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The potential of leveraging electrostatics for improved inhaled drug delivery to the lungs

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In this short perspective, we explore the potential of leveraging electrostatic forces in the lungs to enhance pulmonary drug delivery methods and optimize drug delivery efficiency and therapeutic outcomes. Alongside conventional mechanisms such as diffusion, gravitational sedimentation, and impaction, we delve into electrostatic mechanisms, utilizing a non-dimensional analysis approach for insights into aerosol drug delivery. While often overlooked in inhalation therapy, our considerations emphasize the significance of electrostatic interactions on drug deposition, particularly in the deep lung, where, in the future, tailored electrostatic charges can strategically offer new possibilities for localized therapeutic effects for respiratory diseases.

KEYWORDS

electrostatic forces, drug delivery, pulmonary administration, respiratory medicine, charged aerosols

Introduction

Inhaled aerosol therapy represents a cornerstone in treating respiratory conditions and diseases including asthma, chronic obstructive pulmonary disease (COPD), and cystic fibrosis (CF) to name a few (Laube, 2005; Stein and Thiel, 2017). Concurrently, beyond the delivery of inhaled medication for topical airway treatment, the lungs present a potent gateway for systemic delivery. Due to the high permeability of the thin alveolar-capillary barrier (~1 μm thick) combined with the vast pulmonary surface area (on the order of ~100 m^2 in an adult), deposited molecules can be rapidly absorbed into the systemic circulation (Ji et al., 1995; Patton, 1996). Despite the clinical prevalence of inhalation therapy, pulmonary deposition efficiencies remain typically low (i.e., often <50% of a nominal dose inhaled), a reality that leads, for example, to over-compensation by administrating larger doses (de Boer et al., 2017; Choi et al., 2019). This situation is even more dire in young pediatric populations where deposition efficiencies can lie well below 10% using conventional inhalers (Amirav and Newhouse, 2012; Das et al., 2018). While the respiratory community has long recognized the pitfalls in the efficiency of inhalation therapy, understanding the transport dynamics of inhaled aerosols can help shed light on novel approaches to enhance deposition in targeted areas of the lungs while reducing superfluous deposition in undesired airway sites.

From an evolutionary perspective, the respiratory tract is well adapted to protect the delicate airway milieu from the deposition of undesired inhaled particulate matter (PM), e.g., airborne pathogens, smoke, debris, etc., via mucociliary clearance (King, 2006) and immune responses (Diamond et al., 2000), in conjunction with filtering occurring from the anatomic intricacies of the lungs (e.g., mouth-throat region). Most notably, the nasal

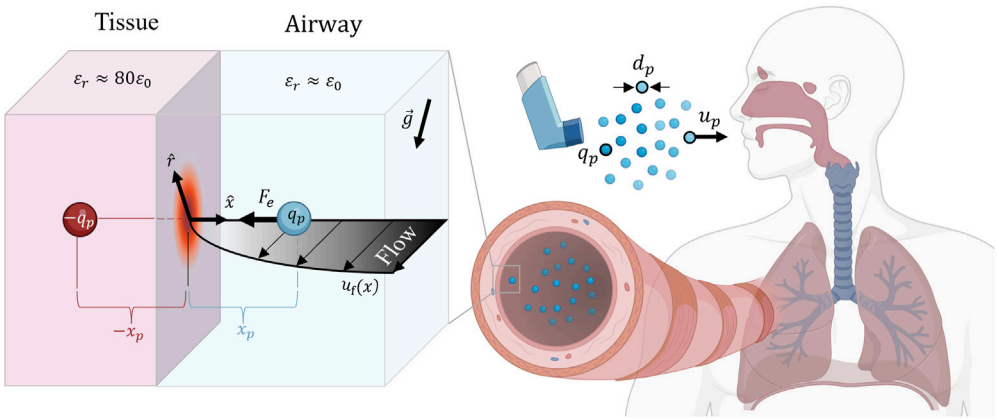

FIGURE 1
Schematic of the journey of an inhaled aerosol with mass m_p. Initially, aerosols of size d_p (blue particle) are produced in the inhaler, acquiring a net charge q_p and initial momentum $m_p u_p$ within the respiratory tract. The particle is then carried deeper into the lungs by the airflow velocity profile u_f. In the vicinity of the airway lumen, electrostatic interactions between the particle and the polarized tissue surface dominate over other mechanisms (i.e., gravity, impaction or diffusion), leading to eventual deposition. Mathematically, the polarized charge on the tissue surface (red circle) can be replaced using image charge methods (red particle) to solve the particle dynamics.

cavities are highly efficient in screening and trapping coarse PM of ~10 μm in diameter or larger (Schwab and Zenkel, 1998). In turn, pharmaceutical aerosols follow broad design recommendations within the size range of 1–5 μm for improved deposition in the peripheral airways (Darquenne, 2012). An often less recognized aspect lies in the tendency of off-the-shelf inhaler devices to accumulate high amounts of electrostatic charges on the generated airborne particles (Kwok and Chan, 2010), a phenomenon characterized by the electric charge q_p on an aerosol that arises during dispersion from physical contact with the inhaler components or by inner interactions between the particles. Additionally, spontaneous disruption of the electrical double layer (EDL) can create highly charged droplets in a fluid (e.g., atomizer generators) (Swarbrick, 2006). As a result, typical inhalers hold electric charges ranging from single (e.g., nebulizers) to hundreds of electrons (e.g., metered dose inhalers and DPI).

Although the effect of electrical charge has been recognized for nearly a century (Wilson, 1947), the discussion of electrostatic forces on inhaled aerosols is often overshadowed by the role of traditional deposition mechanisms (i.e., inertial impaction, gravitational sedimentation, Brownian diffusion). When electrical charges are indeed addressed, they are mostly alluded to as a source for additional losses in the extra-thoracic (e.g., mouth, throat) and upper respiratory airways (Cohen et al., 1995; Azhdarzadeh et al., 2014a; Azhdarzadeh et al., 2014b; Xi et al., 2014; Azhdarzadeh et al., 2015), thereby reducing the net dose available for effective treatment in the distal lungs. Since the electrostatic force F_{elec} is inversely proportional to x_p, which represents the shortest distance from the airborne particle to the airway lumen wall ($F_{elec} \propto x_p^{-2}$; see Figure 1), this effect is anticipated to become increasingly significant in the peripheral regions of the lungs where airway diameters are as small as a few several hundred microns (e.g., small bronchioles and acinar airways) (Melandri et al., 1983).

To date, the role of electrostatic forces on aerosol deposition in the distal lungs has received relatively little attention in either experiments or simulations (Bailey et al., 1998; Majid et al., 2012), with many questions remaining. In this short perspective, we first briefly revisit the physical underpinnings of electrostatic forces on inhaled aerosols and extract, via non-dimensional analysis, the relevant parameter spaces in which electrostatics appear to dominate aerosol deposition quickly. Furthermore, we discuss the potential of leveraging such electrostatic properties for improved pulmonary drug delivery and the outstanding engineering challenges to overcome in ultimately leveraging such effects. In a final step, we identify a number of clinical scenarios in which electrostatics effects deserve further consideration in inhalation therapy.

Electrostatics in off-the-shelf inhalers

In the realm of inhaler devices, a wide range of electric charges is observed, varying from single electrons, as seen in the case of nebulizers (Kwok and Chan, 2010), to several hundred electrons, such as in metered-dose inhalers (MDI) and Dry Powder Inhalers (DPI). For instance, a particle generated from DPI Pulmicort was estimated to carry approximately q_p ~200 e (Byron et al., 1997). MDI particles exhibit even higher charges, with chlorofluorocarbon (CFC) based Ventolin estimated to produce net charges of about ~300e and hydrofluoroalkane (HFA) based Airomir generating ~490 e (Kwok and Chan, 2010). Past computational models have suggest that these charge levels are significant enough to impact deposition in the lungs (Balachandran et al., 1997).

Moreover, spacer devices, which play a pivotal role in enhancing MDI aerosol drug delivery, are found to be susceptible to the charged aerosols produced by MDIs. Spacers are predominantly constructed from non-conductive materials, leading to the accumulation of charges when handled by patients (Newman, 2004). These charges can interact with the highly charged aerosol produced by the MDI, potentially affecting drug output. Fortunately, effective solutions exist to mitigate this issue, including the use of conductive metal spacers (e.g., the Nebuchamber) (Janssens et al., 1999;

Janssens et al., 2000), and the application of detergent or surfactant coatings (Waterer et al., 1998; Piérart et al., 1999; Kwok et al., 2006). These materials prevent the retention of charge concentrations, ultimately enhancing the efficiency of MDIs' drug delivery.

It is important to note that there are various ways to adjust the mentioned inhalers to achieve desired aerosol charge levels. For MDIs, factors like propellant type (Kwok et al., 2005), water content (Chi Lip Kwok et al., 2008), drug formulation (Kwok and Chan, 2010), and inhaler components (Carter et al., 2011), influence charge levels. DPIs can be manipulated through component selection and particle surface properties (Amorphous vs Crystalline) (Bailey, 1993; Kwok and Chan, 2010), as well as Relative Humidity (RH) during storage and dispersion (Young et al., 2007; Kwok and Chan, 2008). Nebulizers exhibit charge modulation based on parameters such as temperature, pH, ionic content, and conductivity (Kwok and Chan, 2010; Yatsuzuka et al., 1994; Yatsuzuka et al., 1996; Vaaraslahti et al., 2002).

Particle dynamics and the electrostatic force

Various mechanistic forces act on an aerosol of diameter d_p along the respiratory tract. Such forces include gravitational sedimentation, stochastic Brownian diffusion, viscous drag, hygroscopic growth, and electrostatic forces among the leading ones (Bailey et al., 1998). Aerosols are typically small in size ($\sim O(10^{-6})$ m), resulting in a relatively small ratio of volume to area (for spherical particles $V_p/A_p \propto d_p$) that leads to the dominance of electrostatic forces even with a small amount of net charge q_p. This characteristic is not only prominent in nature (England et al., 2023), but it is well recognized in the aerosol industry where there are various applications (Hinds and Zhu, 2022).

Inhaled charged aerosol particles can interact with surrounding tissue and with one another. Notably, particles carrying similar charges exhibit more rapid dispersion of the droplet cloud (Balachandran et al., 1997). This behavior can be attributed to the fundamental principle of electrostatic repulsion between the aerosols and is referred to as "*space charge*" (Spc). This becomes particularly significant in environments with dense aerosol clouds characterized by high concentrations ($>10^{12}$ particles/m^3) and charge levels on the order of hundreds of electrons, as often used in industrial applications (Osman et al., 2015). However, it is important to note that this phenomenon is generally absent in the context of inhalation therapy due to notably lower aerosol concentrations. While it may occur near the device's exit and within the mouth region, such phenomenon weakens considerably within the main respiratory tract. (Kwok et al., 2005). Hence, in the realm of aerosol deposition within the lungs, the primary electrostatic effect steams from the interaction between charged airborne particles and the lung tissue (Balachandran et al., 1997; Finlay, 2021).

While the airway surface epithelium typically maintains a negative charge, with ion transport regulating lung cell homeostasis (Zhao et al., 2022; Yeung et al., 2008), the electrical charge within human airways, from the perspective of an airborne particle, remains neutral (Kwok and Chan, 2010). Human mucus, composed of water, glycoproteins, and various molecules (Bansil and Turner, 2018) functions as a dielectric material, capable of storing electrical charge and responding to external electric fields, similar to liquid water. Although the electrical properties of both inflated and deflated lungs have been collectively measured (Sasaki et al., 2022), direct electrical measurements of tissue from the perspective of aerosol deposition remain unestablished. Techniques such as conductive atomic force microscopy (cAFM) could potentially verify tissue conductivity, but have never been reported, possibly due to the existence of robust *in vivo* data supporting the notion of electrostatic enhancement in deposition (Fraser and Hill, 1966; Biology, 1983; Prodi and Mularoni, 1985; Cohen et al., 1998; Kwok et al., 2021). The lung tissue exhibits an electrical conductivity and a dielectric constant (ε) similar to that of conducting saline water (Bailey et al., 1998). When a particle with charge q_p is present, it induces an external field on the neutralized tissue resulting in a dielectric effect. This effect causes charged or dipole molecules to reorient themselves on the tissue surface to counter the external field. In the vicinity of the parenchymal tissue ($x_p \ll R$ where R is the airway radius) one may assume that this tissue acts as a semi-infinite equipotential conducting surface. The surface charge density distribution is given by $\sigma(r, x_p) = -q_p x_p / 2\pi (r^2 + x_p^2)^{1.5}$ in (e/m^2), where r is the projected radial distance on the tissue surface away from the particle (i.e., depicted as the red circle in Figure 1), q_p is the net electrical charge of the aerosol and x_p the shortest distance from the airborne particle to the airway lumen wall (Halliday et al., 2013). This arrangement creates attractive forces between the aerosol and the tissue surface. Due to the symmetry of the charge density, the resultant force (F_e) is directed toward the tissue ($-\hat{x}$) and known from fundamental physics textbook examples, e.g., a particle above a charged ring or disk (Halliday et al., 2013). The complex ensemble of electrostatic forces arising from the charge distribution $\sigma(r, x_p)$ on the tissue surface can be simplified using a similar problem: an opposite mirror image charge $-q_p$ located at equal and opposite distance $-x_p$ in the tissue (Figure 1). Both problems follow Laplace's equation and satisfy identical boundary conditions. By applying the uniqueness theorem, their solutions must be identical. This simplification enables a more straightforward derivation of the electrostatic attraction force known as the induced image charge, i.e., $F_e = k_e (q_p/x_p)^2/4$ where k_e is the Coulomb constant.

As a final remark, one must recognize that none of the forces acting on an inhaled airborne particle is specifically oriented to enhance airway deposition. For example, the gravitational force is directed toward the Earth's center, diffusion involves a random walk and impaction depends on the particle's flight trajectory (Hinds and Zhu, 2022). In contrast, electrostatic charge is at the source of the only mechanism that actively encourages a particle to deposit along its shortest trajectory to the airway surface (Bailey et al., 1998).

Non-dimensional analysis

Despite the above simplification to quantify the electrostatic force (i.e., induced image force), the particle transport equations (in Newton's second law) nevertheless remain a challenging nonlinear second-order ordinary differential equation with no simple analytical solution. In turn, much research in the field has benefited from numerical approaches, most notably

TABLE 1 Summary of the leading mechanisms contributing to aerosol deposition within the lungs, presented as non-dimensional numbers.

Mechanism	Non-dimensional number	Key parameters
Impaction (Stokes Number)	$\mathrm{Stk} = \frac{\tau_p U_c}{L_c}$	$\tau_p = \frac{C_c \rho_p d_p^2}{18\mu_f}$ is the particle relaxation time C_c is the Cunningham slip correction factor (Cu, 1910)
Gravitational Sedimentation	$\mathrm{H} = \frac{\tau_p g}{U_c}$	g is the Earth's gravitational constant of 9.81 m/s^2
Brownian Diffusion (Inverse Péclet Number)	$\mathrm{Pe}^{-1} = \frac{D_{diff}}{U_c L_c}$	D_{diff} is the Stokes-Einstein diffusion coefficient
Induced Charged	$\mathrm{Inc} = \frac{k_e B}{4U_c}\left(\frac{q_p}{L_c}\right)^2$	$B = \tau_p/m_p = \frac{C_c}{3\pi\mu_f d_p}$ is the particle mechanical mobility and m_p is the particle's mass

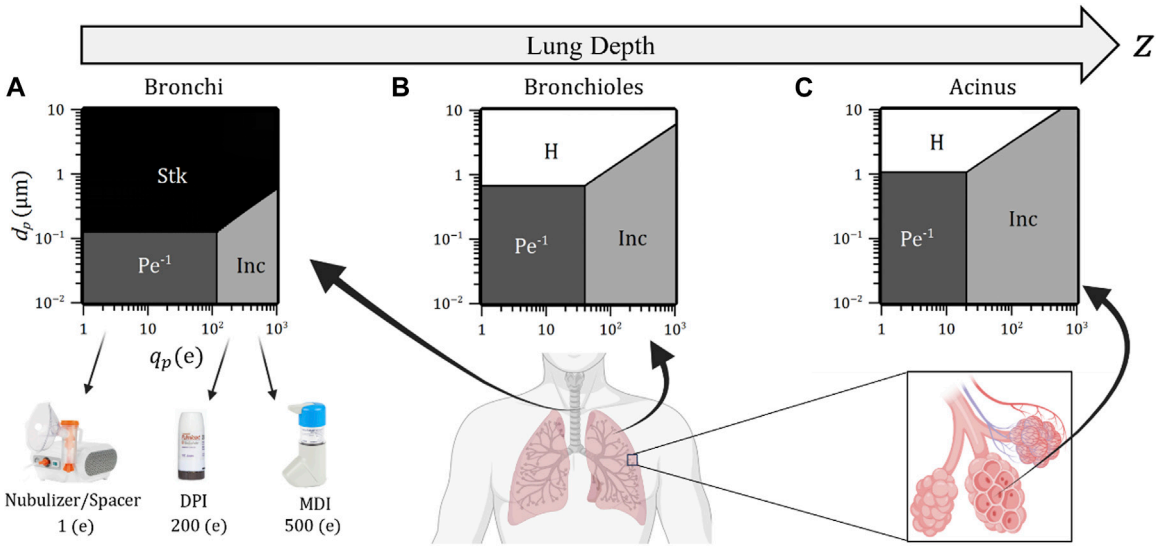

FIGURE 2
Phase maps depicting the leading dimensionless numbers (Stk, H, Pe^{-1} and Inc.) at various depths of the lungs: **(A)** bronchi, **(B)** bronchioles, and **(C)** in the acinus. The dimensionless numbers are plotted against units of elementary charge q_p (horizontal axis) and particle diameter d_p (vertical axis), both on a logarithmic scale. Each phase map reveals distinct zones, relating the dominance of one group over the others, with delineations between indicating regions where two groups are of comparable magnitude. The characteristic length $L_c = 0.05R$ is selected to denote the particle's proximity to the tissue, while the velocity $U_c = u_f(L_c)$ is based on Hagen-Poiseuille flow under quiet breathing conditions (see SM for derivations).

computational fluid dynamics (CFD) (Osman et al., 2015; Koullapis et al., 2016). Yet, much insight can be immediately gained via non-dimensional analysis in assessing the relative importance of each contributing force, as highlighted below.

We recall that the lungs encompass a complex multiscale problem, spanning approximately twenty or so bifurcating airway generations (z). At the trachea (z=0), the characteristic length $L_c(z)$ is related to the airway diameter (~2 cm), reducing down to ~300 μm in the acinar airways (16<z<23) and just ~100 μm in the alveolar cavities (Haefeli-Bleuer and Weibel, 1988). Additionally, as air is transported distally into the lungs, the characteristic airflow velocities $U_c(z)$ decrease according to mass conservation across the tree network.

Following traditional dimensional analysis for airborne particle (Bailey, 1993), we recover four non-dimensional groups summarized in Table 1 (see Supplementary Material for further details), underlining impaction (Stk), sedimentation (H), diffusion (Pe), and electrostatics (Inc). We may assess their relative importance by plotting corresponding phase maps as a function of aerosol diameter and net electric charge for common inhalers across the lung regions (Swarbrick, 2006; Sznitman, 2013; Hofemeier and Sznitman, 2015), as shown in Figure 2. Distinct areas in the phase map highlight regions where one group dominates over the others, whereas lines between regions delineate when two groups have equal magnitude signifying the superimposition of their effects.

Role of electrostatics in the conducting regions of the lungs

As a general rule, in the extrathoracic and upper airway regions of the lungs (Figure 2A) the main deposition mechanism for particles larger than 5 μm is often attributed to impaction (corresponding to large values of Stk). Nevertheless, sedimentation still plays a significant role for particles larger than approximately 1 μm in the main conducting airways. This

phenomenon largely overshadows diffusion and electrostatic effects. However, for high amounts of charge (Bailey et al., 1998) or in the case of ultrafine particles ($d_p < 0.1\,\mu$m), electrostatics can rapidly dominate deposition. This has been witnessed in past simulations (Koullapis et al., 2016) and *in vitro* deposition studies of fine particles in a trachea-like model (Bailey et al., 1998) and in the upper airways (Cohen et al., 1998). We recall that the electrostatic force is superimposed on the other acting forces and will direct an airborne particle toward the shortest path to the tissue. Hence, even if not dominant, electrostatics still alter the deposition characteristics as previously discussed (Bailey et al., 1998; Cohen et al., 1998; Koullapis et al., 2016). Given that off-the-shelf inhaler devices deposit aerosol in the upper airways, particularly in the mouth and throat, there has been a drive for innovation to develop mechanisms that can mitigate these outcomes. Such mechanisms include the utilization of spacers, adjustments in volume, or control over airflow (Ari and Fink, 2020). Consequently, there is a compelling need for additional research to delve into the electrostatic effects within these regions. However, beyond the bronchial generations, there is a noticeable dearth of literature addressing deposition characteristics influenced by electrostatics. Despite the pressing need for improved regulation of electrostatic charging in various inhalers (Kwok and Chan, 2010), a comprehensive understanding is still lacking.

In the small bronchioles, with the rapid decrease in airflow velocities the Stk number becomes less dominant than the gravity number H. Two interesting phenomena may be observed. Firstly, due to the smaller characteristic length L_c, electrostatics gain an advantage over the other mechanisms $\left(\frac{Inc}{H} \propto \frac{1}{L_c^2}\right)$ and $\left(\frac{Inc}{Pe^{-1}} \propto \frac{1}{L_c}\right)$. This advantage can be visually observed in Figure 2B, where various scenarios in which the combination of charge and size can alter anticipated deposition outcomes. With further constriction in diseased airways (e.g., asthma, COPD, etc.) the role of electrostatics could be advantageous, assuming that the nominal inhaled aerosol bolus would, despite decreased ventilation, be able to reach such constricted lung regions.

When considering airway sizes and anatomy, the case of pediatric patients is of particular relevance, where deposition efficiency (DE) is often underwhelming, with typical results reaching only around 30% of the provided dosage and dropping as low as 5% depending on age and condition (Schueepp et al., 2009). Recent reviews continue to highlight this issue (Amirav and Newhouse, 2012; Schüepp et al., 2004), pointing out the rule of thumb that "the younger the patient, the worse the targeting efficiency" (Oakes et al., 2023). Contrary to common intuition, smaller lungs in children do not imply weaker airflows, since children's lungs have narrow airways (i.e., smaller cross-sectional areas) but faster breathing rates, leading to higher velocities (Das et al., 2018; Oakes et al., 2023; Oakes et al., 2018). We recall that Inc, Pe^{-1} and H are inversely proportional to the characteristic velocity ($\propto U_c^{-1}$), ensuring that the interplay between them remains unaffected by slower or faster airflows during inhalation. This interplay favors electrostatic effects due to the small airways of infants since the ratio between Inc/Stk ~ L_c^{-1} is biased towards the smaller airway sizes (Diamond et al., 2000; Yatsuzuka et al., 1996; England et al., 2023).

To the best of our knowledge, the smallest models used to explore electrostatic effects *in vitro* have been hollow casts of adult human airways that span down to the sixth generation (Cohen et al., 1998). For infants, despite the considerations we described, research has largely focused on the upper airways (Azhdarzadeh et al., 2014b) and the effect of neutralizing charge via spacers (Osman et al., 2015; Finlay, 2021), underlining the need for further research.

Role of electrostatics in the deep acinar regions

Gravitational sedimentation (H) and Brownian diffusion (Pe^{-1}) are most often recognized as the dominant processes determining particle deposition in the acinar regions (Kwok et al., 2006; Kwok et al., 2005; Bailey, 1993; Yatsuzuka et al., 1994). However, upon examination of the phase map (Figure 2C) it becomes evident that the acinar regions would be most susceptible to the influence of electrostatic forces, as Inc. is inversely proportional to the square of the characteristic length (Inc $\propto L_c^{-2}$). Although it is widely accepted that diffusion governs the behavior of submicron particles in the acinar region, we observe that this is only true when the charge $q_p <$ 20 e. This result depends on the characteristic length L_c, but not on the velocity U_c nor size d_p (see SM). This threshold value has also been observed *in vivo* for particle sizes of 0.3, 0.6, and 1.1 μm (Melandri et al., 1983) and is an order of magnitude smaller than the common amount of charges acquired in inhalers such as DPI and MDI (Das et al., 2018). Consequently, when using DPI and MDI devices (but not the case with nebulizers (Kwok and Chan, 2010) and spacer extensions (Osman et al., 2015; Finlay, 2021), electrostatically-induced deposition would plausibly become the most significant determinant for submicron aerosols in the alveolar space.

We recall that aerosols in the size range of 5–10 μm are mostly susceptible to deposition in proximal airway regions (i.e., extra-thoracic and upper airways), regardless of charge. Even for smaller particles, such as those between 1–5 μm, a substantial proportion will not successfully reach the deeper regions of the lungs without careful adjustment of inhalation flow rates (Koullapis et al., 2016; Heyder et al., 1986; Kleinstreuer et al., 2008; Kleinstreuer and Zhang, 2010; Islam et al., 2017). For example, the broad deposition efficiency of 2 μm particles is less than ~15% in the acinar regions (Piérart et al., 1999; Prodi and Mularoni, 1985). Yet, such assessments are typically based on spherical particles and alternative particle shapes could be considered (Kleinstreuer et al., 2008; Kleinstreuer and Zhang, 2010; Islam et al., 2017). For example, long straight fibers align with the flow due to fluid shear stress, enabling them to penetrate deeper into the lungs than spherical particles with the same diameter as the fiber length (Asgharian and Yu, 1988; Harris and Timbrell, 1975). Fibers experience stronger drag forces that hinder gravitational sedimentation, leading to longer air retention compared to spherical particles of the same mass (Shachar-Berman et al., 2018). Asbestos fibers, for instance, with lengths of 50–200 μm, yield significant deposition in the alveolar space, causing a dramatic decline in health conditions (Timbrell, 1965; Donaldson et al., 1989; Kamp, 2009; Barlow et al., 2017; Tsuda et al., 2013; Stahlhofen et al., 1989; Velkov et al., 2015; Sznitman et al., 2016). *In vivo,* studies have shown that charged asbestos fibers exhibit much more acinar deposition than neutralized ones (Davis et al., 1988). Hence, the combination of fiber particles with electrostatics offers a potential strategy for targeted drug delivery to the acinar regions. This is particularly relevant for therapeutic agents, which when deposited in the upper airways, can cause important side effects. For instance,

pentamidine, an effective antifungal medication used in chemotherapy, can only be prescribed to individuals allergic to alternatives due to its harmful side effects in the upper airways (Hofemeier and Sznitman, 2015; Ari and Fink, 2020). Such considerations embody the potential of combining shape and electrostatic charge to design airborne carriers tailored to reach the deep lungs.

As a final remark, we recall that the deep respiratory regions encompass ~90% of the total lung volume (Knudsen and Ochs, 2018). Therefore, when examining the phase map in the acinar space (Figure 2C), it becomes even more striking that from a non-dimensional perspective the vast majority of the lung space is susceptible to electrostatic effects.

Conclusion

In this short perspective, we revisited the significance of electrostatics in inhalation therapy with special consideration to deposition in the distal regions of the lungs. Our non-dimensional analysis reveals the crucial importance of this mechanism, showing its potential for improved pulmonary delivery strategies. Until now, little attention has been paid to how electrostatic mechanisms alter aerosol deposition at the smallest scales of the lungs, while there has been extensive research on such phenomenon in the upper airways (Kwok and Chan, 2010). Most notably, the well-known ICPR reference curves entirely overlook the role of electrostatic and charge (ICRP, 1994). The quest to identify the electrostatic window of opportunity should inspire drug delivery researchers to engineer novel deposition strategies for both higher drug efficiency and targeted delivery within the lungs. Integrating charge as a key design parameter, alongside more traditional factors such as particle size, shape, characteristic airflow velocity, can provide a more comprehensive framework to enhance the current state of pulmonary drug delivery.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Author contributions

RB: Conceptualization, Data curation, Formal Analysis, Investigation, Visualization, Writing–original draft. JS: Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Writing–original draft.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmede.2023.1298251/full#supplementary-material

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