Towards Controlling the Rapid Hygroscopic Response of Aerosols for Use in Drug Delivery to the Lungs

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Summary

The correlation between aerosol size and the deposited fraction within the lung can be used to greatly improve drug efficacy through fine tuning the hygroscopic properties of the aerosols used in drug delivery so as to specifically target locations within the lung to deliver the dose. The rapid change in RH, from ambient to >99%, to which an aerosol is exposed affects its size, and the magnitude of size change will dictate the site of particle deposition. Currently, the degree to which the aerosol changes in size during the brief period of time that encompasses inhalation is not well understood. In this preliminary study, we looked at the potential of using Pluronic polymers as the basis of an aerosol by which to deliver drugs to the lung. A new type of electrodynamic balance (EDB) was used to probe these rapid changes in size of Pluronic polymer containing aerosols.

Introduction

One of the more versatile methods employed in delivering drugs to the lung is the metered-dose inhaler (MDI). Modern MDI formulations contain three components, the drug (an inhaled corticosteroid (ICS) or β-adrenergic agonist), a co-solvent (e.g. ethanol), and the propellant (hydrofluoroalkane (HFA)). Combined, the ICS and β-adrenergic agonist are termed the active pharmaceutical ingredient (API). The preferential targeting of the regions of the respiratory tract requiring intervention with an appropriate API dose, while decreasing the delivery to non-diseased sites, would prove to be advantageous. The co-solvent is present to dissolve the drug as well as aiding in its nebulisation by the propellant, HFA. The residual API particles generated from the HFA-MDIs have a mean mass aerodynamic diameter (MMAD) of approaching 1µm.¹

Diffusion and impaction govern particle deposition within the lung. Impaction typically occurs with larger aerosols at branching locations within the lung (upper airways) whereas smaller particles are lost via diffusion are removed from the air deeper within the lung. In terms of size, particles ranging from 10µm to ~0.7µm are typically removed from the air via impaction, while particles ~0.4µm and below are deposited onto lung tissue via diffusion. This means that there is a size, ~0.5µm, where particle removal from the air reaches a minimum.

The size distribution of an aerosol from nebulisation to deposition is dynamic even though the overall lifetime of an inhaled aerosol generated with a MDI is under a second (Figure 1). Upon generation, the MMAD is ~50µm. Three processes then begin in concert: the evaporation of the propellant, the evaporation of the solvent, and the adsorption of water. The rapid evaporation of the HFA and ethanol from the aerosol leads to a depression of the surface temperature, radial inhomogeneities in composition and a time-dependant mass flux as the surface composition and temperature change.³ Aerosols generated from the MDI are created in an atmosphere with a relative humidity (RH) ~75% and inhaled into the lungs where the RH increases to ~99.5%.⁴ Once in this environment, the aerosols will begin to take up water, with the rate and degree to which this occurs depending on the hygroscopic properties of the aerosol. Until recently, the ability to study these three processes in real time, at sub second resolution has not been possible and as a result is not well understood. Recent work at the University of Bristol has led to the development of new techniques that can allow these processes to be probed directly and in real time. Presented here is an initial study of the influence of FDA approved triblock polymer, Pluronic F127, in a saline solution on the growth dynamics on aerosol produced by that solution. The potential to tailor the final size of the aerosols produced are explored.

Methods and Materials

The real-time non-intrusive monitoring of an aerosol droplet in this study relies on a combination of spectroscopic and light scattering techniques. Three different single particle analysis techniques were employed; an optical tweezers (OT) setup⁵, a standard double ring electrodynamic balance (EDB), and a modified electrodynamic balance wherein the electrodes are four cylinders rather than the conventional double ring setup (CEDB)⁶.

The single particle analysis techniques of the EDB and OT are garner similar results to each other. They both measure the equilibrium hygroscopicity of the aerosol to be mapped out.

Figure 1 Schematic of the expected change in droplet radius during inhalation.
Optical tweezing is the more sensitive technique in the collection of size and composition information, whereas the EDB is able to study an aerosol across a wider RH range. With these instruments, the analysis of an aerosol takes place over a time frame from hours to days, to potentially weeks. For both the double ring EDB (DREDB) and the OT, the state of the aerosol, in both size and composition, measured with these techniques during the course of this experiment is understood to be at equilibrium, and thus in a thermodynamically limited state.

CEDB is the most versatile in monitoring rapid changes in aerosol mass. When compared to the conventional EDB, the orientation of the electrodes of the CEDB results in a much stronger electric field within the trap which in turn makes a rapid capture of the aerosol possible. Once held within the electric field of the trap, the properties of the aerosol can be readily probed using Raman (for composition probing) and Mie (for size probing) scattering. The restoring forces of the trap hold the aerosol in the path of the laser beam which allows for the probing of the aerosol as its overall mass rapidly changes. The Mie scattering of the laser by the aerosol is collected with a camera operating at upwards of a 400 Hz which means the size of the aerosol is measured at a resolution ±400 nm every millisecond.

The growth factor profile of various salt-polymer mixtures were measured using both an EDB and an OT. The evaporation profiles of various solvent/polymer formulations on timescales relevant for pulmonary drug delivery were measured with a CEDB.

Results

The growth factor (mass of the aerosol at a given RH divided by the mass of the dry weight of the aerosol) of aerosols containing various weight percents of NaCl and Pluronic F127 measured with an EDB, an example of one particle type is shown in figure 2A. The E-AIM model is a common model used in the prediction of the uptake of water by a given aerosol at any RH. For multicomponent aerosols, the model predicts the growth factor profile with the Zdanovskii-Stokes-Robinson (ZSR) equation. ZSR states that the amount of water absorbed by a multicomponent aerosol at a given RH can be calculated from the sum of the water taken up by each component independently within the aerosol at that RH. Figure 2 demonstrates that the water absorbed up by the salt/F127 aerosol (red squares) is far below the ZSR predicted value (blue diamonds). The difference between the predicted value and the experimental value appears to be a function of the RH, where the higher the RH, the larger the difference (figure 2B). This suggests that there is a significant interaction between the salt and the polymer which limits the amount of water that can be taken up by the aerosol, and this polymer/salt interaction appears to be at the per molecule, or per micelle, basis. Taken together, the data from figure 2 show that the thermodynamically determined size of aerosols containing Pluronic aerosols are much smaller than would be expected where the largest differences between the expected and experimental growth factor are seen for the lowest polymer mass fractions. Also, the difference increases exponentially as the RH increases, and is greatest at the highest RH, such as the RH experienced within the lung. This suggests that the addition of even a small mass fraction of polymer to the total solute mass suppresses the hygroscopic growth of the aerosol particle significantly.

The rapid rate of evaporation of various by weight aqueous solutions of different ratios of F127 and NaCl were measured (figure 3). Like in the thermodynamic data, the larger the proportion of polymer added to the starting solution, the smaller the radius of the final droplet. Given the humidity in which the experiments were undertaken, gel formation was not observed in any of the cases. For the 1% and 5% F127 solutions, when compared to the model, the presence of the polymer was found to slightly slow down the evaporation of water from the aerosol. For the 1% solution, no change in the final size was observed. For the 5%, like in the thermodynamic data, the final size of the droplet was slightly smaller than that predicted by the model.
For the 50% F127 solution, the rate of evaporation of the model and experimental samples were similar, but the final size was found to be much smaller than that predicted by the model, which correlates well with the thermodynamic data.

Conclusions
The addition of F127 to the formulation of an MDI solution should serve to add a few advantages. The addition of a trace amount of polymer lead to an overall reduction in the final size of the aerosol produced, significantly suppressed size at the high RHs experienced with the lungs, and reduced the rate at which the aerosol loses water. Compared to other polymers, the advantage of using F127 as a drug delivery substrate is that there is no loss of the drug into the F127, and the ability to control the overall size of the final aerosol produced should serve to greatly increase the overall efficacy of the drug itself.

Acknowledgements
JPR acknowledges financial support from the EPSRC through the support of a Leadership Fellowship. AEH acknowledges the University of Bristol for the support of a post-doctoral research fellowship.

References
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Figure 3 Growth factor of aerosols of various ratios of F127 and NaCl by weight as measured with a CEDB as a function of time. Red line is the model prediction and the black line is the experimental data.