The effects of inhaler type and orientation at inhalation on dosing efficiency—a study of the SMI, pMDI and DPI

An investigation of factors to consider when choosing inhalers to optimize disease control—dose delivery to the lungs and inhaler robustness to misuse

Sabrina Strohe, BSc[a]; Herbert Wachtel, PhD[b]; Rachel Emerson-Stadler, MSc[b] and Omar S. Usmani, MBBS, PhD, FHEA, FRCP, FERS[c]
[a]Hochschule Darmstadt, University of Applied Sciences
[b]Boehringer Ingelheim
[c]National Heart and Lung Institute (NHLI), Imperial College London

Abstract

This *ex vivo* study was designed to compare the dosing efficiency of different inhaler devices (soft mist inhaler [SMI], pressurized metered dose inhaler [pMDI] and dry powder inhaler [DPI]) and investigate their robustness to inhaler orientation. Stiolto® Respimat® SMI, Trimbow® pMDI, Fostair NEXThaler® DPI and Trelegy Ellipta® DPI were each tested using the Alberta Idealized Throat model, with realistic inhalation patterns for very severe chronic obstructive pulmonary disease generated by a lung simulator. The *in vitro* distribution of dose to the mouth/oropharynx and availability to the lungs were assessed with the inhalers adapted to the throat model in the normal upright orientation and effectively leaning forward at a 45-degree angle. The Stiolto Respimat SMI was superior in dosing efficiency and dose to the lungs compared with Trelegy Ellipta DPI, Fostair NEXThaler DPI and Trimbow pMDI. Irrespective of the inhaler position, the Stiolto Respimat SMI was associated with the lowest dose to the mouth/oropharynx and the highest dose delivered to the lungs. These benefits are expected to translate into the robustness of Stiolto Respimat SMI in routine clinical use, ensuring consistently high dose delivery to the lungs even when patients do not follow instructions regarding inhaler orientation.

Introduction

Inhaled therapy is a key component in the management of chronic obstructive pulmonary disease (COPD) and asthma, and many different delivery devices have been designed to optimize drug delivery to the target organ, the lungs [1, 2]. Selecting the optimum delivery system is essential to ensure that patients obtain the maximum benefit from inhaled therapies [1]. Multiple variations of three key design types are available, namely soft mist inhalers (SMIs), pressurized metered dose inhalers (pMDIs) and dry powder inhalers (DPIs) [1, 3]. Each inhaler has advantages and disadvantages, and it is important for physicians to optimally match not only the therapies to the condition to be treated (e.g., long-acting muscarinic antagonists or long-acting β_2-agonists for COPD, with inhaled corticosteroids (ICS) for asthma), but also the type of inhaler with the specific patient [3, 4]. Patient-centered product design is also critical to ensure that the device remains robust for routine use by patients [5].

One of the principal differences between inhalers is the mechanism of drug delivery, which is active in the case of SMIs (mechanical energy) and pMDIs (propellant) and passive in the case of DPIs (aerosol generated by the patient) [6, 7]. Consequently, the challenges of effective drug delivery associated with each inhaler type are different. In the case of the

pMDI and, to a lesser extent the SMI, lack of coordination between aerosolization and inhalation can be an issue [8]. In contrast, DPIs, which are activated on inspiration, do not require coordination but can be associated with poorer disease control in cases of suboptimal inhalation [9, 10].

The aerosol generated by inhaler delivery devices differs in multiple aspects, each of which can affect drug delivery to the lungs. Particle size and fine particle fraction, for example, are critical. If the particles are too large, the aerosol is retained in the oropharynx; however, if the particles are too small, they can be exhaled, particularly by patients with insufficient breath-hold [11]. Particle velocity is also key; being slow enough to navigate the approximately right-angled bend at the back of the throat is an issue for pMDIs, which have the highest velocity and tend to be associated with higher oropharyngeal deposition [11, 12]. Conversely, with DPIs, if the inhalation rate is too slow, drug and carrier deagglomeration is suboptimal and a patient can suffer higher oropharyngeal deposition, with an associated reduced lung deposition [11]. A key technological breakthrough for the Stiolto® Respimat® SMI was the development of the Uniblock—a nozzle system that ensures that fine jets of solution converge at a precise angle to create a slow-moving aerosol of inhalable fine droplets [7].

Patient factors, such as the inhalation maneuver, can also affect drug delivery. Patients can be trained in the correct inhalation technique for their inhaler type; however, some factors such as meeting a required strength of inhalation cannot be overcome by training [3, 13]. With SMIs, patients should breathe slowly and deeply because inhalations that are too fast increase oropharyngeal deposition; reducing inhalation speed is something that can be adapted by training [3, 13]. For DPIs, fast and strong inhalation is required, which some patients might be unable to achieve [3]. A relatively high proportion of patients (~45%) suffer suboptimal peak inspiratory flow (PIF) with their DPI device, particularly at times of exacerbation [14], a factor that could be further worsened by body position [15]. Training can improve a patient's inhalation technique and inhalation education is essential; however, it has been shown that patients make many errors when using inhalers routinely [6, 16, 17]. Effective inhaler therapy requires training and inhalers that operate independently of the patients' inhalation profiles could be expected to be more robust in routine use [17].

The objective of this study was to investigate the dosing efficiency (ratio of the dose available to the lungs against the dose retained in the oropharynx) of different inhaler devices (SMI, pMDI and DPI) and to compare their robustness to inhaler orientation, synonymous with a patient being in either an upright position or leaning forward at a 45-degree angle.

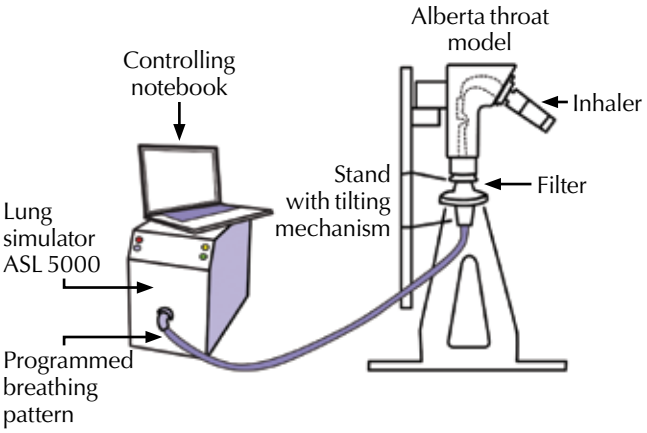
Methods

An *in vitro* model was used to mimic aerosol flow in the mouth/oropharynx region, with data obtained at the exit of the modeled throat, simulating the dose reaching the lung.

The following inhalers were studied: Stiolto (US)/Spiolto (Europe) Respimat (fixed-dose combination of 2.5 µg tiotropium and 2.5 µg olodaterol; TIO/OLO): SMI, Boehringer Ingelheim, Ingelheim am Rhein, Germany [18, 19]; Trimbow® (87 µg beclometasone dipropionate, 5 µg formoterol fumarate dihydrate, 9 µg glycopyrronium [corresponding to 11 µg glycopyrronium bromide]): pMDI, Chiesi, Parma, Italy [20]; Fostair NEXThaler® (200 µg beclometasone dipropionate, 6 µg formoterol fumarate dihydrate [delivered dose: 158.8 µg beclometasone dipropionate and 4.9 µg formoterol fumarate dihydrate]): DPI, Chiesi, Parma, Italy [21]; and Trelegy Ellipta® (92 µg fluticasone furoate, 65 µg umeclidinium bromide [corresponding to 55 µg umeclidinium] and 22 µg vilanterol [as trifenatate]): DPI, GlaxoSmithKline, Brentford, United Kingdom [22, 23].

Figure 1

1A. Laboratory setup



1B. Inhaler angle/cross-section of the Alberta throat model. a) Tilted forward by 45 degrees; b) Upright position (closed); c) Upright position (open, only one half of the cast is shown).

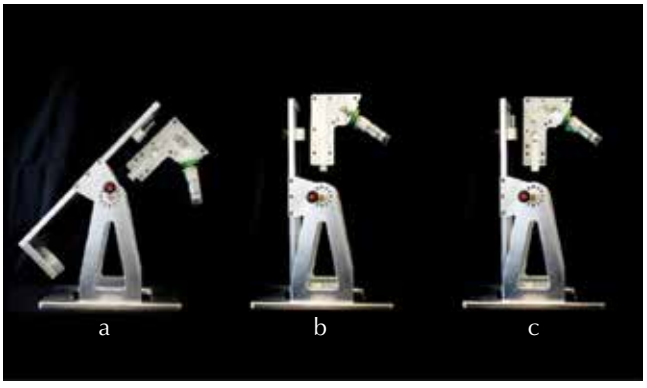
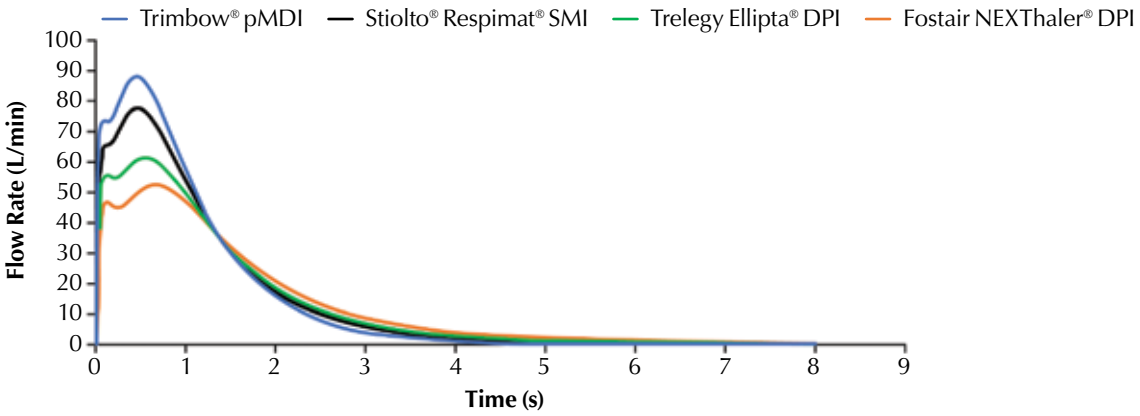


Figure 2

Inhalation patterns used to program the lung simulator



Laboratory setup

The equipment included a lung simulator, the Alberta Idealized Throat model (Warren Finlay, University of Edmonton, Alberta, Canada), a filter and a tilting mechanism (Figure 1). The lung simulator (ASL 5000 Active Servo Lung, IngMar Medical, Pittsburgh, PA, US) was programmed with the inhalation patterns of patients with very severe COPD (forced expiratory volume in one second (FEV_1) < 30% of predicted), according to the Global Initiative for Chronic Obstructive Lung Disease FEV_1 cutoffs for disease classification [2]) that had been generated in a previous study (Figure 2) [24, 25]. Because patients adapt their inhalation profiles depending upon the internal resistance of an inhaler [17], each inhaler was tested using a specific inhalation profile. The inhalation profiles selected were spontaneous (i.e., inspiration during uncoached and normal inhaler use) for Stiolto Respimat SMI and Trimbow pMDI and maximal (i.e., forceful and deep inhalation) for the Fostair NEXThaler and Trelegy Ellipta DPIs [17].

The Alberta throat model is an aluminum cast that simulates the internal anatomy of an adult oropharynx [26-29]. In Figure 1B, the Alberta throat model is shown with the cast closed (as used in the experimental setup) and open (to display, in cross-section, the internal anatomy of the modeled throat/oral cavity, pharynx, epiglottis, larynx and trachea). To mimic the wet mucosal surface of the oropharynx, a thin layer of Brij-glycerol emulsion (Brij 35®, polyoxyethylene monolauryl ester, Serva, Electrophoresis GmbH, Heidelberg, Germany) was used to coat the inside of the oropharynx mode. This coating is not essential for aerosols of aqueous solutions but is required for testing dry powder aerosols to eliminate particle bounce-back [24]. Humidity was not controlled, consistent with patients breathing ambient air.

A filter (to capture the inhaled medication leaving the throat [dose to the lungs]) and a tilting mechanism (upright and leaning forward 45 degrees) completed the equipment, the details of which have been described previously [24]. Each device (Stiolto Respimat, Trimbow, Fostair NEXThaler, Trelegy Ellipta) was tested in triplicate for each inhaler at each orientation.

Each product constituent was quantitated using a validated, high-performance liquid chromatography method. The oropharynx deposition (dose retained in the Alberta throat model) and lung deposition (dose retained in the filter) were expressed as a percentage of the delivered dose (equaling the dose per actuation according to recent pharmacopeial definitions [30]). The sum of the doses recovered from the Alberta throat model and filter was compared with the delivered dose as a quality check. Eight doses were accumulated during the analysis to obtain a good signal-to-noise ratio.

Endpoints

The primary endpoint was the dosing efficiency, expressed as the ratio of the dose delivered to the lungs/dose delivered to the oropharynx. The secondary endpoint was the dose delivered to the lungs.

Statistical analyses

For both endpoints, the constituent compounds and inhaler orientations were pooled for each inhaler. For the primary and secondary endpoints, fixed-effects analysis of covariance models was used to test for superiority of the SMI vs. the alternative inhalers, with factors including inhaler, compounds and orientation. A Wilcoxon nonparametric test was used to test the robustness of the primary endpoint. Descriptive statistics (mean ± standard deviation [SD]) were calculated for oropharyngeal and lung deposition per inhaler per orientation.

Results

In terms of overall oropharynx deposition (pooled constituents and inhaler orientations), the Stiolto Respimat SMI showed the lowest proportion of the

Table 1

Dose Proportion to the Oropharynx and Lungs

Product	Constituents	Dose Proportion to the Oropharynx, %				Dose Proportion to the Lungs, %				Recovered Dose	Dosing Efficiency
		Angle (Degrees)	n	Mean	SD	Angle (Degrees)	n	Mean	SD	Mean (SD)	Ratio Mean (SD)
Stiolto® Respimat® SMI	Olodaterol	0	3	30.7	6.9	0	3	70.2	3.1	100.9 (10.0)	2.4 (0.5)
		45	3	23.2	2.2	45	3	68.7	3.2	91.8 (5.5)	3.0 (0.2)
		All	6	26.9	6.2	All	6	69.4	3.0	–	2.7 (0.5)
	Tiotropium	0	3	32.6	6.9	0	3	70.1	2.9	102.7 (9.8)	2.2 (0.4)
		45	3	23.6	2.0	45	3	68.6	3.4	92.1 (4.2)	2.9 (0.3)
		All	6	28.1	6.7	All	6	69.3	3.0	–	2.6 (0.5)
	All	All	12	27.5	6.2	All	12	69.4	2.8	–	2.6 (0.5)
Trimbow® pMDI	Beclometasone dipropionate	0	3	43.2	5.4	0	3	59.5	2.1	102.6 (3.4)	1.4 (0.2)
		45	1	32.2	–	45	1	48.2	–	80.4 (–)	1.5 (–)
		All	4	40.4	7.0	All	4	56.6	5.9	–	1.4 (0.2)
	Formoterol fumarate dihydrate	0	3	49.7	5.7	0	3	64.9	2.3	114.7 (3.4)	1.3 (0.2)
		45	1	39.5	–	45	1	59.2	–	98.7 (–)	1.5 (–)
		All	4	47.2	6.9	All	4	63.5	3.4	–	1.4 (0.2)
	Glycopyrronium	0	3	42.8	5.3	0	3	63.4	2.5	106.2 (5.7)	1.5 (0.2)
		45	1	39.4	–	45	1	54.1	–	93.6 (–)	1.4 (–)
		All	4	42.0	4.6	All	4	61.1	5.1	–	1.5 (0.2)
	All	All	12	43.2	6.4	All	12	60.4	5.3	–	1.4 (0.2)
Fostair NEXThaler® DPI	Beclometasone dipropionate	0	3	37.7	1.8	0	3	68.0	0.8	105.7 (1.8)	1.8 (0.1)
		45	3	38.2	1.8	45	3	67.4	0.5	105.6 (1.6)	1.8 (0.1)
		All	6	37.9	1.6	All	6	67.7	0.7	–	1.8 (0.1)
	Formoterol fumarate dihydrate	0	3	33.0	2.6	0	3	59.9	4.4	92.9 (4.9)	1.8 (0.2)
		45	3	33.8	5.0	45	3	60.0	4.8	93.7 (8.0)	1.8 (0.3)
		All	6	33.4	3.6	All	6	59.9	4.1	–	1.8 (0.2)
	All	All	12	35.7	3.6	All	12	63.8	5.0	–	1.8 (0.2)
Trelegy Ellipta® DPI	Fluticasone furoate	0	3	63.6	2.8	0	3	36.8	1.6	100.4 (2.1)	0.6 (0.05)
		45	3	63.3	1.5	45	3	39.7	0.9	102.9 (2.0)	0.6 (0.02)
		All	6	63.4	2.0	All	6	38.3	1.9	–	0.6 (0.04)
	Umeclidinium bromide	0	3	46.7	2.7	0	3	58.3	1.4	105.0 (3.7)	1.3 (0.06)
		45	3	43.8	1.2	45	3	60.4	1.4	104.2 (2.5)	1.4 (0.02)
		All	6	45.3	2.5	All	6	59.3	1.7	–	1.3 (0.08)
	Vilanterol	0	3	55.6	5.5	0	3	55.6	2.0	111.2 (4.1)	1.0 (0.1)
		45	3	47.3	2.9	45	3	56.1	3.9	103.4 (3.6)	1.2 (0.1)
		All	6	51.5	6.0	All	6	55.8	2.8	–	1.1 (0.2)
	All	All	18	53.4	8.6	All	18	51.1	9.7	–	1.0 (0.3)

dose retained in the oropharynx (27.5% ± 6.2%), followed by the Fostair NEXThaler DPI (35.7% ± 3.6%), the Trimbow pMDI (43.2% ± 6.4%) and the Trelegy Ellipta DPI (53.4% ± 8.6%). For individual constituent compounds, the highest dose retained in the oropharynx (63.4% ± 2.0%) was observed for fluticasone furoate, the ICS component of the Trelegy Ellipta DPI. The lowest dose delivered to the oropharynx (26.9% ± 6.2%) was observed for the olodaterol constituent of the Stiolto Respimat SMI (Table 1). The device that delivered the highest proportion of the dose to the lungs was the Stiolto Respimat SMI (69.4% ± 2.8%), followed by the Fostair NEXThaler DPI (63.8% ± 5.0%), the Trimbow pMDI (60.4% ± 5.3%) and the Trelegy Ellipta DPI (51.1% ± 9.7).

The dosing efficiency of the Stiolto Respimat SMI was statistically superior to that of the Trelegy Ellipta DPI, the Fostair NEXThaler DPI and the Trimbow pMDI (Table 2A). The dosing efficiency superiority results were robust, with one-sided Wilcoxon (non-parametric test) p values of < 0.0001 when comparing the Stiolto Respimat SMI with each alternative inhaler; results were below the limit of 0.025. The dose delivered to the lungs was also statistically superior for the Stiolto Respimat SMI compared with the other delivery devices (Table 2B).

In terms of confidence in the analytical methodology, the recovered dose (Alberta throat model and filter) was within 100.0% ± 15.0% of the delivered dose (Table 1), with one exception: the recovery of the beclometasone component of the Trimbow pMDI at an angle of 45 degrees was 80.4%, with the recovery of the other components (formoterol fumarate dihydrate and glycopyrronium) also lower than in the upright orientation. An X-ray of the Trimbow pMDI inhaler (Figure 3) indicated a potential aspiration issue when the inhaler was tilted forward, because the liquid in the canister was no longer above the valve in this orientation. Inhaler position (upright or 45-degree angle) had little impact on the results for oropharynx and lung deposition for the Stiolto Respimat SMI, Fostair NEXThaler DPI and Trelegy Ellipta DPI (Figure 4).

Discussion

The Stiolto Respimat SMI was found to be statistically superior in dosing efficiency and the dose available to the lungs compared with the Trelegy Ellipta DPI, Fostair NEXThaler DPI and Trimbow pMDI. This is supported by previous *in vivo* and *in vitro*/*in silico* models, which also showed that the dose to the lungs achieved with the Stiolto Respimat SMI was higher than that achieved with alternative devices [24, 31, 32]. The high dose of both tiotropium and olodaterol administered to the lungs, delivered using the Stiolto Respimat SMI, is supported by a further *in vitro*/*in silico* model in which the Stiolto Respimat SMI achieved high particle deposition of both tiotropium and olodaterol deep into the lung periphery [33, 34]. A study by Iwanaga, et al., using functional respiratory imaging, showed results similar to those presented here, with the Stiolto Respimat SMI having the highest drug deposition to the peripheral

Table 2

Test for Superiority (CI: confidence interval; LCL: lower confidence limit; UCL, upper confidence limit)

2A. Dosing Efficiency

		95% CI for Difference of Means			
Product 1	Product 2	Difference	LCL	UCL	One-sided p value
Stiolto® Respimat® SMI	Trelegy Ellipta® DPI	1.6	1.4	1.8	< 0.0001
Stiolto® Respimat® SMI	Fostair NEXThaler® DPI	0.8	0.5	1.1	< 0.0001
Stiolto® Respimat® SMI	Trimbow® pMDI	1.1	0.8	1.4	< 0.0001

2B. Modeled Dose to the Lung

		95% CI for Difference of Means			
Product 1	Product 2	Difference	LCL	UCL	One-sided p value
Stiolto® Respimat® SMI	Trelegy Ellipta® DPI	18.2	16.3	20.2	< 0.0001
Stiolto® Respimat® SMI	Fostair NEXThaler® DPI	5.6	3.0	8.1	0.0001
Stiolto® Respimat® SMI	Trimbow® pMDI	10.2	7.3	13.0	< 0.0001

airways, ahead of a pMDI (Flutiform® [a combination of fluticasone propionate/formoterol fumarate hydrate; Kyorin Pharmaceutical, Tokyo, Japan]) and DPIs (Symbicort® [a combination of budesonide/formoterol fumarate hydrate; AstraZeneca KK/Astellas Pharma Inc., Tokyo, Japan] and Relvar® [a combination of fluticasone furoate/vilanterol trifenatate; GlaxoSmithKline, Brentford, United Kingdom]) [35].

The lowest dose to the oropharynx was achieved with the Stiolto Respimat SMI, independent of the constituents studied. The dose to the oropharynx with the Trimbow pMDI was, as anticipated, higher than that with the Stiolto Respimat SMI, as a result of the faster aerosol velocity associated with the inhalant propulsion delivery mechanism. The Trelegy Ellipta DPI was associated with the highest oropharyngeal deposition, particularly with the ICS component. In clinical practice, this increase in oropharyngeal deposition observed with Trelegy Ellipta could lead to the common side effect (≤ 10% of patients) of oral candidiasis [22, 23], which occurs as a result of ICS affecting the oral microbiome [36]. The Fostair NEXThaler DPI outperformed the Trelegy Ellipta DPI, irrespective of inhaler position, but was not as effective as the Stiolto Respimat SMI in limiting off-target dosing.

In our model of very severe COPD (FEV_1 < 30%), the dose available to the lungs was consistently low with the Trelegy Ellipta DPI, associated with the higher oropharyngeal deposition observed with this inhaler.

Several studies have demonstrated that suboptimal PIF is associated with a more severe disease [37]. A study (n = 30) of patients with severe COPD showed that the chance of responding to Trelegy Ellipta was significantly lower in patients who had PIF ≤ 45 L/min than in those who had PIF > 45 L/min (2% vs. 17%; p = 0.04) [38].

The 45-degree position (leaning forward) resulted in a lower recovered dose for the Trimbow pMDI, which should be kept upright during inhalation [20] or the solution to aspirate will no longer be above the valve mechanism. The Stiolto Respimat SMI, which also contains a solution rather than a powder, was

Figure 3

X-ray of the Trimbow® pMDI showing the liquid level. The X-ray is copied on top of an image of the pMDI, illustrating the inhaler orientation.

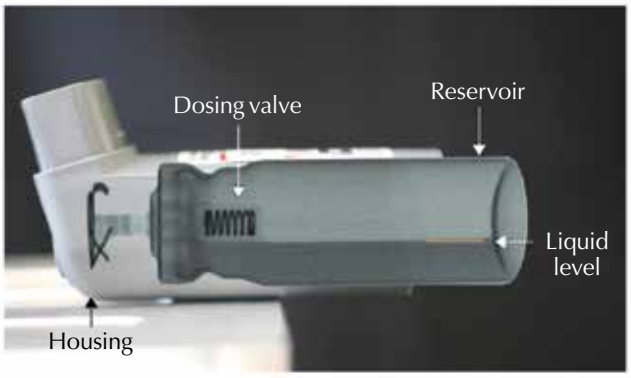
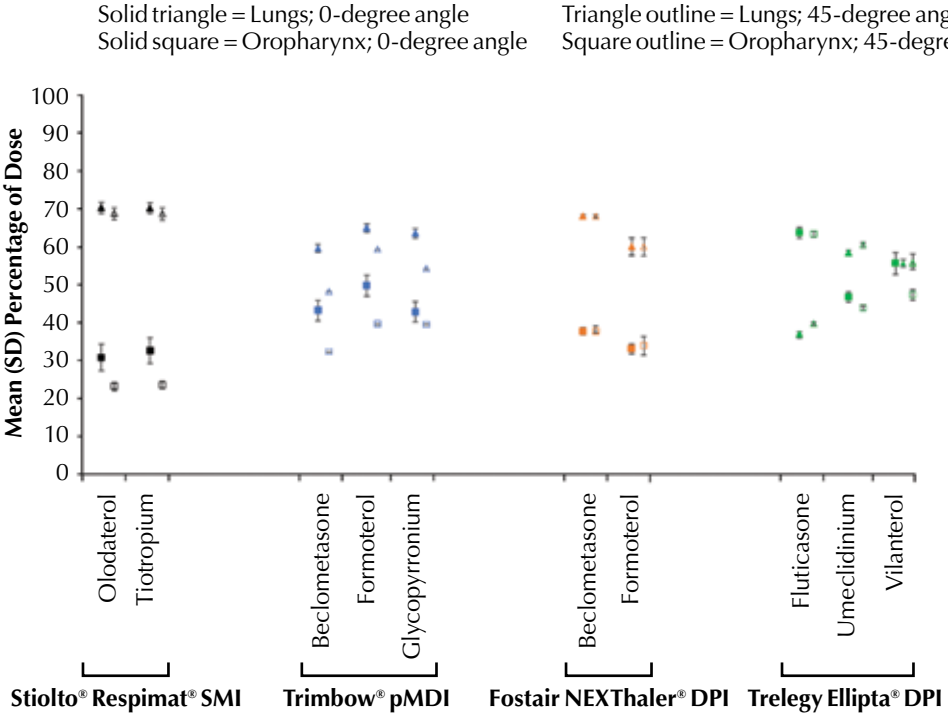


Figure 4

Doses to the oropharynx and lungs for each inhaler (individual components) at each orientation. Data are mean ± standard deviation (SD).



unaffected by the inhaler orientation. The Stiolto Respimat device has a double-walled, plastic, collapsible bag contained within the drug cartridge that contracts as the drug solution is used, such that the capillary is always immersed in the solution, irrespective of the orientation of the inhaler [5].

Considering the DPIs and inhaler orientation, we found very little difference between the upright and leaning-forward positions in this analysis. However, Drummond, et al. have shown that PIF changes with patient position, with the PIF being highest in a standing position and lowest in a supine position, regardless of the DPI type [15]. A limitation of the present study is that the lung simulator did not include a different inhalation profile when the patient orientation (inhaler angle) was changed. Therefore, our DPI lung deposition results are potentially better in the leaning-forward orientation than could be expected in routine practice. Indeed, for both DPIs tested in our study, patients are required to sit or stand upright and hold their inhalers horizontally [21-23].

Although this work is *ex vivo* in nature, it is anticipated that the robustness of the Stiolto Respimat SMI to inhaler orientation would result in clinical benefits in routine inhaler use/misuse. Previous laboratory work has been replicated clinically—an experiment of similar design, using the Alberta throat model, demonstrated that the Stiolto Respimat SMI is robust to inhalation profile, with high *in vitro* lung deposition irrespective of profile characteristics [24]. This was corroborated by the Phase IV, randomized, double-blind, placebo-controlled TRONARTO study, which showed that using the Stiolto Respimat SMI, the improvement in lung function was irrespective of PIF in patients with moderate-to-severe COPD at baseline [39].

As for measuring the dose available to the lungs, namely, the amount of drug exiting the Alberta throat model and being retained in the filter, it is recognized that the dose deposited centrally/peripherally in the lungs or exhaled will depend on factors including aerosol particle size, fine particle fraction (FPF), airflow profile and duration of breath-hold. FPF represents the fraction or percentage of the drug in an aerosol cloud that consists of particles considered small enough (< ~5-µm diameter) to penetrate the lungs and exert a clinical effect [40]. Particle size and distribution were not investigated in this study, although they are also factors affecting the clinical efficacy of inhaled aerosols generated by various inhaler devices [41].

Of the different inhaler types in this study, the DPIs and pMDIs can have a broader distribution of particle size than the SMI, resulting in a lower FPF: Trelegy Ellipta DPI, 24%-40%; Fostair NEXThaler DPI, 68%-74%; Trimbow pMDI, 42%-44% and Stiolto Respimat SMI, 66%-72% [24, 42-45]. DPIs are uniquely vulnerable to inhaled airflow, requiring sufficient airflow to cause deagglomeration and create small inhalable particles; however, airflow that is too fast (especially with devices that have lower internal resistance) can be associated with higher oropharyngeal deposition [46]. This creates issues at both ends of the inspiratory spectrum with inspiratory inability (inhalable particles not disassociated from the carrier) and excessive inspiratory effort (particle velocity that is too high), both resulting in increased oropharyngeal deposition [46]. With pMDIs, the particle distribution tends to be broad, relying on the fast evaporation of the propellant to generate inhalable particles by the time the aerosol reaches the back of the throat [47]. The high particle velocity in pMDIs also tends to increase oropharyngeal deposition [48]. With the SMI, if patients' inhalation is too fast, then it can result in high oropharyngeal deposition, but inhalation speed can be modified through training [16]. FPF with the SMI is high, nearly 70% [45], and the particle size is optimal for lung deposition by direct impaction rather than as a result of collision with the airway wall following Brownian motion diffusion [5, 49]. With very fine particles, the proportion of particles exhaled may be increased as a result of reduced lung deposition in the case of reduced breath-hold [11]. The median particle sizes for the inhalers studied are as follows: Trelegy Ellipta DPI, 1.8-3.2 µm; Fostair NEXThaler DPI, 1.4-1.5 µm; Trimbow pMDI, 1.1 µm; and Stiolto Respimat SMI, 4.2-4.6 µm [24, 43-45].

Considering the wide range of inhaler types available, patient preference will play a key role in selecting the optimal inhaler for a given patient [3]. Besides disease control and the ease of use, other factors that patients consider when choosing a device include the design, cost (insurance and reimbursement restrictions) and environmental impact [3]. Due to the hydrofluoroalkane propellants they contain, pMDIs have a higher carbon footprint than DPIs and SMIs, which are propellant-free [3, 50]. In addition, a reduction in carbon footprint has been associated with reusable vs. single-use inhalers, with refill cartridges reducing the carbon footprint of SMIs by 71% over 6 months [3, 50]. Shared decision-making will play a key role in selecting the best inhaler for a given patient, and improved patient satisfaction may help promote long-term adherence.

Inadvertent nonadherence may also be an important consideration when choosing an inhaler because patients who use their inhaler incorrectly do not receive the optimal dose [34]. Inadvertent underdosing has been observed with pMDIs due to the need to coordinate actuation and inhalation, and patients can believe their inhaler is working when it is empty [34]. The latter is not possible with the SMI, which has a cartridge lock that prevents the release of a dose from an empty device [51]. Inadvertent overdosing has also been seen when an inhala-

tion is tasteless, with patients using the Turbuhaler® (AstraZeneca, Cambridge, United Kingdom) DPI, for example, sometimes administering a second dose "just in case" [34].

Physicians have a wide range of inhalers available, each with its own advantages and disadvantages, and they therefore need to take many factors into consideration when matching a patient with an appropriate inhaler [3]. We suggest that inhaler robustness to misuse in routine clinical practice should be one of the factors considered.

Conclusion

The Stiolto Respimat SMI was found to be superior in dosing efficiency and dose to the lungs compared with the Trelegy Ellipta DPI, Fostair NEXThaler DPI and Trimbow pMDI. The Stiolto Respimat SMI was associated with the lowest dose to the oropharynx and the highest dose to the lungs, irrespective of the inhaler position. These benefits are expected to translate into the robustness of the SMI in routine clinical use, especially in cases where patients do not follow instructions regarding inhaler orientation.

Acknowledgments

The authors thank Volker Brenk, Christoph Kraft and Dr. Thomas Hoffelder for their support during the analytical work.

References

1. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for prevention, diagnosis and management of COPD: 2023 report. 2023. https://goldcopd.org/2023-gold-report-2.

2. Global Initiative for Asthma, Global Initiative for Chronic Obstructive Lung Disease. Diagnosis and initial treatment of asthma, COPD and asthma-COPD overlap. A joint project of GINA and GOLD. Updated April 2017. https://ginasthma.org/wp-content/uploads/2019/11/GINA-GOLD-2017-overlap-pocket-guide-wms-2017-ACO.pdf.

3. Peché R, Attar-Zadeh D, Scullion J, et al. Matching the inhaler to the patient in COPD. Journal of Clinical Medicine 2021; 10:5683.

4. Oba Y, Anwer S, Maduke T, et al. Effectiveness and tolerability of dual and triple combination inhaler therapies compared with each other and varying doses of inhaled corticosteroids in adolescents and adults with asthma: A systematic review and network meta-analysis. Cochrane Database of Systematic Reviews 2022; 12:CD013799.

5. Wachtel H, Kattenbeck S, Dunne S, et al. The Respimat® development story: Patient-centered innovation. Pulmonary Therapy 2017; 3:19-30.

6. Usmani OS. Choosing the right inhaler for your asthma or COPD patient. Therapeutics and Clinical Risk Management 2019; 15:461-472.

7. Gupta A, de la Hoz A. Boehringer Ingelheim: Reshaping the course of chronic obstructive pulmonary disease. Nature Research Custom 2020; https://www.nature.com/articles/d42473-020-00171-3.

8. Cataldo D, Hanon S, Peché RV, et al. How to choose the right inhaler using a patient-centric approach? Advances in Therapy 2022; 39:1149-1163.

9. Berkenfeld K, Lamprecht A, McConville JT. Devices for dry powder drug delivery to the lung. AAPS PharmSciTech 2015; 16:479-490.

10. Kocks JWH, Wouters H, Bosnic-Anticevich S, et al. Factors associated with health status and exacerbations in COPD maintenance therapy with dry powder inhalers. NPJ Primary Care Respiratory Medicine 2022; 32:18.

11. Laube BL, Janssens HM, de Jongh FH, et al. What the pulmonary specialist should know about the new inhalation therapies. European Respiratory Journal 2011; 37:1308-1331.

12. Levy ML, Dekhuijzen PN, Barnes PJ, et al. Inhaler technique: Facts and fantasies. A view from the Aerosol Drug Management Improvement Team (ADMIT). NPJ Primary Care Respiratory Medicine 2016; 26:16017.

13. Chen SY, Huang CK, Peng HC, et al. Peak-inspiratory-flow-rate guided inhalation therapy reduce severe exacerbation of COPD. Frontiers in Pharmacology 2021; 12:704316.

14. Mahler DA, Demirel S, Hollander R, et al. High prevalence of suboptimal peak inspiratory flow in hospitalized patients with COPD: A real-world study. Chronic Obstructive Pulmonary Diseases 2022; 9:427-438.

15. Drummond MB, Henderson AG, Shaikh A, et al. Effect of physical position on peak inspiratory flow in stable COPD. European Respiratory Journal 2021; 58(suppl 65):PA1831.

16. Brand P, Hederer B, Austen G, et al. Higher lung deposition with Respimat® soft mist inhaler than HFA-MDI in COPD patients with poor technique. International Journal of Chronic Obstructive Pulmonary Disease 2008; 3:763-770.

17. Quint J, Montonen J, Singh D, et al. New insights into the optimal management of COPD: Extracts from CHEST 2021 annual meeting (October 17-20, 2021). Expert Review of Respiratory Medicine 2022; 16:485-493.

18. Stiolto® Respimat® US prescribing information. Updated November 2021. https://content.boehringer-ingelheim.com/DAM/7fe8a4a7-9ed3-41ef-a565-af1e0120af14/stiolto%20respimat-us-pi.pdf.

19. Spiolto® Respimat® Summary of product characteristics. Updated December 2020. https://www.medicines.org.uk/emc/product/6902/smpc.

20. Trimbow® Summary of product characteristics. Updated July 2022. https://www.medicines.org.uk/emc/product/761.

21. Fostair NEXThaler® Summary of product characteristics. Updated November 2018. https://www.medicines.org.uk/emc/product/5075/smpc#gref.

22. Trelegy Ellipta® US prescribing information. Updated December 2022. https://gskpro.com/content/dam/global/hcpportal/en_US/Prescribing_Information/Trelegy_Ellipta/pdf/TRELEGY-ELLIPTA-PI-PIL-IFU.PDF.

23. Trelegy Ellipta® Summary of product characteristics. Updated 12/08/2022. https://www.medicines.org.uk/emc/product/8666.

24. Ciciliani AM, Langguth P, Wachtel H. *In vitro* dose comparison of Respimat® inhaler with dry powder inhalers for COPD maintenance therapy. International Journal of Chronic Obstructive Pulmonary Disease 2017; 12:1565-1577.

25. Wachtel H, Flüge T, Gössl R. Flow - pressure - energy - power: Which is the essential factor in breathing patterns of patients using inhalers? Respiratory Drug Delivery 2006; 2:511-514.

26. Golshahi L, Noga ML, Vehring R, et al. An *in vitro* study on the deposition of micrometer-sized particles in the extrathoracic airways of adults during tidal oral breathing. Annals of Biomedical Engineering 2013; 41:979-989.

27. Grgic B, Finlay WH, Heenan AF. Regional aerosol deposition and flow measurements in an idealized mouth and throat. Journal of Aerosol Science 2004; 35:21-32.

28. Johnstone A, Uddin M, Pollard A, et al. The flow inside an idealised form of the human extra-thoracic airway. Experiments in Fluids 2004; 37:673-689.

29. Wei X, Hindle M, Kaviratna A, et al. *In vitro* tests for aerosol deposition. VI: Realistic testing with different mouth-throat models and *in vitro-in vivo* correlations for a dry powder inhaler, metered dose inhaler, and soft mist inhaler. Journal of Aerosol Medicine and Pulmonary Drug Delivery 2018; 31:358-371.

30. European Directorate for the Quality of Medicines & Healthcare. European Pharmacopoeia (Ph. Eur.) 11th ed. EDQM Council of Europe 2023.

31. Newman SP, Brown J, Steed KP, et al. Lung deposition of fenoterol and flunisolide delivered using a novel device for inhaled medicines: Comparison of Respimat with conventional metered-dose inhalers with and without spacer devices. Chest 1998; 113:957-963.

32. Pitcairn G, Reader S, Pavia D, et al. Deposition of corticosteroid aerosol in the human lung by Respimat Soft Mist Inhaler compared to deposition by metered dose inhaler or by Turbuhaler dry powder inhaler. Journal of Aerosol Medicine 2005; 18:264-272.

33. Ciciliani AM, Denny M, Langguth P, et al. Lung deposition using the Respimat® Soft Mist™ inhaler mono and fixed-dose combination therapies: An *in vitro/in silico* analysis. Journal of Chronic Obstructive Pulmonary Disease 2021; 18:91-100.

34. Iwanaga T, Tohda Y, Nakamura S, et al. The Respimat® soft mist inhaler: Implications of drug delivery characteristics for patients. Clinical Drug Investigation 2019; 39:1021-1030.

35. Iwanaga T, Kozuka T, Nakanishi J, et al. Aerosol deposition of inhaled corticosteroids/long-acting β2-agonists in the peripheral airways of patients with asthma using functional respiratory imaging, a novel imaging technology. Pulmonary Therapy 2017; 3:219-231.

36. Abdel-Aziz MI, Vijverberg SJH, Neerincx AH, et al. The crosstalk between microbiome and asthma: Exploring associations and challenges. Clinical & Experimental Allergy 2019; 49:1067-1086.

37. Leving MT, Kocks J, Bosnic-Anticevich S, et al. Relationship between peak inspiratory flow and patient and disease characteristics in individuals with COPD—A systematic scoping review. Biomedicines 2022; 10:458.

38. Ferguson GT. Suboptimal peak inspiratory flow (PIF) in patients with severe COPD does not impact effective drug delivery of an inhaled triple therapy dry powder inhaler (DPI). Chest 2022; 162:A1881-A1883.

39. Mahler DA, Ludwig-Sengpiel A, Ferguson GT, et al. TRONARTO: A randomized, placebo-controlled study of tiotropium/olodaterol delivered via soft mist inhaler in COPD patients stratified by peak inspiratory flow. International Journal of Chronic Obstructive Pulmonary Disease 2021; 16:2455-2465.

40. Newman SP. Fine particle fraction: The good and the bad. Journal of Aerosol Medicine and Pulmonary Drug Delivery 2022; 35:2-10.

41. Newman SP. Aerosol deposition considerations in inhalation therapy. Chest 1985; 88:152S-160S.

42. Lavorini FL, Janson C, Braido F, et al. What to consider before prescribing inhaled medications: A pragmatic approach for evaluating the current inhaler landscape. Therapeutic Advances in Respiratory Disease 2019; 13:1753466619884532.

43. Usmani OS, Mignot B, Kendall I, et al. Predicting lung deposition of extrafine inhaled corticosteroid-containing fixed combinations in patients with chronic obstructive pulmonary disease using functional respiratory imaging: An *in silico* study. Journal

of Aerosol Medicine and Pulmonary Drug Delivery 2021; 34:204-211.

44. Virchow JC, Poli G, Herpich C, et al. Lung deposition of the dry powder fixed combination beclometasone dipropionate plus formoterol fumarate using NEXThaler® device in healthy subjects, asthmatic patients, and COPD patients. Journal of Aerosol Medicine and Pulmonary Drug Delivery 2018; 31:269-280.

45. Wachtel H, Ziegler J. Improved assessment of inhaler device performance using laser diffraction. Respiratory Drug Delivery 2002; 8:379-382.

46. Weers J. Suboptimal inspiratory flow rates with passive dry powder inhalers: Big issue or overstated problem? Frontiers in Drug Delivery 2022; 2:855234.

47. Hochrainer D, Hölz H, Kreher C, et al. Comparison of the aerosol velocity and spray duration of Respimat Soft Mist inhaler and pressurized metered dose inhalers. Journal of Aerosol Medicine 2005; 18:273-282.

48. Dhand R. Aerosol plumes: Slow and steady wins the race. Journal of Aerosol Medicine 2005; 18:261-263.

49. Labiris NR, Dolovich MB. Pulmonary drug delivery. Part I: Physiological factors affecting therapeutic effectiveness of aerosolized medications. British Journal of Clinical Pharmacology 2003; 56:588-599.

50. Hansel M, Bambach T, Wachtel H. Reduced environmental impact of the reusable Respimat® Soft Mist™ inhaler compared with pressurised metered-dose inhalers. Advances in Therapy 2019; 36:2487-2492.

51. Dhand R, Eicher J, Hänsel M, et al. Improving usability and maintaining performance: Human-factor and aerosol-performance studies evaluating the new reusable Respimat inhaler. International Journal of Chronic Obstructive Pulmonary Disease 2019; 14:509-523.

Sabrina Strohe, BSc, Hochshule Darmstadt, University of Applied Sciences, Darmstadt, Germany, is a Compliance Specialist, Boehringer Ingelheim, Ingelheim am Rhein, Germany. Herbert Wachtel, PhD, is a Senior Principal Scientist, Boehringer Ingelheim, Ingelheim am Rhein, Germany. Rachel Emerson-Stadler, MSc, is a Global Medical Advisor, Global Medical Affairs, Boehringer Ingelheim, Ingelheim am Rhein, Germany. Omar S. Usmani, MBBS, PhD, FHEA, FRCP, FERS, is a Professor of Respiratory Medicine & Consultant Physician, National Heart and Lung Institute (NHLI), Imperial College London, London, United Kingdom. Corresponding author: Herbert Wachtel, PhD, +49 6132 77 98552, herbert.wachtel@boehringer-ingelheim.com. www.boehringer-ingelheim.com.