Point of View: The role of *in silico* models in accelerating and de-risking inhaled drug development

In this opinion article, the authors discuss potential benefits of utilizing both empirical methods and *in silico* models for inhaled drug development

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Introduction

Traditional inhaled formulation development can be a costly, slow and iterative process, with no assurance of clinical or commercial success. On average, the development of a successful new drug formulation takes 14+ years and costs $1.5 billion [1] . However, as few as 3% of developed inhaled drug formulations eventually reach the market, with the majority failing during clinical trials due to efficacy or safety issues [1, 2]. Furthermore, even for formulations that reach patients, drug deposition and uptake are often suboptimal, with the efficiency of inhaled drug delivery typically remaining below 50% for most devices [3-5].

The development process itself is inherently risky. Even minor changes in manufacturing or formulation composition can have unforeseen effects on drug deposition and therapeutic outcomes. Furthermore, external market pressures, such as environmental considerations around propellant use [6], can significantly impact drug formulation development. Reducing these risks and enhancing the prospect of clinical and commercial success within shorter timelines is a critical objective for many inhaled formulation development teams. While experienced formulators bring invaluable expertise that can expedite the process and lead to successful solutions, using traditional approaches might overlook promising novel technologies or development routes. Teams might be unfamiliar with such alternatives or may previously have had limited success with them, even if those approaches could offer faster, better or lower-cost outcomes. Consequently, integrating predictive *in silico* methods and artificial intelligence (AI) to guide drug development may offer a more efficient and informed path forward.

From a regulatory perspective, *in silico* modeling is gaining traction as an important tool within the drug development pathway, and regulatory agencies are increasingly recognizing its potential as a complementary approach to experimental methods. The United States Food and Drug Administration (FDA), in particular, has been a strong proponent of computational modeling as part of its commitment to modernize drug development under the 21st Century Cures Act and the FDA Modernization Act 2.0 [7]. These initiatives actively encourage the adoption of model-informed drug development (MIDD) approaches, which utilize *in silico* models to support formulation optimization, bioequivalence assessments and risk mitigation strategies [8]. According to the FDA's 2018 guidance on MIDD, computational models can provide critical insights that may reduce the need for extensive clinical studies, thereby accelerating regulatory review and approval processes [8]. *In silico* tools can provide supplementary data and may reduce the need for extensive clinical testing, particularly in demonstrating bioequivalence or supporting formulation changes [9].

The European Medicines Agency and other global regulatory bodies have also acknowledged the potential of *in silico* methods [10]. Given this clear regulatory push towards embracing *in silico* methods, it is timely to explore how these tools can assist in the development of inhaled drug formulations.

Iterative inhaled formulation development

The selection of an optimal formulation for active pharmaceutical ingredients (APIs) in inhaled drug delivery is a complex process. The performance of an inhaled therapeutic depends upon the successful combination of API, formulation and drug delivery device, and the selection of each element for compatibility directly influences drug development timelines. The optimal formulation for a drug is influenced by the characteristics of the API, such as its solubility, stability and potency, and selection of the drug delivery device, particularly where novel technologies are being co-developed. Identifying these inherent API characteristics and delivery device is also essential for defining the target product profile (TPP), with each API requiring a unique optimization strategy [11].

There are advantages and limitations to each inhaled drug delivery device, including payload capacity, moisture protection, turbulence generation, airflow resistance and dose isolation [12]. Availability can also be a key consideration, as many inhalation devices are protected by intellectual property rights or exclusivity agreements, so the choice of device for proof-of-concept work is often limited to what is accessible. Additionally, formulators are often guided in their choices by prior successes; however, each novel API presents distinct challenges. The physical properties of an API may limit certain development approaches, potentially demanding a more "engineered particle" strategy to succeed. Furthermore, knowledge of the pharmaceutical modality may influence the lung target, thereby affecting the optimal particle size and morphology of the formulation. Ultimately, there is no "one-size-fits-all" formulation approach and navigating the learning curve associated with unfamiliar APIs demands significant time and resources, often resulting in an iterative development process that may be influenced by luck.

One of the most persistent challenges in inhaled drug development is the lack of predictive tools that reliably reflect *in vivo* performance. While initiatives such as the inhalation-based Biopharmaceutics Classification System (iBCS) [13] aim to systematize our understanding of inhaled drug behavior, conventional *in vitro* assays still offer limited insight into the fate of aerosolized formulations after inhalation, particularly for biologics. Unlike small molecules, biologics such as peptides, proteins and nucleic acids are structurally fragile and require specialized evaluation following aerosolization, as the process may compromise their integrity and therapeutic effect [14-17]. However, most *in vitro* cell culture studies apply these compounds in bulk liquid form rather than as aerosols, failing to replicate deposition and delivery mechanisms within the lungs or to assess whether biological activity is retained post-aerosolization. The development of inhaled biologics therefore demands greater mechanistic understanding and more physiologically relevant tools capable of simulating lung delivery, evaluating post-aerosolization activity and accurately predicting deposition and uptake. The current lack of such tools may limit progress in the field and highlights a critical opportunity for innovation in inhaled formulation science.

Beyond formulation-specific challenges, inhaled drug development faces broader issues. Significant time commitments can be required to refine formulations, complete preclinical assessment and progress through clinical phases. Correspondingly, costs may escalate, driven by the need for multiple formulation iterations, device compatibility testing and extensive *in vivo* studies. This extended timeline can also reduce the effective patent life of new drugs, impacting commercial returns.

Overall, inhaled drug formulation development is a multifaceted challenge that spans scientific, technical, commercial and environmental domains. Overcoming these hurdles requires expert formulation knowledge but also may benefit from the integration of innovative predictive methodologies that could reduce reliance on trial-and-error and accelerate the path to successful therapies.

An empirical approach to overcoming formulation challenges

Traditionally, inhaled formulation development has relied on empirical methods, supported by the expertise of formulation teams and iterative laboratory testing. "Design of experiments" approaches have been widely adopted to provide greater structure and efficiency to this process. To mitigate risks and improve the chances of success, formulators often deploy a range of experimental techniques to analyze and optimize key parameters such as particle size, morphology and device compatibility. One common approach involves the extensive physicochemical characterization of an API and any excipients utilized. Techniques such as laser diffraction, scanning electron microscopy and calorimetry methods provide critical insights into particle size distribution, surface morphology and thermal behavior. Similarly, impactor measurements enable the detailed characterization of aerodynamic particle size distribution (APSD) and fine particle fraction (FPF) for different formulation-device combinations. This data can then be used to inform formulation decisions to modify and tailor particle properties or incorporate excipients to modify the formulation properties for optimal lung deposition.

While these laboratory-based methods provide a strong foundation for inhaled product development, they are often resource-intensive and time-consuming. Early-stage formulation development can involve numerous iterations, with no guarantee

that changes will result in *in vitro* improvements or translate into clinical efficacy and efficiency. The high attrition rates of drug candidates observed in the late stages may be partly attributable to the limitations of utilizing purely empirical approaches in predicting product performance *in vivo*.

Integrating computational tools with established experimental techniques may instead provide a promising path forward. Combining computational simulations with hands-on formulation expertise may offer a more data-directed and efficient development process, reducing reliance on experimentally guided lab work and may improve the probability of clinical success.

In silico modeling: Applications in inhaled drug development

In silico modeling is emerging as an important tool to support the increasingly complex task of developing inhaled drug formulations. Leveraging computational simulations can enable researchers to better predict, and therefore optimize, critical aspects of drug delivery, from the physicochemical properties of aerosols upon generation through their regional and total deposition in the lungs [18, 19]. These tools can complement traditional experimental techniques by reducing reliance on extensive *in vitro* and *in vivo* testing, and may thereby accelerate development timelines and reduce costs.

Computational methods are impacting early-stage drug development, particularly in the identification of novel drug candidates [20]. The ability to screen billions of molecules from extensive virtual libraries has increased the likelihood of discovering potent, selective compounds with favorable properties. In particular, structure-based virtual screening can enable accurate docking of molecules into 3D-receptor models, accelerating the identification of drug-like compounds and improving pharmacokinetic (PK) profiles early in development [21]. While these approaches are more established in systemic drug discovery, their direct application to inhaled medicines remains limited but holds considerable promise.

However, challenges such as high computational costs, the need for extreme predictive accuracy and limited generalizability of some deep learning models, especially when training data lacks diversity, continue to constrain broader adoption of computational methods [21]. Nonetheless, the integration of computational modeling is steadily progressing, with emerging technologies opening new avenues for inhaled drug development. In particular, the application of AI to pharmaceutical development is becoming increasingly prevalent and has significant scope to affect the industry [22]. A recent survey found that 80% of professionals in the pharmaceutical and life sciences sectors now use AI for drug discovery [23]. While at the time of writing this article, no AI-generated drug has yet received FDA approval, Insilico Medicine (Boston, Massachusetts, United States) recently published promising Phase IIa clinical trial results for its AI-identified candidate, Rentosertib, a novel serine/threonine kinase (TNIK) inhibitor [24]. The results indicate that the drug is effective, well tolerated and suitable for Phase III trials. This may mark a pivotal moment, with an AI-identified drug candidate now advancing into later-stage clinical trials and approaching regulatory submission. Insilico Medicine's success is particularly relevant for the respiratory and inhaled drug development community, as Rentosertib is being trialed for the treatment of idiopathic pulmonary fibrosis, a degenerative lung condition with limited treatment options. Furthermore, Insilico Medicine has also announced the development of an inhalable formulation of its lead candidate [25].

AI is also used in other stages of drug development including formulation optimization, material characterization and clinical trial design [26, 27]. For example, AI-driven platforms are now being used to optimize formulation design, predict ideal compositional ratios and refine release characteristics, such as identifying component combinations to achieve co-amorphous systems [28], moving beyond traditional screening methods [21]. These innovations may offer the potential to streamline development, reduce costs and minimize reliance on individual expertise, and could signal a future role in computationally guided inhaled therapeutics [29, 30].

In silico modeling can also be used in inhaled drug development to predict particle behavior following inhalation. Computational simulations can play a role in understanding inhaled aerosol deposition in the human respiratory tract, particularly where direct experimental determination is challenging or unfeasible. These models can help predict the regional and total deposited fractions, and therefore the deposited dose, of inhaled particles within the lungs, which is vital for health risk assessment and aerosol therapy. Various modeling approaches exist, categorized by their structure and focus: whole-lung models, which can compute deposition across the entire lung, and local-scale models, which can provide detailed information on deposition patterns within specific lung regions like bronchial bifurcations [31]. Whole-lung models often use analytical equations for particle deposition efficiencies and specific flow conditions, while local-scale models solve particle transport and deposition equations using computational fluid and particle dynamics (CFPD) methods, offering insights into individual particle behavior [32, 33].

In silico approaches are also being used to simulate the impact of formulation variables on aerosol performance. For example, models can assess how changes in excipient composition or propellant type influence aerosolization efficiency, droplet size and

plume geometry [34-37]. This is particularly relevant in light of regulatory pressures to phase out propellants with high global warming potential (GWP), which necessitates pressurized metered dose inhaler (pMDI) reformulation without compromising delivery performance. Similarly, computational fluid dynamics (CFD) may support and help optimize the development of inhaler devices, whether adapting pMDIs to accommodate new propellants or enhancing dry powder inhalers (DPIs), which are breath-actuated [6, 38-40].

Simulating airflow through DPIs and pMDIs can provide insight into device resistance, emitted dose and FPF. For both device types, the efficiency of drug delivery is closely tied to the internal airflow dynamics and the interaction between the formulation and device architecture. CFD can therefore be an important computational tool for understanding and optimizing these interactions. By simulating airflow patterns, pressure gradients and turbulence within the device, CFD can help developers visualize how design changes affect aerosol generation, particle dispersion and, ultimately, lung deposition [41]. CFD modeling also can help identify design inefficiencies, such as regions of particle stagnation, excessive retention or suboptimal flow pathways, all of which may compromise dose delivery or reproducibility [41]. Whether refining valve and actuator configurations in pMDIs to accommodate new propellant behaviors, or refining chamber geometries in DPIs to enhance powder deagglomeration, CFD can help provide mechanistic insight to inform rational design improvements [42, 43]. Furthermore, it can allow developers to explore the effects of patient variability, such as differences in inspiratory flow profiles, on device performance. While CFD remains resource-intensive and its predictive power can be limited by assumptions around complex aerosol behavior, continued advancements in computational methods and data integration are helping to overcome these limitations [41]. Consequently, as both DPI and pMDI platforms evolve under environmental and regulatory pressures, CFD could play a central role in the design of more efficient, robust and sustainable inhalation products.

In addition to modeling aerosol dynamics, inhaler devices and deposition, *in silico* PK models are gaining prominence in inhaled drug development. These models can simulate the absorption, distribution, metabolism and excretion of inhaled compounds once deposited in the lungs. By integrating regional deposition data with lung physiology and systemic circulation parameters, *in silico* PK models can predict local drug concentrations within various lung compartments and systemic exposure over time [44]. This capability could be particularly important for assessing the therapeutic window and safety profile of inhaled drugs without the immediate need for extensive *in vivo* studies. *In silico* PK modeling can also support the optimization of formulation and dosing regimens by enabling virtual trials that can explore how formulation changes or patient variability affect drug bioavailability and clearance [45]. Moreover, these models could be coupled with pharmacodynamic (PD) simulations to forecast the clinical effect of a drug, offering a more comprehensive understanding of dose-response relationships.

Several PK modeling platforms are available for inhaled drug development, each providing important insights into the absorption, distribution, metabolism and excretion of inhaled compounds. Well-established tools such as GastroPlus® (Simulations Plus, Inc., Lancaster, California, United States) [46, 47], Mimetikos Preludium™ (Emmace, Lund, Sweden) [48], and Open Systems Pharmacology (Open Systems Pharmacology) [49, 50] integrate lung physiology parameters, including regional blood flow and tissue permeability, to simulate local and systemic drug concentrations post-inhalation. These models may then facilitate virtual PK profiling, enabling optimization of dose regimens and prediction of lung retention and systemic exposure. By reducing the reliance on early-stage *in vivo* studies, they can help streamline development timelines and inform clinical study design.

However, some PK platforms may have limitations when used for inhaled drug products by relying on simplified or empirical particle deposition inputs. Such inputs can be based on *in vitro* APSD data or standard deposition fractions that do not account for key factors such hygroscopic growth, which is dependent on initial ambient humidity. This is turn can limit the mechanistic fidelity of aerosol transport and deposition predictions [51].

Generally, although *in silico* tools have seen recent advancements and growing adoption for drug development, certain limitations remain. Computational models are only as good as the input data they receive, such as the physicochemical properties of APIs and excipients, as well as comprehensive models of respiratory physiology, and this data is still scarce within the literature. Furthermore, computational predictions, however useful, still require rigorous experimental validation in robust *in vitro* and *in vivo* assays at each step of the pipeline. This experimental testing also serves a critical purpose in providing feedback data that can further refine and improve the models. Nevertheless, ongoing improvements in computational power and algorithms, integration with experimental data and the use of AI to identify connections and correlations are enhancing predictive capabilities. Overall, current applications of *in silico* modeling in inhaled drug development can provide a versatile platform for optimizing formulations, accelerating product development and meeting increasingly stringent regulatory demands. As these tools continue to mature, they are poised to become part of the inhaled

pharmaceutics development landscape. Figure 1 displays a flow chart of some of the inhaled drug development steps and associated computational tools.

To illustrate how *in silico* approaches can be practically applied to overcome key challenges in inhaled drug development, two case studies are presented here. The first focuses on the reformulation of pMDIs with low global warming potential propellants, demonstrating how mechanistic evaporation modeling can guide efficient, environmentally responsible product development. The second explores the use of deposition modeling to predict aerosol behavior and optimize formulation-device combinations, highlighting how virtual screening can streamline early development and reduce the risk of clinical failure. Together, these examples underscore the potential value of computational tools in supporting informed decision-making across the development lifecycle, accelerating formulation design and enhancing mechanistic understanding.

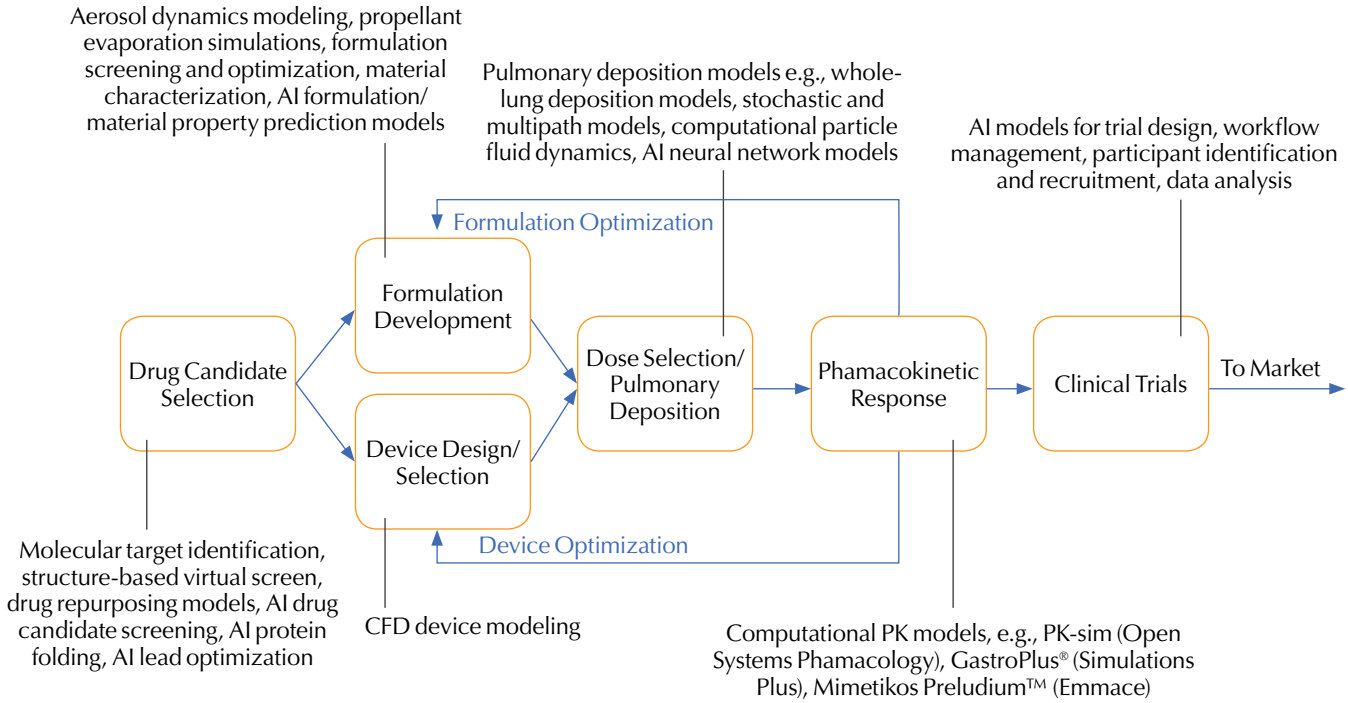
Case study 1. Modeling and the transition to low-GWP propellants

The transition to low-GWP propellants in pMDIs is one of the most significant technical and regulatory challenges currently facing the inhalation industry. Among challenging regulatory and economic pressures, the replacement of traditional hydrofluoroalkane (HFA) propellants such as HFA-134a and HFA-227 with more climate-friendly alternatives, HFA-152a and HFO-1234ze, is progressing. However, these new propellants differ in their physicochemical properties, raising complex issues in formulation design, device compatibility and aerosol performance. These changes in propellant characteristics, such as vapor pressure, density and volatility, can have far-reaching effects on plume dynamics, droplet evaporation, and ultimately, drug deposition in the lungs. Reformulating a pMDI with a new propellant is therefore not a simple matter of substitution; it requires comprehensive re-optimization of actuator design, valve function, excipient or cosolvent composition and suspension stability, in order to maintain bioequivalence and therapeutic consistency.

To navigate the transition, a range of experimental tools is being deployed to characterize the behavior of low-GWP formulations in real-world conditions. High-speed imaging of spray plumes can provide insights into aerosol formation and expansion, revealing differences in spray angle, velocity and evaporation profiles. In-canister X-ray fluorescence spectroscopy is being employed to monitor the physical distribution and chemical stability of formulations over time [52]. Laser diffraction and impactors are being used to assess particle size distributions and respirable fractions. These methods collectively build a comprehensive understanding of how changes at the formulation level affect aerosol performance [53]. However, these experimental approaches are often labor-intensive, time-consuming and resource-heavy. Moreover, they each provide only a partial picture, focused on output characteristics rather than the mechanistic processes driving them. Computational

Figure 1

Inhaled drug development stages and examples of *in silico* modeling techniques that can be utilized at each stage.



modeling can offer the potential to simulate pMDI aerosol generation and evolution processes in a way that complements and enhances experimental data.

To control the performance of formulations based on low-GWP propellants and to demonstrate the equivalence of reformulated products, a deeper understanding of droplet evaporation kinetics is essential. Droplet evaporation plays a central role in determining the efficiency of drug delivery, as it directly influences the physical properties of the aerosol during inhalation. As a pMDI droplet evaporates, after emission and during inhalation through the airways, its composition, aerodynamic diameter and phase evolve due to complex interactions involving heat and mass transfer. Since respiratory tract deposition is highly sensitive to these changes, particularly to aerodynamic size, particle shape and density, accurate modeling of these processes becomes critical in predicting and optimizing *in vivo* drug performance. Consequently, the development of a novel *in silico* model that simulates propellant evaporation dynamics could be of particular use in formulation design and development. This capability could enable developers to identify and address performance differences early in the reformulation process, significantly reducing the need for iterative physical testing. It could also allow for the predictive comparison of formulation performance between propellants and could support the rational design of actuators and valves tailored to the specific evaporation kinetics of a given formulation. Furthermore, by capturing the interplay between vapor pressure, heat transfer and droplet dispersion, the model could provide important insight into how formulation changes affect plume behavior and particle size evolution from the nozzle to the lung, which ultimately affects aerosol deposition and uptake.

Methods

To demonstrate how such models might be used, we present a simulation of the evaporation of HFA-152a (Figure 2) using a model based upon that published by Wang, et al [54]. This model is a quasi-steady state numerical model that simulates the kinetics of coupled heat and mass transfer between droplets with multicomponent compositions and the surrounding gas environment. Given initial conditions, including droplet size, composition and ambient conditions, the system is treated as an initial value problem and integrates over time, with the simulation timesteps dynamically adjusted according to the rate of the droplet kinetics. While the model does not account for temporal or spatial variations in the ambient conditions that droplets experience, it provides insights into the kinetics of propellant droplets during concurrent evaporation and condensation. In this case, the evaporation of a single droplet of pure propellant (initial radius 26.5 µm), into air at 90% relative humidity (RH) and 20 °C, was simulated and compared to experimental measurements.

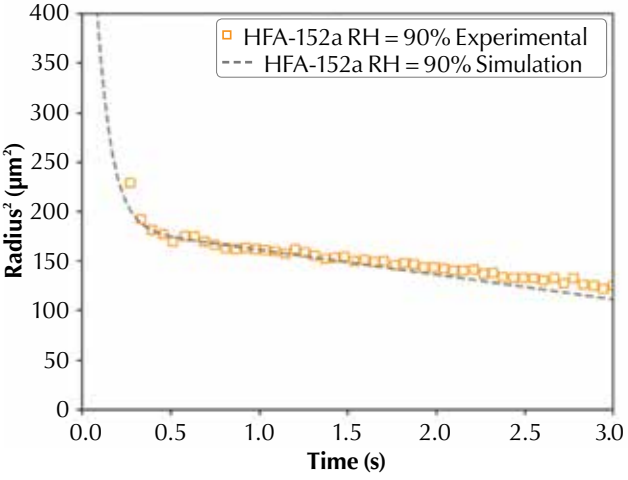
Full details of the experimental method of these measurements have been published previously [55]. In brief, a stroboscopic droplet analysis technique was coupled with single-particle electrodynamic balance measurements to image and measure the evaporation of single droplets of the HFA propellant on both the sub-micron timescale and over longer time periods in various RH conditions. For both methods, the propellant was maintained at ambient pressure but chilled to prevent premature evaporation.

Results and discussion

The experimental observations revealed that when droplets are formed from pure propellant, their evaporation follows a two-stage process [55]. Initially, there is a rapid phase where the propellant evaporates while water simultaneously condenses from the ambient air. This is followed by a slower phase where the condensed water evaporates once the propellant is depleted. However, in high humidity environments (e.g., the lung), second phase hygroscopic condensational growth may occur instead of evaporation of the water droplets. Although water is not present in the original formulation, its condensation from the surrounding environment has a substantial impact on the droplet's evolution and must be taken into account. As Figure 2 shows, the two-stage evaporation process is fully captured by the computational model, with the initial rapid decrease in size of the droplet as the HFA-152a propellant evaporates, followed by a slowing of the reduction in size as water condenses onto the droplet due to the rapid reduction of its temperature. After this point, the droplet

Figure 2

Simulation of the evaporation of a droplet of HFA-152a with a starting size of 26.5 µm into 90% RH compared to the experimental, measured evaporation in the same conditions. Experimental data from Hardy, et al. [55] reproduced with permission.



transforms from being a propellant-water solution to a pure water droplet and then follows the evaporation profile of water.

Furthermore, this simulation was found to demonstrate excellent agreement with the single-particle experimental data [55]. The transition of propellant to water can be significantly quicker than the duration of a single breath, with the propellant evaporation happening very rapidly, within 0.3 seconds. Consequently, the majority of propellant evaporation and conversion of the droplet to water is likely to occur between the aerosol plume leaving the spray orifice and reaching the upper airways or bronchiolar region. By capturing these multicomponent and multistage dynamics, the model is able to provide important insight into how formulation choices and environmental conditions can influence aerosol performance. This can allow developers to explore the impact of changes in propellant composition and droplet properties early in the development process, supporting more targeted and efficient reformulation. Ultimately, this kind of mechanistic modeling could strengthen the scientific basis for demonstrating product equivalence and accelerate the development of environmentally sustainable pMDI products. When linked with pulmonary deposition models, this approach could also facilitate the early prediction of regional lung delivery, thereby informing PK and PD modeling without the need for extensive *in vivo* testing.

Still, this model is not without limitations. The simulated evaporation profile of the droplets is highly dependent on the parameterization of the physicochemical properties of the evaporating species. Many of these properties are well defined and can be found in literature values or calculated from them. However, the diffusion coefficient data of the substance within vapor (humid air) at a given temperature, which is used within the model and strongly affects the resulting evaporation profile, is not always readily locatable. Single-particle aerosol measurements in controlled humidity conditions can be used to calculate this parameter for the model, as was the case for the HFA-152a simulation presented. Yet, the need for these measurements prevents the model from being fully computationally predictive for all volatile species or formulation mixes at present. Despite these limitations, the model offers an important tool for formulation scientists that can enable more informed decision-making early in development and could also provide useful input for developing more accurate CFD models. Continued development and validation from single-particle aerosol measurements could support the virtual screening of formulation and device parameters, potentially reducing experimental workload, shortening timelines and improving confidence in product performance. Moreover, as more accurate input data become available, this modeling approach may be well-positioned to help drive the development of effective and environmentally sustainable inhaled therapies.

It is also important to recognize that pMDIs are frequently used with spacers. Prior research has shown that the use of a spacer can alter the initial particle size distribution at inhalation, thereby affecting pulmonary deposition [56, 57]. Therefore, it would be beneficial to extend the model in future work to simulate evaporation and make comparisons to experimental data under a range of RH conditions that better reflect clinical-use scenarios with and without spacers.

Overall, as regulatory expectations shift towards greener inhalation products, the integration of advanced modeling with targeted experimental techniques could play an essential role in the pMDI transition. *In silico* evaporation models, in particular, represent a promising step forward that could help enable an environmentally responsible approach to the challenge of high-GWP propellant inhalers.

Case Study 2. Predicting particle deposition

As inhaled therapies continue to evolve, computational tools are playing an increasingly important role in drug development. *In silico* modeling can offer a faster, lower-risk route through early formulation screening, enabling researchers to concentrate laboratory efforts on the most promising candidates. By simulating aerosol deposition both in standardized *in vitro* setups, such as the Next Generation Impactor (NGI), and anatomically realistic models of the human lung, developers can more quickly and effectively evaluate and optimize formulations and delivery devices.

Historically, the development of inhaled products has relied heavily on *in vitro* performance indicators such as FPF and mass median aerodynamic diameter (MMAD). While these metrics are useful for characterizing aerosol generation and estimating respirable dose, they offer limited insight into the actual *in vivo* distribution of drug within the lung. FPF, for example, quantifies the proportion of aerosol particles below a threshold aerodynamic diameter, presumed to be small enough to enter the lungs. However, it provides no spatial resolution and cannot account for individual physiological variability, deposition site or regional clearance, all of which significantly influence PK and PD outcomes, and, in our opinion, should not be used as a measure of *in vivo* performance.

In silico deposition models can provide a more mechanistic and anatomically grounded understanding of aerosol behavior and deposition. By combining representations of airway geometry with models of airflow and particle dynamics, these simulations can predict where aerosolized drug particles are likely to deposit under a variety of breathing conditions

and disease states. This can enable drug developers to assess central versus peripheral deposition, evaluate dose delivery to specific lung regions, and estimate the proportion of drug likely to be systemically absorbed or remain locally active.

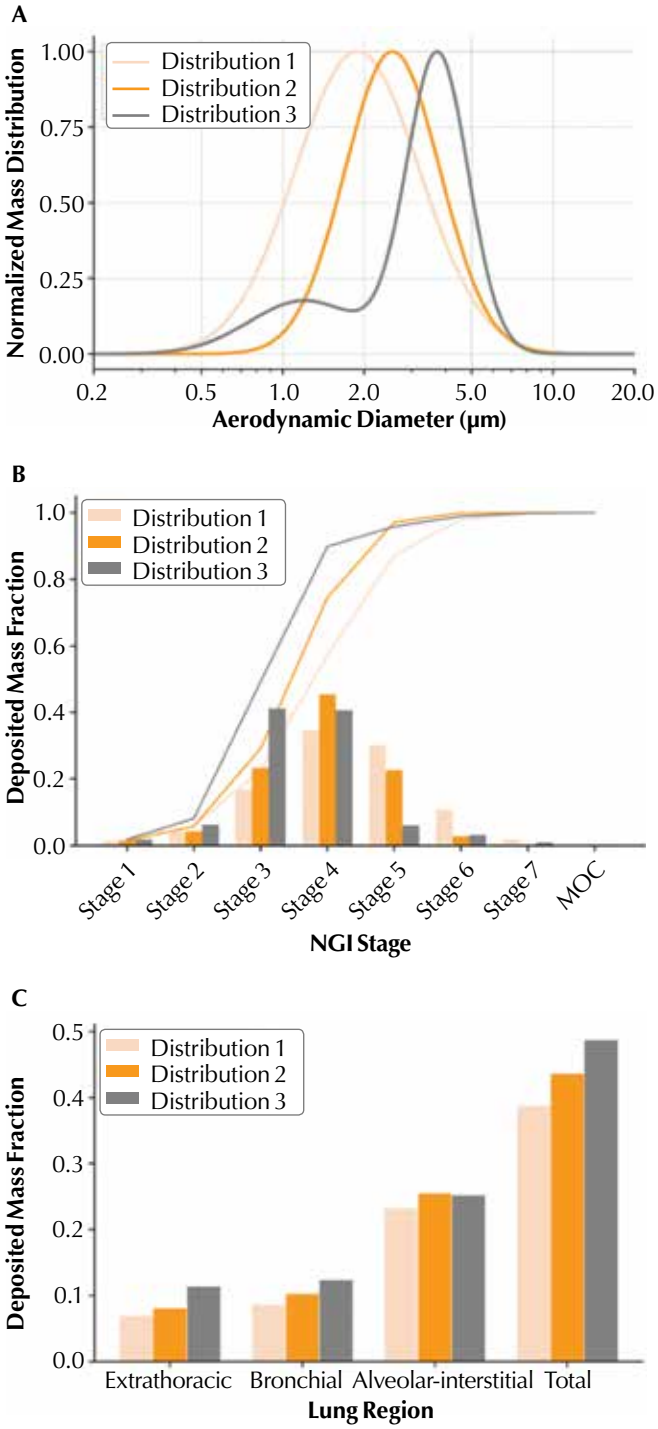
Simulating deposition profiles in an NGI can allow researchers to predict stage-by-stage deposition within the impactor without the need for physical experiments. However, digital tools such as the simulated NGI can do more than replicate *in vitro* results; they can enable the controlled exploration of the ways aerosol particle size distributions behave under conditions not easily reproduced in a laboratory setting. For example, *in silico* simulations can model the warm and humid environment of the respiratory tract, conditions that are not typically captured during NGI experiments, which are often performed with low-humidity, high-flow air and sometimes even chilled impactors to minimize aerosol evaporation. This can lead to discrepancies between the MMAD measured *in vitro* and the particle size presented to the lung during inhalation. By simulating these dynamic conditions, *in silico* NGIs can allow researchers to assess whether a formulation is susceptible to evaporation or condensation, and help them understand how the aerosol size distribution may evolve prior to lung deposition. In doing so, simulations can reveal nuances that may be lost in single-parameter metrics like FPF, which can oversimplify the complexity of aerosol behavior.

Methods

To illustrate how NGI simulations and pulmonary deposition models can be used to provide greater insight into *in vivo* product performance, we simulated *in vitro* deposition profiles for three representative APSDs, each chosen to reflect a range of realistic aerosol device outputs (Figure 3). A single proxy compound was used across all three simulations, ensuring that any differences in deposition behavior were attributable solely to particle size distribution rather than physicochemical properties. Furthermore, the simulations intentionally excluded aerosol dynamics such as solvent evaporation and hygroscopic growth, allowing for a focused examination of how initial APSD influences deposition behavior. Notably, this approach enables detailed predictions of stage-by-stage deposition across cascade impactors, an aspect traditionally accessible only through experimental studies. The resulting profiles reveal how relatively small changes in APSD can lead to pronounced differences in regional deposition, highlighting the potential of computational modeling to detect formulation-dependent effects that may not be apparent through single-metric analysis alone. More broadly, the development of a reliable *in silico* NGI predictor could offer a tool for streamlining inhaled drug development, which could have the potential to reduce the number of physical NGI experiments required, support formulation screening and accelerate decision-making in the early stages of product development.

Figure 3

A) Three APSDs used in the simulated NGI model: Distribution 1 (MMAD 2.50 µm, GSD 1.70), Distribution 2 (MMAD 3.00 µm, GSD 1.50), and bimodal Distribution 3 (MMAD 1.50 µm, mode GSDs 1.60 and 1.30). B) Simulated NGI stage and cumulative mass deposition at 60 L/min for each APSD. C) Regional and total deposition for each APSD based on the ICRP pulmonary deposition model.



We then modeled the pulmonary deposition for the same APSDs within the human lung using the International Commission of Radiological Protection (ICRP) model [58], as shown in Figure 3C. This allowed us to simulate aerosol deposition within the extrathoracic, bronchial and alveolar regions of the respiratory tract.

To further illustrate how *in silico* deposition models can provide significantly greater information than single-term metrics such as FPF to support inhaled drug development, we present here a previously published study we conducted in collaboration with Copley Scientific [59]. In this study, four NGI datasets sourced from the literature on salbutamol sulphate and tiotropium bromide were re-analyzed using Inhalytix® software (Copley Scientific, Nottingham, United Kingdom) to calculate mass median aerodynamic diameter and geometric standard deviation (GSD). Each dataset corresponded to a different type of inhaled drug delivery device: nebulizer (MMAD: 5.02 µm, GSD: 2.17, [60]), pMDI (MMAD: 2.23 µm, GSD: 1.88, [61]), DPI (MMAD: 4.71 µm, GSD: 1.80, [62]), and soft mist inhaler (SMI) (MMAD: 4.89 µm, GSD: 2.01, [63]).

From these data, log-normal particle size distributions were generated and converted from mass to number distributions, assuming a consistent particle density, enabling standardized comparisons between drugs and devices. Particle sizes ranging from 0.001 to 100 µm were simulated through the ICRP lung deposition model [58]. Number distributions were then converted back into mass distributions to predict regional and total lung deposition as a percentage of the emitted dose. This approach predicts where the portion of the emitted dose measured by NGI impactor stages would deposit during inhalation.

Results and discussion

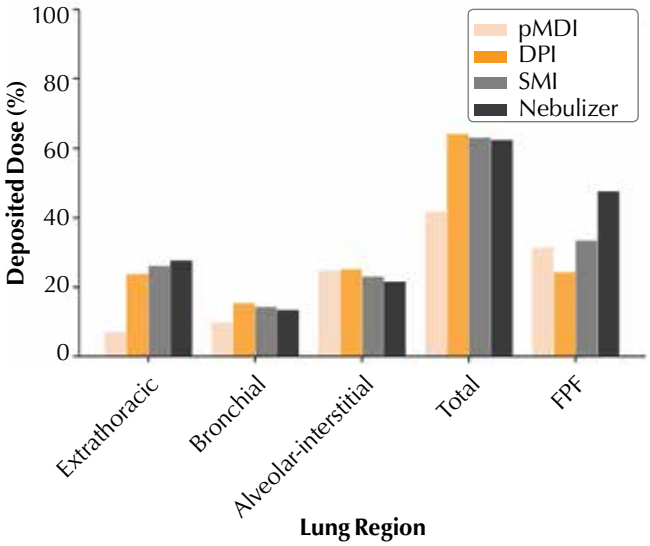
As shown in Figure 3, the NGI simulation successfully predicted the deposited mass fractions for each NGI stage across the three simulated aerosol distributions. While some experimental NGI testing will always be required for confirmation and regulatory submission, such simulations can offer the potential to screen and optimize formulation characteristics prior to laboratory testing. This could reduce the number of necessary experiments, accelerate formulation development and allow for normalization of literature NGI data that has been collected under differing environmental conditions (e.g., temperature and humidity), thereby improving the reliability of comparisons.

Figure 3C presents the simulated predictions of the regional and total deposited dose for each of the three distributions; although the total delivered doses were comparable, the resulting regional deposition profiles differed significantly. These differences in regional deposition are clinically relevant, as they influence both therapeutic efficacy and systemic exposure. While experts may qualitatively interpret NGI profiles, conventional outcome metrics such as FPF, which is often incorrectly used as a surrogate for *in vivo* performance [64], provide only a single summary value. As a result, they do not accurately represent how the dose is distributed throughout the lung nor capture important differences in regional deposition between the aerosols produced from different formulations or device types. In contrast, the computational model can provide detailed predictions of regional deposited dose, delivering more comprehensive and practically useful data to inform formulation decisions. Furthermore, these simulations could be employed early in development to identify the optimal APSDs that would achieve targeted drug delivery to specific lung regions or receptor sites. This example also illustrates how formulation choices made early in development can have downstream effects on clinical performance, effects that may go unnoticed when relying solely on traditional *in vitro* characterization.

Similarly, as can be seen from the results in Figure 4, the distributions generated by the pMDI and SMI devices, despite having very similar FPF values, exhibited markedly different lung deposition profiles. The SMI achieved higher total lung deposition, whereas the pMDI delivered more drug to the alveolar region. Depending on the lung target site, the higher alveolar deposition of the pMDI may be preferable for deep lung delivery, or the greater and more uniform total lung deposition of the SMI might be more

Figure 4

Regional and total deposited dose percentages for four aerosol distributions, each representing a different inhaled drug delivery device, plotted against their respective FPF values (calculated from literature data [60-63] using Copley Scientific Inhalytix® software). Data adapted from work of the author [59] and reproduced with permission.



appropriate. Additionally, the DPI showed the highest alveolar deposition despite possessing the lowest FPF. Depending on the target receptors of the drug, this information could be used by drug formulation developers to identify the device that would likely yield the best drug deposition and therefore produce the greatest therapeutic effect. Similarly, simulations such as these could be used for different particle size distributions to identify an optimal APSD of a formulation for a particular device. By enabling detailed calculation of regional and total deposited doses from standard NGI data, this combined experimental and computational approach could offer drug developers more detailed information to guide formulation and device optimization decisions.

These observations underscore the limitations of FPF as a standalone predictor of *in vivo* drug delivery and may reinforce the value of integrating computational modeling in formulation and device development. Furthermore, model data can offer an enhanced prediction of *in vivo* drug delivery compared to single-term metrics. Such simulations could therefore be used early to aid drug development in selecting devices for delivery and identify the best aerosol compositions or APSDs to move forward for further development.

It should be noted that losses in the NGI induction port (IP) are not accounted for in this model. As a result, extrathoracic and total lung deposition are underestimated. This is especially true for the pMDI device, which emits the aerosol plume most rapidly among the devices, causing a large proportion of this ballistic fraction to deposit in the IP. Additionally, some particles produced by the pMDI are so small they lack sufficient inertia to deposit and are consequently exhaled. Together, these factors can explain the pMDI's low total lung deposition despite having the smallest APSD.

The absence of IP deposition also accounts for why the FPFs of the SMI and DPI differ, despite having similar APSDs: significant particle deposition can occur in the IP for the DPI due to higher velocity during testing, whereas SMIs tend to produce slower-moving particles that largely bypass the IP. Nevertheless, this limitation does not diminish the key finding that combining NGI impactor data with *in silico* lung modeling can offer greater and more mechanistic insights than FPF alone.

Both the NGI and pulmonary deposition simulations show how linking impactor data with physiologically realistic deposition modeling can accelerate design decisions and reduce the risk of late-stage formulation failure. A particularly important extension of this modeling would be its integration with PK and PD simulations. By predicting where in the lung a drug is likely to deposit, and in what proportion, these models could help bridge the gap between formulation design and therapeutic effect. This could support more informed decisions around dose selection, device design and delivery strategy, while reducing reliance on extensive early-stage animal or clinical studies.

Like the *in silico* models discussed earlier, these models have limitations. The accuracy of *in silico* predictions depends heavily on the quality of input data; formulation properties, particle size distribution, breathing profiles and anatomical detail must all be accurately captured; and oversimplified or low-resolution inputs can yield misleading results. While regulatory bodies are beginning to acknowledge the value of these models, wider acceptance will require robust validation against *in vivo* or clinical data [9]. In addition, the technical complexity of these simulations may be a barrier for some development teams, particularly those without access to specialized expertise or computing infrastructure.

Conclusions

From fluid dynamics and propellant evaporation to PK and regional lung deposition simulations, *in silico* models can help reveal the complex interplay of formulation, device and patient physiology. These approaches could therefore assist in decreasing reliance on trial-and-error experimentation and support faster, more targeted development while reducing the risk of failure in later stages. When combined with experimental techniques and AI, *in silico* models could help provide a more efficient, evidence-based route to designing inhaled therapies to be clinically effective as well as commercially and environmentally sustainable.

Despite remaining challenges in areas such as data quality, model validation and regulatory alignment, *in silico* pulmonary deposition models are becoming an integral part of inhalation product development. Ongoing improvements in computational capability, imaging resolution and modeling standards are helping broaden their use across the pharmaceutical industry. Rather than replacing traditional performance metrics, these models can enhance them by offering new layers of insight that can help bring formulation science closer to clinical reality. Furthermore, by assisting researchers in exploring the link between formulation properties and therapeutic outcomes, these tools can support the development of more effective, targeted inhaled therapies. As the field moves increasingly towards precision medicine, *in silico* modeling could offer a means of predicting patient-specific outcomes, with the goal of improving the efficiency, safety and clinical success of inhaled treatments.

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