How Particle Size Changes Lung Deposition: A Physical Modeller's Perspective

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Summary

The aerodynamic particle size of an inhaled medicine plays a very important role in determining the drug dose delivered to the lung and also how that dose is partitioned between the different types of lung airways. Dose delivered to bronchi, bronchioles and alveolated airways may be expected to result in different pharmacological and clinical outcomes as a result of the differing physiologies of these airway regions[1]. Unfortunately it is not yet possible to directly measure the exact drug dose delivered to each region so inferences are made by comparing pharmacokinetic and pharmacodynamic outcomes with other surrogate measurements of the regional lung dose[2]. Here it is demonstrated using illustrative examples from the literature how use of a simple mathematical model can help ensure that interpretations of experimental data are consistent with lung deposition physics. These include two validation datasets and one example of a combination Dry Powder Inhaler (DPI) product. Both the math model and the reference experimental literature (Stahlhofen *et al*[3]) indicate that particles of all sizes in the range 6-0.5µm deposit in all airway regions to some degree. Changes in particle size within this range cause a quantitative shift in the dose delivered to the larger and smaller airways but there is no qualitative change in the location of deposition. This is at variance with some interpretations of experimental data in the literature, thus the value of referring to a simple math model to obtain a physics-driven analysis is demonstrated.

Introduction

The aim of this work is to evaluate the benefit of using a simple math model to interpret lung deposition data, This is achieved by analysing three example datasets. The first two are well-established examples from the *in vivo* lung deposition experimental literature which, as well as providing validation exercises for the math model also evaluate its ability to propose physical processes that explain the experimental trends. These datasets are also compared with a popular schematic diagram for the relationship between particle size and lung deposition. The final example shows how the model can be used to make predictions regarding the lung deposition of a marketed combination DPI.

Case Study 1: The Stahlhofen *et al* Lung Deposition Dataset

The most comprehensive, physiologically meaningful and highly cited dataset on lung deposition is that of Stahlhofen *et al*[3], which is a collation of data from different laboratories. These experimenters assumed that the fraction of an inhaled dose of radiolabelled insoluble aerosol particles remaining in the lung after 24 h provides an indication of the dose delivered initially to the non-ciliated alveolar ducts. The dose fraction that had cleared within 24 h was similarly used as a surrogate measure for the dose delivered to the ciliated bronchi and bronchioles. The curves fitted to their data are reproduced in Figure 1. Also included in Figure 1 is data obtained from the MPPD lung deposition model[4], both for resting breathing conditions approximating the Stahlhofen experiment and also for an inhalation more typical of DPI use. MPPD is a first-principles model based on basic lung flow physics (incorporating deposition by impaction, sedimentation and diffusion) and is not fitted to any lung deposition dataset. The good agreement between the model at resting conditions and the Stahlhofen experimental curve therefore provides a cross-validation of the two datasets with the model providing physical explanations of why the experimental data follows the curves depicted while the data lends *in vivo* credence to the model results.

High intersubject variability for lung delivery makes precise quantitative dose predictions a somewhat elusive goal, however useful qualitative trends are obtained from the experimental and model data. At an aerodynamic diameter of 30 µm oropharyngeal deposition is 100% and no particles reach the lung but as particle size decreases, oropharyngeal deposition decreases and particles become available in the lung. Moving down in particle size from 30 µm, deposition in the bronchial and bronchiolar region increases as particles become available beyond the oropharynx. Continuing to move down in particle size, however, the deposition in this region reaches a local maximum and then decreases again. Deposition in the alveolated airways follows a similar pattern, with an increase in deposition with decreasing particle size as particles become available beyond the bronchial and bronchiolar region before reaching another local maximum and decreasing again. Particles not deposited are exhaled. As will be explained more fully in the next section, the math model indicates that impaction and sedimentation are the dominant processes for bronchial and bronchiolar deposition and sedimentation is the dominant mechanism for deposition in the alveolar airways for particles of this size range. Both impaction and sedimentation efficiency decrease with decreasing particle size so the local maxima reflect a trade-off between the availability of particles beyond upstream airways versus declining deposition efficiency with decreasing particle size.

It is instructive to compare the data of Figure 1 with a popular schematic, reproduced in Figure 2, which outlines a relationship between particle size and lung deposition. Dunbar and Mitchell[5] noted a quantitative difference in the

particle size range required to reach the lung between data from the Stahlhofen *et al* workgroup[6] and Figure 2; specifically that Stahlhofen *et al* predict that half of all particles in the range 9-5.8 µm will deposit in the lung whereas Figure 2 indicates otherwise. Figure 2 suggests also that the penetration depth of lung deposition increases as particle size decreases, in this instance Figure 1 shows a qualitatively different relationship. While it is true that the peak for deposition in the alveolated airways is shifted to smaller particle sizes compared to the deposition peak for the bronchial and bronchiolar region, there is considerable overlap between the two and, more importantly, the data follows a 'peak' shape with a decline in deposition efficiency in both lung regions as the particle size approaches 1µm. This latter aspect is thus both qualitatively and quantitatively different from Figure 2 which suggests that particles smaller than 1 µm play the most important role in alveolar deposition. Therefore Figure 2 shows significant quantitative and qualitative differences from the data of Figure 1.

Finally it is particularly interesting to note from the data of Stahlhofen *et al* that, as a result of the significant overlap between deposition curves for the larger and smaller airways, targeting one region in isolation is difficult and, further, particles comprising the respirable dose of most inhaled medicines (for example those in the range 6-0.5 µm as considered in more detail in the next section) deposit in all lung regions. These observations are in line with those made by Clarke and Hartman[7] during their analysis of the same dataset.
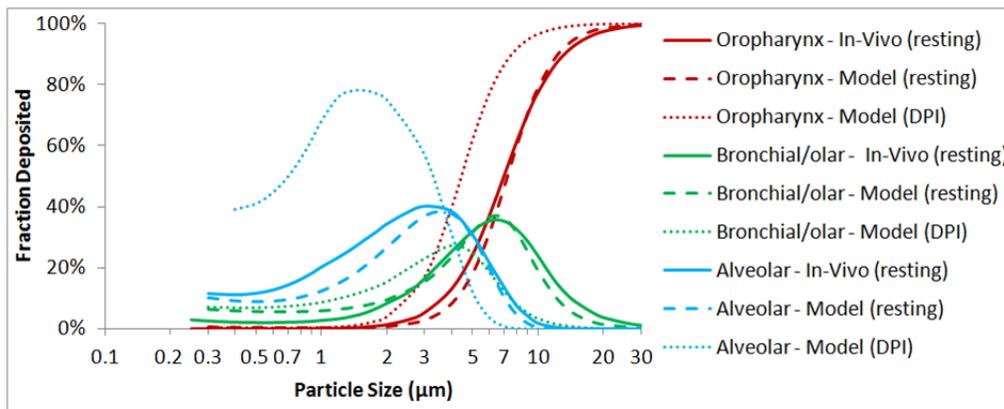

Figure 1. Stahlhofen *et al* Lung Deposition Data and MPPD Model Predictions; Resting (1 L, 30 L/min) and DPI = 60 L/min, 2.5 L Inhalation and 10 s Breath Hold
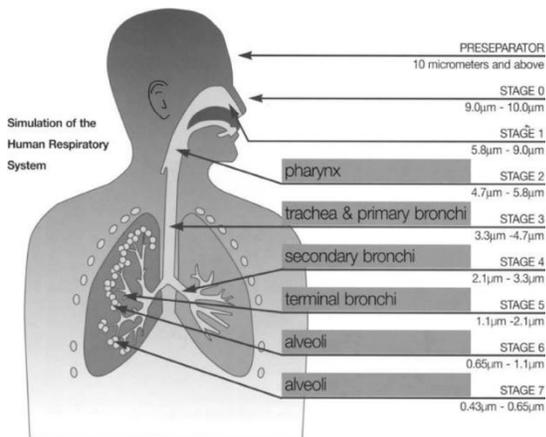

Figure 2.   Popular Schematic Relating Lung Deposition to Particle Size (Courtesy of Westech Instrument Services, UK)
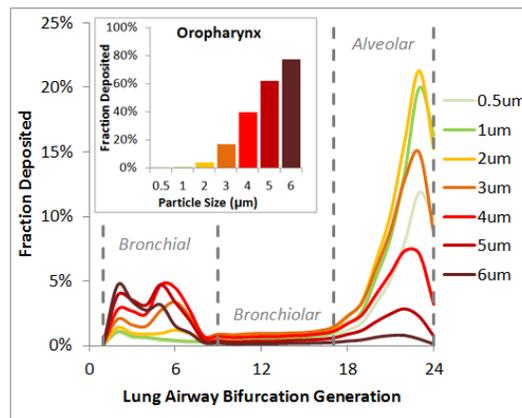

Figure 3. Predicted Lung Deposition Distribution for Various Particle Sizes at 60 L/min, 2.5 L Inhalation and 10 s Breath Hold

A Detailed View of Lung Deposition

A more detailed picture of lung deposition is obtained by presenting the math model results as shown in Figure 3 where the deposition in each airway bifurcation generation of the lung is shown for various aerodynamic particle sizes. The deposition is broadly bimodal, similar to other published models of this kind[8]. Examination of the efficiencies for each deposition mechanism shows that the peak in the bronchial region is impaction dominated and the peak in the alveolar region is sedimentation dominated for particles of this size range. This pattern is driven by the fact that impaction efficiency decreases as air and particle velocity decrease exponentially with deeper lung penetration, and that conversely sedimentation (and diffusion) increases as airway diameter (and hence the distance required for a particle to sediment in the available time) decreases exponentially. Thus the greatest deposition for most particles in

this size range is seen to occur in the smallest airway penetrated by the dose (bar the final portion comprising air that was originally in the lung at the start of inhalation).

This shows therefore that while total quantitative dose to the smallest airways has a strong particle size dependency, the limits of penetration of the dose into the lung is predicted to be independent of particle size. This supportive of the experimental data which shows that particles of all sizes in the considered range deposit in both conducting and alveolated airways but differs from the schematic diagram of Figure 2 which suggests increasing lung penetration depth with decreasing particle size. Finally, an additional prediction made by the model is that only a small portion of the lung dose is estimated to deposit in the bronchiolar region since the physics suggests this has low deposition efficiency by all mechanisms.

Case Study 2: Usmani *et al* Gamma Scintigraphy Data

Usmani *et al* carried out gamma scintigraphy imaging measurements for various near-monodisperse particle sizes and inhalation rates so their dataset provides an interesting and useful model validation. Predictions were carried out for each subject using measured lung volumes, inhalation metrics and particle sizes. The model predictions and experimental data are plotted in Figure 4 where it is seen that there is a quantitative difference in total lung deposition but that the qualitative trends for the different particle sizes and inhalation flowrate show excellent agreement. A comparison for the penetration index was achieved by transposing the model predictions for each airway generation using the model of Schroeter *et al*[9] for the distribution of different airways within the central, intermediate and peripheral imaging zones. The penetration index therefore shows remarkably good agreement considering the variations and assumptions underlying the datasets.
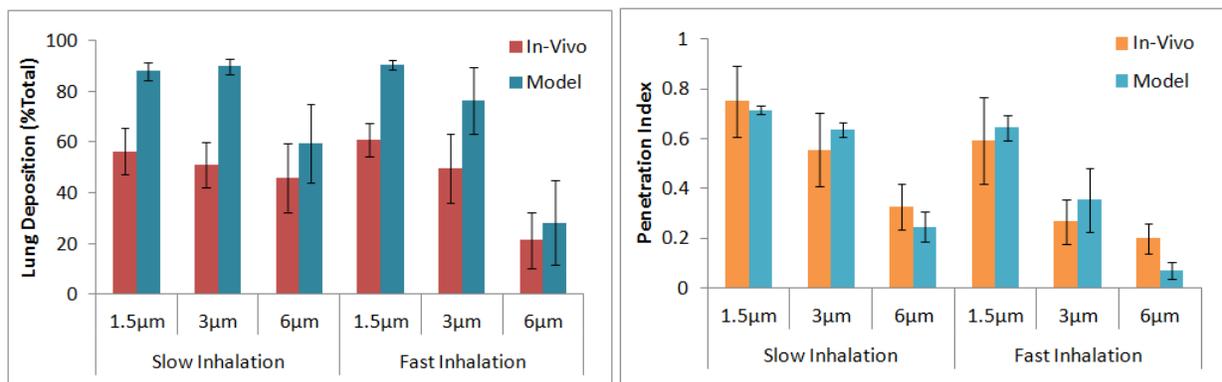

Figure 4. Usmani *et al In Vivo* Experimental Data and MPPD Model Predictions (Means and Standard Deviations)

Case Study 3: Combination Dry Powder Inhaler

The implications of these findings for inhaled medicines are illustrated by applying the model to aerodynamic particle size data obtained via Next Generation Impactor (NGI) for a combination dry powder inhaler containing fluticasone fuorate and vilanterol. The predicted deposition distributions for each drug component are shown in Figure 5. Though this approach may also be applied to standard NGI data, in this instance the particle size distributions were obtained from particles that were aerosolised with an air flow profile replicating a measured patient inhalation and then passed through 3D printed models of *in vivo* oropharyngeal geometries[10]. Inhalation flowrates representing the median, min, max and quartile of 90 asthmatic and COPD subjects ranging from mild to very severe were included. Disease effects were also accounted for in the model by using the same individual patient inhalation flow measurements, functional residual lung volume and also disease-specific bronchial geometries obtained from CT-scans (thanks to an adaption of the model by the developers, ARA). Figure 5 shows that, as expected, the modelled lung deposition of both fluticasone fuorate and vilanterol, follow the general trends of Figure 3 with drug predicted to reach all airway regions. This is predicted even for the Very Severe COPD subject. As might well be expected medicine delivered to this subject is predicted to achieve a reduced penetration into the alveolated region as result of their disease state (specifically, a small inhaled volume in conjunction with a very large Functional Residual Capacity), yet drug is nonetheless predicted to deposit in the alveolated airways of this subject.
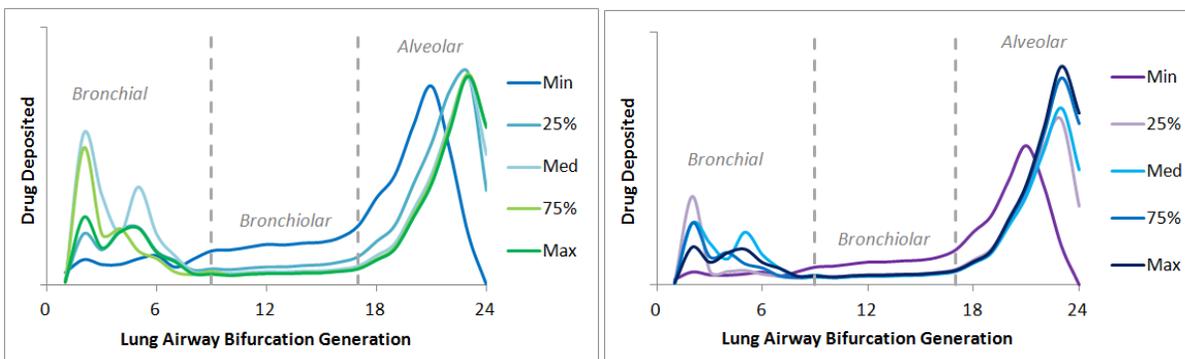
Figure 5. Predicted Lung Deposition for Various Asthmatic and COPD Subjects. Fluticasone Fuorate (left) and Vilanterol (right) Delivered from a Combination Dry Powder Inhalation Product

Conclusions

The use of a simple math model has helped give physical interpretations to *in vivo* deposition data (Stahlhofen *et al*[3] and Usmani *et al*[2]) as well as to particle size data for a DPI product[10]. *In vivo* trends were confirmed by the model and points of general interest in both *in vivo* and model data include the finding that particles of all sizes typical of inhaled products (6-0.5 µm) deposit in all airways meaning that changes in particle size result in differing efficiencies/doses to different lung regions rather than specific delivery to or avoidance of a particular lung region. Additionally, a reduced deposition efficiency in the alveolated airways for particles smaller than around 1 µm was observed suggesting that any changes in the mass of drug at an aerodynamic diameter smaller than 1 µm has a smaller impact on dose delivered to alveolated airways than does a similar change for particles of 3-1 µm. The model also provided some insight into detailed aspects of deposition for which direct measurements do not exist at present, firstly that lung penetration depth is independent of particle size and secondly that deposition in the bronchiolar region is very low. These observations point towards complex and challenging future work both in understanding implications for the delivery of drugs believed to act in these regions and also in obtaining an experimental validation of the model predictions. In the absence of such validation data the model is therefore a useful tool providing physical grounding for intuitive judgements.

Acknowledgements and Declarations of Interests

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