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Journal of Pulmonary Medicine and Respiratory Care

Research Article

Do You Really Need a 10-Second Breath-Hold? Unraveling the Quest for Optimal Drug Deposition with the QVAR Device using the Quasi-3D Whole Lung Model for Healthy Adults

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Received: 29 September 2023; Accepted: 09 October 2023; Published: 13 October 2023

Citation of this article: Kannan, R. (2023) Do You Really Need a 10-Second Breath-Hold? Unraveling the Quest for Optimal Drug Deposition with the QVAR Device using the Quasi-3D Whole Lung Model for Healthy Adults. J Pulm Med Respir Care, 5(1): 13-22.

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Abstract

Aims: In the realm of oral medication delivery through metered dose inhalers (MDIs) like QVAR, this study investigates the influence of breath-holding on lung penetration and deep lung deposition. Advanced deposition simulations using the Quasi-3D whole lung model form the core of our analysis.

Methods: The Quasi-3D whole lung model, constructed from CT scan data of healthy individuals, is utilized to perform deposition simulations. These simulations are meticulously validated against experimental QVAR data, ensuring accuracy in the analysis of drug delivery efficiency.

Results: Our study reveals three vital findings. Firstly, within breath-hold durations of 1-2.78 and 1-8.3 seconds, the Central: Peripheral (C:P) ratio and respiratory generation (beyond the 15th airway) deposition fraction significantly improve. The C:P ratio rises from 1.5597 to 1.6858, while the deposition fraction increases from 26.0435% to 39.7854%, indicating enhanced deep lung deposition. Secondly, extending the breath-hold to 10 seconds yields minimal impact, with metrics increasing < 5%, suggesting diminishing returns. Lastly, a critical breath-hold of around 8.3 seconds achieves 95% of the peak drug dosage, enhancing patient comfort and adherence.

Conclusion: Contrary to conventional wisdom, our research challenges the necessity of the currently recommended 10-second breath-hold duration for optimal QVAR drug delivery. Furthermore, our simulations indicate that the respiratory

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generation deposition fraction serves as a more informative indicator of regional deposition than the C:P ratio. These insights hold significant potential for enhancing patient comfort and adherence to inhaler therapy regimens, fostering a more patient-centered approach to oral medication delivery via MDIs.

Keywords: Oral medication, Metered dose inhaler (MDI), QVAR, Lung deposition, Breath-holding, Quasi-3D whole lung model, Drug penetration metrics, Patient comfort, Treatment adherence

Introduction

Metered dose inhalers (MDIs) are fundamental in delivering inhaled medications, playing a crucial role in the management of respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD). Achieving optimal drug deposition and penetration into the deeper lung regions is pivotal for the therapeutic efficacy of MDIs. QVAR, an MDI formulation delivering beclomethasone dipropionate, is widely used in respiratory therapy [1-3]. Beclomethasone dipropionate (BDP) has been reconfigured using a chlorofluorocarbon-free propellant known as hydrofluoroalkane-134a beclomethasone dipropionate (HFA-BDP), as seen in the QVAR inhaler (developed by 3M Pharmaceuticals in St. Paul, MN) [2]. In this particular formulation, BDP is in solution (with ~40% of the dosage mass having droplet sizes < 1 μm diameter [4]), thereby resulting in an improved deep lung penetration [1,5]. One traditional approach to enhance deep lung deposition from the QVAR device is through pre-exhalation breath-holding [4]. This maneuver extends the time for drug particles to settle within the airways, increasing their chances of reaching the desired lung regions. While Leach, et al. [4] provided the amount of drug exhaled after a breath-hold of 1 and 10 seconds, the temporal variation of hard-to-obtain deposition metrics like (1) the deposition fraction in the respiratory region (beyond airway generation 15), (2) the Central: Peripheral (C:P) ratio are still unknown. The optimal breath-hold time, for maximizing the above metrics, while retaining a certain degree of patient comfort (by not allowing the patient to not have a long breath-hold duration) has not been discussed by researchers.

The impetus driving this investigation is the pursuit of computational solutions to address the challenges outlined in the preceding paragraph. Accordingly, this study leverages the recently developed Quasi-3D (Q3D) whole lung framework [6,7] to assess regional lung depositions of the HFA-BDP drug delivered through the QVAR device for healthy adults. The construction of the healthy lung model was facilitated through the retrospective acquisition of CT scan data. Five distinct variants of drug delivery in healthy subjects were simulated, corresponding to experimentally derived PSDs. The consistency between the simulated deposition metrics and existing experimental data was exceptionally robust, with the simulated C:P ratio, exhalation ratio, and mouth deposition fraction closely aligning with multiple experimental measurements conducted at two distinct breath-hold durations. Further simulations yielded three pivotal observations: (1) Within the 1-2.78 and 1-8.3 second breath-hold duration range, both the C:P ratio and the deposition fraction beyond the 15th airway generation exhibited significant increases respectively, indicating a notable enhancement in deep lung deposition within this time frame. 95% of the peak deposition metrics were attained at these critical breath-hold durations. This suggests that 8.3 seconds is an adequate duration to reach 95% of the therapeutic drug dosage. (2) Thus, extending the breath-hold duration beyond these critical breath-hold duration yielded only marginal additional improvements in these deposition metrics. (3) This demonstrates that the deposition fraction within the respiratory generation, as opposed to the commonly employed C:P ratio, acts as the determining factor influencing optimal breath-hold conditions.

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These observations challenge conventional wisdom regarding the necessity of a 10-second breath-hold for optimizing drug delivery via the QVAR device. Furthermore, our study questions the suitability of the C:P ratio as the primary metric for quantifying deep lung deposition, as discussed in subsequent sections. These insights suggest that an extended breath-hold may not be obligatory for achieving optimal drug delivery efficiency, and we delve further into these findings in the following sections. These results have significant implications for enhancing patient comfort and adherence to inhaler therapy regimens, highlighting the potential for a more patient-centric and device-centric approach to oral inhalation delivery through metered dose inhalers (MDIs).

Materials and Methods

The Quasi-3D (Q3D) whole lung model

In this program, the spatio temporal lung deposition profile was simulated using the Q3D whole lung model. The Zygote geometry data (STL file) was used to create this whole lung model [17]. Most known lung models typically contain the geometry of only the first 6-9/3-4 branch generations at-best/average, respectively. Recently Kannan, et al. [6,7] developed a first of its kind – a full 24 generation lung model of an adult male human. This adult lung model was created from the zygote STL [17]. In this section, we will summarize the process for (i) using the CT scan imaging data to extend the Q3D lung till the end of the tracheobronchial (TB) limit (i.e., 15 generations), and (ii) constructing "sac-trumpet" like control volumes at the end of the TB exits to mimic the alveoli. The detailed procedure is provided in the earlier publication of Kannan, et al. [6]. As the first step, the truncated Q3D lung was extended to the end of the TB limit. The lung lobes provide the outer boundary, for the extension process. Figure 1 shows the lung lobes, enclosing the original truncated Zygote Q3D lung enclosed in the lung lobes. We then (i) adapted the algorithm of Karch, et al. [8] to extend the current Q3D airways, to the end of the TB limit and (ii) implemented sac-trumpet-like control volumes, at each of the TB outlets. Figure 2a shows the lung extended to the TB limit. The final step is the insertion of alveolar "trumpet-sac" control volumes, at each of the TB outlets. Figure 2b shows the complete Q3D lung, i.e., after the insertion of the trumpet-sac control volumes. This was described in detail in our recently published study for adults [6], including the algorithm to penetrate to the end of the TB limit (determined by the lobe geometry) and the construction of alveolar trumpet-sacs. The dimensional metrics are as follows: (i) the whole lung Q3D model has a Functional Residual Capacity (FRC) of 2611 ml, (ii) the constructed model has a TB FRC of 165 ml. The whole lung Q3D model was generated to match the measured FRC and TB-FRC (155 ml [9]).

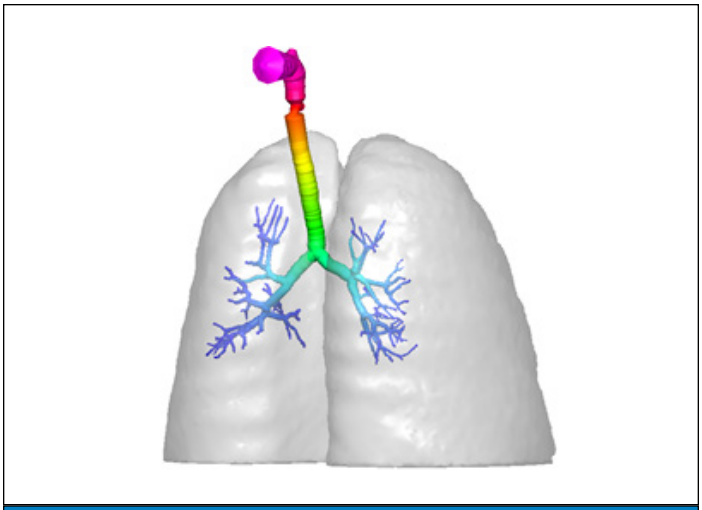

Figure 1: The original truncated Zygote Q3D lung, enclosed in the lung lobes

Inhalation inputs for the model

To the best of our knowledge, there is no inhalation flowrate profile (flowrate as a function of time) for the QVAR device. Hence, in this work, we reconstructed the flowrate using available metrics for QVAR: (1) an inspiratory time of 3 seconds [10,11], (2) a peak inspiratory flow of 2800 +/- 690 ml/s, (3) time to actuate = 0.417 +/-0.234 seconds. Hence, we were able to adapt the inhalation profile of Taylor et al [12] to attain an inspiratory time of 3 seconds, a peak inhalation flowrate of 2236 ml/s. The actuation started at 0.417 seconds and continued for 0.215 seconds [14]. An actuation velocity of 5 m/s was used [13] in the simulations. After the breath-hold, the inhaled air was exhaled in 3 seconds. The inhalation flowprofile is presented in Figure 3.

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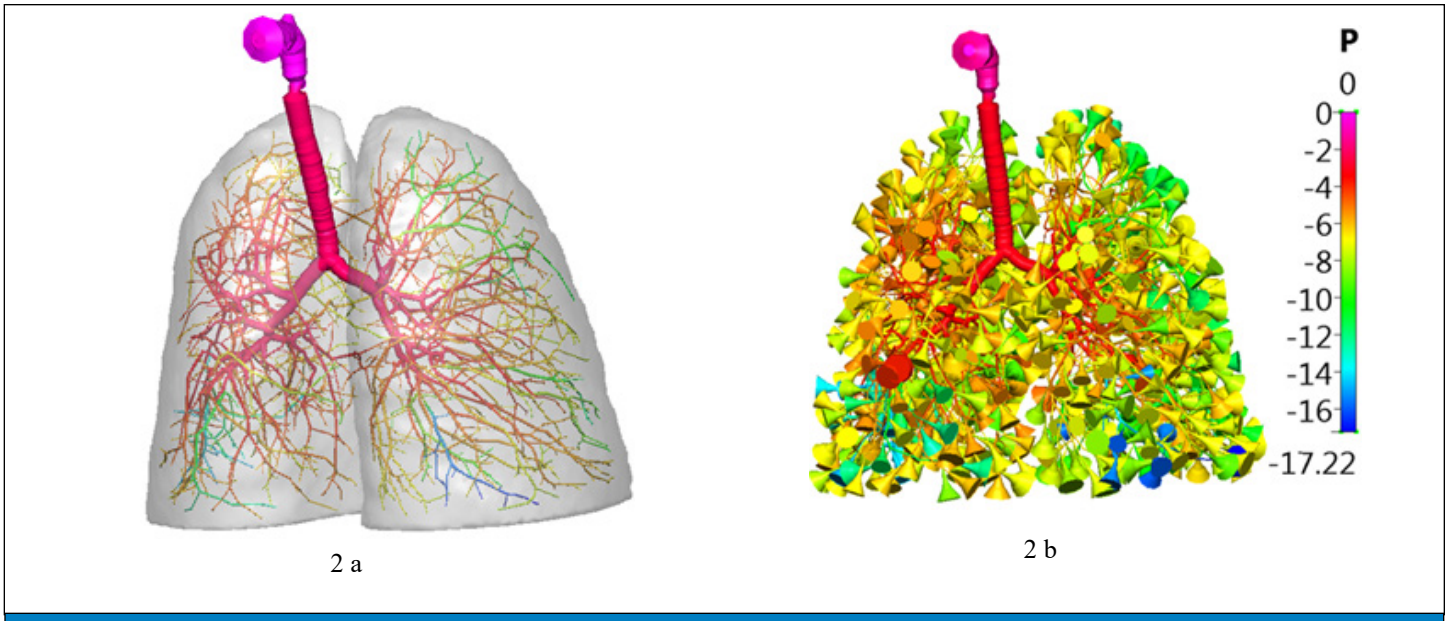
Particle size distribution (PSD) for the model

Five stage-wise distribution measurements from QVAR were reported by Leach, et al. [4]. Table 1 provides these stage-wise dose depositions.

Results

Model validation

A Comparative Assessment of Deposition Metrics against Experimental Measurements at 1-Second and 10-Second Breath-Hold Duration. In this section, we present the results of our deposition simulations, expressed as deposition fractions relative to the dose administered at the mouth (without a spacer), for two distinct breath-hold durations: 1 second and 10 seconds. Table 2 summarizes key deposition metrics, including the exhalation fraction, mouth deposition fraction, Central:Peripheral (C:P) ratio, and the deposition fraction in the respiratory region, as computed using the Quasi-3D (Q3D) whole lung model with the healthy lung



2 a 2 b

Figure 2: The Zygote tracheobronchial Q3D lung. Case (a): Extended to the TB limit. Case (b): The Zygote whole lung (mouth + TB + sac-trumpet Q3D lung) model. The entire whole lung, coloured by pressure, for an inhalation flowrate of 5 L/min.

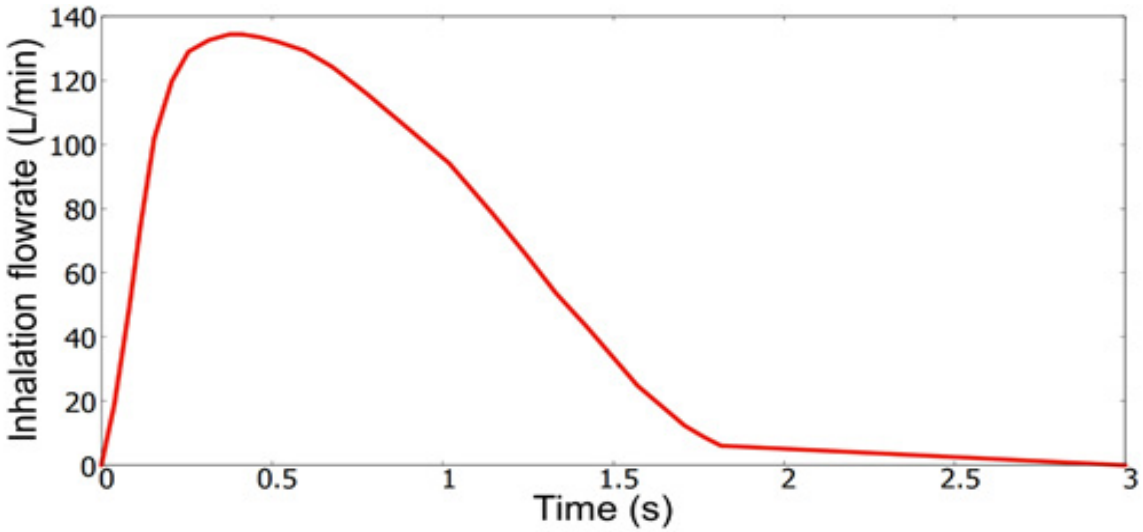


Figure 3: The inhalation profile, used for the simulation of the QVAR device.

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configuration. We juxtapose these simulation results against corresponding experimental measurements obtained from the work of Leach, et al. [4,11,15]. The main observations are as follows:

Agreement in exhalation and mouth deposition fractions

In general, our simulations exhibit an excellent agreement with the experimental results reported by Leach, et al. [4] particularly noteworthy is the close correspondence observed in both the exhalation fraction and mouth deposition ratios.

C:P Ratio Comparison

It is worth noting that, as of the current literature, there are no available experimental measurements for the Central:Peripheral (C:P) ratio in healthy subjects using the QVAR device. Therefore, we have chosen to compare our calculated C:P ratios for the 10-second breath-hold scenario with those obtained from (a) mildly asthmatic subjects as reported by Leach, et al. [15] and (b) healthy subjects who were given a mix of beclomethasone dipropionate (BDP)/formoterol (100/6 μg) [16]. Notably, our simulated C:P ratio for the 10-second breath-hold duration appears to exhibit a lower value in comparison to the measurements observed in asthmatic subjects by Leach, et al [15]: which is physiologically consistent due to higher depositions occurring in asthmatic lungs. Simultaneously, it falls well within the bounds of the BDP/Formoterol study [16]. This alignment between our simulations and available data from asthmatic subjects, along with consistency with a study involving BDP/Formoterol administration, augments our confidence in the reliability and robustness of our computational simulations.

Significance of respiratory region deposition

An essential metric of interest is the deposition fraction within the respiratory generations. This fraction is known to be rapidly absorbed into the bloodstream due to the thin-walled barriers in the respiratory generations. Furthermore, it plays a pivotal role in therapeutic effectiveness for asthma management, particularly in the lower airways where most asthmatic effects occur. Given the impracticality of experimental measurements for this specific metric, our computational model serves as a valuable indicator for distinguishing the deposition fraction at the two distinct breath-hold durations.

Significance of sedimentation

A notable finding emerges from the comparison of the deposition fractions within the respiratory region at 1-second and 10-second breath-hold durations. It becomes evident that gravitational sedimentation plays a pivotal role in driving deposition within these lower airway generations.

Figure 4 illustrates the complete Q3D lung model, with color-coding indicating the deposited drug fractions for a breath-hold of 10 seconds. The visualization includes scenarios for the largest droplet size (10 μm diameter), smallest droplet size (0.4 μm diameter), and the entire spectrum of droplet sizes (using a weighted average from the APSD1 profile). The drug dose administered at the mouth is normalized to 1.0. The main observations include: As anticipated, a significant portion of the drug is deposited in the mouth region for the largest droplet size. Intriguingly, we observe a substantial fraction deposited in the larynx region for the largest droplet sizes and for the entire spectrum of droplet sizes, with in the latter accounting for approximately 15% of the total deposition, as evident in Figure 4c. This notable accumulation within the larynx area implies the potential occurrence of localized side effects, such as hoarseness of the voice (dysphonia), which can be attributed to the action of the steroid inhaler on the larynx. Conversely, in the case of the smallest droplet size, a majority of the deposited droplets can be found in the terminal generation (generation-24). This concentration results from minimal deposition in the mouth or upper airways, primarily due to the negligible impaction, sedimentation, or diffusion processes occurring in these regions. Instead, the deposition at generation-24 primarily occurs through sedimentation.

In summary, this comparative analysis bridges our simulation results with experimental data, demonstrating strong alignment in critical deposition metrics. Moreover, our model's ability to differentiate deposition fractions in the respiratory region provides valuable insights into the potential therapeutic benefits of opti-

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Table 1: Stagewise deposition fraction (%) measured by the impactor for QVAR device (Leach et al [4]).

Stage	APSD1	APSD2	APSD3	APSD4	APSD5
S00 (S0 and earlier)	50.2446	49.80638	50.18214	49.9529	50.11048
S1	0.438836	0.661676	0.795763	0.351694	0.485537
S2	0.27608	0.350537	0.38794	0.351694	0.388903
S3	0.49802	0.795021	0.944063	1.206432	1.243742
S4	3.272258	4.943531	5.504273	7.26392	7.339118
S5	16.69957	19.01883	17.21993	19.93633	19.90154
S6	13.92534	12.42567	12.21483	10.7572	10.23814
S7	7.378132	6.610343	6.727744	5.368632	5.406438
Filter paper	7.267162	5.388014	6.023321	4.811195	4.886101

Table 2: Deposition metrics at 1 and 10 seconds of breath-hold for the QVAR device. Format for the simulations: average [minimum-maximum].

	Simulation	Measurement	Simulation	Measurement
Breath-hold time(s)	1		10	
Exhalation ratio (%)	27.0955[25.4128 -29.4902]	29 ± 13 (Leach et al [4])	13.3639[12.0473 -15.2476]	11 ± 4 (Leach et al [4]), 13.11 ± 5 (Leach et al [11]),
Mouth deposition (%)	34.3066 [34.1037-34.4611]	26 ± 12 (Leach et al [4])	33.2061 [33.0394-33.3505]	29 ± 20 (Leach et al [4]), 34.6 ± 15.84 (Leach et al [11]),
C:P ratio	1.6858 [1.6701-1.7067]		1.5597[1.5543-1.5652]	1.6 ± 0.8 (Leach et al [15]), 1.42 ± 0.32 (De Backer et al [16])
Respiratory generation deposition (%)	26.0435[24.2918-27.2852]		39.7854[38.5417-40.7861]	

mizing breath-hold durations for QVAR device users, as discussed in the next subsection.

Optimal Breath-Hold Duration for 95% Peak Deposition Metrics with the QVAR Device

Our simulations yield a crucial insight: achieving peak deposition performance with the QVAR device does not necessitate a 10-second breath-hold. In fact, our findings suggest that a breath-hold duration of just 2.78 and 8.3 seconds is sufficient to attain 95% efficiency of the peak Central:Peripheral (C:P) ratio and deposition fraction in the respiratory generations respectively. In these

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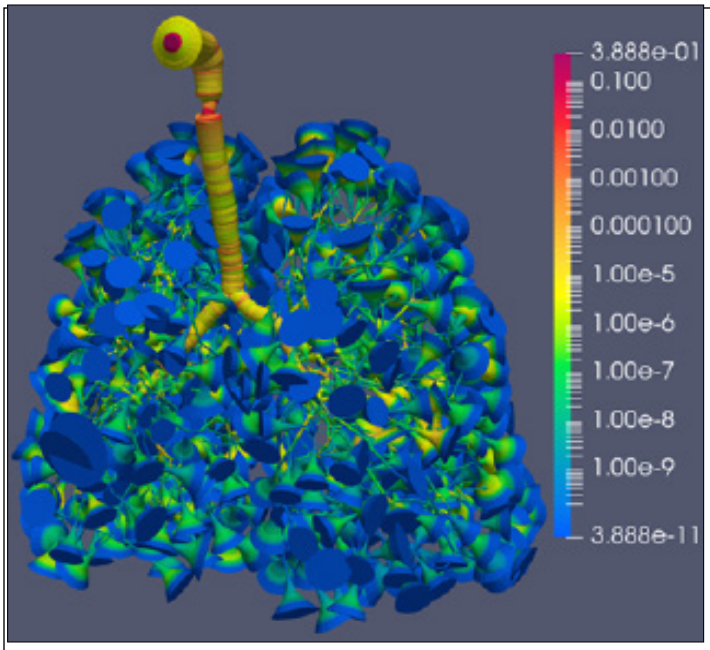
critical breath-hold durations, the average C:P ratio was 1.6377 and the average respiratory generation deposition fraction was 37.7961% (averaged over the five APSD datasets) respectively. This significant reduction (17%) in the required breath-hold time not only enhances patient comfort but also ensures the delivery of a therapeutic dosage of the QVAR drug. The analyses presented above also suggest that the deposition fraction within the respiratory generation is a more reliable metric for assessing deep lung deposition compared to the C:P ratio. The C:P ratio is determined through the projection of regional depositions onto a 2D plane, resulting in minimal variation over time, with values shifting only slightly from 1.5597 to 1.6858 over the 9-second breath-hold pro-



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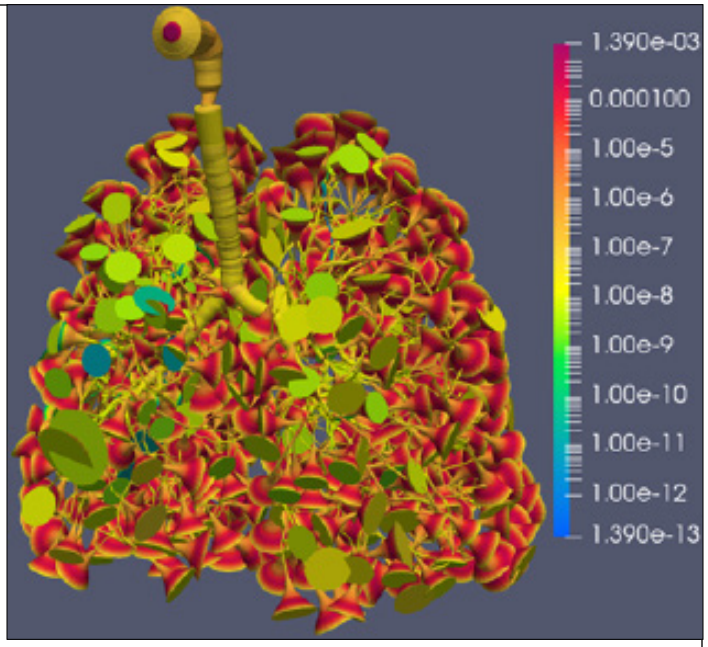

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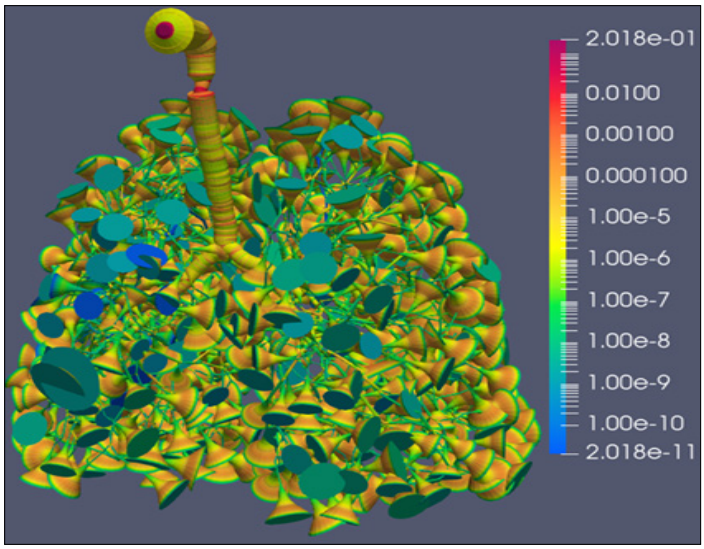

4c

Figure 4: The depositions from the QVAR device on the Q3D whole lung for a breath-hold of 10 seconds. Case (a): For the largest droplets, Case (b): for the smallest droplets, Case (c): for the entire spectrum of droplet sizes (using a weighted average from the APSD1 profile). The drug dose entering the mouth is normalized to 1.0.

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cedure. Consequently, placing sole reliance on the C:P ratio might lead to an underestimation of both deposition timing and the deep lung deposition fraction. This discovery carries profound implications for inhaler therapy, streamlining the process and potentially improving treatment adherence. By optimizing the breath-hold duration, we can strike a balance between efficacy and patient comfort, ultimately enhancing the overall inhalation experience.

Discussions and conclusions

In this comprehensive study, we embarked on a journey to harness the power of the Q3D whole lung modeling to elucidate and optimize the drug delivery efficiency of the QVAR metered dose inhaler (MDI) for the benefit of respiratory therapy. Our investigation spanned the domains of deposition simulations, comparative analysis with experimental data, and the determination of critical breath-hold duration for peak deposition metrics. The culmination of these efforts has yielded valuable insights and transformative implications for the field of inhaler therapy.

Validation and comparative analysis

Through meticulous validation of our Q3D whole lung model, we rigorously compared deposition metrics obtained through simulations with experimental measurements for different breath-hold durations. This multifaceted approach provided us with a high degree of confidence in the accuracy of our model. Notably, our findings demonstrated remarkable concordance between the simulated and experimental exhalation and mouth deposition fractions. These results underscore the credibility of our computational framework and its ability to faithfully replicate real-world inhaler dynamics.

The quest for optimized breath-hold duration

One of the most compelling outcomes of our study pertains to the determination of the critical breath-hold duration required to achieve 95% of the peak deposition metrics, including the Central:Peripheral (C:P) ratio and deposition fraction in the respiratory generations. Contrary to conventional wisdom, our simulations unveil that a breath-hold duration of around 8.3 seconds is adequate to reach this threshold. This conclusion is rooted in the more stringent respiratory generation deposition metric, as opposed to the C:P metric. This revelation holds substantial promise as it noticeably enhances patient comfort during inhaler use, a factor often implicated in treatment adherence.

Patient-Centered inhaler therapy

The implications of our findings reverberate throughout the landscape of inhaler therapy. By optimizing the breath-hold duration, we not only alleviate patient discomfort but also bolster the likelihood of adherence to prescribed regimens. The patient's experience with inhaler therapy is intrinsically tied to its success, and our research offers a pivotal stride toward a more patient-centered approach. Enhanced comfort fosters cooperation, potentially improving the overall therapeutic outcomes for individuals relying on the QVAR MDI.

Future Directions

Our study opens the door to several promising avenues of future research. Further refinements and validations of our computational model can enhance its accuracy and applicability to a broader patient population. Additionally, investigations into the real-world clinical implications of shorter breath-hold durations, including their impact on drug efficacy and patient outcomes, warrant exploration.

In conclusion, our computational model has not only elucidated the intricacies of QVAR MDI drug delivery but has also revolutionized our approach to inhaler therapy. By redefining the optimal breath-hold duration, we have unlocked the potential for improved patient comfort and adherence while maintaining therapeutic efficacy. As we traverse this evolving landscape of inhaler science, our findings pave the way for a future where patient-centricity and therapeutic excellence coalesces seamlessly, transforming the lives of individuals managing respiratory conditions.

Author Contributions

Sole contribution from Ravi Kannan

Funding

Amneal Pharmaceuticals, Inc. (Partial)

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Institutional Review Board Statement

NA (since this is a 100% computational effort)

Informed Consent Statement

NA (since this is a 100% computational effort)

Data Availability Statement

NA, since all the data have been reported in the paper.

Acknowledgments

None

Conflicts of Interest

None

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