Revisiting hygroscopic growth of nebulized pharmaceutics during inhalation: A novel strategy to use single droplet analysis to design nebulizer formulations for targeted dosing

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Summary

Hygroscopic growth of nebulized pharmaceutics is believed to be minimal as the range of relative humidity experienced by a nebulized aerosol is thought to be saturated from generation to inhalation. However, recent studies have challenged this core belief. Shown here is that nebulized pharmaceutics experience a range of relative humidities, and the potential to improve the drug efficacy of existing pharmaceutics by controlling their hygroscopic properties through the tailoring the starting formulations for targeted deposition within the lung.

Three different single droplet analysis techniques were used to analyze existing nebulizer formulations. These techniques were used to measure the necessary water activity/mass fraction of solute and water activity/density relationships to accurately model rapid droplet mass flux, and to experimentally verify the aerosol dynamic model.

The improved hygroscopic growth data were then used to predict the aerodynamic diameter of a population of polydisperse droplets from nebulization to inhalation. The treatment of the aerosol prior to inhalation (ie. changes in the relative humidity, etc.), were modelled. The size of the aerosol was input into a whole lung model based on the International Commission on Radiological Protection lung model. When integrated with the starting number density of a nebulized aerosol, the overall dose was estimated. The makeup of the starting formulation and the treatment of the aerosol prior to inhalation, were found to have a profound effect on both the overall amount and site of the dose, demonstrating the need to investigate the influence of hygroscopic response on lung deposition more completely.

Introduction

Nebulizers have been used for nearly a century to administer pharmaceutics in the treatment of diseases of the lung. Given that the aerodynamic diameter of an aerosol has a significant effect on the site of deposition within the lung, a detailed understanding of the particle size distribution of the aerosol throughout the inhalation process is necessary. Conventional wisdom is that the net mass flux to and from a nebulized aerosol from generation to deposition within the lung is minimal. The reasoning behind this is that the sheer number of droplets in a nebulilzed airflow will serve to buffer the mass flux from any given droplet; the mass of water in the airflow will remain saturated throughout the inhalation process. A series of recent publications have served to challenge this assumption (1-3). In these studies, the aerodynamic diameter of nebulized droplets was found to be affected by the ambient relative humidity (RH). In this study, the actual RH of a nebulized airflow as a function of device orientation, airflow rates, and ambient RH was measured. The findings made here (section 1) bolster the argument that aerosol produced by a nebulizer may, depending on numerous factors such as device construction, experience a range of RH, resulting in the droplets of the aerosol drastically changing size during their lifetime (figure 1).

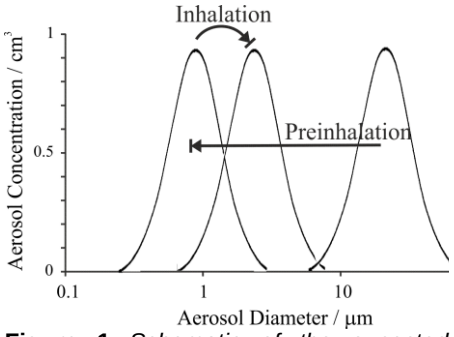

Figure 1 *Schematic of the expected change in droplet radius of a nebulized droplet during its lifetime.*

Single droplet analysis has become a useful tool to understand a wide range of issues ranging from climate change to drug delivery to the lung. Detailed understanding of the behavior of a single droplet can be used to accurately predict the behavior of multiple droplets within a population of polydispersed aerosol (eg. a cloud). In this study, the hygroscopic growth of single droplets generated from nebulization formulations as a function of RH were measured using a single droplet analysis technique (double ring electrodynamic balance (EDB)). From the water activity/mass fraction of solute relationships measured using this technique, the rapid mass flux to and from a droplet was modeled using a series of equations based on the semi-analytical solution to the mass and heat flux equations of Kulmala *et al.* (4). The hygroscopic growth dynamics of droplets generated from nebulization formulations were then directly measured using the recently developed concentric cylinder electrodynamic balance (CCEDB) (5) and optical tweezers (OT), and used to verify mass flux predictions derived from the model. From this data, the ability to predict the dynamic response of a polydisperse population of droplets as it experiences changes in RH is possible.

Whole lung models have been used for many years to predict the eventual site of aerosol deposition within the lung as a function of droplet diameter and composition. The International Commission on Radiological Protection (ICRP) lung model is one of the oldest and most commonly used whole lung models, and is considered the standard. In this study, the ICRP lung model was modified to consider detailed hygroscopic growth rather than the originally used crude estimation. With this modified model, the relative deposition pattern of various nebulized pharmaceutics was modeled using the dynamic hygroscopic properties measured with single droplet analysis techniques, and overall dose estimated.

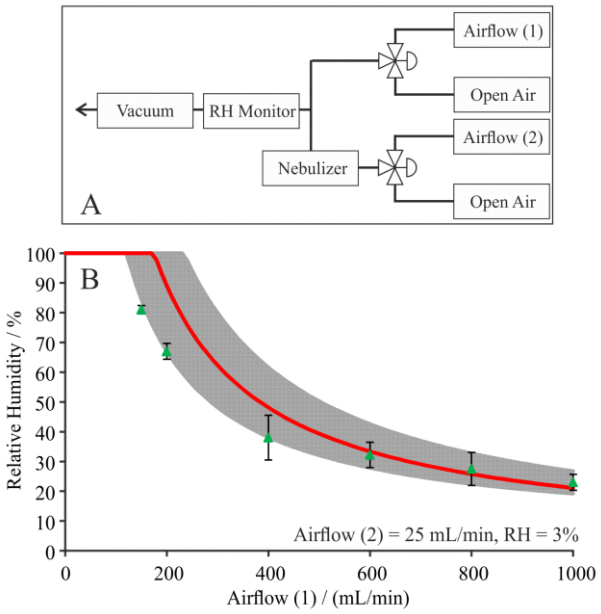

Figure 2 *RH of a nebulized airflow (B) as a function of the airflow rate through the device (A).*

Methods and Materials

Section 1: RH in a nebulized airflow

Based solely on the mass of water ejected from a nebulizer as a function of time, the RH of airflows through the device (figure 2A) was predicted and measured directly (figure 2B). The vacuum was used solely to balance the airflows through the system.

Section 2: Single aerosol analysis

Numerous commercially available nebulisation formulations were studied. A sterile saline product (Steri-Neb®, 0.9% w/v) was used. Breath® (Salbutamol 5 mg/2.5 mL nebulizer solution) and Flixotide® Nebules (Allen & Hanburys Ltd., Uxbridge, UK) were sourced from the manufacturer and used without dilution. Tobramycin powder was purchased from Sigma Aldrich and dissolved in water to produce a Bramitob® (Chiesi) mimic and dissolved in dilute saline to produce a Tobi® (Novartis) mimic (the pH of both Tobramycin solutions was adjusted to ~6).

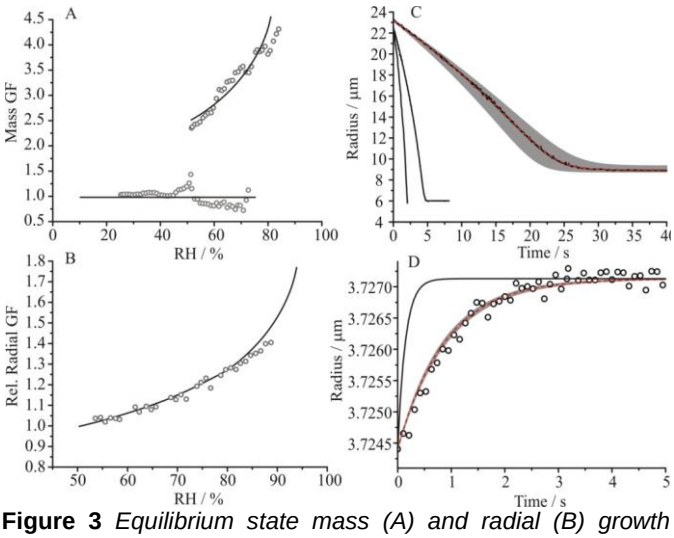

Figure 3 *Equilibrium state mass (A) and radial (B) growth factors (GF) of saline as a function of RH, as measured with the EDB. (C) The time-dependence of the size of saline aerosol droplets injected into an air flow with relative humidity of 90% (right curve), 50% (mid curve) and <10% (dry air; left curve), as measured with the CCEDB. (D) The time-dependence of the radius of a saline droplet during condensational growth from an initial state to a final equilibrium state, as measured with OT.*

Detailed descriptions of the operation of the EDB (6), CCEDB (5) and OT (7) have been published previously, and for brevity, only what the various techniques were used to measure will be given. Note that all three techniques involve the probing of a single levitated droplet (radius between 2 and 30 µm) in a controlled and variable atmosphere.

The relative mass and absolute radius of a single droplet levitated in an electric field was measured using an EDB while the RH was change from <20% to >85% and back to <20% over the course of a >30 hour period. For all of these measurements, the droplet was at a thermodynamic equilibrium with the surrounding air. A series of equations based on the semi-analytical solution to the mass and heat flux equations of Kulmala *et al.* incorporated this data to predict the rapid mass flux to and from a droplet.

The rapid mass flux from droplets in rapidly changing environments was measured using OT and CCEDB to verify the model. For the OT, measured single droplet was exposed to laser induced temperature changes and the resulting size change measured as a function of time. For the CCEDB, a droplet of pure nebulisation formulation was injected into an environment of a given RH, and the rapid change in aerosol diameter was measured as the droplet evaporated to a size and concentration with water activity equal to the gas phase RH.

Section 3: Incorporation into a lung inhalation model

The ICRP model was modified to include accurate droplet growth as a function of RH. To estimate the dose in a given region in the lung, the size distribution of a nebulized aerosol at the point of nebulisation was used to define the aerosol counts at time point zero (1). The mass flux rate verified in section 2 was then used to model the size of each size fraction of a polydisperse aerosol from generation to deposition under a range of conditions and factors (eg. patient sex, activity level, ambient RH, length of hose in the nebulizer, etc.). This size data was then input into the whole lung model to estimate the overall dose of drug as a function of these various conditions.

Results

Section 1: RH in a nebulized airflow

Through controlling all the airflows through the nebulizer (figure 2A), direct measurements of the RH verified that the RH in the nebulized airflow can be predicted solely on the mass of water being ejected by the nebulizer. When the flow rate through the nebulisation region is lowered, or the secondary airflow rate is increased, the RH range that an aerosol can reach is below 20% (figure 2B). Additionally, the ratio of the pipe diameters of the T-junction can be used to control the RH in the primary airflow while leaving the airflow through the nebulization region at a constant 6 L/min (data not shown). A reduction in RH is observed when the diameter of opening to the ambient air (Airflow (1) in figure 2B) was more than double greater than the primary airflow. The reason for this is that even though nebulizers operate at a fairly high flow rate, they also operate at a very low pressure. This data, coupled with prevous studies (1-3), demonstrate that a nebulized aerosol may experience an RH range well below saturation prior to inhalation.

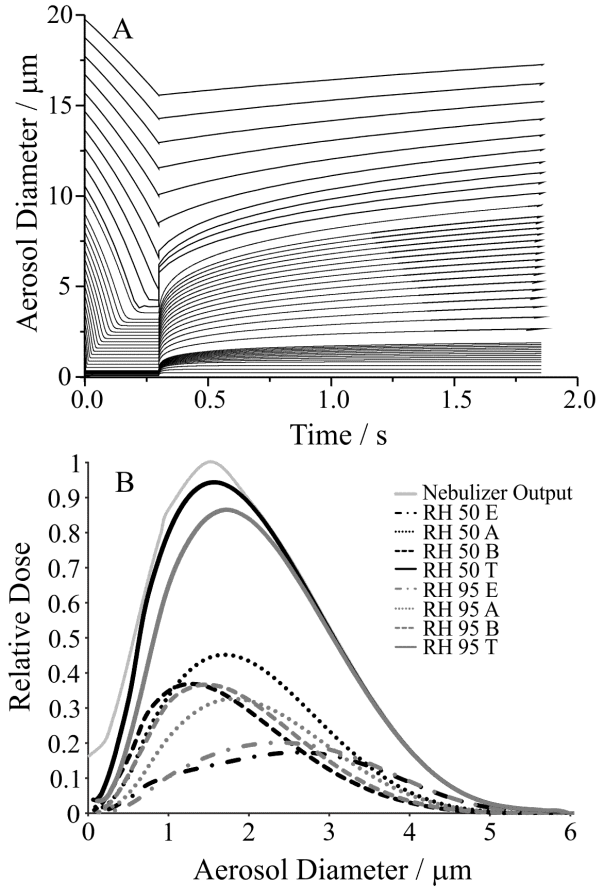

Figure 4 *(A) Example of the radial data model inputted into the whole lung model. In this example, saline droplets are generated into an airflow with an RH of 50% prior to inhalation at a time of 0.3 seconds. (B) The effect of ambient RH on the relative dose of saline in the various areas of the lung (where 'E' is the head and throat, 'A' is the alveolar interstitial region, 'B' is the combined bronchial bronchiolar regions, and 'T' is the total deposition.*

Section 2: Single droplet analysis

The hygroscopic properties of the nebulizer formulations were measured, and an example of the data generated, in this case for pure saline, is shown in figure 3. The data collected from the droplet at a thermodynamic equilibrium (figures 3A and 3B) were used to model the mass flux from (figure 3C) and to (figure 3D) a saline droplet during a period of instability. The red lines in figures 3C and 3D indicate the model prediction, and what is immediately apparent is the strong correlation between the model prediction and the experimental result. This data demonstrates a detailed understanding of aerosol mass flux in a variable environment.

Section 3: Incorporation into a lung inhalation model

The absolute size change of a population of polydisperse aerosol as a function of various conditions (ie. ambient RH, nebulizer orientation, etc.) was modelled (figure 4A). In this situation, the diameter of a saline aerosol, where the RH experienced by the aerosol is 50% for a period of time of 0.3 seconds prior to inhalation, is shown. Note that many of the larger droplets fail to reach equilibrium prior to inhalation.

The radial data as a function of time were input into the adapted ICRP model, and the deposition fraction was calculated (data not shown). The deposition fraction within each region in the lung was then used to estimate relative dose using the initial size distribution of a nebulized aerosol (1) (figure 4B). In this example, by reducing the humidity the nebulized saline experienced prior to inhalation, the overall dose was increased. The increase in dose was found to be primarily in the alveolar interstitial region with little changes in the rest of the airways observed. This data shows that to increase the dose of nebulized saline to deep within the lung, the RH within the nebulized airflow should be reduced. In addition, figure 4B shows that an understanding of hygroscopic growth of aerosols during inhalation can be used to target specific regions in the lung with increased doses of pharmaceutics.

Conclusions

A novel strategy to tailor nebulizer formulations through the use of single aerosol analysis techniques coupled with a whole lung model has been introduced. The potential to control hygroscopic aerosol mass flux prior to and during inhalation to target the deposition of pharmaceutics into a specific region within the lung has been demonstrated.

Acknowledgements

AEH acknowledges the Elizabeth Blackwell Institute for the support of a post-doctoral research fellowship and support from the Wellcome Trust Institutional Strategic Support Fund. We thank the EPSRC for financial support through a Leadership Fellowship awarded to JPR (grant reference EP/G007713/1).

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