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The effect of lung emptying before the inhalation of aerosol drugs on drug deposition in the respiratory system

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ABSTRACT

The amount of drug depositing in the airways depends, among others, on the inhalation manoeuvre and breathing parameters. The objective of this study was to quantify the effect of lung emptying before the inhalation of drugs on the lung doses. Thirty healthy adults were recruited. Their breathing profiles were recorded while inhaling through six different emptied DPI devices without breathe-out and after comfortable or forced exhalation. The corresponding emitted doses and aerosol size distributions were derived from the literature. The Stochastic Lung Model was used to estimate the deposited doses. In general, forceful exhalation caused increased flow rate and inhaled air volume. Increased flow rate led to the increase of the average lung dose for drugs with positive lung dose-flow rate correlation (e.g. Symbicort®: relative increase of 6.7%, Bufomix®: relative increase of 9.2%). For drugs with negative correlation of lung dose with flow rate (all the studied drugs except the above two) lung emptying caused increased (Foster® by 2.7%), almost unchanged (Seebri®, Relvar®, Bretaris®) and also decreased (Onbrez® by 6.6%) average lung dose. It is worth noting that there were significant inter-individual differences, and lung dose of each drug could be increased by a number of subjects. In conclusion, the change of lung dose depends on the degree of lung emptying, but it is also inhaler and drug specific. Forceful exhalation can help in increasing the lung dose only if the above specificities are taken into account.

1. Introduction

The effects of therapeutic particles deposited on the airway surface depend on the complex particle-lung interactions (Gehr and Hexder, 2000). However, the first condition of any interaction between the epithelial surface and the drug is that the drug particle deposits in the airways by one of the physical mechanisms of deposition, that is, impaction, stochastic processes (turbulent and thermal diffusion), sedimentation and electrostatic attraction (Rosati et al., 2013). Inertial impaction is the dominant mechanism for large particles (with aerodynamic diameter bigger than 1 μm) especially at high air velocities which are generally characteristic of the larger airways, such as the upper airways and large bronchi (Stahlhofen et al., 1989). The probability of deposition by Brownian diffusion increases by the decrease of particle size and increase of particle residence time. This mechanism is significant in the case of ultrafine particles (< 0.1 μm), but it is the most effective for the smallest nanoparticles (< 0.01 μm) (Cheng and Swift, 1995). It is worth noting that most of the currently marketed drugs do not contain a significant fraction of particles prone to deposition by Brownian motion. Deposition by turbulent diffusion is characteristic of the anatomical airway regions characterized by turbulent flows, namely the upper airways and the large bronchi at high inhalation flow rates (Hamill, 1979; Ounis and Ahmadi, 1990). Gravitational settling is dependent on particle size, but it is also affected by the residence time of particle within the airways. Consequently, big particle size, low airflow velocity and long breath-hold time after the inhalation increase the chances of deposition by sedimentation (Heyder et al., 1986; Yu and Thiagarajan, 1978). As low air velocities are characteristic of the deeper airways (bronchioli, alveoli), particles that were not filtered out by the larger airways either by impaction or diffusion (aerodynamic diameter between 0.1 and 1 μm) deposit mainly in these deeper regions. Finally, deposition by electrostatic attraction is relevant only in the case of

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charged drug particles (Xi et al., 2014), its likelihood increases with an increasing number of electrical charges and decreasing size of the particles (Finlay, 2021). It is clear from the above statements that the probability of particle deposition is highly dependent on particle density, size and shape, but also on the breathing pattern of the patient. By the same token, size of the drug particle may change inside the airways depending on its hygroscopicity and the moisture content of the airways (Farkas et al., 2022). In addition, the geometry of the airways inherently affects the amount of the deposited drug particles and the spatial distribution of the deposition within the airways. In the case of aerosol drugs emitted by dry powder inhalers (DPIs) both the amount (dose) and size of the inhaled particles depend on the properties of the drug formulated and metered in the device, the inner geometry of the inhaler and the breathing manoeuvre of the patient. In conclusion, a large set of parameters characterizing the drug particles, the inhaler and the patient's airways and breathing will influence the deposition of drug particles. The knowledge-based choice of drug-inhaler pair and the optimisation of breathing mode is necessary to deliver the right amount of the right active substance to the right place in the airways. This implies that we know and control the effect of each relevant parameter influencing the deposition, which is a highly complex task.

In order to control the breathing manoeuvres and parameters influencing the deposition we need to know their exact effect on the deposition relative to each other. There are a number of studies in the open literature aiming for the quantification of the effect of different breathing parameters on lung dose. In this context, the most studied parameter is the inhalation flow rate. There were several attempts in the past to experimentally determine the effect of this breathing parameter, especially on the upper airway deposition of micron sized particles (e.g. Stahlhofen et al., 1989; Usmani et al., 2005; Cheng, 2003) demonstrated that for a given particle size (aerodynamic diameter $>$ 0.5 μm) the extrathoracic deposition fraction of the orally inhaled particles increases exponentially with the increase of inhalation flow rate. Though the deposition efficiency of the same particles increases also in the lungs, the deposition fraction will decrease, as upper airway deposition means less particles entering the lungs. However, aerosol drugs are polydispersed and their size distribution also depends on the inhalation flow rate. The emitted particles become smaller and the number of emitted particles becomes higher by the increase of flow rate. Moreover, even constant lung deposition fraction could lead to increased lung dose as a result of higher emitted dose (higher number of inhaled particles) at higher flow rates. Since the increase of emitted dose and the decrease of particle size with the increase of flow rate is drug specific, a universal (valid for any drug dispensed in any inhaler) relationship for the dependence of the lung dose on the flow rate does not exist. This is in agreement with the observation of Weers and Clark (2017) that the total lung dose of dry powder drugs can exhibit either negative, neutral, or positive flow rate dependence. Horváth et al. (2020) have also found that correlation of lung dose with inhalation flow rate was inhaler and drug specific. According to the same publication, the dependence of lung dose on the inhaled air volume was also highly device and formulation dependent. When considering the determinants of drug airway deposition besides the breathing parameters characterizing the inhalation (flow rate, inhaled volume, inhalation time) of the drug, pre- and post-inhalation phases should also be considered. The dependence of lung dose on the breath-hold time after the inhalation was also the subject of experimental (Leach and Colice, 2010) and computational (Horváth et al., 2017) studies. Here the correlation was always positive, but the extent of lung dose enhancement due to longer breath-hold was drug and inhaler specific.

A relatively unexplored phase of aerosol drug delivery is the lung emptying before the inhalation. Although many studies revealed that lack or insufficient lung emptying is one of the most frequent errors (Sanchis et al., 2016; Vytrisalova et al., 2019; Molimard et al., 2003, among others), to the best of our knowledge, there is no publication in the open literature reporting on the quantification of the effect of lung emptying preceding the inhalation of aerosol drugs on the drug dose depositing in the lungs, as a target site. Therefore, the main objective of this study was to apply complex numerical techniques to calculate the dose deposited in the extrathoratic and lung regions as a result of the lack of lung emptying, slight lung emptying and forceful lung emptying in the case of six different inhalers and drugs based on the measured breathing patterns of adult volunteers.

2. Methods

2.1. Experimentally measured input data

This computational study is based on experimentally measured and calculated input parameter values. The two major groups of input data are represented by breathing parameters of the subjects and the individual-specific aerodynamic characteristics of the studied drugs.

The measurement of breathing parameters when inhaling through different inhalers was the subject of a previous publication (Farkas et al., 2023), thus it will not be repeated here. However, the salient features of the study will be briefly recalled for the sake of the reader. The inhalation patterns of 30 healthy adult volunteers were recorded while they inhaled through six different emptied dry powder inhalers (Breezhaler®, Easyhaler®, Ellipta®, Genuair®, NEXThaler® and Turbuhaler®). The inhalation manoeuvre was repeated based on three different scenarios: (i) without lung emptying before the inhalation; (ii) with slight and comfortable lung emptying and (iii) with forceful exhalation preceding the inhalation (preferably lasting for at least 6 s). These three scenarios were considered in accordance with the indications in the SPCs (Summary of Product Characteristics) and PILs (Patient Information Leaflet) of the marketed drugs. Key inhalation parameters were derived from the measured inhalation patterns (flow rate versus time curve) of each subject inhaling in the above three modes, such as inhaled volume (IV), peak inspiratory flow (PIF), mean inspiratory flow (Q) and inhalation time (t_{in}).

The number and size of the drug particles emitted by dry powder inhalers depend on the above breathing parameters. Individual-specific emitted doses (ED), aerosolized fractions (AF), fine particle fractions (FPF), large particle fractions (LP), mass median aerodynamic diameters (MMAD) and geometric standard deviations (GSD) were computed from analytical formulas yielding their values as a function of the inhalation flow rate. These formulas were derived based on experimentally measured data retrieved in the open literature.

The relationship connecting the inhalation flow rate (Q) with the emitted dose (ED) expressed as a percent of the metered dose can be written as.

$$ED = \frac{a_1 Q}{a_2 + Q} \tag{1}$$

A similar empirical function describes the flow rate dependency of the fine particle fraction (FPF), expressed as a percent of the metered dose.

$$FPF = \frac{a_3 Q}{a_4 + Q} \tag{2}$$

By the same token, the mass median aerodynamic diameter is a linear function of flow rate expressed by.

$$MMAD = a_5 - a_6 Q \tag{3}$$

Assuming that the emitted drug size follows a lognormal distribution, the aerosolized fraction (AF) expressed as a function of metered dose can be written as.

$$AF = \frac{2FPF}{\left(1 + erf\left(\frac{ln5 - lnMMAD}{\sqrt{2}\ln GSD}\right)\right)} \tag{4}$$

where *erf* is the error function and GSD the geometric standard

deviation.

Finally, the large particle fraction (LP) can be calculated as.

$$LP = ED - AF \quad (5)$$

The values of a_1, a_2, a_3, a_4, a_5, a_6 and *GSD* for the seven studied drugs were tabulated (Table 1).

2.2. Calculation of individual-specific airway deposition distributions

The fraction of particles depositing in different parts of the airways were estimated by an in-house deposition model, the Stochastic Lung Model. In this model the inhaled particles are tracked in a stochastic airway structure. Deposition fraction in the upper airways is computed by empirical formulas, while deposition fractions in the intrathoracic airways are calculated by analytical formulas taking into account sedimentation and impaction and diffusion deposition mechanisms. A more detailed description of the model can be found in Madas et al. (2020) and other publications. The model has been validated against experimental data and successfully applied in the past to simulate the deposition of different aerosol drugs (e.g. Farkas et al., 2016; Horváth et al., 2020).

The model was applied to simulate the airway deposition of Seebri® Breezhaler®, Onbrez® Breezhaler®, Bufomix® Easyhaler®, Relvar® Ellipta®, Bretaris® Genuair®, Foster® NEXThaler® and Symbicort® Turbuhaler®. These drugs were selected to model the airway deposition of both monocomponent (either LAMA- long-acting muscarinic antagonist or LABA – long-acting beta agonist) and combination (ICS + LABA – inhalation corticosteroid and long-acting beta agonist) drugs. In addition, we aimed to simulate the cases of two drugs dispensed in the same inhaler (Onbrez® and Seebri®) and the same ingredients metered in different inhalers (Bufomix® and Symbicort®). Finally, we wanted to span the whole spectrum of recommendations regarding the breath-out before the inhalation that can be found in the SPCs and PILs.

3. Results and discussion

The results of the simulations of lung deposition fractions in the cases of 'no lung emptying', 'slight emptying' and 'forceful emptying' are summarized in Table 2. The lung dose values are expressed as a percent of the metered dose. Average values and standard deviations of the calculated deposition fractions of 30 individuals are demonstrated. The table also presents the average values of the relative change of the deposition fraction (in percent) and the significance level of the deposition change due to 'slight emptying' and 'forceful emptying' in comparison with 'no emptying'. Besides the dose values averaged over the whole study population, the number of subjects who increased their lung dose after a forceful breathe-out and the maximum value of relative dose increase is also provided.

As Table 1 demonstrates, there are relevant differences among the deposition fractions of different aerosol drugs in the same airway region (lung) for the same population. More importantly, there are clear differences among the studied drugs in terms of their deposition change as a result of lung emptying before the inhalation. The change of lung dose can be both negative and positive, statistically significant or not (with $p = 0.05$ significance threshold). Therefore, it is plausible to analyse the results on a drug-by-drug basis. It is also important to define fine and extrafine particles, as the discussion of the results is based also on these quantities. By definition, Fine particles are those particles whose aerodynamic diameter is smaller than 5 μm. By the same token, extrafine particles are those particles whose aerodynamic diameter is smaller than 2 μm.

There was a significant increase (average relative increase of 4.5% and 7.8%) of upper airway deposition due to lung emptying in the case of Seebri® Breezhaler®. This increase is strongly related to the higher inhalation flow rates. The average flow rate increased from 58 L/min without lung emptying to 67.8 L/min and 79.2 L/min, characteristic of the slight and forceful lung emptying modes, respectively. The higher flow rates resulted in higher deposition by impaction in the extrathoracic airways. As the upper airways filtered out more particles, the lung dose should have decreased significantly. However, the results showed only an insignificant relative decrease of lung dose (by 0.6% and 1.1% at slight and forced lung emptying, respectively). This was possible due to the higher emitted doses (the average values of the emitted doses expressed as a percent of the metered dose increased from 83.4% to 85.4% and 87.1%), but also because of the better detachment of the drug from the carrier particles (the fine particle fraction increased from 45.8% to 48.4% and 50.5%). The patient information leaflet (PIL) of this drug emphasizes the need for forceful lung emptying before the inhalation of the drug. Our results revealed that despite the negative average change, 16 subjects managed to increase their lung dose (the maximum relative increase was 7.1%) after a forceful lung emptying. The examination of their breathing parameters revealed that lung dose increase was achieved by those who managed to increase their inhaled volume, rather than their inhalation flow rate. This was achievable by increasing both the inhaled volume and the inhalation time, without a significant increase of the inhalation flow rate.

The case of Onbrez® Breezhaler® is instructive because it shows the importance of the formulation. Although Seebri® and Onbrez® are two ingredients dispensed in the same device which was used by the same study participants, the outcome was different. While the average value of the change of lung dose was insignificant in the case of Seebri®, a significant decrease of the lung dose was calculated for Onbrez®. As the breathing parameters of the subjects were the same, the difference can be attributed to the differences in the aerosolization properties of the

Table 1
Parameter values characterizing the emitted dose, fine particle fraction, mass median aerodynamic diameter, aerosolized fraction and geometric standard deviation of the drug particles of Seebri® Breezhaler®, Onbrez® Breezhaler®, Bufomix® Easyhaler®, Relvar® Ellipta®, Bretaris® Genuair®, Foster® NEXThaler® and Symbicort® Turbuhaler®.

Aerosol drug name	a_1	a_2	a_3	a_4	a_5	a_6	*GSD*
Seebri® Breezhaler®	89.47	4.79	58.27	16.83	2.93	0.003	1.9
Onbrez® Breezhaler®	96.50	7.34	40.33	17.64	3.65	0.011	2.0
Bufomix® Easyhaler®	83.35	5.09	91.93	100.33	3.19	0.010	1.9
Relvar® Ellipta®	98.04	5.45	43.48	27.88	3.79	0.038	2.2
Bretaris® Genuair®	92.62	6.47	45.82	28.63	2.71	0.013	2.0
Foster® NEXThaler®	80.42	0.03	40.39	0.13	2.29	0.016	2.4
Symbicort Turbuhaler®	101.28	24.94	117.55	116.34	3.25	0.013	1.9

Table 2
Calculated values of deposited lung doses of seven aerosol drugs as a percent of metered dose after no lung emptying, slight lung emptying and forceful lung emptying, relative change of the lung dose at different degrees of lung emptying relative to the case of no emptying, the number of participants who increased their lung dose by forceful lung emptying, and the maximum value of relative lung dose increase.

Aerosol drug name		Lung dose (%)			Number of subjects increasing their lung dose at forceful emptying	Maximum relative lung dose increase (%)
		no emptying	slight emptying	forceful emptying		
Seebri® Breezhaler®	avg (std)	36.0 (1.7)	35.7 (1.4)	35.6 (6.5)	16	7.1
	rel. Increase		−0.8	−1.1		
	significance (p)		not sig. (0.25)	not sig. (0.51)		
Onbrez® Breezhaler®	avg (std)	26.9 (3.3)	25.7 (2.3)	25.2 (1.8)	8	8.7
	rel. Increase		−4.6	−6.6		
	significance (p)		sig. (0.04)	sig. (0.02)		
Bufomix® Easyhaler®	avg (std)	25.6 (1.1)	26.6 (1.0)	26.9 (0.9)	28	15.0
	rel. Increase		4.0	6.7		
	significance (p)		sig. (<0.01)	sig. (<0.01)		
Relvar® Ellipta®	avg (std)	25.1 (0.8)	24.8 (1.3)	25.0 (1.1)	17	13.5
	rel. Increase		−1.2	0.22		
	significance (p)		not sig. (0.1)	not sign. (0.9)		
Bretaris® Genuair®	avg (std)	26.0 (1.1)	25.7 (0.9)	26.1 (1.1)	16	9.9
	rel. Increase		−1.1	0.4		
	significance (p)		not sig. (0.1)	not sig. (0.9)		
Foster® NEXThaler®	avg (std)	36.7 (2.9)	37.0 (6.6)	37.7 (2.5)	20	15.0
	rel. Increase		0.8	2.7		
	significance (p)		not sig. (0.4)	sig. (0.02)		
Symbicort® Turbuhaler®	avg (std)	28.3 (2.7)	29.7 (2.7)	30.9 (2.8)	28	31.8
	rel. Increase		4.9	9.2		
	significance		sig. (<0.01)	sig. (<0.01)		

two drugs. The emitted dose and the size of the emitted particles are less sensitive to the inhalation flow rate in the case of Onbrez®, thus the loss in lung dose due to the enhancement of upper airway deposition at higher flow rates was less compensated by the increase of the emitted dose and fine particle fraction than it was for Seebri®.

Any kind of lung emptying slightly increased both the extrathoracic and lung deposition fractions of Bufomix® Easyhaler®, and the increase of lung dose was higher after forceful exhalation. The average value of relative lung dose increase was 4% and 6.7% for the slight and forceful lung emptying modes, respectively. The PIL of this generic drug indicates that patients should exhale before the inhalation of the drug without pressing on the forcefulness of the exhalation. Although our results demonstrated that the lung dose of Bufomix® Easyhaler® increased even after slight exhalation, the extent of the increase could be much higher, if the subjects exhaled deeply.

The PIL of Relvar® Ellipta® instructs the patients to exhale comfortably before the inhalation of the drug, without asking for a deep exhalation. Our computer simulation results revealed that averaged over the whole study population the change of lung deposition fraction remains insignificant. As the increase of throat deposition does not have any positive therapeutic effect, it seems that optimization of other inhalation manoeuvres (e.g., inhalation time or breath-hold time) could have stronger effects in the case of this drug. The reason why deep exhalation preceding the inhalation of the drug did not significantly increase the lung dose, relies in the relatively stable aerosol parameters as a function of the patient's breathing. The relatively small increase in the emitted dose, aerosolized fraction and fine particle fraction which promotes higher lung deposition could not overbalance the higher extrathoracic deposition due to the increased inhalation flow rate. The advantage of this characteristic is that patients who are not able or fail to empty their airways before the inhalation of the drug will not experience a significant disadvantage. On the other hand, patients who were able to correctly empty their lungs would not improve their lung deposition significantly.

Similar to the deposition of Seebri® Breezhaler® and Relvar® Ellipta®, Bretaris® Genuair® exhibited an insignificant level of average lung dose change as result of lung emptying, though 16 individual patients managed to increase their lung dose by higher inhaled volume and longer inhalation time. The PIL of this drug warns the patients to breathe out completely. It seems that deep exhalation can lead to higher lung dose of this drug by allowing for higher inhaled air volume values, but only if this is not accompanied by significantly increased flow rate.

Foster® NEXThaler® contains a breath actuated mechanism (BAM) with the role of retaining the release of the drug until the patient's inhalation flow rate reaches a value of about 35 L/min. After reaching this flow rate the drug is released in about 0.1–0.3 s. As a result, the emitted dose is almost independent of the patient's inhalation capabilities (assuming that the peak flow is higher than 35 L/min). Similarly, the size distribution of the emitted particles is nearly constant. Therefore, any increase of the flow rate causes a decrease of lung dose. However, this decrease could be compensated by the increase due to higher inhaled volume and especially due to the increase caused by longer inhalation time. Foster® contains the highest fraction of fine and extrafine particles among the studied drugs. These tiny particles deposit in the lungs by mostly gravitational settling which is proportional to the time they spend in this region. As the increase of lung dose was significant only at forced breathe out, the instruction from the PIL and the Summary of Product Characteristics (SPC) documents on the importance of total lung emptying makes sense.

The highest increase of lung deposition fraction was achieved for Symbicort® Turbuhaler®. 76.7% of the study participants increased their theoretical lung deposition by exhaling gently before inhalation and 93.3% of the subjects increased the same dose after exhaling forcefully. It is known that among the studied aerosol drugs the aerodynamic parameters of Symbicort® Turbuhaler® are the most sensitive to the individual's inhalation flow rate and the inhaled air volume (Farkas et al., 2016). The emitted amount of drug increases, while the size of the emitted particles decreases by the increase of inhalation flow

rate. The higher aerosolized and fine particle fractions and the higher emitted dose led to the increase of lung dose. In addition, the increase of the inhaled air volume contributes to the increase of lung deposition fraction. These effects counterbalanced the potential lowering of the amount of drug entering the lungs due to higher upper airway deposition. As the increase of lung dose was significantly higher after deep exhalation, the 'breath out forcefully' instruction seems to be more efficient than the currently used 'breathe out gently (as far as is comfortable)'requirement.

As highlighted by the above statements, the change in lung dose at different levels of lung emptying, compared to the case of no emptying, is device- and formulation-specific. Although deep exhalation caused the increase of inhalation volume, inhaled flow rate and inhalation time for all the studied inhalers (Farkas et al., 2023), the average value of the relative change of lung dose could be negative, slightly negative, slightly positive, and also positive. In order to explain this large variability of the results an in-depth analysis of the dependence of lung deposition on different parameters was performed. In the followings mathematical and phenomenological (physical) explanations will be provided. Aa a starting point, it is worth reminding the observations on the effects of individual breathing parameters on the lung deposition of aerosol particles. At constant inhaled volume and particle size distribution characteristic of aerosol drugs the increase of inhalation flow rate in the interval of 0–120 causes the decrease of the lung deposition. This is a consequence of the increasing upper airway deposition due to impaction. By the same token, at constant flow rate lung deposition increases with the increase of the inhaled volume and by the increase of the inhalation time (see *Supplement 1*). Increased inhaled volume means deeper penetration of particles into the lungs, while longer inhalation time promotes the deposition by gravitational sedimentation. These two parameters hardly affect the upper airway deposition. It converges from the above statements that lung deposition can increase, if the increase due to longer inhalation time and higher inhaled volume overcompensates for the decrease due to higher inhalation flow rate, at least for constant particle size and inhaled particle number. However, the situation is more complex in the case of aerosol drugs as breathing parameters influence both the emitted dose and the size distribution of the inhaled particles. An increasing flow rate leads to higher emitted (inhaled) dose and higher fine particle (with diameter smaller than 5 μm) fraction both contributing to the increase of lung dose. Finally, the resulting change depends on the above competitive effects and can lead to any result, as it happened in our case. To illustrate this, Fig. 1 depicts two cases with opposing correlation of lung dose with flow rate. The plot depicts the emitted doses, fine particle doses and lung doses of Onbrez® Breezhaler® and Symbicort® Turbuhaler® as a function of the mean inhalation flow rate (Q) for the 30 participants including all the three breathing modes. All doses are expressed as a percent of the dose metered in the capsule (Onbrez®) or reservoir (Symbicort®). All the results are calculated values, the emitted doses and fine particle doses are based on formulas (1) and (2).

As the figure demonstrates, lung doses of both drugs depend strongly on the inhalation flow rate (high values of correlation coefficients). However, the lung dose-flow rate function is monotonously decreasing for Onbrez® and increasing for Symbicort®. This is due to the differences between the two drugs in terms of emitted dose and fine particle dose dependence on the flow rate. While for Onbrez® the increase of ED and FPD is moderate especially after certain flow rate value (say 60 L/min), they increase abruptly and constantly for Symbicort®. As a result, the increase of ED and FPD can compensate for the decreasing lung dose due to higher flow rates only in the case of Symbicort®. Therefore, lung deposition of Symbicort® increases for any increase of flow rate, inhaled volume and inhalation time due to forceful lung emptying. At the same time, lung dose of Onbrez® would increase only if inhalation flow rate did not increase significantly, while inhaled volume and inhalation time increased markedly. Similar plots for all the studied drugs are available in *Supplement 2*.

According to the spirometry measurements, the inhalation flow rate increase due to forced lung emptying was higher for low resistance devices and lower for high resistance inhalers, that is, the correlation between ΔPIF (or ΔQ) and device resistance was strong and negative ($r = -0.96$). At the same time, the increase of inhalation time (Δt_{in}) correlated strongly and positively with device resistance ($r = 0.86$). It results that in the case of a drug with negative lung dose –flow rate correlation (e.g., Seebri®, Onbrez®, Relvar®, Genuair®, Foster®) the chances of increasing the lung dose as a result of lung emptying are higher, if the device resistance is higher (e.g., Foster®). Following this rationale, drugs dispensed in low resistance devices with negative lung dose-flow rate correlation are less likely to increase their lung dose as a result of strong lung emptying.

Summarizing the above results, the present study clearly demonstrated that lung emptying does have a major effect on the subsequent inhalation pattern. The amount of inhaled air generally increased as a result of lung emptying. The increase of inhaled volume caused the increase of lung dose. At the same time, the duration of the inhalation became longer. However, the relative increase of the inhaled air volume usually exceeded the relative increase of the inhalation time. As a consequence, in most of the cases the average flow rate characterizing the inhalation also increased. The enhancement of the flow rate resulted in higher emitted dose, higher aerosolized particle fraction and higher fine particle fraction. All these contributed to the increase of lung dose.

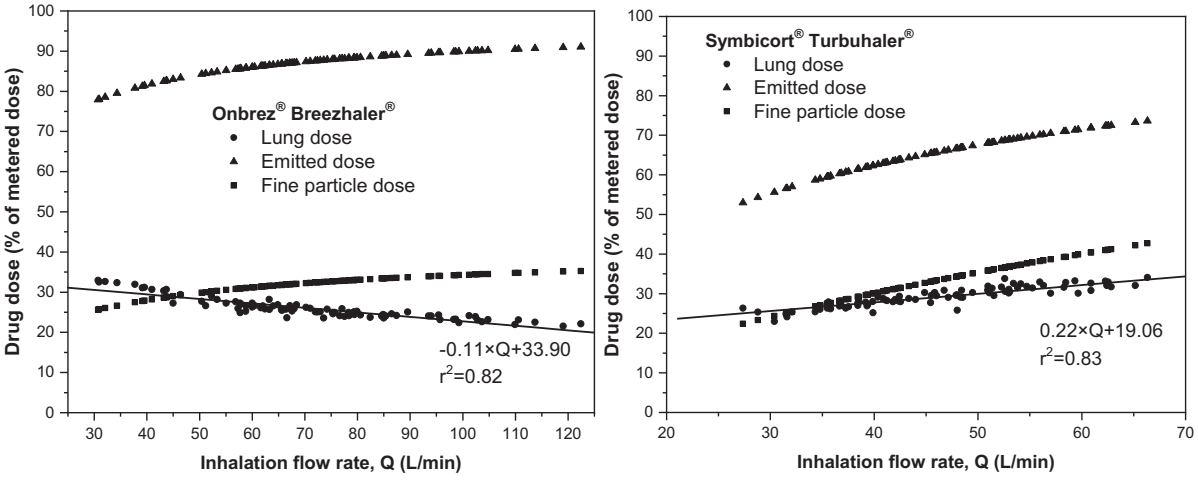

Fig. 1. Emitted doses (ED), fine particle doses (FPD) and lung doses of Onbrez® Breezhaler® and Symbicort® Turbuhaler® as a function of inhalation flow rate. Each symbol corresponds to one subject and one of the three exhalation modes before inhalation.

On the other hand, the increased inhalation flow rate resulted in higher upper airway deposition fractions which means lower fraction of dose available for deposition in the lungs. The resulting change in the lung dose was the result of the competing effect of the above phenomena. This proved to be drug and inhaler specific. From this perspective the studied drugs could be grouped into four categories. The first group was represented by drugs with significant increase of lung dose even for a slight lung emptying, and further increase of the lung dose for deep exhalation before the drug inhalation (Symbicort® Turbuhaler®, Bufomix® Easyhaler®). In the case of the second category of drugs slight exhalation resulted in minor and not significant lung dose change, but deep exhalation caused moderate, but statistically significant enhancement of the lung dose (Foster® NEXThaler®). For the third category of drugs the change of lung dose was not significant even after a deep exhalation (Relvar® Ellipta®, Seebri® Breezhaler®, Bretaris® Genuair®). Finally, there are drugs (e.g., Onbrez® Breezhaler®), which exhibit reduced lung dose as a result of lung emptying. It is worth noting that even for the drugs with insignificant lung dose change or lung dose decrease, there were individuals who managed to increase their lung dose by increasing their inhaled volume and inhalation time without an increase of the inhalation flow rate. Therefore, it is important to emphasize the necessity of a strong exhalation before the inhalation of all aerosol drugs, but also to emphasize that the inhalation should be longer, rather than more powerful.

Though the presented simulations provided reliable results and useful information on the effect of breathing out before the inhalation of aerosol drugs on the deposited lung dose, there are also a few limitations of this study. First of all, the participants of the study were healthy subjects with normal lung capacity. Most of them were able to achieve relatively high lung deposition fractions even without a forceful exhalation before the drug inhalation. Therefore, it is expected that the effect of deep exhalation on the lung dose would be more accentuated for individuals affected by lung diseases (e.g., asthma or COPD). For most of the drugs the emitted dose reduces drastically under 30 L/min inhalation flow rate. For those patients even an increased flow rate due to deep exhalation may lead to enhanced lung dose. On the other hand, it is uncertain to what extent the patients with different degrees of disease severity would be able to fully breathe out, then correctly execute the remaining manoeuvres of the device handling and drug inhalation. The change in health status involving functional and structural alterations can affect not only the effects of the already deposited aerosols but it can also influence their primary deposition pattern. There is substantial experimental and computational evidence that the change of morphology in pathological airways affects the airway deposition fractions of the inhaled particles at both local and regional scales (e.g. Choi et al., 2018; Farkas and Balásházy, 2007; Kadota et al., 2022; Farkas et al., 2020). Moreover, breathing capacity of COPD patients may be restricted, which also influences the amount and size of the particles emitted by DPIs and the fate of drug particles after their inhalation (Farkas et al., 2020). To reveal the effect of the disease also in the context of lung emptying before the inhalation of drugs will be the subject of a future study, the related work being in progress in the frame of a project registered at ClinicalTrials.gov (ID: NCT05445349) Protocol Registration and Results System.

Though the transport of particles within the airways is governed by the laws of physics, the interaction of the deposited drug particles with the complex system of the airways involves both chemical and biological phenomena. While the anatomy of the airways directly affects the amount of drug depositing on the airway wall, airway physiology is a major determinant of the ultimate effect of aerosol drugs. From this perspective, inter- and intrapersonal variability of lung fluid composition and respiratory microbiota may play a key role. After the deposition, the lung-particle interaction is affected by different non-epithelial clearance mechanisms (e.g. mucociliary clearance or macrophage uptake, Gehr and Hexder, 2000), but different transport systems can also translocate the inhaled particles into epithelial cells and/or across the epithelia into the interstitium and to the blood and lymph (Zhang et al., 2011). Therapeutic effect of aerosol drugs is very much dependent on their dissolution in the lung lining fluid (Eedara et al., 2022). Besides particle properties (size, shape, surface morphology, porosity, solid state nature, and surface hydrophobicity), dissolution depends on the properties of lung lining fluid which is different in different regions of the lungs and exhibits large inter-individual differences even in healthy subjects, and much consistent inter-individual scatter in the case of diseased airways (Patton et al., 2010). As the process of dissolution is highly complex and there is a consistent lack of mechanistic knowledge about the details, it is not straightforward to estimate whether the effect of different breathing parameters overweighs the effect of biological and physiological parameters of the airway lining fluid. The mechanistic and predicting understanding of drug-microbiome interactions and bicrobiota chemistry that shapes drug efficacy and toxicity is also a promising avenue (Guthrie and Kelly, 2019). Although the microbial drivers of variability in drug response are more and more revealed, a quantitative analysis of the relevance of physical parameters influencing drug deposition relative to the effect of individual specific microbiome cannot be performed at this moment. While it is important to recognise that the final health effect cannot be predicted solely by the quantification of the deposited drug amount, it is equally true that no effect can be expected without the drug entering and depositing in the airways. Finally, the main scope of this work was to assess the deposited dose, rather than to assess the dose-response relationship.

Last but not least, there is a lack of data in the open literature regarding the effect of inhaled volume on the aerosol characteristics. Such data is available only for certain drugs at specific flow rates (typically only 30 L/min or 60 L/min), but not for a broad range of flow rates. For most of the drugs this information is completely missing. Therefore, in the present study the effect of inhaled air volume on the deposition was considered only after the drug inhalation and the effect of it on the emitted particle number and particle size was neglected.

4. Conclusions

Airway deposition of aerosol drugs is the result of a complex particle-device-human interaction. The breathing pattern of the subject influences the aerodynamic characteristics of the dry powder drugs and their fate after inhalation. The present study demonstrated that emptying of the lungs has a major effect on the breathing parameters characterizing the subsequent inhalation. This may translate in modified deposited drug doses and dose distributions along the airways. According to present numerical simulation results, the lung dose of some drugs increased as a result of lung emptying before the inhalation of the drug, though the dose enhancement was regularly not drastic. The drugs with strong dependence of aerosol parameters on the inhalation pattern are more likely to deposit with higher efficiency in the lungs, if a deep exhalation preceded their inhalation. For other drugs, lung dose increase was achievable only by higher inhaled volume and longer inhalation time. Therefore, it is plausible to warn the patients on the importance of exhalation and even deep exhalation before the inhalation of the drug, but it should also keep in mind the inter-inhaler and inter-drug differences.

Declaration of Competing Interest

None.

Data availability

Data will be made available on request.

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in the study record NCT05445349 available on clinicaltrials.org.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijpx.2023.100192.

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