Estimation of Particle Deposition in the Airways From Different Inhaler Formulations Using an In Silico Model†

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Abstract

The objective of these studies was to evaluate the use of an in silico model for predicting lung deposition of inhaled therapeutic aerosols. A range of input data derived from our own in vitro data and published clinical studies was utilized. The in silico model ran simulations for these propellant driven metered dose inhaler formulations across a range of conditions. Firstly, a range of pressurized metered dose inhaler formulations were evaluated in the in silico model and compared to the in vitro aerosol performance data. Limitations of using in vitro cascade impaction data were observed. Then, using in vivo data from healthy human subjects using metered dose inhalers, lung deposition profiles were compared with the in silico model predictions. Despite differences in oropharyngeal deposition the model predicted lung deposition accurately. We conclude that the in silico model can be applied to various conditions for particulate based inhalation aerosol systems.

Keywords: Aerosol, Metered dose inhalers, hydrofluoroalkane, pMDI, in silico, prediction

1. Introduction

The efficacy of aerosolized drugs would be enhanced if they could be selectively deposited (i.e. targeted) at appropriate sites within the human respiratory system. This targeting may be interpreted from a macro-scale (regional lung targeting) to a micro-scale (cellular or receptor targeting). To achieve selective regional deposition within the airways, aerosol administration has traditionally been achieved using nebulized liquids, propellant driven aerosols, or dry powder inhaler systems. As these technologies have advanced, their efficiencies have improved but little has been intentionally introduced to effect more selective targeting of different regions of the airways. This is despite recent evidence from clinical studies that indicate improved therapeutic efficacy when laboratory engineered mono-dispersed aerosols were delivered to asthmatics (Usmani et al., 2003).

Of the current aerosol delivery systems, propellant driven metered dose inhalers (pMDIs) predominate, with sales that reached an estimated 4.6 billion dollars in 2007. These systems have also witnessed significant change in recent years due to the transition from chloroflorocarbon (CFC) based propellants to hydrofluorocarbon (HFC) based propellants as required by international agreements2,3. The redesign of pMDIs led to significant changes in the formulation of new and existing inhaled drug products4. Most notably, lung deposition patterns were significantly altered due to the different formulations and the physicochemical properties of the propellants that drive the atomization process5. As a consequence of the change in performance, prediction and extrapolation of lung deposition profiles has been challenging. In particular, those wishing to match the performance of the predecessor CFC-based systems to a reformulated HFA-based system requires large design of experiment studies so that equivalence between the two could be achieved. Alternatively, utilizing formulations to more appropriately target therapeutic agents within the airways appears a logi-
and in silico – in vivo correlations. Specifically, to study the effects of formulation design on lung deposition and evaluate the in silico – in vitro, findings by applying the currently described in silico model to further elucidate the implications of both formulation changes and the utility of spacers with these newer HFA 134a based pMDIs. We also extended these findings by applying the currently described in silico model to study the effects of spacer devices used with solution HFA 134a pMDIs. In addition, we reported in vitro performance data on the effect of spacer devices used with solution HFA 134a solution pMDIs. We also extended these in vitro cascade impaction studies that does not represent the human physiology.

In particular, we previously reviewed the significant differences in HFA propellant characteristics that give rise to major changes in pMDI performance compared to the CFC predecessor devices. Interestingly, in these studies, spacer devices had little effect on in vitro performance of HFA 134a solution pMDIs. We also extended these studies we show the limitations of using in vitro data to predict lung deposition patterns.

In the present studies we employed an in silico aerosol dosimetry model and compared the results of in silico predictions to experimentally determined data in both in vitro and in vivo conditions. Specifically, to study the effects of the factors addressed in our work (e.g. HFA versus CFC based pMDI systems) we employed an in silico aerosol dosimetry model and compared the results of in silico predictions to experimentally determined data in both in vitro and human subjects. The in silico model had been previously tested extensively via comparisons of its predictions with in vivo data from human subject experiments. The validated in silico model allowed us to consider drug delivery conditions and inhaler performance where in vitro data are not currently available extrapolating to new situations.

2. Methods

The mathematical calculations and computer simulations performed in this study used the in silico dosimetry model which has evolved through the works of Martonen and Martonen et al. The in silico model was tested by comparing its theoretical predictions with in vivo data from the work of Heyder et al. The excellent agreement between theory and experiment over the wide range of conditions validate the in silico model and support its use for extrapolation purposes in our analyses.

For orientation we shall provide a few salient details in this METHODS section. However, a comprehensive review of the theoretical concepts and related software development is beyond the scope of this text. The mathematical techniques and computational protocols can be found in the aforementioned citations.

The behavior and fate of inhaled particles (i.e. micronized powders and atomized droplets) can be formulated in terms of three families of variables which describe respiratory system morphology, ventilation parameters, and aerosol characteristics. Let us consider these factors, albeit briefly.

Respiratory System Morphology

This topic considers the shapes and dimensions of individual airways and their spatial arrangement in a 3D branching network. In this work we shall employ the morphometric data published by Soong et al., as augmented by clinical studies from our laboratory. To produce an anatomically realistic system, the tubular network was positioned within patient-specific left and right lungs whose boundary surfaces were generated via computer reconstructions of magnetic resonance images. The lungs were coupled with extrathoracic data describing the head and throat from high resolution computed tomodraphy to produce a 3D computer depiction of the complete respiratory system from the nose and mouth to the alveoli. The resulting contiguous system is presented in Fig. 1.

Ventilatory Parameters

To describe breathing conditions during the administration of aerosolized drugs the salient parameters are tidal volume (TV), breathing frequency (f), and breath-hold time (Dt). The differences in these factors pertaining to spontaneous versus controlled breathing regimens have been addressed in an earlier work (see Fig. 8.6 of reference 9 and related text). We shall employ ventilatory parameters consistent with the outpatient use of MDIs and the details of which are included for each simulation below in the results section.

Aerosol Characteristics

The size distribution of an aerosolized drug may be defined by the mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD)
of its constituent particles. Herein, practical MMAD and GSD values were considered; that is, representative values used in particle dosimetry simulations will be within the range of commercially available inhalers. The details for each simulation performed are described below in the results section.

We shall now demonstrate how the three families of variables outlined above may be integrated to create a biologically realistic in silico aerosol dosimetry model.

**In Silico Dosimetry Model**

The factors (TV, f, and Δt) are used with airway dimension measurements to calculated airstream velocity values which, in turn, are used in published formulas to determine particle deposition probabilities within the respiratory system. Particle deposition is described by the processes of inertial impaction, sedimentation, and diffusion which simulate particle trajectories due to momentum, gravity, and Brownian motion, respectively. The three deposition mecha-

![Three-dimensional computer reconstruction of the entire human respiratory system. With permission (14).](image-url)
nisms are shown in Fig. 2. A comprehensive review of various deposition probability formulae has been conducted by Isaacs et al.\textsuperscript{9}. We shall use the coupled (i.e. mathematically consistent) system of equations derived by Martonen\textsuperscript{15}.

To simulate the behavior and fate of aerosolized drug produced by a particular device, its MMAD and GSD values are used as input to the aforementioned deposition probability equations. The deposition values within individual airways are computed, which can then be summed appropriately to describe deposition patterns to desired levels of spatial resolution. For example, output can be presented for total lung deposition, compartmental (i.e. tracheobronchial (TB) and pulmonary (P)) deposition fractions of the total, and generation-by-generation deposition fractions of the total.

For our purposes, the aforementioned particle deposition fractions are acceptable computational endpoints. However, in future drug efficacy studies aerosol dose delivered values may be the desired computational endpoints. It may be incumbent on us, therefore, to explain how to make the conversion from particle deposition fractions to aerosol dose delivered. The \textit{in silico} model predicts the number of particles of a prescribed size deposited in a specified region, for example, in a given airway generation. That number can be normalized in a manner selected by the investigator. For instance, a clinician may elect to normalize the deposition to the number entering the trachea. This would actually be the standard technique because experimental data have been routinely based on TB and P clearance measurements which are inherently related to the quantity entering the lungs. When the MMAD and GSD of an aerosolized drug are known, particle deposition fractions can be converted to corresponding particle mass values in a straightforward manner. For a prescribed size distribution of constituent particles the aerosol mass deposition fraction can then be determined. The aerosol dose delivered can then be calculated using the computational endpoint desired by the investigator. For instance, when the aerosol mass deposited is divided by the cumulative airway surface area in a generation the aerosol dose delivered units would be µg/cm\textsuperscript{2}.

In this METHODS section, we would be remiss if the subject matter of computational fluid dynamics (CFD) was not recognized. Several third party CFD packages are commercially available and permit particle trajectories to be mapped within branching networks. We have utilized such CFD codes, and although they allow localized deposits to be discerned in networks containing only a limited number of airways, they are not of practical application when considering complete lungs which, obviously, must be addressed in the medical arena\textsuperscript{16, 17, 18}.

Isaacs et al.\textsuperscript{19} compared the \textit{in silico} aerosol dosimetry model with CFD techniques. The respective outputs of the two approaches were compared with particle deposition data from experiments with human replica casts\textsuperscript{20}. Whereas the \textit{in silico} model accurately predicted airway surface-average values the deterministic manner in which computations are performed did not allow it to produce the hot-spots at airway bifurcations detected by CFD analyses.

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\textbf{Fig. 2}  Mechanisms of particle deposition in the human airways are schematically illustrated. With permission (9).
must be emphasized that, pertaining to the in vivo delivery of aerosolized drugs to patients, the in vitro data from replica casts are obviously of a much finer degree of spatial resolution than can be measured within human lungs per se. CFD analyses of are of limited practical use at this time simply because they cannot be reasonably used for complete lungs consisting of several millions of individual airways. For instance, the Soong et al. geometry used in this work consists of approximately $17 \times 10^6$ airways. The in silico model, therefore, is the most viable alternative for implementation in drug delivery studies.

Finally, we shall note that Martonen et al. have recently evaluated the methodology of the in silico model using single photon emission computed tomography (SPECT) observations as benchmark testing criteria. The findings support the in silico model’s use in the medical arena.

3. Results and Discussion

In vitro – in silico correlations

In Fig. 3, the fine particle fraction (FPF) as determined by Andersen Cascade impaction studies and laser diffraction, is shown for four HFA 134a formulations with increasing concentrations of added ethanol (2.5% to 50% w/w). Previously we had shown that multimodal particle size distributions are generated from these solution based HFA 134a systems. Increasing ethanol concentrations did not lead to a shift in the particle size distributions such that the distribution modes were changed. Rather, the particle populations in either the “respirable” (less than 5 microns) or “non-respirable” (distribution mode at around 10 microns) would be increased or decreased according to the formulation composition. This is reflected in Fig. 3 where increasing the ethanol concentration in the formulation leads to a decrease in the fine particle fraction emitted from the inhaler. The performance of these formulations were then assessed using the in silico model.

In Fig. 4 the predicted deposition patterns for the four HFA 134a/ethanol formulations is shown. The in silico model calculates the deposition fractions for oropharyngeal, total lung, central and peripheral lung zones. For oropharyngeal and central airway deposition the model predicts an increase in deposition with an increase in ethanol concentration in the formulation. However, for total lung and peripheral lung deposition the model predicts that maximal deposition will be achieved using the 20% ethanol formulation. Peripheral deposition was reduced in both the highest ethanol concentration (50% w/w) and the lowest (2.5% w/w).

Comparing the in silico and in vitro results several areas of agreement and disparity were identified and can be observed in Fig. 5. In Fig. 5 the predicted deposition fraction is plotted against the in vitro determined fine particle fraction for each of the different pulmonary regions calculated by the model. Correlations are generally not good for in vitro determined data. Maximum peripheral deposition was predicted for the 20% and 10% w/w ethanol HFA formulations, whereas the in vitro cascade impactor and laser diffraction studies indicate that maximal deposition should be attained when ethanol concentrations

![Figure 3](image_url)

**Fig. 3** Effect of ethanol concentration on the fine particle fraction (fraction of particles less than 5 microns) in HFA 134a metered dose inhaler aerosols.
are minimized and only 2.5% ethanol is present. The disparities between the data sets are derived from the more realistic in silico breathing model, whereby the high proportion of extra fine particles present in these aerosols are governed by diffusion based lung deposition mechanisms and, therefore, are more susceptible to exhalation. Exhaled particles are generally not accounted for when performing analysis on cascade impaction data and therefore are counted as respirable despite their propensity for avoiding lung deposition without a breath hold during inhalation. The in vitro fine particle fractions did appear to correlate with central deposition predictions (linear negative correlation) and oropharyngeal deposition (negative correlation). The model may be useful in directing formulation studies to achieve desired deposition profiles, that are perhaps more meaningful than standard cascade impaction or laser diffraction studies. To determine the potential for prediction of deposition for these inhaler types in humans, we used data obtained from clinical lung imaging dosimetry studies in the next part of the study.

**In vivo – in silico Correlations**

Four additional simulations were performed, using the data presented in a paper by Leach et al.²³ in
which in vitro and in vivo data were obtained for CFC and HFA based inhaler systems. In these studies, four experimental groups were assessed in normal subjects:

1) HFA-BDP-50 (HFA-BDP, 50 microgram shot)
2) HFA-BDP-100 (HFA-BDP, 100 microgram shot)
3) CFC-BDP-50 (CFC-BDP, 50 microgram shot)
4) CFC-BDP-250 (CFC-BDP, 250 microgram shot)

The model input parameters were derived from the data published in the paper by Leach et al. Specifically, the input particle size distributions are shown in Fig. 6 for both the HFA and CFC based systems. Table 1 shows the physiological parameters input into the in silico model. The flow profile for both propellants was assumed parabolic. Airway morphology was assumed to be represented by Weibel Symmetric A, adult model.

Model predictions over estimated performance of the CFC-based inhaler formulations used in these experiments (Fig. 7). Experimentally determined oropharyngeal deposition was underestimated significantly and, therefore, total lung deposition was overestimated. This was similar to the findings for the HFA formulations (also a HFA-ethanol based solution formulation) where the model also underestimated oropharyngeal deposition. Despite this, the model accurately predicted total lung deposition.

The oropharyngeal predictions are likely to underestimate deposition due to limitations in the input data. In particular, input data is derived from measures of the particle size distributions of the inhaled aerosols. In most cases this is obtained from cascade impaction studies which truncates the particle size distribution as its upper particle size limit is around 10 microns. This truncation likely leads to underestimation of the emitted particle size and, therefore, underestimates the aerosol potential for inertial impaction on the oropharnyx.

The good agreement between total lung deposition predicted and that experimentally measured confirms earlier research using this model in other systems that showed good predictability. Fig. 8 shows that HFA solution based systems are predicted to yield much greater peripheral deposition than central.

![Fig. 6](image-url)

**Fig. 6** Particle size distributions used as input data for the in silico model predictions of lung deposition.

| Table 1 | Physiological parameters measured during the in vivo lung deposition studies comparing HFA and CFC formulations |
|---------|---------------------------------------------------------------------------------------------------------------|
| Formulation | Tidal Volume | Inspiration/Expiration Time | Breath-Hold Time |
| HFA-BDP-50 | 5295 ml | 3.1 sec | 10.4 sec |
| HFA-BDP-100 | 4503 ml | 3.4 sec | 10.0 sec |
| CFC-BDP-50 | 5388 ml | 3.2 sec | 10.3 sec |
| CFC-BDP-250 | 5190 ml | 3.1 sec | 10.2 sec |
Fig. 7  Comparison of the model predictions of lung deposition to the in vivo experimentally determined lung deposition fractions for CFC based inhalers (upper graph) and HFA based inhalers (lower graph).

Fig. 8  Central versus peripheral lung deposition fractions for HFA based metered dose inhalers as predicted by the in silico model.
4. Conclusion

We believe the validated in silico aerosol dosimetry model used in this work is a valuable research tool. It can be employed in a complimentary manner with technological (e.g., inhaler design and development) and medical (e.g., targeted drug delivery) issues of importance to inhalation therapy. Additional studies designed specifically to address the limits of the model with respect to input data for the major categories of inhaler (pMDI, dry powder inhaler and nebulizer) and implications for clinical impact would be desirable.

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Ted Martonen, Ph.D., is a research physicist. His research has primarily focused on the development of mathematical models which describe the behavior and fate of inhaled substances for risk assessment. Through his collaborations with pharmaceutical scientists, Dr. Martonen has shown that there is a great commonality between the fields of toxicology and medicine. Specifically, he realized that dosimetry models for air pollutants, since they quantitate the toxic particulate matter delivered to airway cells, could be integrated into the treatment of airway diseases caused or exacerbated by those same air pollutants.

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