Refining Regional Deposition Predictions in MDIs: A Comparison of Static and Dynamic ICRP Models

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Introduction

The accurate prediction of regional deposition for aerosols delivered by pressurized Metered Dose Inhalers (pMDIs) is essential for optimizing therapeutic efficacy, particularly as the industry transitions from traditional propellants (HFA-134a, HFA-227ea) to alternatives (HFA-152a, HFO-1234ze). These new propellants introduce challenges due to their distinct properties: reduced viscosities, higher vapor pressures, and faster evaporation rates [1,2].

The International Commission on Radiological Protection (**ICRP**) model, widely adopted for predicting deposition across extrathoracic (**ET**), bronchial (**BB**), bronchiolar (**bb**), and alveolar (**AL**) regions, is a **static framework** that fails to account for:

1. **Dynamic Droplet Size Evolution:** Evaporation of propellant and condensation of water, influenced by relative humidity (RH), significantly alter droplet size, affecting aerodynamic properties and deposition efficiency [4].
2. **Plume Dynamics:** Key factors such as plume velocity, spray angle, and duration directly interact with formulation properties and inhalation flow, impacting deposition patterns [5, 6].

To address these limitations, we combined the D^2-law and plume dynamics into the ICRP framework, creating the **Extended D^2-law** [7]. This approach integrates experimentally derived evaporation (K_e) and condensation (K_c) constants to dynamically model droplet size evolution as a function of time and environmental conditions.

> **Study Objective:** To compare the regional deposition predictions of the static ICRP model with those of the modified framework using literature data for Flovent HFA.

Experimental Data

Determination of Deposition Parameters

Key input parameters for the ICRP model were derived from experimental data for Flovent HFA (44 µg/inh). Values were averaged across multiple anatomical throat models: USP throat, Alberta Idealized Throat (AIT), and Virginia Commonwealth University (VCU) models [8].

ET Deposition (MT Deposition): 61.5% ± 13.3%
Lung Dose (Impactor-Sized Mass): 38.5% ± 13.2%
Mass Median Aerodynamic Diameter: 2.23 µm ± 0.07
Geometric Standard Deviation: 1.75 µm ± 0.05
Source: Kaviratna et al. [8]

Plume Characteristics

Plume Velocity: 20.1 m/s
Median Droplet Size (D_0): 11.7 µm
Measured at 3 cm from nozzle (Liu et al. [9])

Spray Duration: 0.25 seconds
Corresponds to discharge of 50-100 µL under standard actuation (Wachtel et al. [10])

These parameters were used to initialize the ICRP model and the Extended D^2-law model for comparing regional deposition predictions.

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Theoretical Framework

Modified ICRP Model with Environmental Effects and Plume Dynamics with Extended D^2-Law for Droplet Size Evolution

The Extended D^2-Law builds upon the classical D^2-Law by integrating experimental findings on evaporation and condensation dynamics under varying relative humidity (RH). Using Stroboscopic Droplet Analysis and Electrodynamic Balance provided insights into propellant behavior [4][5].

Evaporation Dynamics:

The evaporation constant (K_e) was refined based on experimental measurements. HFA134a had evaporation kinetics of ~10,000 µm²/s [4].

Condensation Dynamics:

A condensation term ($K_c \cdot RH$) accounts for water uptake at elevated RH. Hardy et al. [4] showed that at 90% RH, condensation slowed evaporation and stabilized droplet sizes.

The Extended D^2-Law now models droplet size evolution as:

$$D^2(t) = D_0^2 - (K_e - K_c \cdot RH) \cdot t$$

Where:

- D(t): Droplet diameter at time t
- D_0: Initial droplet diameter
- K_e: Evaporation constant, dependent on propellant properties
- K_c: Condensation constant (µm²/s per RH unit) from Hardy's observations [4]
- RH: Relative humidity

The ICRP framework was not used for extrathoracic deposition, which came from experimental in vitro analysis. The ICRP framework with/without the extended D^2-law and plume dynamics was used for Bronchial (BB), Bronchiolar (bb), and Alveolar (AL) regions using ICRP parameters:

$$\eta = 1 - e^{-a(Rd)^p}$$

Where:

- a, R, p: Empirical constants specific to each lung region
- d: Aerodynamic particle diameter

The BB deposition fraction was adjusted based on plume velocity and duration:

$$\textit{Adjusted BB Fraction} = \textit{Base BB Fraction} + 0.03(t_p - 0.7) - 0.02(V_p - 8.5)$$

- t_p: Plume duration (s) • V_p: Plume velocity (m/s)

Remaining lung dose is redistributed proportionally across the bb and AL regions.

Pharmacokinetic Modeling

Fluticasone Propionate PBPK model

A PBPK model was developed to simulate regional deposition and absorption kinetics of fluticasone propionate via pMDI.

The model incorporates three lung compartments (**BB**, **bb**, **AL**) with distinct dissolution, mucociliary clearance, and permeability.

Dissolution used a squared-radius approach. Regional absorption followed first-order kinetics, with clearance rates from measured mucociliary velocities.

Systemic circulation was modelled via plasma compartment, with drug flux determined by lung-to-blood partitioning.

The model used numerical integration for concentration-time profiles.

Key PK metrics provided:
- Maximum plasma concentration (C_{max})
- Time to C_{max} (t_{max})
- Area under the curve (AUC)

For lung and plasma compartments

Results and Discussion

The Extended D^2-law and plume dynamics significantly altered predicted regional deposition patterns (Figure 1).

Traditional Model: Higher deposition in **BB** region, lower in **bb** and **AL** regions due to static assumptions ignoring dynamic droplet behavior.

Modified Model: Dramatic shift with decreased **BB** deposition and increased **bb** and **AL** deposition.

> This redistribution shows the importance of modeling droplet evaporation, condensation, and plume dynamics for accurate regional deposition prediction.

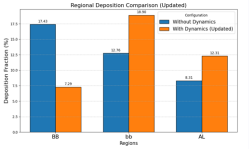

Figure 1. Comparison of regional deposition predictions using the static ICRP model versus the modified framework with Extended D^2-law.

PBPK Simulations

Changes in deposition influenced lung PK (Figure 2). Drug deposition varied between simulations without dynamics (● blue) or with dynamics (● orange). With-dynamics led to **lower bronchial deposition** but **higher alveolar and total lung deposition**, enhancing deeper lung penetration.

Without Dynamics:
- C_{max}: 32.14 pg/mL
- AUC: 1,264.4 pg·min/mL
- t_{max}: 9.05 min

With Dynamics:
- C_{max}: 47.51 pg/mL (+47.8%)
- AUC: 1,870.9 pg·min/mL (+48%)
- t_{max}: 9.05 min (unchanged)

While drug absorption dynamics were altered, the consistent t_{max} suggests the overall rate of absorption remained unchanged across models.

The increases support that plume dynamics improves delivery to deeper lung regions. Slower velocities and longer plume durations reduced upper airway deposition, allowing aerosols to penetrate where absorption is more efficient. This shows limitations of standard ICRP models in capturing droplet evolution and plume behavior.

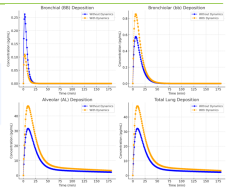

Figure 2. PBPK simulations of fluticasone propionate absorption from Flovent HFA across different lung regions with and without plume dynamics.

Conclusion

By incorporating plume dynamics into the regional deposition model, the predicted total lung drug exposure (AUC) increases by nearly **50%**, highlighting the importance of considering aerosol physics in PBPK modelling.

> This refined approach more accurately reflects patient-device interactions and plume behaviour, particularly with new propellants such as HFA-152a and HFO-1234ze.

We will validate our model by comparing predicted regional deposition and total lung exposure with in vitro and in vivo PK data.

Future Validation Steps

1. Benchmarking against experimental lung PK data
2. Utilizing physiologically relevant deposition studies
3. Refining predictions with data-driven optimizations to align with observed aerosol dynamics and systemic drug levels

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