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Dynamics of aerosol size during inhalation: Hygroscopic growth of commercial nebulizer formulations

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ABSTRACT

The size of aerosol particles prior to, and during, inhalation influences the site of deposition within the lung. As such, a detailed understanding of the hygroscopic growth of an aerosol during inhalation is necessary to accurately model the deposited dose. In the first part of this study, it is demonstrated that the aerosol produced by a nebulizer, depending on the airflows rates, may experience a (predictable) wide range of relative humidity prior to inhalation and undergo dramatic changes in both size and solute concentration. A series of sensitive single aerosol analysis techniques are then used to make measurements of the relative humidity dependent thermodynamic equilibrium properties of aerosol generated from four common nebulizer formulations. Measurements are also reported of the kinetics of mass transport during the evaporation or condensation of water from the aerosol. Combined, these measurements allow accurate prediction of the temporal response of the aerosol size prior to and during inhalation. Specifically, we compare aerosol composed of pure saline (150 mM sodium chloride solution in ultrapure water) with two commercially available nebulizer products containing relatively low compound doses: Breath®, consisting of a simple salbutamol sulfate solution (5 mg/2.5 mL; 1.7 mM) in saline, and Flixotide® Nebules, consisting of a more complex stabilized fluticasone propionate suspension (0.25 mg/mL; 0.5 mM in saline. A mimic of the commercial product Tobi© (60 mg/mL tobramycin and 2.25 mg/mL NaCl, pH 5.5–6.5) is also studied, which was prepared in house. In all cases, the presence of the pharmaceutical was shown to have a profound effect on the magnitude, and in some cases the rate, of the mass flux of water to and from the aerosol as compared to saline. These findings provide physical chemical evidence supporting observations from human inhalation studies, and suggest that using the growth dynamics of a pure saline aerosol in a lung inhalation model to represent nebulizer formulations may not be representative of the actual behavior of the aerosolized drug solutions.

1. Introduction

For nearly a century, nebulizers have been used to administer medication to the lungs and account for ~13% of all inhaler retail sales in Europe as of 2008 (Lavorini et al., 2011). During this time, the use of the respiratory tract for drug delivery has proven highly successful for treating not only diseases of the lung, such as delivering bronchodilators to treat asthma (Johnson, 1989), but also in the treatment of systemic diseases, such as delivering insulin to treat diabetes (Dubus and Luc, 2003; Watts et al., 2008). In diseases of the lung, and to a lesser extent systemic diseases, the efficacy of the drug can be correlated to the site of drug deposition and delivery (Labiris and Dolovich, 2003). For this reason, the ability to effectively model the eventual site of drug deposition as a function of the composition, size distribution and phase of the nascent aerosol could prove to be advantageous in the design of nebulizer formulations and devices.

Although the importance of the aerodynamic diameter of an aerosol particle in determining the likelihood and site of deposition within the lung is well appreciated (Carvalho et al., 2011), the role of the hygroscopic growth of the aerosol, when produced with a nebulizer, remains a contentious issue. While the hygroscopic growth of fine and ultra-fine aerosol (diameter <1 μm) during inhalation is widely recognized to occur (Asgharian, 2004; Kim et al., 2012), the degree of hygroscopic growth of 'coarse' respirable aerosol (diameter >1 μm) is speculated to be minimal (Dennis, 2009; Finlay, 1998; Finlay and Smaldone, 1998). Given that the aerosol generated by many nebulizers has an aerodynamic size distribution

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concentrated in the coarse mode (Kallstrom et al., 2008), this assumption suggests that nebulized aerosol will not significantly change size during inhalation, regardless of composition. There are four commonly held reasons that may support the assumption that hygroscopic growth can be neglected. The first reason is that the large number of droplets per unit volume in a nebulized aerosol will stabilize individual particles against hygroscopic size changes. The large evaporating mass of water from the aerosol on nebulization is sufficient to ensure the relative humidity (RH) remains high and, thus, the aerodynamic diameter of all the droplets in the nebulized aerosol will remain approximately constant prior to inhalation (Dennis, 2009).

The second reason hygroscopic aerosol growth is sometimes thought to be minimal during inhalation is that the RH range that a nebulized aerosol experiences during inhalation is considered to be minimal (Dennis, 2009). As with the first reason, this is attributed to the large number of droplets in the aerosol which are believed to sustain the RH at or above 99.5%. When the nebulized airflow encounters any change in RH, the high RH is maintained by a net mass flux of water from the large number of droplets present into the gas phase (Ferron et al., 1997). This, however, is not the case (Prokop et al., 1995), and a series of recent publications have explored this process further (Krajnik et al., 2009; Nerbrink et al., 2003; Zhou et al., 2005). In these studies, the aerodynamic diameter of droplets in a nebulized aerosol is measured as a function of the ambient RH of the air that is mixed with the nebulized aerosol prior to inhalation. The influence of the ambient RH on the size distribution was found to be very much dependent on the pathway of the airflows through the nebulizer. When the only airflow in the system passes through the nebulized region (Fig. 1A(i)), also known as a breath enhanced nebulizer (*e.g.* Pari LC+ (Pari GmbH, Starnberg, Germany)), the RH throughout the system remains at or near saturation (Berg et al., 2007). This results from the ambient air becoming saturated in the nebulization region. As a result, for these types of nebulizers the degree of size change of the aerosol prior to inhalation is expected, and observed (Nerbrink et al., 2003), to be minimal. When the pathway of the ambient airflow instead meets the nebulized airflow at a T-junction (Fig. 1A(ii)) the volume of air and amount of time that the aerosol and ambient air spend mixing are controlled by the breathing rate of the patient and the breathing circuit design. For these systems, it was consistently observed that the RH of the ambient air had a significant and direct effect on the aerodynamic diameter of the aerosol exiting the nebulizer prior to immediate inhalation and the degree of the size change was found to be a function of the ambient RH (Krajnik et al., 2009; Nerbrink et al., 2003; Zhou et al., 2005).

The third reason that hygroscopic growth is sometimes assumed to be minimal during inhalation is the absence of any measurements that allow direct access to the rapid and significant changes in aerosol particle size that can occur at the near-saturation RH and elevated temperature characteristic of the respiratory tract. Specifically, measurements of both the magnitude and rate of condensational growth for aerosols generated from nebulizer formulations have not been possible until recently (Davies et al., 2012b). Without such data, the rate of growth of hygroscopic aerosol has been assumed to be that of pure saline (Xi et al., 2011), precluding any quantitative assessment of the role of hygroscopic growth of coarse nebulized aerosols during inhalation and the dependence on aerosol composition. The approach proposed here is to exploit recently developed single droplet analysis techniques to measure the time dependence of the mass flux to and from an aerosol of known composition as a function of the RH. An improved understanding of the mass flux from a single droplet will enable parameterization of a more accurate condensational growth model compared to previous reports. This new parameterization will then be used to predict the dynamic changes in aerosol size during a variety of hypothetical inhalation scenarios. One example is depicted in Fig. 1B for a constant output jet nebulizer with a T-junction.

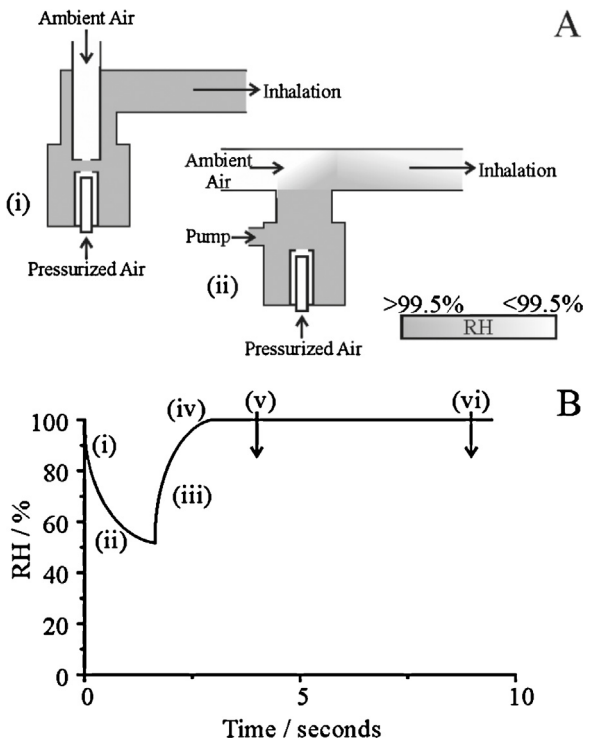

Fig. 1. (A) Two common airflows found in commercially available nebulizers. (B) A hypothetical representation of changes to relative humidity (%) during a wet nebulization inhalation process: (i) represents the aerosol generation process, (ii) denotes aerosol transport phase from the nebulization chamber to the mouthpiece (2 s), (iii) represents onset of aerosol inhalation and (iv) depicts the period aerosol residence in the lower respiratory tract. Points (v) and (vi) represent two different exhalation scenarios: (v) describes a relatively rapid exhalation based on tidal breathing and (vi) represents a hypothetical scenario in which the breath is held for ~10 s prior to exhalation. In both scenarios it is assumed that the RH% will remain at near saturation until exhalation is completed. This representation is based on experimental data from a combination of sources (Ferron, 1994; Martonen et al., 1982; Morrow, 1986).

The fourth reason that hygroscopic growth is often ignored is the assumption that there is insufficient water vapor in the lung to fully supply and sustain the growth of a large number of droplets in a nebulized aerosol. As a result, the amount of growth that is possible within the lungs is considered to be limited. It should be noted that the first, second and fourth issues are connected; either the aerosol is able to buffer the change in ambient/lung RH or not; if it is unable to buffer the change the changes in the RH is then large enough to cause a significant change in the aerodynamic size. In this study, each of these issues will be explored, and the potential importance of hygroscopic growth of nebulized pharmaceuticals in the estimation of dose, both overall and targeted, will be discussed.

The thermodynamic and kinetic factors governing the capacity of aerosols containing active pharmaceutical ingredients in saline solutions to undergo hygroscopic growth during inhalation remain ill-defined (Chan et al., 1994; Martonen et al., 1982). To enhance our understanding of the response of aerosol particle size to rapid changes in humidity for typical nebulizer product formulations, two different commercially available nebulizer formulations are compared with 150 mM sodium chloride (NaCl) solution in ultrapure water (referred to as saline in this study) to determine if the low drug content, either in solution or suspension form, influences hygroscopic growth profiles in nebulized products. Saline is the most commonly used vehicle in nebulizer solutions