Respiratory Medicine 224 (2024) 107576

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: www.elsevier.com/locate/rmed

Original Research

Comparative study of the inhalation parameters of COPD patients through NEXThaler® and Ellipta® dry powder inhalers

Árpád Farkas [a,*], Alpár Horváth [b,c], Izolda Réti [c], Norbert Ilyés [c], Botond Havadtői [c], Tamás Kovács [d], Balázs Sánta [b], Gábor Tomisa [b], Péter Czaun [e], Gabriella Gálffy [c]

[a] HUN-REN Centre for Energy Research, Konkoly-Thege Miklós út 29-33, 1121, Budapest, Hungary
[b] Chiesi Hungary Ltd., Dunavirág u. 2, 1138, Budapest, Hungary
[c] Pulmonology Institute of Törökbálint, Munkácsy M. u.70, 2045, Törökbálint, Hungary
[d] Pulmonology Clinic, University of Debrecen, Nagyerdei krt. 98, 4032, Debrecen, Hungary
[e] Bremotech Ltd., Ezred u. 7, 1044, Budapest, Hungary

ARTICLE INFO

Keywords:
COPD management
Dry powder inhaler
Peak inhalation flow
Patient and device specific inhalation parameters

ABSTRACT

The deposition of dry powder aerosol drugs depends on the inhalation parameters of the patients through the inhaler. These data are not directly measured in clinical practice. Their prediction based on the routinely measured spirometric data could help in choosing the appropriate device and optimizing the therapy. The aim of this study was to perform inhalation experiments to find correlations between inhalation parameters of COPD patients through two DPI devices and their native spirometric data, gender, age and disease severity. Another goal was to establish relationships between peak inspiratory flows through NEXThaler® and Ellipta® inhalers and their statistical determinants. Breathing parameters of 113 COPD patients were measured by normal spirometry and while inhaling through the two DPIs. Statistical analysis of the measured data was performed. The average values of peak inspiratory flow through the devices (PIF_{dev}) were 68.4 L/min and 78.0 L/min for NEXThaler® and Ellipta®, respectively. PIF_{dev} values were significantly higher for males than for females, but differences upon age, BMI and disease severity group were not significant. PIF_{dev} values correlated best with their native spirometric counterparts (PIF) and linear relationships between them were revealed. Current results may be used in the future to predict the success of inhalation of COPD patients through DPI devices, which may help in the inhaler choice. By choosing the appropriate device-drug pair for each patient the lung dose can be increased and the efficiency of the therapy improved. Further results of the clinical study will be the subject of a next publication.

1. Introduction

The dose of dry powder aerosol drugs depositing in the lungs of COPD patients is a result of a complex patient-device interaction with many key parameters influencing the outcome. The emitted dose and the size of the emitted particles are dependent on the handling of the device [1], inhalation manoeuvre and breathing capacity of the patient [2,3]. A recent work highlighted the differences between Ellipta® and NEXThaler® in their response to improper use, such as inclined device holding, falling the device, double activation or exhalation into the device [4]. In addition, drug formulation and the internal architecture of the device (shape, size, resistance) are also influencing the number and size of the emitted particles [5]. On the other hand, the fate of the inhaled particles in the airways depends on their aerodynamic properties, the patient's breathing pattern and the morphology of the airways [6]. Besides the inherent high intersubject variability of the breathing parameters and airway morphology (both being influenced also by the status of the disease), the high and continuously increasing number of active pharmaceutical ingredient (API) formulations dispensed in different inhalers makes the choice of appropriate inhaler-API pair really difficult. Once a drug chosen, the optimization of patient's inhalation to obtain low upper airway deposition, high and uniform or receptor specific lung deposition is also a real challenge. Due to the great number of effects and parameters affecting the success of aerosol inhalation, the chance of misunderstandings and misconceptions is also high [7]. This could be diminished by enhancing our empirical and theoretical

* Corresponding author.
E-mail address: farkas.arpad@ek.hun-ren.hu (Á. Farkas).

https://doi.org/10.1016/j.rmed.2024.107576
Received 21 December 2023; Received in revised form 1 February 2024; Accepted 19 February 2024
Available online 23 February 2024

knowledge on the effect of each parameter. Real-life data characterizing the patient's behaviour, habits, manoeuvres and breathing capacity is invaluable in this context.

Collection of data on the breathing parameters during the inhalation through dry powder inhalers (DPI) of patients with very well documented demographic, pathological, anthropometric, and lung capacity characteristics and finding interrelationships between them may lead to better understanding of aerosol drug delivery and may even have predictive power related to the success of drug delivery.

Such clinical studies were conducted in the past on several groups of patients involving a remarkable number of DPIs. Without the intent to provide an exhaustive list, key inhalation parameters were recorded and analysed for example in the case of Turbuhaler® [8], Breezhaler® [9], original Easyhaler® [10], lower resistance Easyhaler® [11], Diskus® [12], Ellipta® [13] and NEXThaler® [14]. These data contributed to a great extent to the understanding of the mode the patients are using these devices. In addition, statistical analysis of the breathing parameter values became possible. However, due to the multiple differences regarding the disease type, severity, age, sex, inclusion/exclusion criteria of the patients, these studies are not appropriate when it comes to the comparison of different devices among them. For this purpose, the same patient group needs to be analysed when inhaling through multiple inhalers. Results of such studies were also published in the open literature. Inhaler pairs were assessed by van der Palen [15] (Diskus® and Turbuhaler®), Magnussen et al. [16] (Genuair® and HandiHaler®) and Azouz et al. [17] (Spiromax® and Turbuhaler®) among others. Inhaler triplets were also investigated, for instance inhalation through Breezhaler®, Ellipta® and HandiHaler® of the same COPD patients was studied by Altman et al. [18], through Breezhaler®, Genuair® and Turbuhaler® by Farkas et al. [19], through Diskus®, Turbuhaler® and lower resistance Easyhaler® by Malmberg et al. [20], while Janssens et al. [21] have measured the PIF values of the same COPD patients through Aerolizer®, Turbuhaler® and Diskus®. More than three inhalers were rarely analysed, as it is tiring for COPD patients to inhale through many inhalers consecutively and the bias due to fatigue can be significant (e.g. Ref. [22]).

Although Ellipta® and NEXThaler® are one of the most modern and most frequently used DPI inhalers with several mono-, bi-, and tricomponent (Ellipta®) and bi- and tricomponent (NEXThaler®) APIs metered in them, a comparative study of the inhalation of COPD patients through NEXThaler® and Ellipta® is still missing. Therefore, the aim of this work was to conduct a clinical study on COPD diagnosed patients focusing on the recording and analysis of their inhalation parameters when using the two inhaler devices, with special emphasis on the value of peak inspiratory flow, which is an important indicator of the successfulness of inhalation [23].

2. Methods

2.1. Study protocol and patient recruitment

The breathing profile measurements of COPD patients were completed within an observational, case-only, cross-sectional study at three medical centres including Pulmonology Institute of Törökbálint (Törökbálint, Hungary), Pulmonology Clinic, University of Debrecen (Debrecen, Hungary) and St. Borbála Hospital (Tatabánya, Hungary). The study has been approved by the National Institute of Pharmacy and Nutrition (OGYÉI/74-3/2022) based on the positive evaluation statement of the Ethical Committee of the National Medical Research Council (ETT TUKEB). The study is also registered as the CHOICE study at ClinicalTrials.org (NCT05445349), where the study protocol and the statistical analysis plan are also available. The inclusion criteria were the diagnosed COPD and proper usage of inhalation device after being educated. The subject also needed to be under outpatient/inpatient therapy capable of acting and cooperating. The exclusion criteria referred to the cases when the patient was incapable of filling out the questionnaire or did not agree to have data collected on her/him. Patients with untreated heavy chronic illness or with not evaluable lung function (spirometry) data were also excluded from this study. This work focused on the analysis of the measured breathing patterns and breathing parameters of COPD patients through NEXThaler® and Ellipta® dry powder inhalers as endpoints, further endpoints being explored in ongoing works. 113 adult patients (39 females and 74 males) with previously diagnosed COPD of different degrees of disease severity were recruited. Written consent was obtained from all participants.

2.2. Patient demographics and native lung function parameters

The native lung function parameters of the patients were measured by Otthon Idegen™ Mobile Handheld Spirometer of Thor Laboratories (Budapest, Hungary) just before the measurement of breathing parameters through the selected inhalers. According to the ERS/ATS guidelines [24] three technically acceptable maneuvers were performed and the best sample (with the highest forced vital capacity) was used. Table 1 summarizes these data, in addition to patient demographics.

2.3. Measurement of inhalation parameters through NEXThaler® and Ellipta® DPI devices

Next to the acquirement of standard spirometric data, inhalation curves (flow rate versus time) of the same patients were digitally recorded while they used the NEXThaler® and Ellipta® inhalation devices. For this purpose, the handheld spirometer was placed between the bacterium filter and the inhaler (see Fig. 1). The spirometer was connected to the inhalers by the help of two 3D printed mouthpiece adapters (one for each inhaler). These adapters were designed by computer aided design (CAD) techniques after laser scanning and digital reconstruction of the two inhalers. Tight contact of the adapter with the mouthpiece of the inhaler was ensured by the application of silicone rubber inside the adapter. Holes in the adapter around the air inlet vent of the inhalers were applied in order to avoid the obstruction of air entering the inhalers during the inhalation. The effect of the adapter on the flow resistance was verified by measuring the pressure drop on the devices at different constant flow rates between 30 and 120 L/min both with the adapter and without, and comparing them. The change of flow resistance was negligible for both adapters. A PBF-100-G-M type bacterium filter was inserted between the patient's mouth and the spirometer. The filtering material was 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 small compared to the resistance of the inhalers. As the handheld spirometer was developed for the measurement of normal spirometric parameters, it needed to be validated before the measurements by a method described in details in Farkas et al. [19].

The patients were instructed on the inhalation through the devices in accordance with the patient information leaflets (PIL). The order of the devices used in the inhalation experiments was randomized among the patients. Original, but emptied (without active substance) inhalation devices were used to ensure realistic airflow resistances. No active substance was inhaled by the patients during the measurements.

The key breathing parameters derived from the recorded inhalation profiles were the peak inspiratory flow through the device (PIF_{dev}), the inhaled volume (IV) and the inhalation time (t_{in}). As the dose of drug depositing in the lungs of COPD patients is dependent also on the length breath-holding after drug inhalation, the breath-hold time (t_{bh}) of each patient was also measured.

2.4. Searching for the predictors of peak inspiratory flow through DPIs

It has been demonstrated that both the amount of the emitted drug (emitted dose) and its size distribution depend on the forcefulness of patient's inhalation represented by the peak inspiratory flow through the inhaler (e.g. Ref. [25,26]). This quantity has a major effect also on

Table 1
Patient demographics and baseline lung function data. Mean values with standard deviations (first row) and ranges (second row) for the population of 113 patients are demonstrated. 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)
67.1 ± 8.1 45–88	34.5:65.5	26.3 ± 6.0 15.6–47.1	0.9 ± 0.5 0.3–4.5	35.3 ± 16.3 12–86	1.8 ± 0.7 0.5-3.5	54.8 ± 19.3 17–112	57.7 ± 9.9 27.0–69.8	136.0 ± 66.3 37.2–299.4	1.6 ± 0.7 0.4-3.6

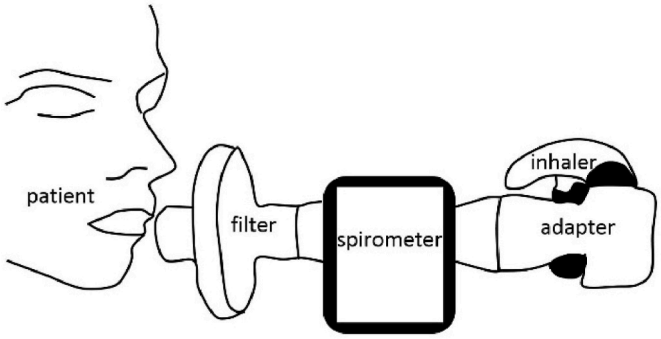

Fig. 1. Schematic illustration of the set-up for the measurement of breathing patterns through the selected DPI devices.

the deposition of drugs within the human airways [27]. As in the everyday clinical practice this inhalation parameter (PIF_{dev}) is not measured, it is worth analysing its dependence on known patient characteristics and routinely measured spirometric parameters. Therefore, the influence of patient demographic data (age, gender), anthropomorphic characteristics (height, weight), disease condition (expiratory volume at the end of the first second of forced exhalation: FEV_1, forced vital capacity: FVC, Tiffeneau-index: FEV_1/FVC, GOLD grades), and baseline spirometric data characterizing the inhalation (peak inspiratory flow without the inhaler: PIF, inspiratory vital capacity: IVC) was studied by statistical methods. A correlation analysis of the above parameters (except GOLD grades and gender) with PIF_{dev} for both devices was performed, the corresponding Pearson coefficients and significant levels were calculated. Any correlation characterized by $p < 0.05$ was considered statistically significant. Predictors of PIF_{dev} were found by stepwise multiple regression analysis using a backward elimination technique. In addition, mean PIF_{dev} values of subject subgroups upon gender, age, body mass index (BMI) and disease stages (GOLD grades) were analysed for both inhalers by conducting two-sample t-tests. Two age groups were formed delimitated by a cut-off age of 70 years. Two subgroups were also considered based on BMI by using a cut-off value of 25 kg/m^2, and another two groups were based on disease severity (GOLD B and GOLD C + D). All the statistical evaluations were performed by OriginPro 2018 (version b9.5.0.193, OriginLab Corporation, Massachusetts, USA) software.

3. Results

3.1. Breathing patterns and breathing parameters through NEXThaler® and Ellipta®

The median (p50) breathing profile, that is, the time dependent median inhalation flow rate of the subjects through NEXThaler® can be seen in the left panel. The right panel of the same figure demonstrates the same profiles for Ellipta®. In addition to p10, the p50 and p90 percentile profiles are also illustrated. As Fig. 2 demonstrates, peak flow values of p10, p50 and p90 profiles are higher for Ellipta®. By the same token, inhalation time is consistently longer through NEXThaler®, which is also reflected by its mean values presented in Table 2 (last two columns). In addition, Table 2 includes the study population averaged values of PIF_{dev} and IV and their standard deviation and range.

Mean PIF_{dev} value through NEXThaler® exactly matches the value measured by Chetta et al. [14] on a population of 97 COPD patients. The value is also very close (68.4 L/min vs. 69.9 L/min) to the one published by Virchow et al. [28], who measured PIF_{dev} on 9 COPD patients. The measured PIF_{dev} values for Ellipta® are in good agreement with those measured by Prime et al. [13] on 60 COPD patients (weighted mean PIF_{dev}: 82.7 L/min) and are exactly matching the ones published by Altman et al. [18] obtained on 97 patients (78 L/min). It is worth noting that in contrast to our study in the above works the patients were different for NEXThaler® and Ellipta®. Table 2 demonstrates that, contrary to the mean PIF_{dev} values, average values of the inhaled volume through the two devices were the same.

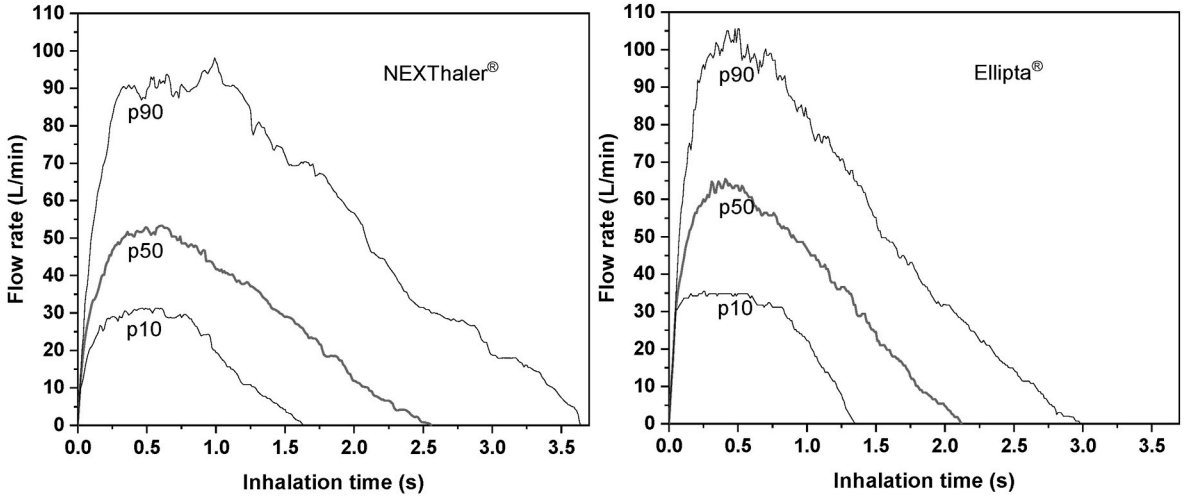

Fig. 2. p10, p50 (median) and p90 percentile profiles based on the 113 measured flowrate-inhalation time curves while COPD patients inhaled through NEXThaler® (left) and Ellipta® (right) dry powder inhalers.

Table 2
Mean values, standard deviations and ranges of peak inspiratory flow (PIF_{dev}), inhaled air volume (IV) and inhalation time (t_{in}) of the 113 patients while inhaling through NEXThaler® and Ellipta® DPI devices.

PIF_{dev} (L/min)		IV (L)		t_{in} (s)	
NEXThaler®	Ellipta®	NEXThaler®	Ellipta®	NEXThaler®	Ellipta®
68.4 ± 32.4	78.0 ± 36.2	1.5 ± 0.9	1.5 ± 0.7	2.4 ± 0.9	2.1 ± 0.6
26.5–184.8	31.8–198.0	0.2–4.7	0.3–3.5	0.7-6.3	0.7-3.8

3.2. Comparison of different subgroups of COPD patients based on PIF_{dev}

Besides the distribution of the key inhalation parameters for the whole population, the comparison of their values among different subgroups is also useful, indicating the influence of characteristics such as sex, age, body mass index or disease stage. Table 3 summarizes the results of two sample t-tests on these subgroups. According to these results, males had significantly higher PIF_{dev} than females in the case of both inhalation devices. Based on the measured datasets, significant differences in terms of peak inspiratory flow through the inhaler between the subgroups upon obesity could not be demonstrated. Mean PIF_{dev} for both inhalers was significantly lower ($p = 0.0002$ for NEXThaler® and $p = 0.00001$ for Ellipta®) for the current COPD patients than for a group of 30 healthy subjects measured earlier by us (92.8 ± 35.8 for NEXThaler® and 114.5 ± 43.8 for Ellipta®, [29]). However, there was no significant difference from this point of view between the two disease severity subgroups (GOLD B vs. C + D).

3.3. Predictors of the peak inspiratory flow through the devices

One of the main strengths of the present study is that it provides the opportunity to find out the predictors of PIF_{dev}, especially those predictors whose value is known for practically every diagnosed COPD patient (anthropometric parameters and baseline lung function data). For this purpose, an extended correlation analysis has been performed. The results are summarized in Table 4. These data demonstrate that peak inspiratory flow through NEXThaler® correlated weakly with FVC% ($r = 0.2$), moderately with FVC in litre ($r = 0.36$) and strongly with native PIF ($r = 0.57$) and IVC ($r = 0.43$). The correlation with height ($r = 0.28$) was stronger than the correlation with body mass ($r = 0.17$). The same key parameter (PIF_{dev}) through Ellipta® correlated weakly with FEV_1 ($r = 0.24$) expressed in litre, and with FVC expressed in percent ($r = 0.26$). The correlation was strong with FVC expressed in litre ($r = 0.46$) and with PIF ($r = 0.71$) and IVC ($r = 0.56$) lung function parameters. As it can be seen, PIF_{dev} was the most strongly correlated with the native PIF for both inhalers.

Based on the currently measured data a quantitative relationship between PIF_{dev} and its predictors can be established. A stepwise multiple regression analysis using a backward elimination technique revealed that the peak inspiratory flow through a device (PIF_{dev}) was best predicted by native peak inspiratory flow (PIF) for both NEXThaler® and Ellipta®. None of the other independent variables (FEV_1(L), FVC%, FVC (L), IVC, h, m) could be retained at the significance level of $p = 0.05$. Although PIF_{dev} correlated strongly with IVC ($r = 0.43$ for NEXThaler® and $r = 0.56$ for Ellipta®), IVC was eliminated because the correlation between native PIF and IVC was also strong ($r = 0.66$) and significant ($p = 0.00001$). The relationship between the two types of peak inspiratory flow (PIF and PIF_{dev}) is demonstrated in Fig. 3 for NEXThaler® (left panel) and Ellipta® (right panel). These relationships allow us to predict the value of peak inspiratory flow (within some uncertainty limits) through the two devices, if the baseline peak inspiratory flow of the patient is known.

Moreover, current measurement results allowed us to assess the ability of a patient to exceed a given flow rate threshold through any of the studied devices based on the available native PIF value without effectively measuring the PIF_{dev} (which is not routinely measured).

Fig. 4 demonstrates the probability that a patient's peak inspiratory flow through the inhaler (NEXThaler® or Ellipta®) exceeds a certain threshold value as a function of here/his native peak inspiratory flow. The thresholds are set to 35 L/min for Foster® NEXThaler® (both the minimum and the optimum) and to 30 L/min and 60 L/min for Relvar® Ellipta®, corresponding to the minimum and optimal values of the peak flow.

Table 3
Mean values of peak inspiratory flow through NEXThaler® and Ellipta® DPI devices of different subgroups upon gender, age, BMI and disease stage. Significance level of the difference between the two subgroups as yielded by the two sample t-tests is also provided. ns means that the difference between the subgroups is not significant ($p \geq 0.05$).

	Gender (female vs. male)	Age (<70 years vs. >70 years)	BMI (<25 kg/m^2 vs. >25 kg/m^2)	GOLD (B vs. C + D)
mean PIF_{dev} (L/min) NEXThaler®	56.8; 74.5 (0.005)	67.8; 69.5 (ns)	66.9; 69.8 (ns)	63.6; 69.6 (ns)
mean PIF_{dev} (L/min) Ellipta®	59.2; 87.9 (0.00004)	76.4; 81.8 (ns)	76.7; 78.9 (ns)	70.1; 79.8 (ns)

4. Discussion

Peak inspiratory flow through the device is one of the main parameters affecting airway deposition both directly by influencing particle impaction and indirectly by influencing he size of the emitted particles. However, the fact that mean PIF_{dev} was higher for Ellipta® does not automatically imply a better performance of this device, being an inherent consequence of lower flow resistance of Ellipta® compared to the resistance of NEXThaler (0.027 $(kPa)^{0.5}$ min/L and 0.036 $(kPa)^{0.5}$ min/L, respectively; [30]). Average PIF_{dev} values obtained in this study (68.4 L/min for NEXThaler® and 78.0 L/min for Ellipta®) are in line with flow resistances, but they also agree with the outcome of our recent measurements involving several dry powder inhalers [29].

A more important question is how the average PIF_{dev} recorded for both devices aligns with the technical specification of the inhalers. It was presented in the technical descriptions of Ellipta® [31] and NEXThaler® [32] that both devices ensure a relatively low variance of the emitted dose and fine particle dose in the flow rate range of 30–90 L/min with the specification that emission from NEXThaler® needs at least 35 L/min inhalation flow rate. The average values of PIF_{dev} obtained in this study fall within the above mentioned flow rate range, suggesting that in general COPD patients are able to efficiently use both devices. Obviously, this does not mean that all patients can achieve the minimum or the optimal flow rate. Regarding the minimum flow rate, the 35 L/min lower threshold limit is obvious for NEXThaler®. From this point of view situation is a bit more complex in the case of Ellipta®. As multiple active pharmaceutical ingredients are filled in Ellipta® device, it is correct to establish the flow rate threshold to a given drug filled in it. For instance, the *in vitro* aerodynamic performance of the ICS-LABA combination drug (Relvar® Ellipta®) has been evaluated by several authors (e.g. Refs. [25,31,33,34]). However, only the work of Saed et al. [33] contains information on the emitted dose below the flow rate of 30 L/min. According to this study, the emitted dose of Relvar® Ellipta® is 91.8% (expressed as a percent of the metered dose) at 40 L/min, 84.7% at 30 L/min, but

Table 4
Pearson correlation coefficients (r) of peak inspiratory flow through NEXThaler® and Ellipta® DPI devices and baseline lung function and anthropometric parameters. Significance values (p) are also provided. FEV_1 – expiratory volume in the first second of forced exhalation; FVC - forced vital capacity; PIF – baseline peak inspiratory flow; IVC – inspiratory vital capacity; h – height; m - mass.

		FEV_1 (%)	FEV_1 (L)	FVC (%)	FVC (L)	FEV_1/FVC (%)	PIF (L/min)	IVC (L)	h (m)	m (kg)
NEXThaler®	r	0.06	0.13	0.20	0.36	−0.10	0.57	0.43	0.28	0.17
	p	ns	ns	0.02	0.0001	ns	0.000001	0.0001	0.003	ns
Ellipta®	r	0.04	0.24	0.26	0.46	−0.18	0.71	0.56	0.38	0.25
	p	ns	0.009	0.005	0.0000003	ns	0.000001	0.0000002	0.00004	0.007

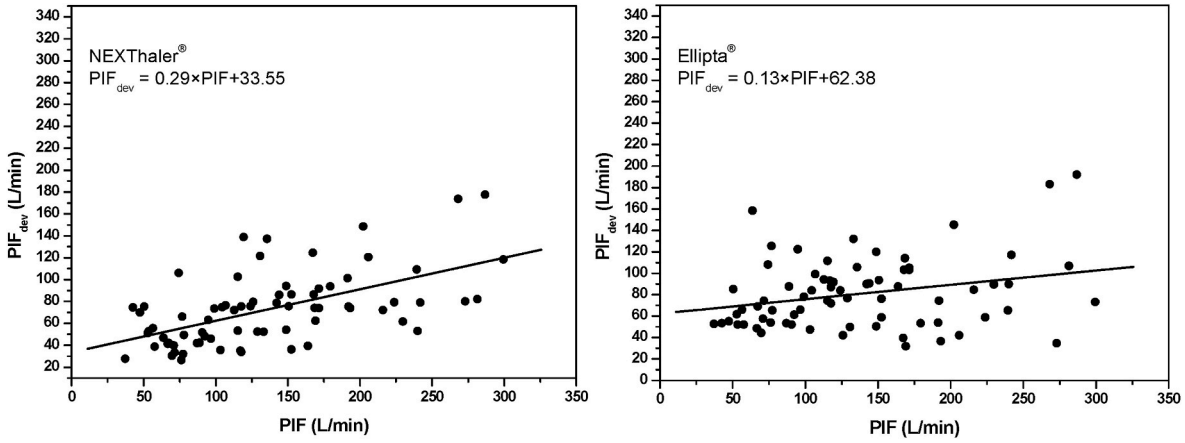

Fig. 3. Peak inspiratory flow (PIF_{dev}) through NEXThaler® (left panel) and Ellipta® (right panel) DPI devices as a function of native peak inspiratory flow. Each symbol represents one patient.

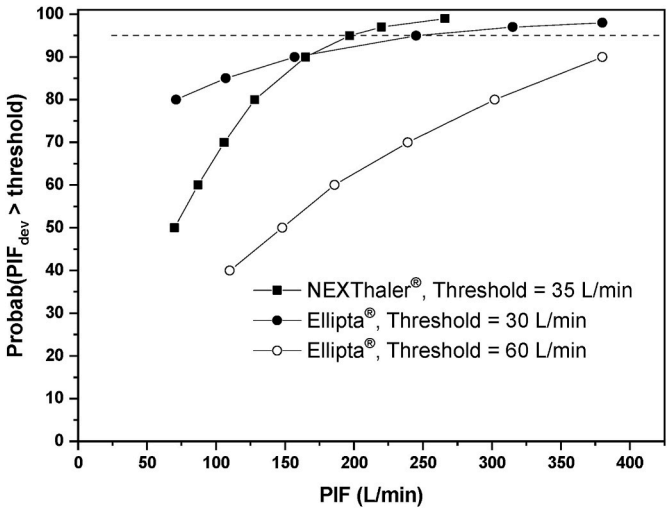

Fig. 4. Probability that a patient's peak inspiratory flow through the inhaler (NEXThaler® or Ellipta®) exceeds a certain threshold value as a function of its native peak inspiratory flow.

only 63.8% at 20 L/min. Due to this sudden decline below 30 L/min, a threshold value of 30 L/min for the peak flow rate seems to be reasonable in the case Relvar® Ellipta®.

In our study, all the subjects were able to produce at least 30 L/min through Ellipta®, but around 7% of the patients did not reach 35 L/min through NEXThaler®. The breath-actuated mechanism (BAM) built in NEXThaler® retains the emission of the dose below 35 L/min and the counter does not advance, providing a feedback to the patient on the low inhalation flow ([32].) As most of the patients who did not reach 35 L/min were very close to it (only one of them performed below 30 L/min), it was expected that they would manage exceeding this value after some more exercise. Although this was not verified in this study, it underpins the necessity of appropriate training frequency and methodology to enhance the correct device use and a more efficient therapy. One of the possible training tools providing immediate feedback on the correctness of patient's peak inspiratory flow value is the In-Check Dial device [35].

Besides exceeding the minimum PIF_{dev} value, another key aspect is the ability of patients to attain optimal peak flow values [36]. Since the emitted dose of Foster® NEXThaler® is almost constant over 35 L/min, the 35 l/min value was suggested also as optimal value [31]. As this is a relatively low flow rate, almost all of the participants managed to reach it (except 7% of them). On the other hand, Grant et al. [31] proposed 60 L/min as the optimal value of peak flow rate for Ellipta®. According to our results, 59% of the COPD patients were able to reach this inspiratory peak flow rate value through this device.

One of the main outcomes of our work is that it can provide predictive PIF_{dev} values for arbitrary COPD patients, whose native PIF values are known. Based on our results (Fig. 4), if we want to be 95% confident that a patient exceeds the above minimum thresholds we must ensure that her/his native PIF value is higher than 197 L/min (NEXThaler®) and 245 L/min (Ellipta®). Obviously, the same threshold value can be achieved also by patients with lower native PIF value, but the associated likelihood is lower. For instance, according to the present data any patient reaching 100 L/min native PIF has 67% chance to reach 35 L/min through NEXThaler® and 84% chance to reach 30 L/min through Ellipta®. By the same token, at 250 L/min native inspiratory peak flow rate the probability of reaching the optimal flow rate through Ellipta® is only 72%, while through NEXThaler® is as high as 96%. In conclusion, the lower threshold is attained with higher probability in the case of Ellipta®, but the optimal value is reached with higher probability in the case of NEXThaler®.It is also clear from the plot that in the case of patients with the lowest native PIF value (some of them were also exacerbating during the study) any extra effort to increase the strength of the inhalation through the device would enhance the chances of reaching the threshold value.

In addition to the capability to predict the likelihood that a patient

reaches minimum or optimum flow rate value, present work shed also light into the factors affecting this. In this context an important question was whether PIF_{dev} depends on disease severity, which according to the present results (see Table 3) is not the case. At first sight, this may seem to be in contradiction with the results published by Prime et al. [13], who found significantly higher PIF_{dev} values for the very severe COPD group compared to the less severe patient's group, but the apparent discrepancy could also be a result of different ages. Janssens et al. [21] argued that the age and not only the disease is the cause for the fall of PIF_{dev}. Indeed, in our case COPD patients were significantly ($p = 0.00001$) older (67.1 ± 8.1 years) than their healthy counterparts (38.3 ± 10.2). To see the effect of disease, healthy and diseased subjects with matching age should be compared. Such a comparison could not be done here, as only a few subjects were from the common age interval (45–57 years) of the two groups. Nevertheless, significant difference between the two COPD subgroups upon age (cut-off age was 70 years) could not be found in this study. The non-existent correlation of PIF_{dev} with FEV_1% (Table 4) supports the above lack of correlation of PIF_{dev} with disease severity, as in this study the earlier GOLD grades which were based on FEV_1% values were used to classify the patients. This is also in agreement with our earlier observations [19], but also in line with a large study by Anderson et al. [37] who assessed more than 33000 COPD patients and concluded that assessing inhalation capability (PIF) by exhalation measurements such as FEV_1% has no practical value.

5. Conclusions

A clinical study involving 113 COPD patients was conducted to measure and analyse the key inhalation parameters through NEXThaler® and Ellipta® dry powder inhalers. Our results demonstrated that peak inspiratory flow through the two devices was higher for males than for females and higher through Ellipta® than through NEXThaler®. Peak inspiratory flow through the device correlated strongly with native peak inspiratory flow and inspiratory vital capacity, but PIF was the only predictor of PIF_{dev}. Our analyses pointed towards no correlation of PIF_{dev} with FEV_1% and no significant difference between the patients from different disease severity groups in terms of their peak inspiratory flow through the two devices. Present data contribute to the better understanding of relationships between different inhalation parameters occurring during the therapy of COPD patients by aerosol drugs emitted by NEXThaler® and Ellipta® inhalers. Present data will also serve as inputs to simulate lung deposition and find correlations between different inhalation and other parameters and the lung dose.

CRediT authorship contribution statement

Árpád Farkas: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Alpár Horváth:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Data curation, Conceptualization. **Izolda Réti:** Writing – review & editing, Validation, Methodology, Investigation, Data curation. **Norbert Ilyés:** Writing – review & editing, Methodology, Investigation, Data curation, Conceptualization. **Botond Havadtői:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Tamás Kovács:** Writing – review & editing, Methodology, Formal analysis, Data curation, Conceptualization. **Balázs Sánta:** Writing – review & editing, Validation, Methodology, Investigation, Formal analysis, Conceptualization. **Gábor Tomisa:** Writing – review & editing, Validation, Methodology, Investigation, Formal analysis, Conceptualization. **Péter Czaun:** Writing – review & editing, Visualization, Methodology, Investigation, Data curation, Conceptualization. **Gabriella Gálffy:** Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Methodology, Investigation, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Alpár Horváth, Gábor Tomisa, Balázs Sánta report a relationship with Chiesi Hungary Kft that includes: employment.

Acknowledgement

Project no. 00057 has been implemented with the support provided by the Ministry of Culture and Innovation of Hungary from the National Research, Development and Innovation Fund, financed under the 2021-1.1.4-GYORSÍTÓSÁV-2022 funding scheme.

References

[1] J. Sanchis, I. Gich, S. Pedersen, Systematic review of errors in inhaler use: has the patient technique improved over time, Chest 150 (2016) 394–406.
[2] H. Chrystyn, Is inhalation rate important for a dry powder inhaler? Using the In-Check Dial to identify these rates, Respir. Med. 97 (2003) 181–187.
[3] M. Abadelah, F. Hazim, H. Chrystyn, G. Bagherisadeghi, H. Rahmoune, H. Larhrib, Effect of maximum inhalation flow and inhaled volume on formoterol drug deposition in-vitro from an Easyhaler® dry powder inhaler, Eur. J. Pharmaceut. Sci. 104 (2017) 180–187.
[4] Varacca G, D'Angelo D, Glieca S, Cavalieri L, Piraino A, Quarta E, Sonvico F, Buttini F. The Impact of Possible Improper Use on the Performance *in Vitro* of NEXThaler® in Comparison with Ellipta® Inhaler.
[5] N.R. Labiris, M.B. Dolovich, Pulmonary drug delivery. Part II: the role of inhalant delivery devices and drug formulations in therapeutic effectiveness of aerosolized medications, Br. J. Clin. Pharmacol. 56 (2003) 600–612.
[6] P. Gehr, J. Heyder, Particle-lung interactions, in: C. Lenfant (Ed.), Book Series: Lung Biology in Health and Disease (Exec, Marcel Dekker Inc., New York, 2000, p. 143.
[7] P. Demoly, P. Hagedoorn, A.H. deBoer, H.W. Frijlink, The clinical relevance of dry powder inhaler performance for drug delivery, Respir. Med. 108 (2014) 1195–1203.
[8] M.H. Dewar, A. Jamieson, A. McLean, G.K. Crompton, Peak inspiratory flow through Turbuhaler in chronic obstructive airways disease, Respir. Med. 93 (1999) 342–344.
[9] R. Pavkov, S. Mueller, K. Fiebich, D. Singh, F. Stowasser, G. Pignatelli, B. Walter, D. Ziegler, M. Dalvi, J. Dederichs, I. Rietveld, Characteristics of a capsule based dry powder inhaler for the delivery of indacaterol, Curr. Med. Res. Opin. 26 (2010) 2527–2533.
[10] L.P. Malmberg, P. Rytila, P. Happonen, T. Haahtela, Inspiratory flows through dry powder inhaler in chronic obstructive pulmonary disease: age and gender rather than severity matters, Int. J. Chronic Obstr. Pulm. Dis. 5 (2010) 257–262.
[11] L.P. Malmberg, M.L. Everard, J. Haikarainen, S. lahelma, Evaluation of in vitro and in Vivo flow rate dependency of budesonide/formoterol Easyhaler®, J. Aerosol Med. Pulm. Drug Deliv. 27 (2014) 329–340.
[12] J.N. Seheult, S. Costello, K.C. Tee, T. Bholah, H. Al Bannai, I. Sulaiman, R. W. Costello, Investigating the relationship between peak inspiratory flow rate and volume of inhalation from a Diskus™ Inhaler and baseline spirometric parameters: a cross-sectional study, SpringerPlus 3 (2014) 496.
[13] D. Prime, W. de Backer, M. Hamilton, A. Cahn, A. Preece, D. Kelleher, A. Baines, A. Moore, N. Brealey, J. Moynihan, Effect of disease severity in asthma and chronic obstructive pulmonary disease on inhaler-specific inhalation profiles through the ELLIPTA dry powder inhaler, J. Aerosol Med. Pulm. Drug Deliv. 28 (2015) 486–497.
[14] A. Chetta, A. Yorgancioglu, M. Scuri, S. Barile, D. Guastalla, P.N.R. Dechuijzen, Inspiratory fow profle and usability of the NEXThaler, a multidose dry powder inhaler, in asthma and COPD, BMC Pulm. Med. 21 (65) (2021).
[15] J. van der Palen, Peak inspiratory flow through Diskus and Turbuhaler, measured by means of a peak inspiratory flow meter (In-Check DIALs), Respir. Med. 97 (2003) 285–289.
[16] H. Magnussen, H. Watz, I. Zimmermann, S. Macht, R. Greguletz, M. Falques, D. Jaretta, E.G. Gil, Peak inspiratory flow through the Genuair® inhaler in patients with moderate or severe COPD, Respir. Med. 103 (2009) 1832–1837.
[17] W. Azouz, P. Chetcuti, H. Hosker, D. Saralaya, H. Chrystyn, Inhalation characteristics of asthma patients, COPD patients and healthy volunteers with the Spiromax® and Turbuhaler® devices: a randomised, cross-over study, BMC Pulm. Med. 15 (2015) 47.
[18] P. Altman, L. Wehbe, J. Dederich, T. Guerin, B. Ament, M.C. Moronta, A.V. Pino, P. Gojal, Comparison of peak inspiratory flow rate via the Breezhaler®, Ellipta® and HandiHaler® dry powder inhalers in patients with moderate to very severe COPD: a randomized cross-over trial, BMC Pulm. Med. 18 (2018) 100.
[19] Á. Farkas, A. Szipőcs, A. Horváth, I. Horváth, G. Gálffy, J. Varga, K. Galambos, S. Kugler, A. Nagy, Z. Szalai, Establishment of relationships between native and inhalation device specific spirometric parameters as a step towards patient tailored inhalation device selection, Respir. Med. 154 (2019) 133–140.

[20] L.P. Malmberg, A.S. Pelkonen, V. Vartiainen, M. Vahteristo, S. Lahelma, R. Jögi, Patients with asthma or chronic obstructive pulmonary disease (COPD) can generate sufficient inspiratory flows via Easyhaler® dry powder inhaler: a pooled analysis of two randomized controlled trials, J. Thorac. Dis. 13 (2021) 621–631.
[21] W. Janssens, P. VandenBrande, E. Hardeman, E. De Langhe, T. Philps, T. Troosters, M. Decramer, Inspiratory flow rates at different levels of resistance in elderly COPD patients, Eur. Respir. J. 31 (2008) 78–83.
[22] W. Azouz, P. Chetcuti, H.S.R. Hosker, D. Saralaya, J. Stephenson, H. Chrystyn, The inhalation characteristics of patients when they use different dry powder inhalers, J. Aerosol Med. Pulm. Drug Deliv. 28 (2015) 35–42.
[23] S. Ghosh, J.A. Ohar, M.B. Drummond, Peak inspiratory flow rate in chronic obstructive pulmonary disease: implications for dry powder inhalers, J. Aerosol Med. Pulm. Drug Deliv. 30 (2017) 381–387.
[24] S. Stanojevic, D.A. Kaminsky, M. Miller, B. Thompson, A. Aliverti, I. Barjaktarevic, B.G. Cooper, B. Culver, E. Derom, G.L. Hall, T.S. Hallstrand, J.D. Leuppi, N. MacIntyre, M. McCormack, M. Rosenfeld, E.R. Swenson, ERS/ATS technical standard on interpretive strategies for routine lung function tests, Eur. Respir. J. 60 (2022) 2101499.
[25] M. Hamilton, R. Leggett, C. Pang, S. Charles, B. Gillett, D. Prime, In vitro dosing performance of the ELLIPTA dry powder inhaler using asthma and COPD patient inhalation profiles replicated with the electronic lung (eLungTM), J. Aerosol Med. Pulm. Drug Deliv. 28 (2015) 498–506.
[26] F. Buttini, G. Brambilla, D. Copelli, V. Sisti, A.G. Balducci, R. Bettini, I. Pasquaki, Effect of flow rate on *in vitro* performance of NEXThaler® in comparison with Diskus® and Turbohaler® dry powder inhalers, J. Aerosol Med. Pulm. Drug Deliv. 29 (2016) 167–178.
[27] A. Horváth, Á. Farkas, A. Szipőcs, G. Tomisa, Z. Szalai, G. Gálffy, Numerical simulation of the effect of inhalation parameters, gender, age and disease severity on the lung deposition of dry powder aerosol drugs emitted by Turbuhaler®, Breezhaler® and Genuair® in COPD patients, Eur. J. Pharmaceut. Sci. 154 (2020) 105508.
[28] J.C. Virchow, G. Poli, C. Herpich, C. Kietzig, H. Ehlich, D. Braeutigam, K. Sommerer, S. Hausermann, F. Mariotti, Lung deposition of the dry powder fixed combination beclometasone dipropionate plus formoterol fumarate using NEXThaler device in healthy subjects, asthmatic patients, and COPD patients, J. Aerosol Med. Pulm. Drug Deliv. 31 (2018) 269–280.
[29] Á. Farkas, G. Tomisa, S. Kugler, A. Nagy, A. Vaskó, E. Kis, G. Szénási, G. Gálffy, A. Horváth, The effect of exhalation before the inhalation of dry powder aerosol drugs on the breathing parameters, emitted doses and aerosol size distributions, Int. J. Pharm. X 5 (2023) 100167.
[30] P. Krüger, B. Ehrlein, M. Zier, R. Greguletz, Inspiratory flow resistance of marketed dry powder inhalers, Eur. Respir. J. 44 (2014) 4635.
[31] A.C. Grant, R. Walker, M. Hamilton, K. Garrill, The ELLIPTA dry powder inhaler: design, functionality, in vitro dosing performance and critical task compliance by patients and caregivers, J. Aerosol Med. Pulm. Drug Deliv. 28 (2015) 474–485.
[32] M. Corradi, H. Chrystyn, B.G. Cosio, M. Pirozynski, S. Loukides, R. Louis, M. Spinola, O.S. Usmani, NEXThaler, an innovative dry powder inhaler delivering an extrafine fixed combination of beclomethasone and formoterol to treat large and small airways in asthma, Expet Opin. Drug Deliv. 11 (2014) 1497–1506.
[33] H. Saed, H.F. Salem, H. Rabea, M.E.A. Abdelrahim, Effect of human error, inhalation flow, and inhalation volume on dose delivery from Ellipta® dry-powder inhaler, Journal of Pharmaceutical Innovation 14 (2019) 239–244.
[34] H. Watz, S. Barile, D. Guastalla, E. Topole, D. Cocconi, B. Mignot, D. Belmans, D. Duman, G. Poli, L.M. Fabbri, Targeting the small airways with inhaled corticosteroid/long-acting beta agonist dry powder inhalers: a functional respiratory Imaging study, J. Aerosol Med. Pulm. Drug Deliv. 34 (2021) 280–292.
[35] M.J. Sanders, Guiding inspiratory flow: Development of the In-Check Dial G16, a tool for improving inhaler technique, Pulmonary Medicine 2017 (2017) 1495867.
[36] P. Haidl, S. Heindl, K. Siemon, M. Bernacka, R.M. Cloes, Inhalation device requirements for patient's inhalation maneuvers, Respir. Med. 118 (2016) 65–75.
[37] M. Anderson, E. Sailer, E. Björk, T. Gustafsson, Ther relationship betweeen peak inspiratory flow rate (PIFR) and COPD severity measured as FEV1%predicted, and other lung function parameters in 33304 tests in patients at two different sites in Karolinska University Hospital in Stockholm, Sweden, Eur. Respir. J. 60 (1105) (2022).