

Validation of In-Silico Lung Deposition Predictions for Inhaled Liposomal Amikacin Against Scintigraphy Data

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Summary

This study presents an in-silico validation of lung deposition for liposomal amikacin delivered via the PARI LC STAR nebulizer. Building on previously published gamma scintigraphy data in healthy adults, we simulated aerosol deposition in three demographically matched subjects using functional respiratory imaging (FRI), which combines high-resolution CT-based airway modeling with computational fluid dynamics (CFD). The same particle characteristics and inhalation conditions used in the scintigraphy study were applied to approximate the experimental setup.

The simulations predicted a mean intrathoracic deposition of $29.09\% \pm 6.54\%$, closely aligning with the $32.33\% \pm 3.41\%$ reported in vivo—demonstrating strong agreement despite the fact that different subjects were used and anatomical variability is naturally expected. Extrathoracic and exhaled fractions also showed reasonable correspondence, with observed differences attributable to inter-subject variability and the use of idealized breathing profiles in silico.

These findings reinforce the predictive capability of FRI-based CFD for nebulized drug products, including complex formulations such as liposomal suspensions. The results further support the accuracy of FRI in modelling aerosol deposition from nebulized liposomal formulations and support its application in the development and optimization of inhaled therapies.

Key Message

In-silico simulations using FRI closely matched gamma scintigraphy data for nebulized liposomal amikacin, with ~3% difference in lung deposition. This highlights the potential value of CFD-based modeling for evaluating and optimizing inhaled drug delivery.

Introduction

Validating in-silico models against in-vivo data is critical for establishing their reliability in predicting pulmonary drug deposition. Functional respiratory imaging (FRI), which combines computational fluid dynamics (CFD) with patient-specific airway geometries derived from CT scans, has been successfully validated across a wide range of inhaled drug products, delivery devices, and disease states. For instance, Sadafi et al. demonstrated strong agreement between FRI-predicted deposition and single-photon emission computed tomography (SPECT) imaging in asthma patients [1], while Costa et al. validated FRI predictions against gamma scintigraphy data for fluticasone/formoterol delivered via a pressurized metered-dose inhaler (pMDI) in patients with chronic obstructive pulmonary disease (COPD) [2].

In the present study, we extend the application of the FRI-based in-silico platform to nebulized liposomal formulations. Inhaled liposomal amikacin, administered via the PARI LC STAR nebulizer, is being developed for the treatment of chronic pulmonary infections, particularly in patients with cystic fibrosis colonized by *Pseudomonas aeruginosa*. The formulation was previously studied by Weers et al. (2009) using gamma scintigraphy in three healthy adult males, reporting a mean lung deposition of $32.3\% \pm 3.4\%$ of the emitted dose [3]. This dataset was used as the reference for comparison in our simulations.

Methodology

Three healthy male subjects were retrospectively selected from FLUIDDA's in-house database (see Table 1) based on demographic similarity (ages 36–38, mean: 37 years) to those studied in the scintigraphy dataset by Weers et al. (mean: 37.7 years). Their three-dimensional airway geometries were segmented from high-resolution CT scans using an automated algorithm, followed by manual correction to remove imaging artifacts. Airway regions were classified into extrathoracic and intrathoracic compartments to enable regional deposition analysis consistent with the available scintigraphy data.

Each airway model was digitally coupled to a detailed model of the PARI LC STAR nebulizer at the oral cavity inlet. A tidal breathing profile was applied with continuous nebulization, replicating the

experimental setup used in the scintigraphy study. Particle characteristics were matched to those reported by Weers et al., with a mass median aerodynamic diameter (MMAD) of approximately 1.6 μm and a geometric standard deviation (GSD) of 2.0.

Eulerian–Lagrangian CFD simulations were conducted to resolve airflow and particle dynamics. Deposition was quantified for three main regions: extrathoracic (mouth and upper airways), exhaled fraction, and intrathoracic (lung) deposition. These regional values were directly compared with the corresponding scintigraphy measurements as the basis for validation. Similar to Weers et al., the exhaled fraction consisted of three components: (1) drug that entered the mouth, throat and lungs but was not deposited and subsequently exhaled, (2) aerosol generated during the exhalation phase, and (3) drug deposited on the mouthpiece. While central and peripheral lung zones were also computed in the in-silico model based on airway diameter and branching, these were not directly compared to scintigraphy-derived values due to differing region definitions.

Table 1: Subject demographics

Subject	Condition	Gender	Age [y]	Height [cm]	Weight [kg]
A	Healthy	M	37	177	93
B	Healthy	M	36	168	82
C	Healthy	M	38	189	95

Results and discussion

The in-silico simulations predicted a mean intrathoracic (lung) deposition of $29.09\% \pm 6.54\%$ of the emitted dose, compared to $32.33\% \pm 3.41\%$ reported in the scintigraphy study by Weers et al. Extrathoracic deposition—representing deposition in the mouth and throat—was $10.03\% \pm 5.80\%$ in the simulations versus $12.03\% \pm 2.72\%$ in vivo. The exhaled fraction was slightly higher in the in-silico group ($60.88\% \pm 0.77\%$) than in the scintigraphy group ($55.64\% \pm 2.62\%$) (Table 2).

Table 2: Deposition fractions (% of emitted dose) for exhaled, extrathoracic, and intrathoracic (lung) regions obtained using in-silico simulations (FRI) and in-vivo gamma scintigraphy. In both groups, subjects are ordered by decreasing intrathoracic deposition.

Method	Patient	Exhaled	Extrathoracic	Intrathoracic
FRI (in-silico)	A	60.01	3.95	36.04
	B	61.18	10.65	28.16
	C	61.45	15.49	23.06
	Mean $\pm$ SD	60.88 ± 0.77	10.03 ± 5.80	29.09 ± 6.54
Scintigraphy (in-vivo)	S102	55.66	8.94	35.41
	S103	53.01	14.07	32.92
	S101	58.25	13.08	28.67
	Mean $\pm$ SD	55.64 ± 2.62	12.03 ± 2.72	32.33 ± 3.41

It is important to note that the airway models used for the in-silico simulations were not obtained from the same individuals who participated in the scintigraphy study. Although the selected subjects were demographically matched to the in-vivo group (in terms of age and sex), anatomical differences between individuals can influence regional deposition patterns. Previous work [4] has demonstrated that even among individuals with similar demographic characteristics, natural variability in airway geometry can affect deposition in both the extrathoracic and intrathoracic regions.

Despite this, the mean intrathoracic deposition values differ by only ~3% between the two methods, highlighting a strong level of agreement. This result supports the ability of the FRI-based CFD approach to accurately capture the lung deposition behavior of nebulized liposomal formulations.

The slightly elevated exhaled fraction in the in-silico group can be attributed to the use of a standardized, repeatable tidal breathing profile in CFD simulations. In contrast, the scintigraphy study involved 20 minutes of active nebulization under free breathing conditions, where variability in inspiratory and expiratory flow across cycles could influence aerosol residence time and deposition dynamics—particularly the amount exhaled before settling in the lungs.

Taken together, the close match in lung deposition, combined with the expected but modest variation in extrathoracic and exhaled fractions, demonstrate the robustness of the FRI-based CFD approach. These findings support the use of in-silico tools for the evaluation of regional aerosol deposition and highlight their potential to accelerate the development and refinement of nebulized therapies.

The in-silico deposition results are visualized in Figure 1 as scintigraphy-like images for three selected subjects (A, B, and C). Brighter regions within the airways and lung lobes indicate higher local deposition, while darker regions correspond to lower deposition. Notable inter-subject variability in regional deposition patterns is observed, despite similar overall lung deposition levels.

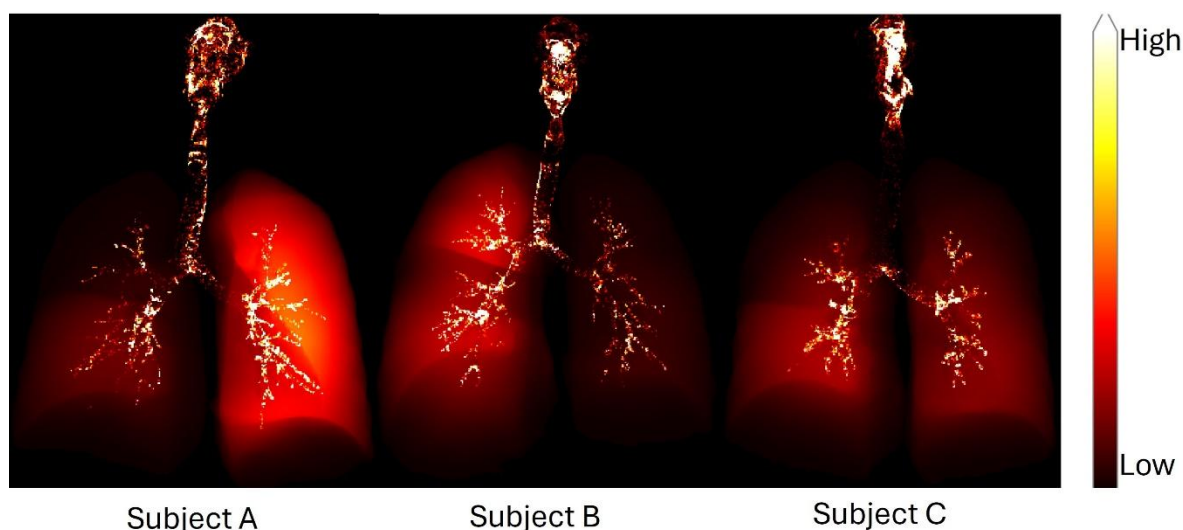


Figure 1: FRI scintigraphy-like images. Patients A, B and C

Conclusion

This study demonstrates strong agreement between in-silico predicted lung deposition of inhaled liposomal amikacin and previously published gamma scintigraphy data. Despite the use of anatomically different but demographically matched subjects, the FRI-based CFD simulations reproduced intrathoracic deposition within 3% of the in-vivo values. Small differences in extrathoracic and exhaled fractions are attributed to natural anatomical variability and differences in breathing profiles used in the two methods. These results further support the accuracy of FRI in modeling aerosol deposition from nebulized liposomal formulations and support its application in the development, optimization, and regulatory evaluation of inhaled therapies.

References

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