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The effect of exhalation before the inhalation of dry powder aerosol drugs on the breathing parameters, emitted doses and aerosol size distributions

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ABSTRACT

Airway deposition of aerosol drugs is highly dependent on the breathing manoeuvre of the patients. Though incorrect exhalation before the inhalation of the drug is one of the most common mistakes, its effect on the rest of the manoeuvre and on the airway deposition distribution of aerosol drugs is not explored in the open literature. The aim of the present work was to conduct inhalation experiments using six dry powder inhalers in order to quantify the effect of the degree of lung emptying on the inhalation time, inhaled volume and peak inhalation flow. Another goal of the research was to determine the effect of the exhalation on the aerodynamic properties of the drugs emitted by the same inhalers. According to the measurements, deep exhalation before drug inhalation increased the volume of the inhaled air and the average and maximum values of the inhalation flow rate, but the extent of the increase was patient and inhaler specific. For different inhalers, the mean value of the relative increase in peak inhalation flow due to forceful exhalation was between 15.3 and 38.4% (min: Easyhaler®, max: Breezhaler®), compared to the case of normal (tidal) exhalation before the drug inhalation. The relative increase in the inhaled volume was between 36.4 and 57.1% (min: NEXThaler®, max: Turbuhaler®). By the same token, forceful exhalation resulted in higher emitted doses and smaller emitted particles, depending on the individual breathing ability of the patient, the inhalation device and the drug metered in it. The relative increase in the emitted dose varied between 0.2 and 8.0% (min: Foster® NEXThaler®, max: Bufomix® Easyhaler®), while the relative enhancement of fine particle dose ranged between 1.9 and 30.8% (min: Foster® NEXThaler®, max: Symbicort® Turbuhaler®), depending on the inhaler. All these effects and parameter values point toward higher airway doses due to forceful exhalation before the inhalation of the drug. At the same time, the present findings highlight the necessity of proper patient education on the importance of lung emptying, but also the importance of patient-specific inhaler-drug pair choice in the future.

1. Introduction

The inhalation of drugs in the form of aerosol particles is a key element of current asthma and COPD (chronic obstructive pulmonary disease) therapy (GINA, 2021; GOLD, 2021). In addition, the delivery of painkillers, insulin, contraceptives, vaccines, chemotherapy drugs and

Abbreviations: AF, aerosolized fraction; BMI, body mass index; CAD, computer aided design; COPD, chronic obstructive pulmonary disease; CT, computed tomography; DPI, dry powder inhaler; ED, emitted dose; FEV_1, expiratory volume at the end of the first second of forced exhalation; FPF, fine particle fraction; FVC, forced vital capacity; GSD, geometric standard deviation; ICS, inhalation cortico-steroid; IV, inhaled volume; IV_{dev}, inhaled volume through an inhalation device; IVC, inspiratory vital capacity; LABA, long-acting beta-agonist; MMAD, mass median aerodynamic diameter; PEF, peak expiratory flow; PIF, peak inhalation flow; PIF_{dev}, peak inhalation flow through an inhalation device; PIL, patient information leaflet; Q, mean inhalation flow rate; Q_{dev}, mean inhalation flow rate through an inhalation device; SPC, summary of product characteristics; t_{in}, inhalation time; $t_{in\text{-}dev}$, inhalation time through an inhalation device.

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other active ingredients through the oral route is under development (Ye et al., 2022). For efficient aerosol drug therapy, it is important to deliver the right amount of drug to the right place in the lungs. To achieve this, knowledge of the effect of each important factor influencing the fate of inhaled drug particles is essential. Particle deposition within the airways depends on three major groups of parameters, that is, airway geometry, the aerodynamic characteristics of drug particles and the breathing parameters of the patient.

The inherent intersubject variability of physiological airways is further diversified by different airway diseases, which can cause narrowing or blocking of the conducting airways, enlargement of alveoli and so on. The complexity of the problem is further enhanced by the fact that airway geometry is constantly changing during breathing and may also change over a longer time (aging, disease progression etc.). The advancement of medical imaging techniques (e.g. computed tomography, magnetic resonance imaging) allows us to more and more precisely reconstruct the realistic 3D geometry of the airways. Among the last tendencies, it is worth noting the efforts to characterize the time-dependent 3D structure of the airways by dynamic computed tomography, also called 4D-CT (e.g. Jahani et al., 2017; Choi et al., 2019).

From the perspective of airway deposition, the most important physical properties of a particle are its size, density and shape. The first two characteristics can be expressed by a single parameter, that is, the aerodynamic diameter. The deposition of aerosol drugs in different anatomical regions of the airways is mostly due to inertial impaction and gravitational settling, which are sensitive to particle size. Deposition by thermal (Brownian) motion is important only for drugs with a consistent fraction of submicron particles. The dependence of deposition efficiency on particle size was extensively studied by both experimental and computational methods. A systematic review of the in vivo and in vitro airway deposition experiments can be found in Lizal et al. (2018), while Hofmann (2011) summarized the most frequently applied analytical and numerical techniques. In the case of DPIs (dry powder inhalers), both the number and size of the emitted particles depend on the breathing pattern of the patient. In this context, it is an important and unexplored question how lung emptying before inhalation affects the emitted dose and particle size distribution.

The values of parameters characterizing the breathing capacity of humans measured during standard spirometry span a large spectrum depending on age, gender, race and health status, among others (Quanjer et al., 2012). The variability can be even more accentuated when the subjects inhale through an inhaler with flow resistance. Breathing during the delivery of aerosol drugs has different phases, such as exhalation before the inhalation of the drug, drug inhalation, breath-hold and exhalation after breath-holding. Each phase can be characterized by key parameters, and it is important to know the effect of each of them.

Since most of the drug particles deposit in the inhalation phase (especially the particles depositing by impaction), this phase is the most studied. The drug inhalation phase is usually characterized by an airflow accelerating at the beginning of inhalation, reaching a maximum, and then gradually decelerating. The most important parameters of this phase are the inhalation time (t_{in}), inhaled air volume (IV), peak inhalation flow (PIF), mean inhalation flow rate (Q) and flow ramp-up (acceleration). Previous research efforts demonstrated that lung dose and dose distribution are sensitive to the above parameters and this dependence is device and drug-specific (Chrystyn et al., 2015; Horváth et al., 2020). In the case of dry powder inhalers, not only the deposited dose but even the inhaled dose (the dose emitted from DPI) and the distribution of particle sizes are dependent on the above parameters (Janson et al., 2017; Buttini et al., 2016; Ung and Chan, 2016).

Much less research data exists in the open literature regarding the effect of breath-hold time after inhalation on the amount of drug depositing in different airway regions. It is usually emphasized that holding the breath at least 5 s after the inhalation of aerosol drugs is important for a high lung deposition. Indeed, deposition by gravitational settling is time dependent and the deposited amount depends on the length of breath-hold. Horváth et al. (2017) demonstrated that longer breath-hold enhanced lung deposition of every studied dry powder drug, though there were significant differences between them in terms of relative lung dose increase. The increase was the most consistent for drugs with high fine and extrafine particle size fractions.

An even less studied phase of aerosol drug delivery is the exhalation of air before the inhalation of the drug, though according to a Ciplamed (2019) study the frequency of errors is the highest in this phase (65.5%). The same conclusion was drawn by Sanchis et al. (2016), who stated that the most frequent error is related to the exhalation before drug inhalation and it is as high as 46%. Vytrisalova et al. (2019) demonstrated that the frequency of errors in this phase is inhaler-specific and varied between 9.5 and 47.5%. Naturally, there are several types of errors even within the exhalation phase, such as insufficient level of lung emptying, emptying in more phases, forgetting to empty, emptying through the inhaler or combination of them. Molimard et al. (2003) and van der Palen et al. (1995) had shown that insufficient emptying of the lungs is more frequent than emptying through the inhaler. In spite of the high probability of patient error during this phase there are currently no studies aiming at the quantification of drug dose loss due to inadequate lung emptying. Lack of pertinent information on the effect of correct exhalation before the inhalation of drug could be also the reason for the reduced awareness on the importance of this phase reflected in the patient information leaflets (PIL) and summary of product characteristics (SPC) of different commercialized aerosol drugs. Our survey on the content of above documents in the case of 34 DPI drugs dispensed in 15 different inhalers (EMC, 2022) revealed that from this point of view the instructions in PILs and SPCs can be categorized into three groups:

(i) Breathe out normally before the inhalation of the drug.
(ii) Breathe out gently (as far as it is comfortable) before the inhalation of the drug.
(iii) Breathe out completely (fully) before the inhalation of the drug.

The aim of this study was to conduct inhalation experiments through several commercially available inhalers in order to study the effect of the above types of exhalation modes on the parameters characterizing the inhalation following it. An additional goal was to quantify the effect of exhalation before the inhalation of drugs on the emitted drug dose and the aerodynamic characteristics of the emitted aerosol particles.

Table 1
Summary of subject demographics and baseline spirometry data. Mean values with standard deviations (first row) and ranges (second row) for the population of 30 volunteers are provided. BMI – body mass index; FEV_1 - expiratory volume at the end of the first second of forced exhalation; FVC – forced vital capacity; PIF – peak inhalation flow; IVC – inspiratory vital capacity.

Age (years)	Gender (F:M %)	BMI (kg/m^2)	FEV_1 (L)	FEV_1 (%)	FVC (L)	FVC (%)	FEV_1/FVC (%)	PIF (L/min)	IVC (L)
38.3 ± 10.2 19–57	60.0:40.0	23.9 ± 3.9 17.8–34.5	3.4 ± 0.7 2.2–5.0	96.6 ± 11.5 77–121	4.2 ± 0.9 2.7–6.4	97.9 ± 12.4 78.0–132.0	97.4 ± 9.0 73.0–113.0	222.2 ± 78.0 88.8–442.8	3.8 ± 0.9 2.4–5.9

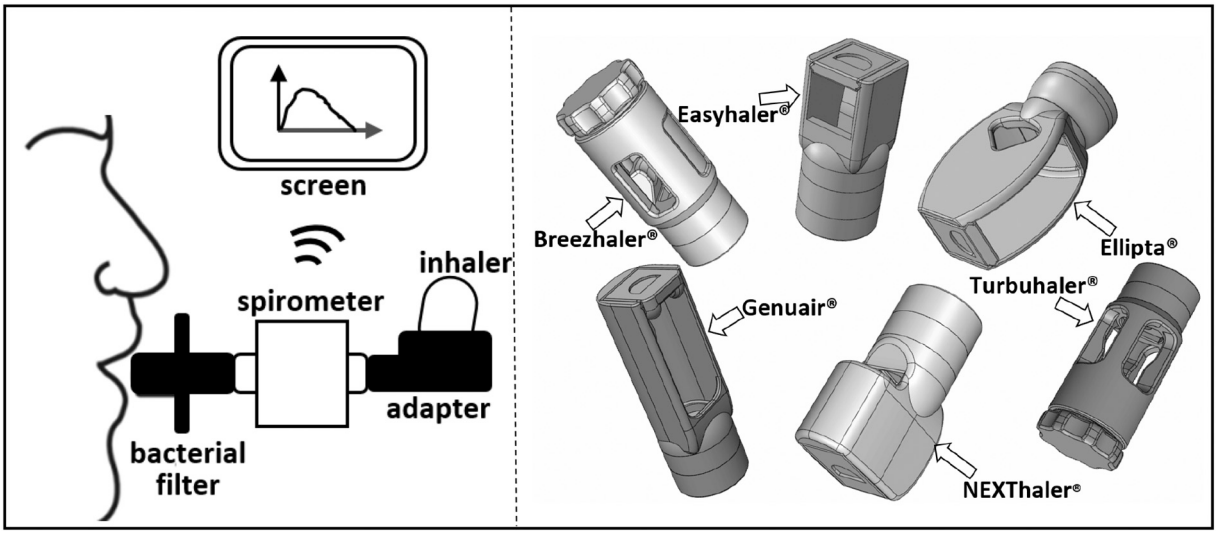

Fig. 1. Experimental setup of the breathing profile measurements (left panel) and 3D models of the six mouthpiece adapters holding the dry powder inhalers and ensuring gapless connections of the inhalers with the spirometer (right panel).

2. Methods

2.1. Experimental measurements

2.1.1. Measurement of inhalation flow profiles

The breathing profile measurements were carried out in the frame of a case-only, observational, non-interventional study according to the study protocol (TBEP-2110/01) approved by National Institute of Pharmacy and Nutrition (OGYÉI/74–1/2022) based on the positive opinion of the Scientific and Research Ethics Committee of the Medical Research Council (ETT TUKEB) of Hungary (registry no IV/657–3/2022/EKU). Thirty healthy adult subjects (18 females and 12 males) were recruited who signed written consent after being informed both orally and in written form. FVC (forced vital capacity) spirometry was performed by the help of a Otthon Idegen™ mobile handheld spirometer of Thor Laboratories (Budapest, Hungary). Three technically acceptable maneuvers were performed and the trial corresponding to the highest FVC value was used. Patient demographics and normal spirometry parameter values measured on the 30 individuals are summarized in Table 1.

Breathing profiles and parameters of the same individuals were also recorded while they inhaled through six different emptied DPI devices (containing no active substances). Each participant performed three inhalation maneuvers: (i) inhalation through the devices preceded by normal exhalation; (ii) gently lung emptying before the inhalation and (iii) forceful exhalation before the inhalation. The order of the devices was randomized. There was a few minutes' relaxation time between the inhalations through every two consecutive inhalers.

The DPI devices selected for this study were Breezhaler®, Easyhaler®, Ellipta®, Genuair®, NEXThaler® and Turbuhaler®. These devices were selected because they are frequently used in the therapy of asthma and COPD, span a large spectrum of flow resistances. The exact values of the flow resistances are 32.3 $Pa^{0.5}s/L$ (Breezhaler®), 67.4 $Pa^{0.5}s/L$ (Easyhaler®), 51.2 $Pa^{0.5}$ s/L (Ellipta®), 58.8 $Pa^{0.5}s/L$ (Genuair®), 68.3 $Pa^{0.5}s/L$ (NEXThaler®) and 66.4 $Pa^{0.5}s/L$ (Turbuhaler®) as measured by Krüger et al. (2014) and Janson et al. (2017). In addition, they represent all the three classes mentioned in the Introduction section upon the instructions on the exhalation before the inhalation of drug. During these measurements one end of the handheld spirometer was connected to the inhalers by 3D printed mouthpiece adapters designed by computer aided design (CAD) techniques. A PBF-100-G-M type bacterium filter was inserted between the spirometer and the mouth of the subject. The filter had circular inlet and elliptical patient side outlet to improve the fitting to the patient's mouth. The filtering material is electrostatically charged tissue (3 M Filtrete) filtering out 99.999% of the bacteria. The resistance of the filter is 1 Pa/L/min, which is negligible compared to the resistance of the inhalers. The effect of the bacterium filter was verified experimentally and no notable change in the total resistance (DPI versus DPI + filter) was observed. A simple sketch of the experimental setup is demonstrated in Fig. 1, left panel. In the right panel of the same figure the pre-print models of the six easy-fits are shown. The mouthpiece adapters needed to fulfil requirements, such as tight contact with the inhaler and the mouthpiece of the inhaler (achieved by design based on laser scanning of exact shapes and sizes and by application of silicone rubber inside the easy-fits), no effect on the airflow entering the inhaler (solved by applying holes in the easy-fit around the air inlet vent of the inhalers) and no effect on the flow resistance. This last criterion was verified by measuring the pressure drop on the devices at different constant flow rates both with the adapter and without, and comparing them. The change of flow resistance was negligible for all adapters (below the measurement error). The handheld spirometer was also validated before the measurements on the patients by the connection of each device to a pump providing constant flow rates of 30, 60, 90, 120 and 150 L/min. Uncertainty of the measured flow rate was also assessed. A detailed description of this procedure can be found in Farkas et al. (2019).

2.1.2. Treatment of the measured breathing data

The individual breathing curves (inhalation flow rate versus time) were processed and one median profile (p50) was constructed for each device and each exhalation mode. The median profiles were obtained by selecting the median value of the flow rates of all individuals at each measurement point (the time resolution was 0.01 s). The main breathing parameter values derived from the measured profiles were the inhaled volume through the device (IV_{dev}), time of inhalation through the device ($t_{in\text{-}dev}$), average flow rate through the device (Q_{dev}) and peak inhalation flow through the device (PIF_{dev}). Mean values, standard deviations and ranges of these device specific breathing data were calculated. The sets of IV_{dev}, $t_{in\text{-}dev}$, Q_{dev} and PIF_{dev} values obtained for the same device at three exhalation modes were inter-compared by two-sample *t*-tests.

Among the above parameters, the key breathing parameter predicting the ability of the patient to optimally use the device is peak inhalation flow through the device (PIF_{dev}). The dose emitted by a DPI, the amount of drug containing particles with aerodynamic diameter smaller than 5 μm and implicitly the fraction of dose depositing within the lungs are influenced by this parameter. The analysis of the dependence of

Table 2
Inhalation drugs considered in the present study.

Name	Manufacturer	Type	Active ingredient(s)		
			ICS	LABA	LAMA
Seebri® Breezhaler®	Novartis	bronchodilator			glycopyrronium bromide
Bufomix® Easyhaler®	Orion Pharma	anti-inflammatory and bronchodilator	budesonide	formoterol fumarate dihydrate	
Relvar® Ellipta®	GlaxoSmithKline	anti-inflammatory and bronchodilator	fluticasone furoate	vilanterol	
Bretaris® Genuair®	Berlin-Chemie Menarini	bronchodilator			aclidinium bromide
Foster® NEXThaler®	Chiesi Farmaceutici	anti-inflammatory and bronchodilator	beclometasone dipropionate	formoterol fumarate dihydrate	
Symbicort® Turbuhaler®	AstraZeneca	anti-inflammatory and bronchodilator	budesonide	formoterol fumarate dihydrate	

PIF_{dev} for each selected device and each exhalation mode on the subject's age, height, weight and baseline spirometric parameters (expiratory volume at the end of the first second of forced exhalation expressed both in L and %: FEV_1; forced vital capacity expressed both in L and %: FVC; Tiffeneau index: FEV_1/FVC; peak inhalation flow: PIF, inspiratory vital capacity: IVC, peak expiratory flow: PEF) was performed by an in-depth statistical evaluation of the inter-relationships. Cross-correlation analysis of the above parameters in connection with each device was performed. The degree of correlation between two different parameters was expressed by the Pearson coefficient (r). Any correlation was considered significant for $p < 0.05$. Predictors of PIF_{dev} were found by stepwise multiple regression analysis using a backward elimination technique. All the statistical analyses were performed by OriginPro® 2021 (version 9.8.0.200, OriginLab Corporation, Northampton, Massachusetts, USA) software.

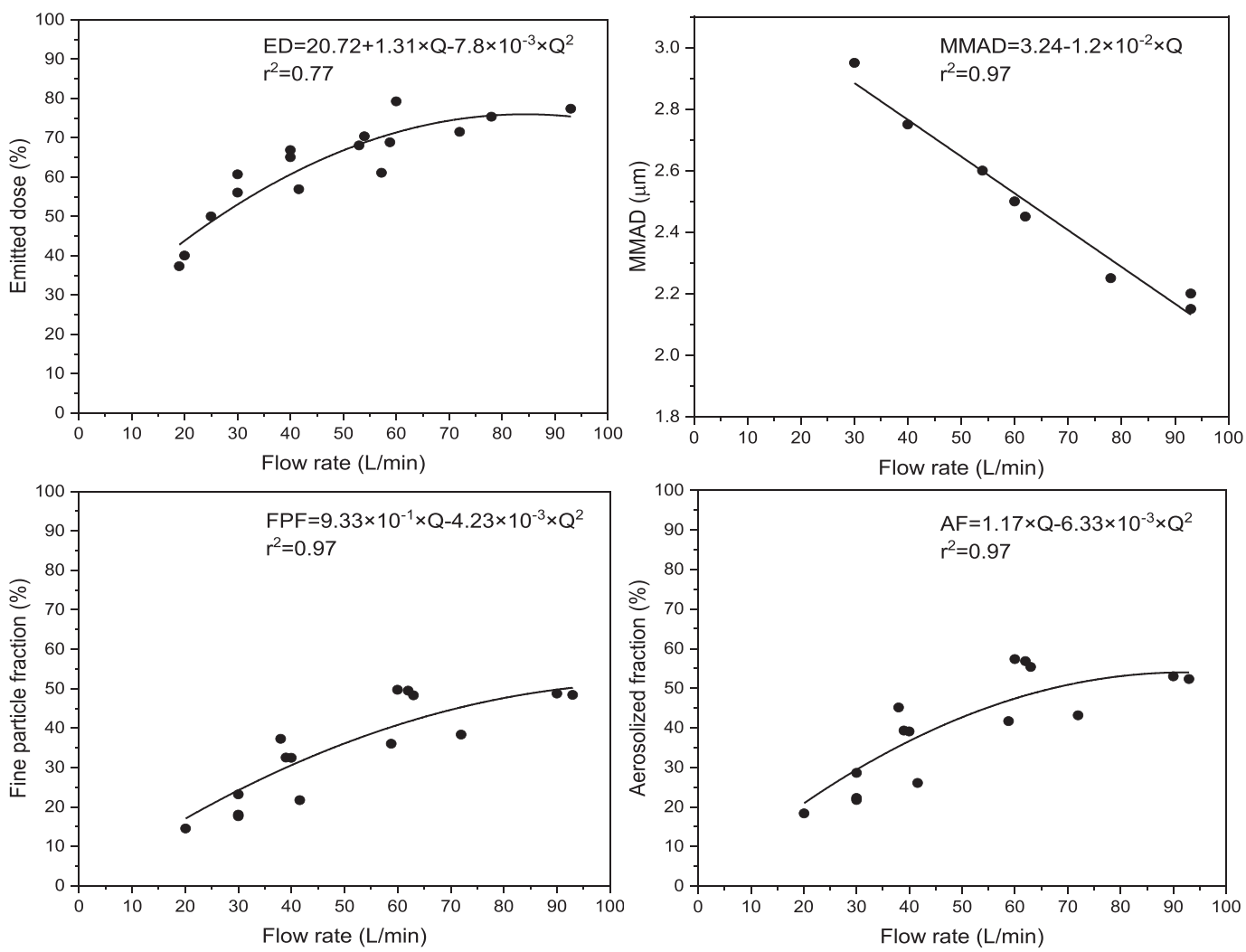

Fig. 2. Flow rate (Q) dependence of the emitted dose (ED, left upper panel), mass median aerodynamic diameter (MMAD, right upper panel), fine particle fraction (FPF, left lower panel) and the aerosolized fraction (AF, right lower panel) of Symbicort® Turbuhaler®. ED, FPF and AF are provided as a percent of metered dose.

2.2. Estimation of personalized emitted drug doses and particle size distributions

Besides the data characterizing the airway geometry and the breathing of subjects, airway transport and deposition of the inhaled aerosol drugs depend on their inhaled amount and aerodynamic properties. However, in the case of drugs emitted by DPIs, both are dependent on the subject's breathing pattern. Therefore, it is necessary to calculate the individual-specific emitted (inhaled) doses and particle size distributions.

Currently, there are several active pharmaceutical ingredients dispensed in Breezhaler®, Easyhaler®, Ellipta®, Genuair®, NEXThaler® and Turbuhaler® inhalers, which may have different aerodynamic properties and airway deposition. In this study, we selected bi-component drugs, assuming that data on their emitted dose and particle size distribution needed for the modelling of airway deposition is retrievable in the literature. For the sake of comparability, we selected only inhalation corticosteroid (ICS) and long-acting beta-agonist (LABA) fixed-dose combination drugs. In two cases (Breezhaler® and Genuair®), only monocomponent (LABA) drugs could be considered, since the ICS + LABA combination is not available in these devices. Therefore, the inhalation drugs considered in this study were Seebri® Breezhaler®, Bufomix® Easyhaler®, Relvar® Ellipta®, Bretaris® Genuair®, Foster® NEXThaler® and Symbicort® Turbuhaler®. The names, manufacturers, types and active ingredients of these aerosol drugs are summarized in Table 2.

2.2.1. Emitted doses

Subject-specific emitted doses (ED) were determined based on the measured data available in the open literature. In the published works, emitted doses are provided for different constant inhalation flow rate values. In this work, these data were used to derive mathematical expressions of the emitted doses as functions of inhalation flow rate. This allowed us to assign an emitted dose to each subject based on her/his individual inhalation flow rate. As an illustration of the emitted dose calculation method, the left upper panel of Fig. 2 demonstrates the emitted dose of Symbicort® Turbuhaler® as a function of inhalation flow rate using experimentally measured dose values from the open literature (Chrystyn et al., 2015; Buttini et al., 2016; Bagherisadegi et al., 2017; de Boer et al., 2015; Haikarainen et al., 2017; Assi et al., 2006).

2.2.2. Size distributions of the emitted particles

A similar method to the one described above (2.2.1.) was applied to calculate patient-specific size distributions of the emitted particles based on published experimental measurement results and individual inhalation flow rates measured within the present work. The personalized size distributions were reconstructed from the available information on the MMADs (mass median aerodynamic diameter), GSDs (geometric standard deviation), fine particle fractions (FPF, the fraction of the metered dose provided by particles with diameter < 5 μm) and aerosolized fractions (AF). Aerosolized fraction is defined here as the fraction of the metered dose represented by smaller particles which in the drug aerodynamic characterization experiments deposit on the impactor plates and on the filter. With the help of AF, it is possible to determine the particle fraction depositing in the impactor inlet throat and in the pre-separator (which are not accounted for when calculating MMAD, GSD and FPF) by extracting AF from ED. Right upper panel of Fig. 2 demonstrates the MMAD of Symbicort® Turbuhaler® as a function of inhalation flow rate, while the lower panels illustrate the fine particle fraction (left) and the aerosolized fraction (right) of the same drug derived from the works of Tarsin et al. (2004), Johal et al. (2013), Watz et al. (2021), Chrystyn et al. (2015), Buttini et al. (2016), Bagherisadegi et al. (2017), de Boer et al. (2015), Haikarainen et al. (2017) and Assi et al. (2006). It is worth noting that the aerosolized fractions are not measured values, but they were calculated assuming lognormal size distribution with the help of the formula

$$AF = \frac{2FPF}{1 + erf\left(\frac{ln(5) - ln(MMAD)}{\sqrt{2}\,ln(GSD)}\right)} \quad (1)$$

where *erf* is the error function.

$$erf(x) = \frac{2}{\sqrt{\pi}}\int_0^x e^{-t^2}dt \quad (2)$$

Though the plot corresponding to AF has a quite similar shape to the shape of the curve depicting the flow rate dependency of FPF, AF values are slightly higher than the FPF values corresponding to the same flow rate. Similar polynomial functions were derived for all the drugs considered in this study. These relationships are presented in Table 3. The presented functions are based on the results of impactor measurements on Seebri® Breezhaler® retrieved in Chapman et al. (2011) and Colthorpe et al. (2013), Bufomix® Easyhaler® available in Malmberg et al. (2014), Lahelma et al. (2015), Janson et al. (2017) and Haikarainen et al. (2017), Relvar® Ellipta® published in Hamilton et al. (2015), Grant et al. (2015) and Saeed et al. (2019), Bretaris® Genuair® published in Block et al. (2010) and Newman et al. (2009), and on Foster® NEXThaler® published by Buttini et al. (2016), Corradi et al. (2014), Mariotti et al. (2011), de Boer et al. (2015) and Watz et al. (2021).

Table 3
Formulas for the determination of the emitted dose (ED), mass median aerodynamic diameter (MMAD), fine particle fraction (FPF) and the aerosolized fraction (AF) of Seebri® Breezhaler®, Bufomix® Easyhaler®, Relvar® Ellipta®, Bretaris® Genuair®, Foster® NEXThaler® and Symbicort® Turbuhaler® inhalation drugs. ED, FPF and AF are expressed as a percent of metered dose.

	Seebri® Breezhaler®	Bufomix® Easyhaler®	Relvar® Ellipta®
ED (%)	$70.63 + 2.05 \times 10^{-1} \times Q$	$2.49 \times Q\text{-}1.95 \times 10^{-2} \times Q^2$	$61.02 + 9.25 \times 10^{-1} \times Q\text{-}6.87 \times 10^{-3} \times Q^2$
MMAD (μm)	$2.93\text{–}3.44 \times 10^{-3} \times Q$	$3.19\text{–}1.01 \times 10^{-2} \times Q$	$3.79\text{–}1.53 \times 10^{-2} \times Q$
GSD	1.90	1.90	2.10
FPF (%)	$29.07 + 2.85 \times 10^{-1} \times Q\text{-}2.18 \times 10^{-4} \times Q^2$	$6.92 \times 10^{-1} \times Q\text{-}2.67 \times 10^{-3} \times Q^2$	$8.42 \times 10^{-1} \times Q\text{-}5.37 \times 10^{-3} \times Q^2$
AF (%)	$36.23 + 3.28 \times 10^{-1} \times Q\text{-}4.47 \times 10^{-4} \times Q^2$	$8.73 \times 10^{-1} \times Q\text{-}4.19 \times 10^{-3} \times Q^2$	$28.80 + 1.74 \times 10^{-1} \times Q\text{-}4.38 \times 10^{-4} \times Q^2$

	Bretaris® Genuair®	Foster® NEXThaler®	Symbicort® Turbuhaler®
ED (%)	$59.71 + 7.16 \times 10^{-1} \times Q\text{-}4.19 \times 10^{-3} \times Q^2$	$80.42 + 2.78 \times 10^{-2} \times Q$	$20.72 + 1.31 \times Q\text{-}7.80 \times 10^{-3} \times Q^2$
MMAD (μm)	2.50	$2.29\text{–}1.57 \times 10^{-2} \times Q$	$3.24\text{–}1.20 \times 10^{-2} \times Q$
GSD	1.80	2.25	1.90
FPF (%)	$7.99 \times 10^{-1} \times Q\text{-}4.48 \times 10^{-3} \times Q^2$	$40.39 + 1.34 \times 10^{-1} \times Q$	$9.33 \times 10^{-1} \times Q\text{-}4.23 \times 10^{-3} \times Q^2$
AF (%)	$9.32 \times 10^{-1} \times Q\text{-}5.81 \times 10^{-3} \times Q^2$	$48.26 + 8.70 \times 10^{-2} \times Q$	$1.17 \times Q\text{-}6.33 \times 10^{-3} \times Q^2$

3. Results

3.1. Airflow measurements

Figure 3 presents the median (p50) inhalation profiles of 30 subjects when inhaling through Breezhaler®, Easyhaler®, Ellipta®, Genuair®, NEXThaler® and Turbuhaler® DPI inhalers after no lung emptying, slight lung emptying and forced lung emptying. As expected, the breathing patterns were inhalation device-dependent. The peak inhalation flow through the device (PIF_{dev}) was the highest in the case of the

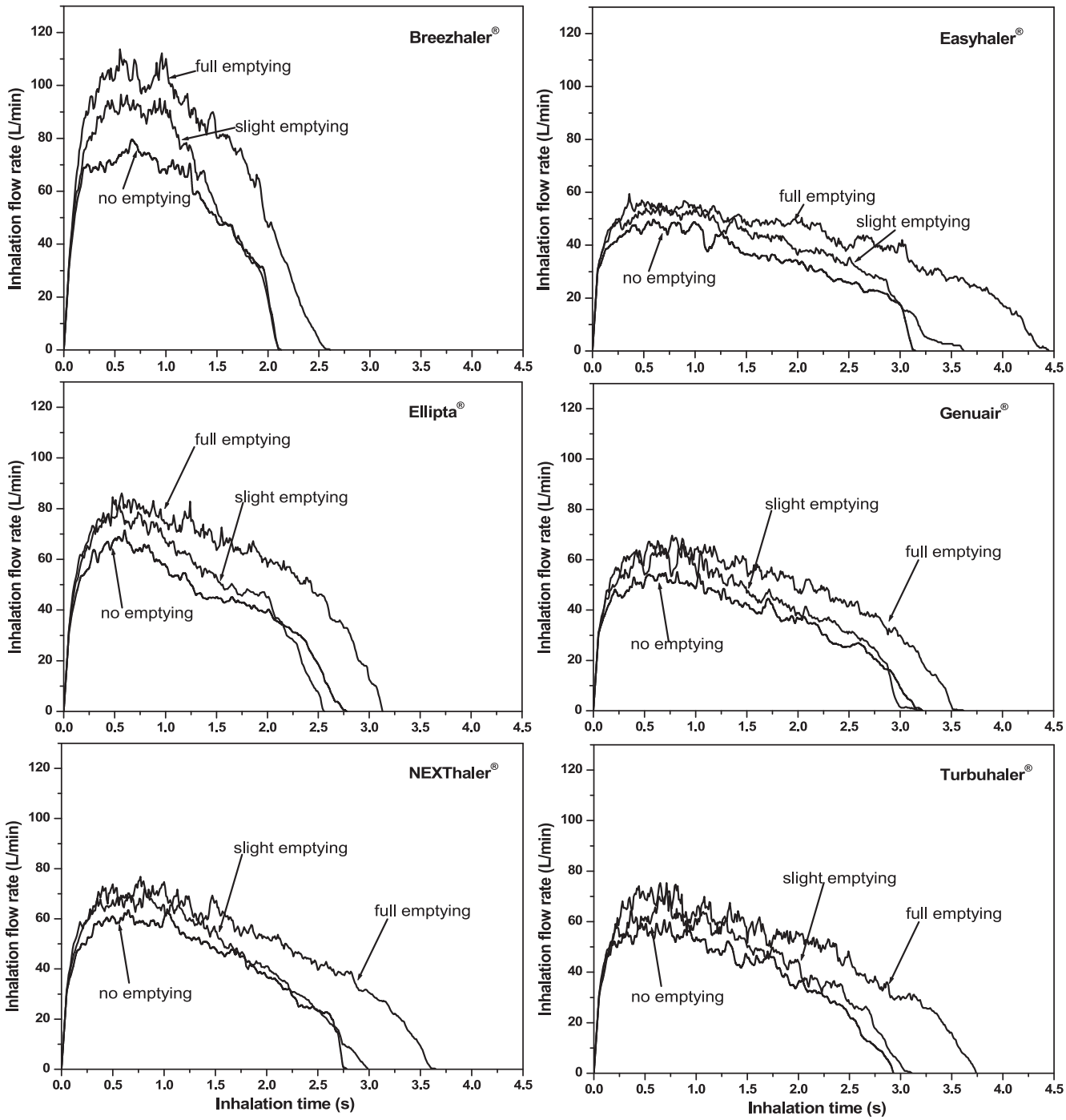

Fig. 3. Median (p50) inhalation profiles of 30 subjects when inhaling through Breezhaler®, Easyhaler®, Ellipta®, Genuair®, NEXThaler® and Turbuhaler® DPI inhalers after no, slight and full lung emptying.

DPI with the lowest flow resistance (Breezhaler®) and it was the lowest for the device with the highest resistance (Easyhaler®). More importantly, for all the DPIs the flow rate maximum increased when the subjects slightly emptied their lungs and further increased when they fully emptied their lungs. Concomitantly, the time of inhalation ($t_{in\text{-}dev}$) increased for some of the inhalers at slight lung emptying and for all the inhalers at forced lung emptying. Inherently, the increase in the flow rate and inhalation time caused the increase in the inhaled volume (IV_{dev}), which is the surface area under the curves in Fig. 3. The same tendencies could be observed in the male and female subgroups, though mean values of PIF_{dev}, $t_{in\text{-}dev}$ and IV_{dev} were lower for females than for males by 30.5%, 6.9% and 34.6%, respectively (averaged over all the devices and lung emptying modes). The mean values, standard deviations and ranges of the three parameters (PIF_{dev}, $t_{in\text{-}dev}$ and IV_{dev}) for the whole population (males and females) are summarized in Table 4.

Table 4 shows that the mean value of the relative increase in peak inhalation flow due to forceful exhalation was device specific and varied between 15.3 and 38.4% (min: Easyhaler®, max: Breezhaler®), compared to the case of normal (tidal) exhalation before the drug inhalation. The relative increase in the inhaled volume was between 36.4 and 57.1% (min: NEXThaler®, max: Turbuhaler®).

Based on the results of statistical tests (two-sample *t*-test), the values of PIF_{dev}, Q_{dev} and IV_{dev} were significantly higher for all the devices after forceful lung emptying compared to no lung emptying. At the same time,

Table 4
Mean values, standard deviations and ranges of peak inhalation flow (PIF_{dev}), inhalation time ($t_{in\text{-}dev}$) and inhaled volume IV_{dev} through six DPI devices and three different lung emptying modes.

	PIF_{dev} (L/min)			$t_{in\text{-}dev}$ (s)			IV_{dev} (L)		
	no emptying	slight emptying	forceful emptying	no emptying	slight emptying	forceful emptying	no emptying	slight emptying	forceful emptying
Breezhaler®	86.0 (31.1)	102.7 (27.8)	119.0 (29.8)	2.4 (0.9)	2.3 (0.8)	2.5 (0.6)	2.3 (0.6)	2.6 (0.7)	3.3 (1.0)
	38.5–149.8	50.9–170.9	62.2–197.1	1.1–4.0	1.3–4.6	1.3–4.1	1.2–4.0	1.4–4.0	1.3–5.2
Easyhaler®	51.6 (14.4)	56.6 (13.4)	59.5 (13.0)	3.4 (1.2)	3.5 (1.1)	4.5 (1.4)	2.0 (0.7)	2.3 (0.7)	3.1 (1.0)
	28.1–84.2	34.5–85.7	38.9–91.9	1.7–6.8	2.2–6.4	1.9–8.1	1.1–3.9	1.2–4.1	1.4–5.1
Ellipta®	74.3 (26.2)	82.5 (22.8)	91.7 (26.2)	2.7 (0.8)	2.7 (0.8)	3.1 (0.8)	2.2 (0.7)	2.5 (0.7)	3.2 (1.0)
	39.1–153.4	45.2–131.3	52.6–158.0	1.3–4.0	1.6–4.4	1.2–4.4	1.1–3.6	1.2–4.1	1.1–5.2
Genuair®	60.2 (20.5)	67.0 (18.7)	73.3 (20)	3.2 (1.1)	3.2 (1.0)	3.7 (1.1)	2.1 (0.7)	2.4 (0.7)	3.1 (1.0)
	32.4–114.3	37.8–116.2	42.5–123.3	1.5–5.8	1.5–5.4	1.3–6.3	0.9–3.4	0.9–4.2	0.7–4.8
NEXThaler®	67.0 (21.4)	70.6 (20.9)	77.8 (20.4)	2.9 (0.9)	3.0 (0.9)	3.5 (0.9)	2.2 (0.7)	2.4 (0.7)	3.0 (0.9)
	33.0–118.4	31.9–115.4	30.1–119	1.0–5.1	1.8–4.8	1.7–5.2	1.1–3.7	1.1–3.7	1.6–4.9
Turbuhaler®	64.8 (19.8)	72.4 (17.1)	78.8 (21.1)	2.9 (0.9)	3.0 (0.8)	3.8 (1.0)	2.1 (0.7)	2.5 (0.8)	3.3 (1.0)
	31.1–127.6	44.3–102.8	48.2–134.1	1.1–4.5	1.3–4.7	1.7–5.6	0.8–3.4	0.8–3.9	1.0–5.0

Table 5
Coefficients describing the linear relationship between peak inhalation flow through the six inhalers and native peak inhalation flow for three different lung emptying modes and the corresponding correlation coefficients.

	Breezhaler®			Easyhaler®			Ellipta®		
	A	B	r	A	B	r	A	B	r
no lung emptying	0.23	35.4	0.57	0.10	29.9	0.53	0.17	36.4	0.51
slight lung emptying	0.19	59.8	0.54	0.09	37.1	0.52	0.18	41.9	0.58
forceful lung emptying	0.28	56.8	0.73	0.10	36.4	0.62	0.19	48.5	0.62

	Genuair®			NEXThaler®			Turbuhaler®		
	A	B	r	A	B	r	A	B	r
no lung emptying	0.12	33.7	0.45	0.14	36.5	0.50	0.09	45.1	0.35
slight lung emptying	0.14	36.7	0.52	0.09	51.6	0.32	0.11	47.4	0.51
forceful lung emptying	0.13	43.7	0.57	0.14	47.7	0.52	0.16	42.9	0.60

the increase of the values of the same parameters due to slight lung emptying was not statistically significant (except for PIF_{dev} through Breezhaler® and Turbuhaler®) at this sample size (30 subjects) and significance level ($p = 0.05$). Peak inhalation flows through the DPIs (PIF_{dev}) regularly correlated with native spirometric parameters FEV_1(L), FVC(L), PEF (L/min), PIF (L/min) and IVC (L). However, only native PIF could be retained as a predictor of PIF_{dev}. The coefficients (slope: A, intercept: B) of the linear relationship ($PIF_{dev} = A \times PIF + B$) between the two peak inhalation flow values and the corresponding correlation coefficients (r) are summarized in Table 5. With the help of these relationships, it is possible to assess the peak flow of a subject through different devices (with a certain probability), if the native spirometric peak flow is known. Based on the values of the correlation coefficient, PIF_{dev} is best predicted by native PIF when the subject exhales forcefully before the inhalation.

3.2. Emitted doses and aerosol size distributions

The breathing parameters and the formulas presented in Table 3 made it possible to calculate individual-specific emitted doses and drug particle size distributions for all 30 volunteers when inhaling through six different DPIs after three different lung emptying modes (see Fig. 4).

The upper left panel of Fig. 4 demonstrates the distributions of emitted doses (ED) of Seebri® Breezhaler® corresponding to three lung emptying modes of 30 subjects. The boxes show the interquartile range (difference between 75% and 25% percentiles), the median value (horizontal line inside the box), the average value (small empty rectangle inside the box) and lower and upper whiskers (from minimum to the lower quartile and from the upper quartile to the maximum). The characteristics of the distributions of fine particle fraction (FPF, upper right panel) and mass median aerodynamic diameters (MMAD, lower left panel) are presented in a similar way. These parameters combined with GSD and AF provided the size distributions depicted in the lower right panel of the same figure corresponding to median inhalation profiles of Fig. 3, left upper panel. As the figure demonstrates, the increase in the degree of lung emptying caused the increase in the emitted dose. By the same token, the emitted particles became smaller suggesting a higher chance for lung penetration. Similar distributions and parameter values were determined for Bufomix® Easyhaler®, Relvar® Ellipta®, Bretaris® Genuair®, Foster® NEXThaler® and Symbicort® Turbuhaler®. It is worth noting that as a consequence of lower flow rate and inhaled volumes, females had lower emitted doses and higher MMAD values than males. Mean values, standard deviations and ranges of ED, MMAD and FPF of these drugs are summarized in Table 6 for the three studied lung emptying modes. The relative increase in the emitted dose varied between 0.2 and 8.0% (min: Foster® NEXThaler®, max: Bufomix® Easyhaler®), while the relative enhancement of fine particle dose ranged between 1.9 and 30.8% (min: Foster® NEXThaler®, max: Symbicort® Turbuhaler®), depending on the inhaler. A low value of the change of these parameters (Foster® NEXThaler®) suggests that airway deposition is relatively insensitive to the lung emptying, while high values indicate that important gain in deposition can be obtained by a forceful lung emptying.

4. Discussion

The present study demonstrated that switching to a more intense lung emptying before the inhalation resulted in higher inhaled volume (IV_{dev}), inhalation flow rate (Q_{dev}) and peak inhalation flow (PIF_{dev}) values for all the inhalers, but the relative increase was inhaler specific.

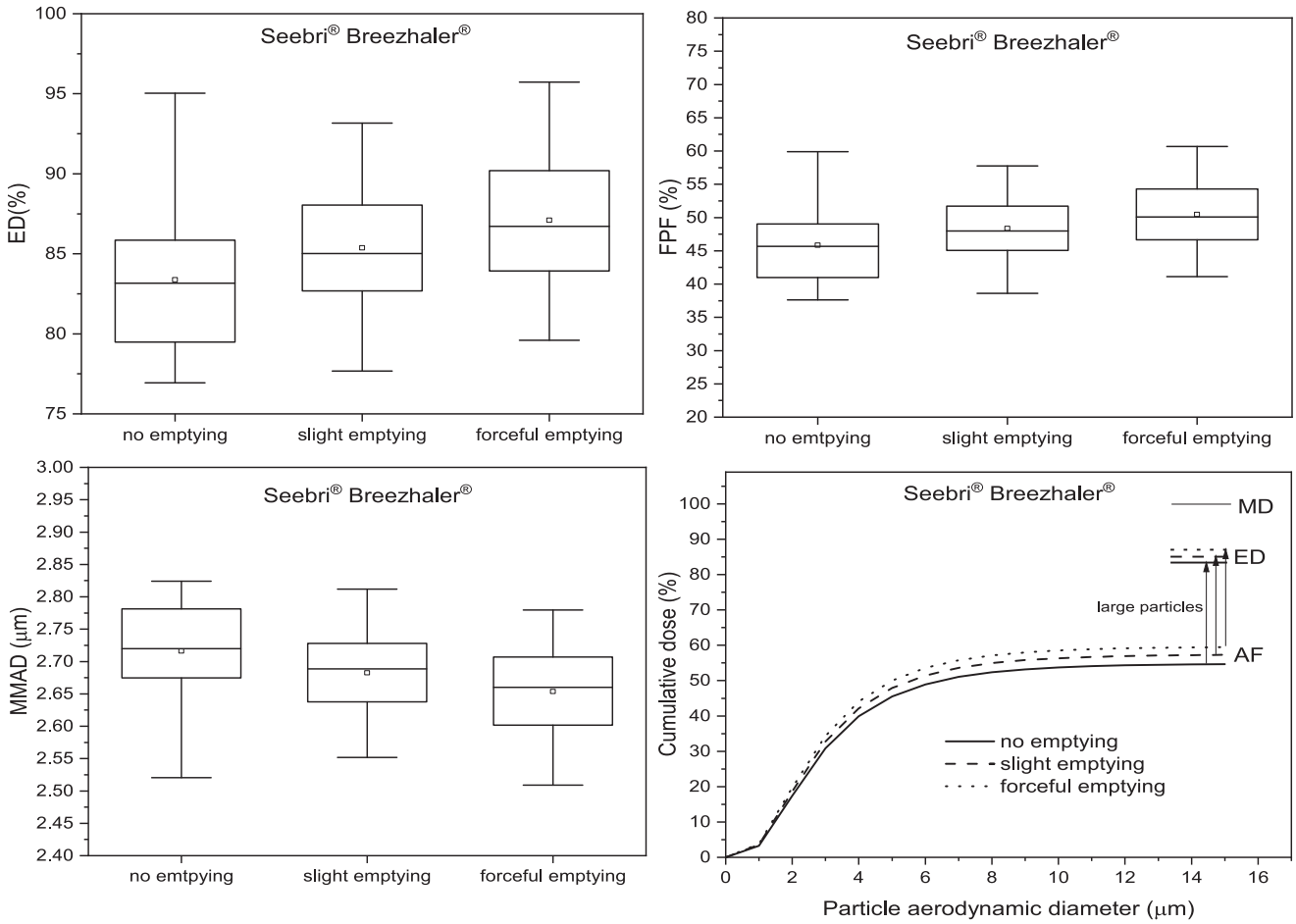

Fig. 4. Box plots of the distributions of emitted doses (ED, upper left panel), fine particle fractions (FPF, upper right panel) and mass median aerodynamic diameters (MMAD, lower left panel) of Seebri® Breezhaler® corresponding to three lung emptying modes of 30 subjects; and cumulative size distributions of the same drug corresponding to medium inhalation profiles depicted in the left upper panel of Fig. 3 (lower right panel). AF – aerosolized fraction; MD – metered dose. ED, FPF and AF are provided as a percentage of the metered dose.

Table 6
Calculated mean values, standard deviations and ranges of the distributions of subject-specific ED, MMAD and AF of Seebri® Breezhaler®, Bufomix® Easyhaler®, Relvar® Ellipta®, Bretaris® Genuair®, Foster® NEXThaler® and Symbicort® Turbuhaler® corresponding to three different lung emptying modes before the inhalation of the drug. In the case of combination drugs the values shown in the table are the averages of the values characteristic of ICS and LABA components (Bufomix Easyhaler: budesonide and formoterol fumarate combined; Relvar Ellipta: fluticasone fourate and vilanterol combined; Foster NEXThaler: beclometasone dipropionate and formoterol fumarate dehydrate combined; Symbicort Turbuhaler: Budesonide and formoterol fumarate dehydrate combined). In the case of monocomponent drugs (Seebri Breezhaler and Bretaris Genuair) the values refer to the LAMA API (glycopyrronium bromide and umeclidinium bromide, respectively).

		ED (%)			MMAD (μm)			FPF (%)		
		no emptying	slight emptying	forceful emptying	no emptying	slight emptying	forceful emptying	no emptying	slight emptying	forceful emptying
Seebri® Breezhaler®	mean	83.4 (4.4)	85.4 (3.8)	87.1 (4.0)	2.7 (0.1)	2.7 (0.1)	2.6 (0.1)	45.8 (5.5)	48.4 (4.7)	50.5 (4.9)
	(STD)	76.9–95.0	77.7–93.2	79.6–95.7	2.5–2.8	2.6–2.8	2.5–2.7	37.6–59.9	38.6–57.8	41.1–60.7
	range									
Bufomix® Easyhaler®	mean	63.8 (9.9)	67.1 (7.4)	68.9 (6.1)	2.8 (0.1)	2.8 (0.1)	2.8 (0.1)	21.7 (4.6)	23.3 (4.1)	24.1 (3.5)
	(STD)	43.8–77.6	51.0–79.5	57.2–78.9	2.6–3.0	2.6–2.9	2.6–2.9	13.4–29.5	16.0–33.1	18.4–31.3
	range									
Relvar® Ellipta®	mean	88.8 (3.3)	89.9 (2.1)	90.7 (2.0)	3.0 (0.2)	2.9 (0.2)	2.8 (0.2)	27.8 (4.0)	29.3 (2.7)	30.7 (2.0)
	(STD)	77.8–92.2	84.1–92.2	52.1–92.2	2.3–3.5	2.2–3.2	2.2–3.1	15.7–33.0	23.6–33.0	26.3–33.0
	range									
Bretaris® Genuair®	mean	81.7 (4.0)	83.6 (3.4)	84.5 (3.1)	2.5	2.5	2.5	24.9 (4.7)	27.1 (4.0)	28.2 (3.7)
	(STD)	74.3–90.0)	77.9–89.5	78.3–90.3	-	-	-	16.4–34.9	20.5–34.3	21.0–35.4
	range									
Foster® NEXThaler®	mean	81.7 (0.4)	81.8 (0.4)	81.9 (0.3)	1.5 (0.2)	1.5 (0.2)	1.4 (0.2)	46.7 (1.9)	46.9 (1.9)	47.6 (1.7)
	(STD)	81.1–82.7	81.1–82.6	81.2–82.6	1.0–1.9	1.0–1.9	1.0–1.9	43.6–51.4	43.8–51.0	43.9–51.1
	range									
Symbicort® Turbuhaler®	mean	62.5 (6.4)	65.6 (5.6)	66.7 (5.4)	2.7 (0.2)	2.6 (0.1)	2.6 (0.1)	32.8 (6.5)	35.4 (5.7)	42.9 (5.6)
	(STD)	50.7–74.7	53.3–75.4	54.3–75.4	2.1–2.9	2.2–2.9	2.3–2.9	22.4–50.7	24.4–49.8	30.7–52.7
	range									

It has been previously shown that, at least for drugs emitted by Breezhaler®, Turbuhaler® and Genuair®, increased inhalation flow results in higher lung deposition. Higher lung doses also correlated with increased inhaled volumes (Horváth et al., 2020). It is most likely that, at least for some drugs, more forceful exhalation leads to a higher lung deposition fraction. This is also underpinned by the effect of lung emptying on the emitted doses and aerosol drug particle sizes. Based on the results highlighted in Table 6, the emitted dose increased in all the studied cases by increasing the degree of exhalation before the inhalation of drugs, though the extent of the increase varied among different drugs. This means higher inhaled doses, that is, a higher amount of drug that potentially deposits in the airways. Theoretically this could also mean higher upper airway deposition, but the decreasing particle size and the increasing fine particle fraction (Fig. 4) promote higher lung doses. The exact change in lung dose could be evaluated by simulating airway transport and deposition based on the breathing and aerosol parameter values determined in this study.

It is worth noting that all the above statements are valid for the average values of the breathing and aerosol parameters (averaged over 30 subjects). However, the present work demonstrated that their inter-subject variability is high and in spite of the general tendencies, it is not excluded that there are some subjects and inhalers that do not exhibit the same tendency. This highlights the importance of choosing the appropriate device-drug pair by taking into account both the device particularities and the individual breathing capability of the patient. As females had significantly lower inhalation flow rates and inhaled volumes resulting in lower emitted doses and larger particle sizes, it is advisable to take into account these gender-related particularities when choosing the appropriate inhaler.

To decide for a given subject which inhaler-drug pair would yield significantly increased lung deposition by intensifying the degree of lung emptying, it is necessary to assess the lung deposition of each drug in the lungs of each subject. This would be an important step toward knowledge-based inhaler choice and aerosol drug delivery optimization. Such deposition modelling efforts, using the current measurement and computational results as inputs, are in progress and the results will be presented in our future publication.

Since present results suggest better lung deposition after an inhalation preceded by full lung emptying, it is advisable that manufacturers revise their summary of product characteristics and patient information leaflet documents to emphasize the role of forceful lung emptying before the inhalation of the drug.

Finally, as a limitation of the study, it is worth mentioning that present results were obtained on healthy volunteers. While well controlled asthmatics could be able to forcefully empty their lungs, severe and symptomatic asthmatic patients may encounter difficulties, especially in more elevated states of the disease or during asthma attacks. Similarly, in the case of COPD patients, bronchial constriction, dynamic hyperinflation, increased residual volume and increased functional residual capacity may lead to reduced chances of full exhalation before the inhalation of the drug. In addition, as severe COPD can lead to cachectization, exhalation capacity of these patients may be further reduced. In order to reveal the differences between healthy and diseased subjects it is planned to repeat the present experimental measurements in both mild and severe asthmatic and COPD patients in the future. However, according to the results of the present study even a weaker exhalation can lead to gains in terms of more optimal amount of drug available for inhalation and higher chances of reaching the lungs compared to the total lack of lung emptying. Therefore, it is highly recommended to draw the patient's attention to exhale as strongly as they are able before the inhalation through the inhaler device.

5. Conclusions

Spirometry measurements on 30 volunteers were performed to study the effect of the degree of lung emptying before the inhalation of aerosol drugs on the breathing patterns through 6 commercially available DPI devices. Published data and numerical schemes were used to assess the effect of exhalation power on the aerodynamic properties of 6 selected drugs which are filled in these devices. The present study demonstrated that the degree of lung emptying before the inhalation of aerosol drugs has a non-negligible effect on the parameters characterizing the inhalation of drugs through different DPIs. As a consequence of the dependence of the amount and size of the emitted particles on the inhalation parameters, these are indirectly influenced by the exhalation phase preceding the inhalation. In the light of these results, the education of patients on the significance of forceful exhalation before inhaling through the device is highly important. The results of this work also revealed that the influence of exhalation on the inhalation manoeuvre and the aerodynamic characteristics of the emitted drug particles depends on the DPI device, active ingredients and carriers metered in the device, breathing capacity and other characteristics (e.g. gender) of the patient. This highlights the complexity of patient-inhaler-drug particle interaction. At the same time, present results demonstrate the necessity of patient tailored device choice and treatment optimization. In this context combination of spirometry measurements with computer simulations can be a powerful tool.

CRediT authorship contribution statement

Árpád Farkas: Conceptualization, Methodology, Writing – original draft, Validation, Writing – review & editing. **Gábor Tomisa:** Conceptualization, Methodology, Writing – original draft. **Szilvia Kugler:** Conceptualization, Validation, Writing – review & editing. **Attila Nagy:** Conceptualization, Validation, Writing – review & editing. **Attila Vaskó:** Conceptualization, Writing – review & editing. **Erika Kis:** Methodology, Visualization, Writing – original draft. **Georgina Szénási:** Conceptualization, Writing – review & editing. **Gabriella Gálffy:** Conceptualization, Methodology, Writing – review & editing. **Alpár Horváth:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Arpad Farkas reports financial support was provided by Centre for Energy Research. Gabor Tomisa, Alpar Horvath, Georgina Szenasi reports a relationship with Chiesi Hungary Kft that includes: employment.

Data availability

Data will be made available on request.

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