that was being recorded with a static locator at set positions. However, it is the charges on the inside surface that are more relevant. This is because charges are not distributed uniformly throughout an insulator, thus the surface potentials on the outside surface may not represent those on the inside.

The effect of new or detergent-coated spacers on MDI aerosol charges was investigated in a comprehensive study conducted by Kwok *et al*.[50] The surface potential on the internal spacer wall circumference was mapped before and after actuation. High surface potentials with variable magnitude and polarity were found on the new spacers.[50] The surface charge distributions appeared to be random, as expected for an insulator. On the other hand, the detergent-coated spacers possessed minimal surface charges. The surface potentials were not altered significantly after aerosol sampling.[50] The aerosol charges were greatly reduced with new spacers but were partially recovered with detergent-coated ones. The charge-to-mass ratios also followed this trend. This implies that the particles that exited from a new spacer, hence were sampled and measured, possessed lower inherent charges. Furthermore, particles carrying higher charges became available by reducing the spacer surface potential with detergent. Thus, essentially, the spacer was analogous to an electrostatic filter such that particles carrying higher charges (i.e. more elementary charges) were more susceptible to the effects of spacer surface charges and became retained. The calculated number of elementary charges per drug particle ranged from zero to several hundred, which may be sufficiently high to potentially affect lung deposition.[50] The effects of detergent-coating on spacer retention, fine particle dose and mass median aerodynamic diameter observed in this study[50] agreed with those reported previously.

A fundamental solution to avoid spacer wall charges is to use non-electrostatic constructing materials. Metals are obvious candidates because being conductors they do not retain charges. The Nebuchamber is a commercially available stainless steel spacer. It has similar in-vitro antistatic properties to detergent-coated plastic spacers[48] and increases in-vivo drug delivery.[51,52] Similarly, drug deposition in metal cylindrical spacers (stainless steel, anodised aluminium and nickel-coated aluminium) was less than that in plastic ones (polycarbonate, styrene–butadiene copolymer and polyester).[53] Spacers manufactured from charge-dissipative polymers are also available. These materials are physically similar to the usual plastics but their electrical conductivity is higher. Detergent-coating was not needed for the non-electrostatic AeroChamber Max and AeroChamber Z-STAT Plus spacers in improving the drug output.[54,55] Zerostat V, a non-electrostatic spacer made with a different polymer to those of AeroChamber Max and AeroChamber Z-STAT Plus, also significantly prolonged the half-life of MDI aerosols inside the chamber.[56]

Nebulisers and liquid sprays

Droplets generated from nebulisers are spontaneously charged. This is because charge separation occurs when a liquid surface is disrupted during atomisation[57–60] or when a liquid flows against a solid surface.[61,62] Droplets of an unknown liquid nebulised from an Inspiron Mini-Neb nebuliser were found to contain bipolar charges using an ion mobility analyser.[63] The charge production rate and the ratio of positive-to-negative charges also increased with the compressed air flow rate. The charge level of the droplets was estimated by assuming that the aerosol charges were shared amongst the droplets in proportion to the droplet surface area.[63] Inferring from the results of computational deposition modelling, the calculated droplet charges were deemed too low to influence lung deposition.[63] In another study, deionised water droplets produced from a Sidestream jet nebuliser carried net positive charges.[64] The net charge of the aerosol also varied with different starting volumes of water in the nebuliser.[64] This may be due to other factors such as the reduction in temperature of the liquid and possible changes in conductivity and pH during nebulisation.

The effect of ionic content and conductivity on spray charging was observed on the polydisperse droplets produced from a wet scrubber nozzle used in industrial cleaning.[65] Positively charged droplets were resulted from the spraying of distilled water, ionic solutions and diluted scrubber liquid, whereas negative charges were measured on undiluted scrubber liquid droplets. Although the exact constituents of the scrubber liquids tested were not disclosed, these products generally contain lime, limestone, sodium hydroxide or sodium carbonate, together with other soluble and insoluble impurities collected through recirculation during cleaning.[65] Varying the nozzle material between stainless steel, brass and polyvinylidene fluoride had no significant effect on charging. The specific charge, expressed as the net charge per unit volume of sprayed liquid, was found to be inversely related to the electrical conductivity of, and hence the concentration of ionic species in, the liquid.[65] This effect of conductivity on charging was also observed by Yatsuzuka *et al*.[61,62]

The inverse relationship between ionic concentration and resultant charges on atomised droplets was exploited to suppress the charging of inhalation aerosols produced from a novel atomiser, AERx.[66] The rationale for reducing aerosol charging is to avoid premature droplet deposition in the oropharynx during inhalation. Ionic salts such as sodium chloride or potassium chloride were added to increase the conductivity of the solution. Droplets of deionised water and Water for Injection USP produced from the AERx atomiser carried high positive charges, whereas those of sodium chloride (5 mM and 10 mM) and sodium cromoglycate (30 mg/ml) solutions had much lower charges.[66] In addition, the output of a non-ionisable drug (details undisclosed) from the same atomiser was increased with the sodium chloride concentration, reaching a maximum plateau at 7.7 mM.[66] Thus low levels of added electrolytes to aqueous solutions are sufficient to reduce droplet charging significantly.

Electrosprays for inhalation

Electrospray, also called electrohydrodynamic or electrostatic spray, is an atomisation technique in which liquids are dispersed solely by the application of high voltages.[67,68] A liquid flows into a metal capillary tube charged to the kilovolt range and emerges from the tip as a conical meniscus, known as a Taylor cone,[68] due to the intense electric field. An unstable jet extends continuously from the apex of the cone and disperses into charged droplets further downstream.[68,69] Electrosprays have been used in industrial and agricultural applications such as ink-jet printing, paint coating and crop spraying for controlled deposition of charged droplets onto specific targets.[68]

The size of electrosprayed droplets can be tightly regulated, depending on the applied voltage, liquid flow rate and physicochemical characteristics of the liquid such as the dielectric constant, conductivity, surface tension and viscosity.[67] Thus the system has been employed to produce monodisperse droplets and particles in size ranges potentially suitable for respiratory delivery.[70,71] Tang and Gomez[70] generated normally distributed saline droplets with a mean diameter of 1.4 μm and a relative standard deviation of 0.14. Gomez *et al*.[71] also electrosprayed an insulin solution and yielded particles between 90 and 110 nm after solvent evaporation. The technique is also suitable for dispersing suspensions without clogging the system, due to the relatively large calibre of the capillary tubes (typically 100 μm).[67,71]

More sophisticated electrospray devices have been designed to produce aerosols for patient use. However, the droplets must be discharged before inhalation to avoid premature deposition from image forces in the oropharynx. The capillary nozzle of the electrospray apparatus devised by Noakes *et al*.[72] is charged to the opposite polarity to a needle discharge electrode (Figure 1). The ions produced from the needle electrode through corona charging neutralise the charges on the droplets. A grounded plate shields the capillary to prevent corona ions from discharging the nozzle and interfering with the electrostatic dispersion. The shield contains a small orifice through which charged droplets pass into the aerosol chamber for neutralisation. A similar mechanism for discharging droplets is used in the breath-

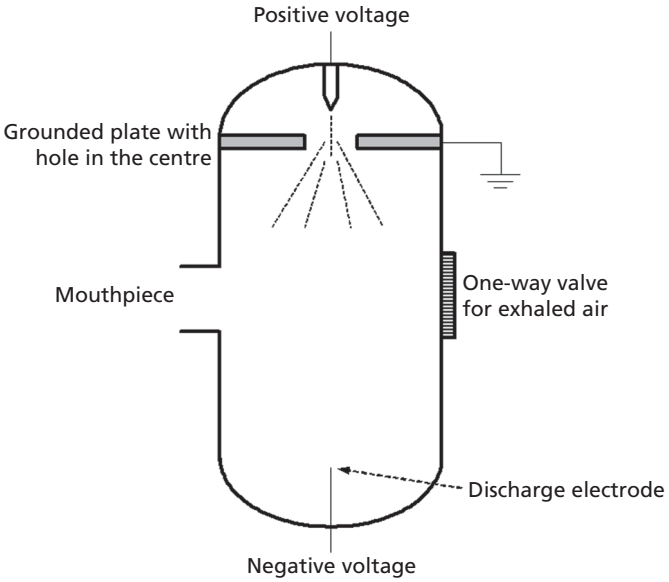

Figure 1 Schematic of the electrospray inhaler.[72] Diagram not drawn to scale.

actuated electrospray nebulisers developed by Battelle-Pharma, including battery-operated portable and bench-top prototypes.[67] Although a high voltage is applied upon atomisation, the nebulisers are claimed to be safe for patient self-operation due to the low electric currents involved.[70] The manufacturing cost of these devices is also relatively inexpensive. Multiple nozzles are used to achieve an optimal drug output. Respirable fractions of nebulised triamcinolone acetonide, albuterol and cromolyn were close to 100%, with narrow geometric standard deviations between 1.2 and 1.5.[67] The average lung deposition was 78% of the emitted dose from a prototype Battelle inhaler in a Phase I scintigraphic study on human subjects.[73] The oropharyngeal deposition was also significantly lower compared with that from a DPI (16 *vs* 67%), thus the electrospray nebuliser has high respiratory delivery efficiency.

Drug molecules should gain no charge upon electrospray atomisation because it is believed that only the liquid carrier, rather than the drug, is charged during the process.[67] Furthermore, the droplets are discharged after their dispersion, thus it is improbable that charges should remain on the drug. Since no heat is applied during electrospraying, heat-labile substances such as proteins may be aerosolised without molecular fragmentation.[67] Owing to this advantage, the technique is used to inject macromolecules into mass spectrometers for analyses.[71] However, a concern for electrospraying macromolecules for inhalation is their potential denaturation due to interferences from intensifying electric fields resulting from the evaporation of highly charged liquid droplets.[71] This may happen without the occurrence of fragmentation and result in altered molecular conformations, as well as loss of biological activity. Nevertheless, the receptor binding ability of electrosprayed insulin was not found to be altered in an in-vitro assay.[71] Further investigations are needed to evaluate the suitability of the electrospray atomisation for other macromolecules.

Table 1 Studies on the electrostatics of pharmaceutical inhalation aerosols

Type of research		Major findings
Deposition	*In vivo* (human subjects)	Deposition of 0.3–1.1-μm particles increased with charge, up to ~200 elementary charges per particle.[4,5]
	In vitro (airway models and casts)	Deposition of 15–125-nm particles carrying one positive elementary charge per particle was higher than that of neutral ones.[6,7]
	Computational models	Deposition of 2.2-μm particles with 1–200 elementary charges per particle increased in all airway generations,[10] similar effects for 0.5-μm and 5-μm particles.[8]
Formulation and device	Dry powder inhalers (DPIs)	Aerosol charge profiles were dependent on the drug, excipients (e.g. lactose carrier), and inhaler.[18–20,22] Respirable particles were estimated to carry charge levels high enough to affect deposition.[18,22] Charge separation occurred from the dispersion of aggregates.[18,19] The extent and trends of charging were affected by storage and dispersion relative humidities.[21,22]
	Metered dose inhalers (MDIs)	Aerosol charge profiles were dependent on the drug, propellant, other excipients (e.g. ethanol) and inhaler components (e.g. valve body and stem materials).[30–35,38] Respirable particles were estimated to carry charge levels high enough to affect deposition.[30–32] Hydrofluoroalkane propellants have net negative charges, attributed to their electronegative nature.[37] Water inverted the polarity of the hydrofluoroalkane net charge, possibly by increasing the electrical conductivity of the propellant and/or decreasing the bulk electronegativity.[37]
	Spacer devices	Spacers have high and variable surface charges on their surfaces.[41,50] Charge profiles of aerosols exiting the spacers were not qualitatively altered.[50] Static spacers retained particles with higher specific charges.[50] Spacer wall charges were effectively eliminated by coating with surfactants, which increased the delivered dose.[46–48,50] Metal[51–53] and charge-dissipative polymers[54–56] have also been used to construct non-static spacers.
	Nebulisers and liquid sprays	Nebulised droplets are charged[63,64] but the levels may be too low to influence lung deposition.[63] Generally, the higher the ionic content (i.e. conductivity) of the liquid, the less the charging.[65,66]
	Electrosprays	Droplets and particles of respirable sizes have been produced by electrospraying.[67,70,71] The technology has also been built into inhaler devices for direct inhalation delivery.[67,70,72,73]

Table 1 summarises the significant research and findings in the field of electrostatics of pharmaceutical inhalation aerosols.[4–8,10,18–22,30–35,37,38,41,46–48,50–56,63–67,70–73]

Electrostatic charge measurement techniques

There is currently no standard technique for measuring electrostatic charges of pharmaceutical aerosols. A wide range of equipment has been applied in this field and can be classified into two categories according to principle of operation, namely, static and dynamic.[74] These techniques are described below.

Static techniques

Static methods involve the transfer of charges from, or induction of charges by, the particles to the measurement device. The Faraday pail, the aerosol electrometer apparatus built by Peart's group,[31,36,38,75] the electrical low pressure impactor (ELPI),[33,76–78] the modified twin stage impinger[79] and the electrical next generation impactor (eNGI)[80] are examples of such instruments. A major drawback of static methods is that only the net charge can be measured on a given size fraction. Thus bipolar charges within that size fraction cannot be quantified separately.

Faraday pail

The simplest instrument for measuring electrostatic charge is the Faraday pail or Faraday well (Figure 2). It consists of two metal containers, one situated inside the other. The outer well is grounded to provide shielding from interferences by stray charges or electric fields in the vicinity. The inner well, connected to an electrometer, is electrically insulated to prevent charge leakage. A charged object in the inner well induces a flow of electrons to or from earth through the electrometer to balance the charge in the well. This results in a charge imbalance across a capacitor in the electrometer and is measured to derive the charge in the inner well.[15]

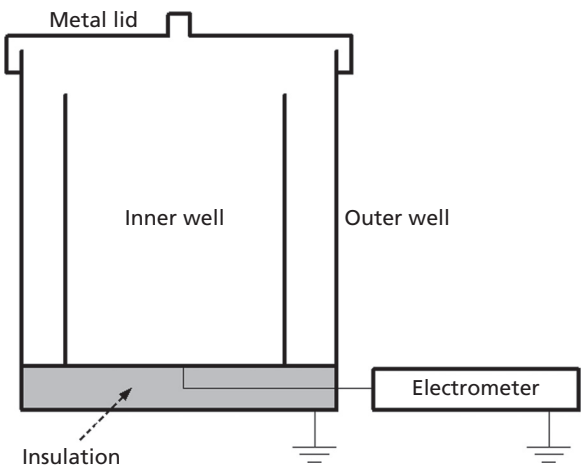

Figure 2 Schematic of a Faraday pail. Diagram not drawn to scale.

Aerosol electrometer apparatus

Electrostatic charge studies of MDIs and DPIs were previously conducted by Peart *et al*. using an aerosol electrometer apparatus that was built in-house.[31,36,38,75] The instrument is essentially a two-stage impactor with a Faraday pail serving as the second stage for collecting fine

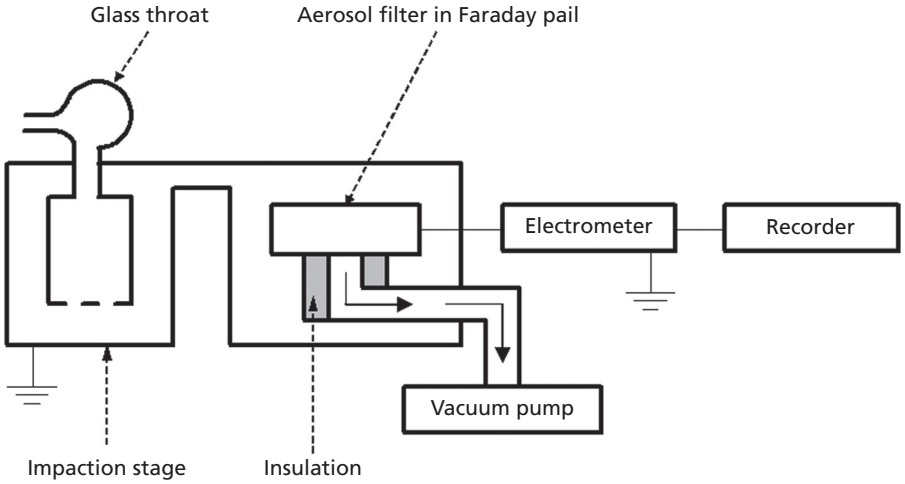

Figure 3 Schematic of the aerosol electrometer apparatus.[75] Diagram not drawn to scale.

particles <5 μm (Figure 3).[75] The net charge on the fine particle mass was measured with an electrometer. The limitation of this setup is that while the net charge of the fine particles was measured, the charges among different size fractions could not be discerned. Thus, if an aerosol carries bipolar charges, the two polarities would mask each other and only the overall charge is detected.

Electrical low pressure impactor

The ELPI was originally designed for near real-time sizing of airborne particles by electrical detection.[76,81] It consists of a 13-stage Berner multijet low pressure impactor with a diode-type corona charger situated directly above the top stage.[76] The size range covered by conventional cascade impactors is usually 0.3–10 μm.[81] By operating the impactor stages below atmospheric pressure, the lower size limit can be extended down to about 30 nm, as it is for the ELPI (Figure 4).[81] In its original mode of operation, the corona charger is charged to +5 kV,[82] and the resulting high electric field imparts a known, size-dependent level of charge to the particles introduced into the impactor by vacuum suction. The jet plate of Stage 1 functions as a critical orifice for establishing the flow rate.[81] All the impactor stages are electrically insulated from each other, with the last twelve stages connected individually to individual electrometers with sensitivity at femtoampere levels. The particles subsequently deposit onto the stages according to their aerodynamic sizes with their charges measured by the respective electrometers. Particle size distribution is then derived from the electric current measurements according to the corona charger efficiency.[76] The computer data collection software has an algorithm to correct for fine particle losses due to space-charge forces. Further details on the theoretical background and electronics of the ELPI were given by Keskinen *et al*.[76]

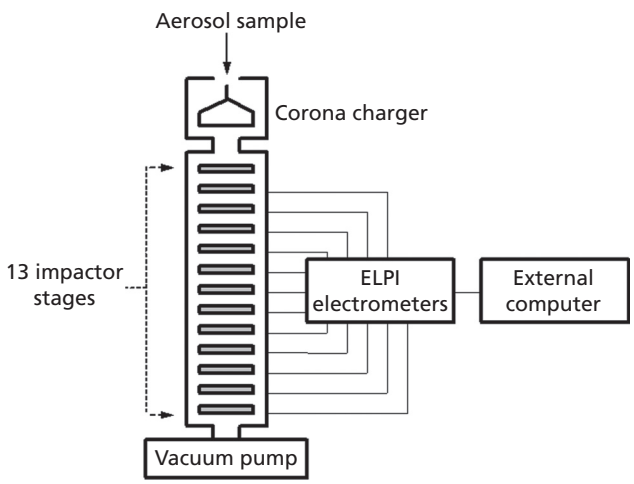

Figure 4 Schematic of the electrical low pressure impactor (ELPI) in its original configuration. Diagram not drawn to scale.

Particle sizing via corona charging and electrical derivation with the ELPI is an indirect method but it is fast and convenient because no gravimetric or chemical analyses are required.[83] These additional assays may still be conducted afterwards if desired. The ELPI has mostly been applied in measurements or real-time monitoring of industrial and environmental aerosols. These include particulate emissions from diesel engines,[84–89] vehicles,[90] burning incense,[91] smoke particles attached with radon decay products,[92] and general atmospheric airborne particles.[93–95] Aerosols generated from MDIs[96] and DPIs[97] have also been sized by ELPI electrical detection, but in general pharmaceutical applications are relatively few. In all the aforementioned studies, aerosol samples were charged with the corona charger. The primary interest was to derive size distributions from electrical signals. However, inherent charges on aerosol particles may also be measured by the ELPI without corona charging.

Although the ELPI is not a pharmacopoeial impactor, it has recently gained popularity for pharmaceutical particle size and charge measurements. Palonen and Murtomaa[19] measured DPI aerosol charges with the corona charger in place but switched off. However, no drug mass was determined. Glover and Chan[33] found no significant

difference in the charge measurement of MDI aerosols with the corona charger in place but switched off and with the charger removed. The charger was thus unnecessary and was removed to eliminate the possibility of artefacts in charge and mass measurements due to unwanted contact charging with, and deposition of particles on, the charger block.[33] A USP throat was also connected to the ELPI inlet. The net charge contributed by particles on each stage is derived from the electrometer readings collected from the individual stages. The deposited drug on the stages may be assayed chemically using high performance liquid chromatography to obtain the particle size distribution by mass.[33] The charge and mass data may be combined to yield charge-to-mass ratios, or specific charges, for the various size fractions.

The modified ELPI has been used to measure charges generated from nebulisers,[64] MDIs[32–34,37,50,77] and DPIs.[19–22,24] However, the ELPI only operates at a fixed air flow rate of 30 l/min, which is too low to disperse DPI aerosols. To achieve a dispersion flow rate of 60 l/min, a Y-tube and other extra parts are added to the setup.[22] Telko *et al*.[20] also employed a similar setup but a custom-made flow splitter with Tygon tubings and an Anderson cascade impactor were used in place of the Y-tube and unit dose sampler, respectively.

An advantage of using the modified ELPI to measure particle charges over the aerosol electrometer apparatus is the higher resolution of size and charge classifications. Variations in both the mass and net charge across the different size fractions can be discerned. However, a shortfall is that measurement of bipolarity within each size fraction is not possible.

Modified twin stage impinger

A glass twin stage impinger was recently modified by Zhu *et al*.[79] for charge measurement. This impinger is a pharmacopoeial apparatus for particle size measurement, with an aerodynamic cutoff diameter of 6.4 μm for the lower stage when operated at 60 l/min.[79] Electrodes from an electrometer were connected to the upper and lower stages. The charges induced in the stages by impacted particles were measured by the electrometer and recorded by a computer. The accuracy of the measurements made using this setup were comparable with those measured with a Faraday pail.[79] However, as with the aerosol electrometer apparatus, the modified twin stage impinger does not provide detailed size and charge classifications for the fine particles.

Electrical next generation impactor

The concept of modifying pharmacopoeial aerosol apparatus to measure charges has been extended to the NGI. The NGI has seven impaction stages and a micro-orifice collector before the exit. It can operate at a range of air flow rates and can accommodate a pre-separator for sampling carrier particles.[98] The USP throat was insulated from the impactor with a polypropylene adaptor.[80] The outer surface of each impaction cup was coated with acrylic latex for insulation, except a small uncoated area onto which an electrometer probe was connected. The charge distributions of three commercial MDI products were comparable between the eNGI and the ELPI.[80] The eNGI offers more detailed size classification than the aerosol electrometer apparatus and twin stage impinger. It is more versatile and efficient than the ELPI because it can operate at a range of air flow rates. The eNGI is also simpler in design and hence easier to operate than the ELPI. However, as with the ELPI, only the net charge of each size fraction is measured.

Dynamic techniques

Dynamic methods primarily measure the electrical mobility of individual particles, instead of the net charge of a population of particles. Electrical mobility (μ_e) is defined as:

$$\mu_e = \frac{v_d}{E} = \frac{neC}{3\pi\eta d} \quad (1)$$

where v_d is the migration velocity of a particle in an electric field of magnitude E, n is the number of elementary charges (e) that the particle carries, C is the Cunningham slip correction factor, η is the viscosity of air, and d is the particle diameter.[74] Depending on its size and charge, an individual particle exhibits a unique electrical mobility, which can be calculated by measuring the velocity of the particle in an applied electric field (Equation 1). Since dynamic charge measurement is based on the electrical behaviour of single particles, bipolarity within an aerosol sample can be detected. This is an advantage over the static methods. Some instruments can determine the charge distribution of aerosols by measuring the electrical mobility and particle size simultaneously. Examples of these include the electrical single particle aerodynamic relaxation time (E-SPART) analyser[99] and a bipolar charge measurement system.[100]

Electrical single particle aerodynamic relaxation time analyser

The E-SPART measures particle size and charge by laser Doppler velocimetry.[99] It can be operated in two modes, namely, DC/acoustic and AC. In both modes, particles are sampled vertically downwards in a slow-moving air stream through a sensing zone formed by two intersecting laser beams. While falling through this zone, the particles are subjected to a DC electric field and an oscillatory acoustic field simultaneously (DC/acoustic mode), or to an AC electric field only (AC mode).[99] In DC/acoustic mode, the acoustic field induces the particles to oscillate horizontally, which is measured by a laser Doppler velocimeter. Due to inertia from mass, each particle will cause a phase lag in its oscillation with respect to the acoustic field.[99] This phase lag is a function of the aerodynamic diameter, thus particle size can be calculated. The DC field induces charged particles to migrate in a preferred direction, depending on the polarity of the particle. Charge magnitude is derived from the induced migration velocity and aerodynamic diameter.[99] Both charged and uncharged particles can be sized in DC/acoustic mode. On the contrary, only charged particles are measured in AC mode. This is because no acoustic field is employed in this mode, thus only charged particles will respond to the AC electric field.[99] A charged particle oscillating in the AC field would cause a phase lag with respect to the field. The aerodynamic diameter can then be derived from this phase lag. The amplitude of the oscillatory velocity is proportional to the charge magnitude and opposite polarities display a 180° phase shift.[99] From these data,

together with the aerodynamic diameter, the particle charge can be calculated.

The E-SPART has been successfully used to characterise electrostatic properties of pharmaceutical aerosols. Mannitol and lactose dispersed with nitrogen in an aerosol chamber were found to carry bipolarly charges the magnitudes of which decreased with increasing particle size.[101] It was observed that 6.4 and 42.2% of the emitted particles were charged for the commercial products Atrovent MDI and Spiriva DPI, respectively.[102] Among the charged particles, the ratio of positively charged to negatively charged particles was 46 : 54% for Atrovent and 60 : 40% for Spiriva.[102]

It must be noted that the size and charge distributions obtained from the E-SPART are primarily number based. The number-based distributions may need to be subsequently converted to mass based distributions,[102] since the latter are usually employed in the pharmaceutical field. However, since large particles have high mass contributions,[3] errors in the count of these particles will be amplified if the number distribution is converted to mass distribution. Thus, the recalculated data should be interpreted with caution.

Bipolar charge measurement system

Balachandran's group at Brunel University, UK, has developed a system for quantifying bipolar charges on pharmaceutical aerosols. The system operates on the principle of electrostatic precipitation to measure charged particles according to their electrical mobility.[100] It consists of a sampling inlet splitting into two cylindrical electrostatic precipitators. The aerosol is sucked vertically through the precipitators at 60 l/min by vacuum. High-voltage electrodes are positioned in the middle of the cylinders, charged to opposite polarities in each precipitator. The internal surfaces of the cylinders are grounded and serve as the measuring electrodes. A charged particle travelling through the precipitator will experience a radial force caused by the electric field generated between the central electrode and the cylinder wall.[100] Particles with the same charge polarity as the central electrode will migrate towards the wall and their charges will be measured upon deposition. The length of the precipitators is divided into five sections. The site of particle deposition is governed by the electrical mobility. The higher the mobility, the earlier a particle will deposit.[100] Thus, each precipitator section has its electrical mobility 'cutoff range'.

Charges generated from a MDI were measured using the bipolar charge measurement system and the ELPI.[100] Bipolar charges were measured in all sections of the precipitator system. To facilitate comparison, particle size ranges of the five precipitator sections were derived from the ELPI net mobility distribution.[100] The proportions of positive and negative charges with respect to the net charge in a precipitator section were defined as 'bipolarity factors'.[100] A hypothetical bipolar charge distribution was calculated by multiplying the net charges obtained from the ELPI by the corresponding bipolarity factors for the various size fractions.[100]

Table 2 summarises the electrostatic charge measurement techniques.[15,19–22,31–34,36–38,50,75,79,80,99–102]

Table 2 Electrostatic charge measurement techniques

Static	Dynamic
Faraday pail[15]	Electrical single particle aerodynamic relaxation time (E-SPART) analyser[99,101,102]
Aerosol electrometer apparatus[31,36,38,75]	Bipolar charge measurement system[100]
Electrical low pressure impactor (ELPI)[19–22,32–34,37,50]	
Modified twin stage impinger[79]	
Electrical next generation impactor (eNGI)[80]	

Future directions

Electrostatics of pharmaceutical inhalation aerosols is an important area that is still in its early stages of development. The core question that needs to be addressed is whether charges carried by respirable particles affect the site and/or extent of deposition in human airways. Although computational simulation results suggest that this may be so (within certain ranges of charge magnitude and particle size), the models must be validated by in-vivo data. There are hitherto no clinical studies employing the administration of charged aerosols to human subjects with precise mapping of deposition in the lungs. Such studies are achievable using currently available techniques. Aerosol electrification may be controlled by corona charging, spray charging or manipulation of the formulation and inhaler components. Three-dimensional gamma scintigraphy such as single photon emission computed tomography[103] may be applied to determine the lung deposition of charged, radiolabelled particles or droplets. The data derived, whether positive or negative, can constitute a major milestone in the advancement of this field.

A related area of research is the relationship between the physicochemical properties of the formulation/inhaler components and the resultant charges. Although charges of various commercial products have been characterised, fundamental studies are still rare. To unravel the underlying charging mechanisms would necessitate further exploration in this direction. Obviously, the practical usefulness of the in-vitro findings should be interpreted in the light of clinical studies. If charges have no or limited influence on deposition, then the pursuit of fundamental studies is only of pure scientific interest. However, significant electrostatic effects on in-vivo deposition would mean not only a new opportunity to control pulmonary drug delivery for optimising clinical outcomes, but also new pharmacopoeial methods and regulatory requirements on charge measurement for pharmaceutical inhalation aerosol products.

Conclusions

Research and innovations in the area of pharmaceutical aerosol electrostatics have been reviewed in this paper. The electrification properties of charged solid particles and liquid droplets and their measurements were discussed. Certain areas have been studied more extensively than others by researchers over the years, such as the

electrostatics of bulk powder handling and spacer devices. On the other hand, interest in the role of charges in inhalation aerosols and lung deposition has only started to grow recently. Data on the clinical significance of electrostatic charges on lung deposition is still lacking. Much is still unexplored and development in this area is anticipated. The knowledge gained may have regulatory implications and further assist the development of aerosol formulations and delivery systems.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

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