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ORIGINAL RESEARCH

Optimizing Fluticasone Propionate and Ciclesonide pMDI Delivery: The Protective Role of Valved Holding Chambers Against Inhalation Timing Errors

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Introduction: Discoordination between inhalation and pressurized metered-dose inhaler (pMDI) actuation when delivering inhaled corticosteroids (ICS) is a common technique error that can lead to worsened treatment outcomes. Valved holding chambers (VHCs) are thought to improve the delivered dose if inhalation is delayed, but this effect has not been sufficiently quantified.

Methods: The aerodynamic particle size distribution of fluticasone propionate (FP) and ciclesonide (CIC) was studied under three conditions: inhalation initiated before actuation without a VHC, inhalation started at actuation without a VHC, and inhalation started at actuation with a VHC. We used a Next Generation Impactor connected to an anatomical adult throat model and a breathing simulator that produced a single, adult-type inhalation.

Results: We found that when inhalation was initiated simultaneously with actuation, the effective dose delivered decreased markedly for both FP and CIC compared to when inhalation was begun correctly, ie, before actuation. However, when a VHC was used and inhalation was started at actuation, delivered dose improved substantially for both medications. This protective effect of the VHC was especially pronounced for CIC, with both the fraction of particles in the 1–5 µm range and those under 1 µm returning to the same levels as when inhalation was initiated correctly.

Discussion: Although our study was conducted in vitro and did not involve patients, the findings likely have relevance for clinical practice. Therefore, promoting the use of VHCs in both children and adults may be beneficial, but this should be confirmed in clinical studies.

Plain Language Summary: Using inhalers correctly is important for people with asthma. Pressurized metered-dose inhalers (pMDIs) spray medication into the lungs and work best when the user begins to breathe in just before actuating the canister. If the timing is off, less medicine may reach the lungs, which can make asthma harder to control. This study examined how timing between inhalation and actuation affects the delivery of two commonly used asthma medications: fluticasone propionate (FP) and ciclesonide (CIC). Researchers also tested whether using a valved holding chamber (VHC) – a plastic attachment that holds the spray momentarily – can improve drug delivery. VHCs are often recommended to make inhalers easier to use correctly. The results showed that when the inhaler was actuated at the exact start of inhalation, the amount of medication reaching the test system was lower compared to when inhalation started just before actuation. This effect was especially clear without a VHC. When a VHC was used, medication delivery improved and was more consistent, particularly for CIC, which may be more sensitive to poor timing due to its finer particles. In real life, many people do not always use their inhalers with perfect technique. Since only the medication that reaches the lungs can help relieve asthma symptoms, tools like VHCs could play an important role in improving treatment effectiveness. However, this was an in vitro study, not done with real patients. More clinical studies are needed to confirm whether the benefits seen with VHCs in the lab lead to better asthma control in practice.

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Introduction

Asthma is a highly prevalent chronic respiratory disease, affecting approximately 340 million individuals globally.[1] It is characterized by bronchial hyperreactivity, resulting in symptoms such as wheezing, shortness of breath, chest tightness, breathlessness, and coughing, along with variable expiratory airflow limitation. As an inflammatory condition, asthma is treated using inhaled corticosteroids (ICS), with fluticasone propionate (FP) and ciclesonide (CIC) being among the most frequently used options. Globally, most ICSs are administered with pressurized metered-dose inhalers (pMDI).

pMDI containing FP is available as a suspension, a heterogeneous mixture where solid particles are dispersed within a liquid. These particles, typically larger than 1 μm, do not dissolve in the solvent. Suspensions are inherently unstable, with the dispersed particles prone to settling under gravity, a process that can be reversed by shaking. In contrast, pMDI containing CIC is prepared as a stable solution, with drug particles evenly distributed and resistant to settling over time.[2] The mass median aerodynamic diameter (MMAD) of an FP pMDI is significantly larger (2.6 μm) compared to a CIC pMDI (1.0 μm).[3]

Particle size plays a pivotal role in the aerodynamic behavior of aerosols and is a key factor in determining how deep inhaled medications travel in the respiratory tract. Particles within the 1–5 μm range, commonly referred to as the respirable range, are considered optimal for traversing the mouth, pharynx, and larynx to reach the lower airways. It is commonly thought that larger particles, exceeding 5 μm, are more likely to deposit in the upper airways or be swallowed, while smaller particles, below 1 μm, are generally exhaled.[4] However, the notion that sub-1 μm particles do not achieve effective lung deposition has been called into question.[5] Nevertheless, correct aerodynamic particle size distribution (APSD) of an aerosol medication is crucial for ensuring effective drug delivery and therapeutic efficacy.

While pMDIs may be used without a valved holding chamber (VHC), the use of a VHC is recommended for ICS delivery to reduce oropharyngeal deposition and minimize the risk of local side effects, such as dysphonia and oral candidiasis.[6–8] VHCs differ significantly in properties such as material composition, aerodynamic characteristics, valve mechanisms, shape, electrostatic properties, and volume, all of which can impact APSD.[9–11]

The effectiveness of ICS administration relies on proper inhaler technique and incorrect use has been associated with poor asthma outcomes.[12] Nevertheless, errors in inhaler technique are common.[13,14] To optimize the delivery of active substances to the lower airways, patients are advised to begin with a slow, steady inhalation and actuate the inhaler immediately after starting to inhale. However, patients may activate the inhaler simultaneously with or even before beginning inhalation, preventing the adequate flow rate from being achieved before actuation. As many as a quarter of patients have been observed making this mistake.[14]

Earlier in vitro investigations have demonstrated that the interval between pMDI actuation and subsequent inhalation can markedly influence the amount of aerosolised medication delivered when used with VHCs.[15,16] Initiating inhalation at the time of actuation may hinder efficient ICS delivery if a VHC is not used, as there is no space for the plume to disperse, unlike when a VHC is used. To the best of our knowledge, the protective effect of VHCs during inhalation delay has not been sufficiently quantified. This in vitro study aimed to assess how initiating inhalation before actuation affects APSD of FP and CIC, compared to when inhalation is started at actuation. We also sought to determine how the use of a VHC influences APSD of FP and CIC when inhalation is initiated at actuation.

Methods

Data Collection

Instrumentation, Drugs, Sample Collection and Analyses

This study was performed in vitro. The VHCs were connected to an anatomical adult throat model (Adult Alberta Idealised Throat, Copley Scientific Limited, Nottingham, UK) with a silicone adapter. The throat model was followed by the mixing inlet (Copley Scientific Limited, Nottingham, UK) and the cascade impactor system Next Generation Impactor (NGI, Copley Scientific Limited, Nottingham, UK).

The pharmaceutical products studied were FP pMDI (Flixotide Evohaler 125 µg/dos, GlaxoSmithKline Inc., Evreux, France) and CIC pMDI (Alvesco 160 µg/dos, AstraZeneca AB, Södertälje, Sweden). The FP pMDI canister was vigorously shaken prior to each actuation. In each test setup, two doses of the drugs were delivered – each puff actuated individually in coordination with inhalation – and the resulting samples were subsequently collected.

The preparation of the test system included coating the cups of the NGI stages with a fixation solution (40 g glycerol + 10 mL of 15% Brij35 in ethanol) to minimize particle bounce and re-entrainment. The samples were collected from the throat model and all eight stages of the NGI. At NGI flow rate of 45 L/min, the particle diameter cut-off values of various stages were as follows: 9.4 µm, 5.2 µm, 3.3 µm, 1.9 µm, 1.1 µm, 0.7 µm, 0.4 µm, and 0.1 µm (Micro-Orifice Collector, MOC). The NGI stage cut-off diameters were calculated based on the constant flow rate within the NGI with interpolation performed between adjacent stages.

To collect the samples, 30 mL of solvent, 50% ethanol (v/v), was added to the throat model and 15 mL to the NGI cups. The outlets of the throat model were covered, solvent added, and the model was then shaken. The cups were shaken with a gentle rocker (Copley Scientific Limited, Nottingham, UK) after adding the solvent for 15 minutes. After adequate mixing, 1.5 mL of each sample was collected to a vial. The NGI samples were analyzed by high-performance liquid chromatography carried out by Emmace Consulting AB (Lund, Sweden) with the following setup: mobile phase: 96% ethanol/0.1% ammonium acetate 43/57 (vol/vol), pump flow rate: 1.5 mL/min, injection volume: 100 µL, detection wavelength: 226 nm, column: Waters XTerra RP18 3.5 µm, 50×4.6 mm. Validation showed linearity 0.03–32 µg/mL. The limit of quantitation (LOQ) was 0.03 µg/mL.

Inhalation Simulations, Timing of Actuation and Valved Holding Chamber

The APSD of FP and CIC was examined using three different setups: 1) inhalation initiated before actuation without a VHC; 2) inhalation started at actuation without a VHC; and 3) inhalation started at actuation with a VHC. Each test setup was repeated four times. To assess how a VHC affects deposition of a suspension and a solution pMDI (FP and CIC, respectively), the reusable plastic (acrylonitrile butadiene styrene) EasyChamber (TriOn Pharma, Hampshire, United Kingdom) with a chamber volume of 175 mL was used. Three separate VHCs from different manufacturing lots were used to ensure reliability of data. Before and in between the experiments the components of the VHCs were washed and dried according to the manufacturer's instructions. To simulate inhalation initiated before actuation, a constant flow of 30 L/min was used. To simulate delayed inhalation, actuation was initiated at the exact start of inspiration using a breathing simulator (Breathing Simulator BRS 3100, Copley Scientific Limited, Nottingham, UK), which was programmed to represent an adult-type single inhalation. The flow rate reached 30 L/min within 0.5 seconds, followed by a steady flow maintained at 30 L/min for 3.5 seconds.[17] The flow then ceased over the subsequent 0.5 seconds, resulting in a total inhalation duration of 4.5 seconds with a total inhalation volume of 2030 mL.

Statistics

The software IBM SPSS Statistics for Windows, version 27 (IBM Corp, NY, USA), was used for the data analysis. Proportions of the label claim of FP and CIC deposited in the throat model and as particles 1–5 µm and under 1 µm in diameter, delivered with inhalation initiated before actuation without a VHC as well as with inhalation started at actuation both without and with a VHC, were compared using the mean. Confidence intervals of 95% were established. To compare APSD of FP and CIC delivered with inhalation initiated before actuation without a VHC as well as with inhalation started at actuation both without and with a VHC, a general linear model of repeated measures was utilized.

Ethical Statement

Due to the in vitro setting of the study, no ethical approval was required.

Results

Figure 1 illustrates the APSD of FP delivered with inhalation initiated before actuation without a VHC as well as with inhalation started at actuation both without and with a VHC. When inhalation began at actuation, the APSD profiles beyond the throat model had a similar shape. However, without a VHC, overall drug delivery was significantly lower

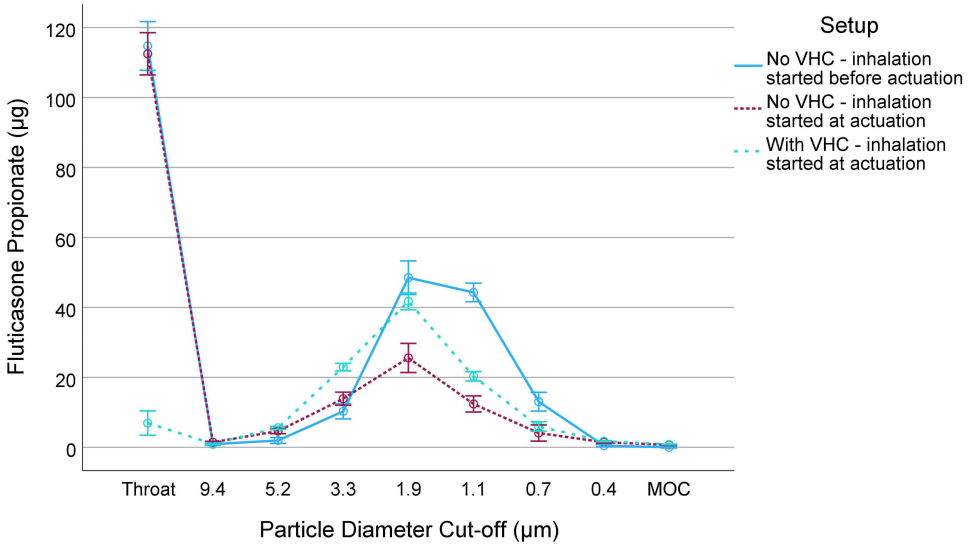

Figure 1 Aerodynamic particle size distribution of fluticasone propionate (250 µg) delivered using three different setups: inhalation initiated before actuation without a valved holding chamber (VHC), inhalation started at actuation without a VHC, and inhalation started at actuation with a VHC. Error bars indicate 95% confidence interval.
Abbreviation: MOC, Micro-Orifice Collector.

than with a VHC. When inhalation was initiated before actuation (without the VHC), particle deposition was slightly more skewed toward smaller particles (Figure 1).

Figure 2 illustrates the APSD of CIC delivered with inhalation initiated before actuation without a VHC as well as with inhalation started at actuation both without and with a VHC. Without considering throat deposition, APSD profile of CIC was almost identical when inhalation started before actuation without a VHC and when a VHC was used with inhalation starting at actuation. However, when no VHC was used and inhalation started at actuation, the APSD changed in both shape and magnitude, leading to a much lower delivered dose and a slight shift toward smaller particles (Figure 2).

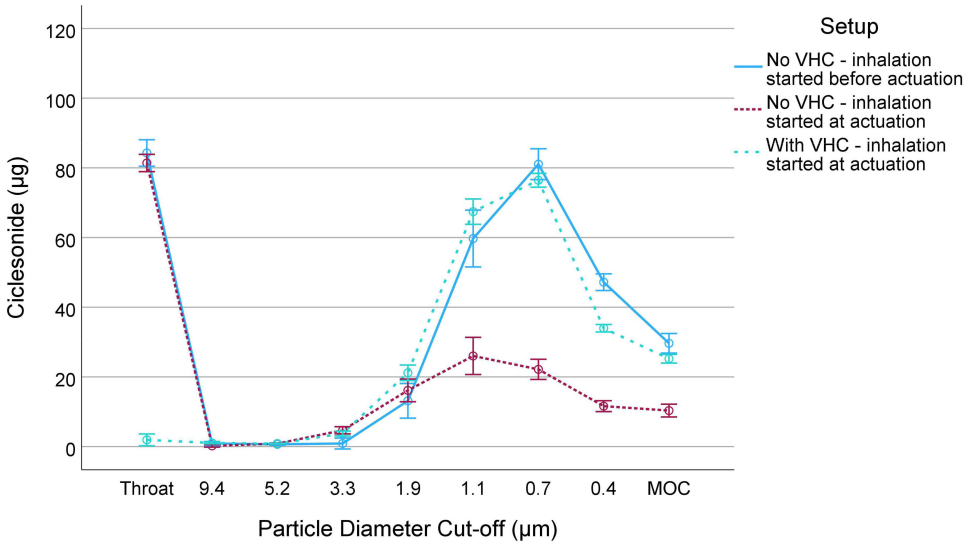

Figure 2 The aerodynamic particle size distribution of ciclesonide (320 µg) delivered using three different setups: inhalation initiated before actuation without a valved holding chamber (VHC), inhalation started at actuation without a VHC, and inhalation started at actuation with a VHC. Error bars indicate 95% confidence interval.
Abbreviation: MOC, Micro-Orifice Collector.

Table 1 Proportions of the Label Claim Deposited in the Throat Model and in the Next Generation Impactor as Particles 1–5 μm and Under 1 μm in Diameter, Delivered Using Three Different Setups: Inhalation Initiated Before Actuation without a Valved Holding Chamber (VHC), Inhalation Started at Actuation without a VHC, and Inhalation Started at Actuation with a VHC

	Throat Model	Next Generation Impactor	
	% of Label Claim (95% CI)	Particles 1–5 μm % of Label Claim (95% CI)	Particles < 1 μm % of Label Claim (95% CI)
Fluticasone propionate (2 × 125 μg = 250 μg)			
No VHC – inhalation started before actuation	45.9 (40.7–51.1)	42.3 (40.1–44.6)	2.1 (0.0–4.5)
No VHC – inhalation started at actuation	45.0 (37.3–52.7)	20.6 (17.4–23.8)	2.2 (1.6–2.8)
With VHC – inhalation started at actuation	2.8 (2.4–3.1)	33.7 (31.7–35.7)	3.0 (2.8–3.2)
Ciclesonide (2 × 160 μg = 320 μg)			
No VHC – inhalation started before actuation	26.3 (19.4–33.2)	36.8 (31.2–42.5)	35.6 (28.7–42.5)
No VHC – inhalation started at actuation	25.4 (24.5–26.4)	15.3 (14.4–16.2)	12.3 (11.5–13.1)
With VHC – inhalation started at actuation	0.6 (0.5–0.7)	31.9 (30.3–33.5)	39.2 (37.7–40.7)

Abbreviations: VHC, Valved Holding Chamber; CI, confidence interval.

Table 1 presents the percentage of the label claim deposited in the throat model and as particles in the 1–5 μm and under 1 μm diameter ranges, delivered with inhalation initiated before actuation without a VHC as well as with inhalation started at actuation both without and with a VHC. The timing of inhalation relative to pMDI actuation did not affect throat deposition of FP or CIC; however, with the VHC, throat deposition was reduced to only a few percent of the label claim for both. Deposition of particles 1–5 μm was lowest for both medications when inhalation was initiated concurrently with actuation without a VHC. The VHC markedly improved the deposition of particles 1–5 μm for both medications, with the effect being especially pronounced for CIC. The proportion of particles under 1 μm for FP was only a few percent of the label claim and increased only slightly with the use of a VHC while remaining unaffected by inhalation timing. In contrast, for CIC, deposition of particles under 1 μm was lower when inhalation was initiated concurrently with actuation and no VHC was used but markedly improved when a VHC was utilized and when inhalation was initiated before actuation (Table 1).

The mass MMAD and geometric standard deviation (GSD), representing the measures of central tendency and spread, respectively, are presented in Table 2.

Table 2 Mass Median Aerodynamic Diameter (MMAD) and Geometric Standard Deviation (GSD) of Fluticasone Propionate and Ciclesonide Obtained from the Next Generation Impactor Using Three Different Setups: Inhalation Initiated Before Actuation without a Valved Holding Chamber (VHC), Inhalation Started at Actuation without a VHC, and Inhalation Started at Actuation with a VHC. Values are Mean ± Standard Deviation (SD)

Drug and Setup	MMAD (μm)	GSD
Fluticasone propionate (2 × 125 μg = 250 μg)		
No VHC – inhalation started before actuation	2.31±0.12	1.55±0.06
No VHC – inhalation started at actuation	2.44±0.03	1.82±0.06
With VHC – inhalation started at actuation	2.45±0.06	1.76±0.04
Ciclesonide (2 × 160 μg = 320 μg)		
No VHC – inhalation started before actuation	1.02±0.03	1.70±0.03
No VHC – inhalation started at actuation	1.12±0.01	2.11±0.02
With VHC – inhalation started at actuation	0.93±0.02	1.76±0.02

Abbreviations: VHC, Valved Holding Chamber; MMAD, Mass Median Aerodynamic Diameter; GSD, Geometric Standard Deviation.

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Discussion

In this in vitro investigation, we found that when inhalation is initiated simultaneously with actuation, the effective dose delivered decreased markedly for both FP and CIC compared to when inhalation was begun correctly, ie, before actuation. However, when a VHC was used and inhalation was started at actuation, delivered dose improved substantially for both medications. This protective effect of the VHC was especially pronounced for CIC, with both the fraction of particles in the 1–5 µm range and those under 1 µm returning to the same levels as when inhalation was initiated correctly.

We hypothesize that when the pMDI is actuated at 0 seconds, or before inhalation, corresponding to a flow rate of 0 L/min at the inlet, the emitted dose lacks sufficient airflow to transport it through the inlet, causing it to stagnate or rebound. This results in a loss of formulation into the surrounding air, which can sometimes be observed as a visible cloud of formulation escaping from the top of the device. In contrast, when the pMDI is actuated into a spacer at 0 L/min flow, the aerosol is captured within the spacer chamber. As airflow increases, this dose is subsequently delivered into the NGI, improving mass balance and dose delivery efficiency.

For FP, the use of a VHC significantly improved the deposition of 1–5 µm particles when the inhalation started at actuation, although still not reaching the level when inhalation was initiated before actuation. In contrast, for CIC, the VHC improved deposition of 1–5 µm particles to a level comparable to that achieved with correctly coordinated inhalation, as indicated by the overlapping 95% confidence intervals (Table 1). A comparison of Figures 1 and 2 reveals that within the 1–5 µm range, the mass of CIC particles was on average more concentrated toward smaller particles compared to FP. This difference in particle size may explain why the VHC provided greater protection for CIC against inhalation and actuation discoordination. This is further supported by previous findings showing that the MMAD of FP pMDI is larger than that of CIC pMDI.[3]

Only a few percent of the label claim for FP were deposited as particles smaller than 1 µm, and the inhalation delay appeared to have no clear effect on these. However, the 95% confidence interval for the mean of measurements with inhalation initiated before actuation was too wide to draw a definitive conclusion about its effect (Table 1). The use of a VHC slightly improved the deposition of FP particles under 1 µm. In contrast, for CIC, the deposition of sub-1 µm particles improved substantially with both the use of a VHC and the early initiation of inhalation. We believe that this is also related to the average particle size within the sub-1 µm particle range, which differed between FP and CIC. Specifically, within the sub-1 µm range, CIC particles were, on average, smaller than FP particles, as illustrated in Figures 1 and 2.

Previous studies have highlighted the impact of delayed inhalation on drug delivery efficiency when using pMDIs with VHCs. For example, Berlinski and Pennington reported that a 10-second delay following actuation led to a significant reduction (between 27% and 42%) in the fine particle fraction of albuterol across several VHC devices.[15] Similarly, Chambers et al found that certain VHC designs, particularly those with smaller volumes or lacking valves, were more prone to dose loss when a delay was introduced during use of a budesonide–formoterol combination inhaler.[16] Although these studies offer important evidence on the role of timing and chamber design, their methodologies differed from ours in several ways. Notably, they did not include physiologically realistic throat models or incorporate breathing profiles that reflect actual patient inhalation patterns. Furthermore, solution-based inhaled corticosteroids and direct comparisons between solution and suspension formulations were not examined, limiting their relevance to the full range of available ICS therapies.

Although recommendations state that ICS delivery from pMDIs should ideally be performed with a VHC, this guidance is often overlooked.[6] It has also been suggested that the delivery of drugs with small MMADs, such as CIC pMDI, may be reliably achieved even without a VHC if the inhalation technique is correct.[18] However, studies indicate that up to 25% of adults use incorrect inhalation timing.[14] It is also important to note that the commonly recommended inhalation time of 3–5 seconds is already long and challenging, so asking patients to extend it further just to avoid using a VHC is not practical. If inhalation begins too early, there may not be enough time to fully inhale the medication, as the lungs will already be full. This could also introduce additional technique-related issues for certain patients, such as those

with obstructive pulmonary disease, neuromuscular disorders and the elderly. Given these factors, can we truly claim that the use of a VHC is unnecessary?

We employed the NGI cascade impactor, a widely used pharmaceutical tool for characterising aerosol particle size distribution. The MMAD and GSD values obtained in our study align with previously reported data for both FP and CIC delivered by pMDI.[3,19] We noted that CIC's GSD increased slightly in the setup where inhalation started at actuation without using a VHC (GSD = 2.11), suggesting a broader particle distribution under less optimal timing conditions. Importantly, the low standard deviations across all replicates reflect good reproducibility.

The use of an anatomical throat model enabled a more precise simulation of airway conditions, facilitating accurate throat deposition estimation. The integration of a breathing simulator further enhanced the realism of our setup by closely mimicking real inhalation conditions. The EasyChamber VHC was selected based on its reliable performance in our previous studies, which enabled us to accurately assess the effects of VHCs under ideal conditions. A significant advantage of our in vitro approach was the ability to control for variables that could confound results in in vivo studies, allowing us to focus solely on the variables of interest.

We used an adult throat model, which may not accurately reflect the conditions of a child's throat. Likewise, the breathing pattern used in our experiments was representative of adult breathing and may not mirror pediatric breathing patterns. Therefore, our findings may not be directly applicable to children. Additionally, since we only tested one VHC and two medications, the results may not be fully generalizable to other devices or drugs. A broader limitation of in vitro studies is their inability to fully replicate the complexity of human organ systems and physiological environments.

In conclusion, initiating inhalation simultaneously with pMDI actuation, a common mistake in real life, reduces the delivered dose of FP and CIC compared to when inhalation is started before actuation. The use of a VHC effectively mitigates this issue, ensuring a higher and more consistent medication dose is delivered, even when actuation timing is suboptimal. This effect was especially pronounced for CIC pMDI, which has a smaller MMAD and may be more sensitive to variations in inhalation technique. Given that correct inhaler use is often challenging in everyday practice and only the medication that actually reaches the lungs can help, it is important to encourage the use of valved holding chambers (VHCs) not just for children but also for adults.

While our results provide mechanistic insight into how inhalation timing and device configuration influence aerosol delivery, they are based on laboratory simulations and do not directly reflect clinical outcomes. Therefore, larger real-world clinical studies are needed to confirm whether the improved drug delivery observed with VHC use in vitro translates into better asthma control, adherence, and health outcomes in diverse patient populations.

Abbreviations

APSD, Aerodynamic Particle Size Distribution; CIC, Ciclesonide; FP, Fluticasone Propionate; ICS, Inhaled Corticosteroid; MMAD, Mass Median Aerodynamic Diameter; NGI, Next Generation Impactor; pMDI, Pressurized Meter-Dosed Inhaler; VHC, Valved Holding Chamber.

Data Sharing Statement

Data collected for the study, along with a data dictionary defining each field in the set, will be made available following publication, pending approval of a proposal and a signed data access agreement. All data requests should be submitted to the corresponding author for consideration.

Generative Artificial Intelligence

AI technology (ChatGTP) was utilized solely for grammar and language refinement in this submission. No AI was used for data analysis, content generation, or research interpretation. The purpose of AI involvement was to ensure clarity and grammatical accuracy while maintaining the original meaning and integrity of the work.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

Professor Lauri Lehtimäki reports personal fees from ALK, AstraZeneca, Berlin Chemie, Boehringer Ingelheim, Chiesi, GSK, Menarini, Novartis, Orion, Sanofi, outside the submitted work. The authors declare no other competing interests related to the manuscript content.

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