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Do we really target the receptors? Deposition and co-deposition of ICS-LABA fixed combination drugs

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ABSTRACT

Fixed dose combinations of aerosolized bronchodilators and steroids are routinely used in current asthma and COPD management. As spatial distribution of their receptors within the human airways is different, it is a challenging task to deliver the right drug component to the right receptor. The aim of this work was to apply numerical methods to analyse the airway deposition distribution of two inhalation corticosteroid (ICS) – long-acting beta-agonist (LABA) combination drugs in comparison with the distribution of the corresponding receptors. Our results revealed that different combination drugs exhibit different co-deposition patterns depending on the aerodynamic properties of their components. While ICS and LABA components of Symbicort® Turbuhaler® had similar deposition efficiencies in the same airway generation throughout the whole respiratory tract, the steroid component of Relvar® Ellipta® had up to 25% higher deposition than its bronchodilator component in the large bronchi and up to 40% lower deposition in the deeper airways. Present results highlight the need for extensive research to elucidate whether each drug component should deposit according to its receptor distribution or similar deposition distribution patterns of the components should be attained to benefit from the synergistic effects documented in the open literature. Once this aspect clarified, the next step will be to tailor the aerodynamic properties of each component of combination drugs to yield the desired deposition distribution in the lungs.

1. Introduction

Inhaled aerosol drugs are key elements of current asthma and COPD therapy (GINA, 2021; GOLD, 2021). Long-acting bronchodilators, such as long-acting muscarinic antagonists (LAMA) or long-acting beta agonists (LABA), and inhalation corticosteroids (ICS) play a major role in the management of these diseases. Besides the simple monotherapy with one of the active ingredient types, different combinations of ICS, LAMA and LABA ingredients are also prescribed to well-defined subpopulations of patients to obtain better therapeutic outcome. Several studies have demonstrated the multiple economic and clinical advantages of the combination of fixed doses of two or even three drug components in a single inhaler over their delivery from different inhalation devices. A review of these studies can be found in the recent paper of Zhang et al., 2020. Amongst other advantages, in this way it is ensured that the ratio of the doses of different components is always the same (which was not ensured in the 'one drug in one inhaler' case, if the patient would forget to use one of them). In reality, the fixed dose ratio can be ensured only at the level of the doses metered in the device, but only to a smaller extent at the level of deposited doses. In order to preserve this ratio at the level of deposited doses, it would be desirable that the different components have the same aerosol aerodynamic properties. However, in this case not only the deposition efficiency would be the same, but also the spatial distribution of different components within the lungs. As the distribution of the targeted receptors of different drug components is different along the airways, at least hypothetically this may lead to suboptimal

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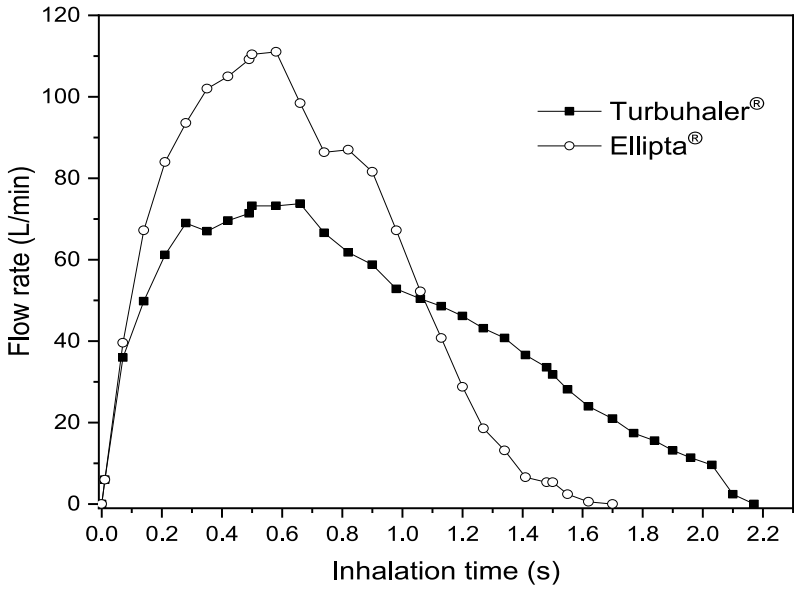

Fig. 1. p50 profiles of COPD patients while inhaling through Turbuhaler® and Ellipta® DPI devices.

effects. However, before entering into the details of clinical effects we must answer some questions, like are indeed the aerodynamic properties of different drug components similar? Is their deposition efficiency the same to preserve the fixed dose ratio? Are all marketed combination drugs the same from this point of view? To answer these questions, in this study we aimed to simulate the deposition of ICS-LABA fixed combination aerosol drugs and examine the deposition of their components from the perspective of the deposited amounts and the spatial distribution of the deposited drug particles starting from realistic breathing patterns of COPD patients. Another aim was to interpret the results in the view of possible synergistic effects of different components documented in the open literature.

2. Methods

In this study, transport and deposition of ICS and LABA components of two well-known fixed combination DPI aerosol drugs was studied. Both drugs are currently widely-used in asthma and COPD therapy. Symbicort® Turbuhaler® was one of the first fixed dose combination drugs, so its use has a twenty years' history. Its ICS component is budesonide, which is combined with formoterol fumarate dehydrate as the LABA component. Relvar® Ellipta® was the first once-daily ICS-LABA drug and also the first to be launched with both asthma and COPD indications. The anti-inflammatory component (ICS) of Relvar® is fluticasone furoate, being combined with vilanterol (trifenatate) as bronchodilator. Besides their widespread use, the reason for choosing these two aerosol drugs was our own data regarding the breathing of patients through the inhalers and the availability of data concerning the aerodynamic properties of the emitted drug particles in the open literature. Both sets of data are necessary for the numerical simulation of airway transport and deposition of the inhaled aerosol drug particles.

2.1. Breathing profiles

Airflow measurements were carried out on COPD patients inhaling through Turbuhaler® and Ellipta®. The corresponding 50 percentile inhalation profiles (p50) are depicted in Fig. 1.

The p50 curve corresponding to Turbuhaler® was generated based on the breathing parameters of a sample of 49 volunteer patients acquired at the Pulmonology Department of Petz Aladár County Teaching Hospital (Győr, Hungary, ethical approval no 76–1–20/2017).

The p50 profile for Ellipta® represents a population of 59 COPD patients whose breathing data were measured at the Pulmonology Clinic of University of Debrecen (Debrecen, Hungary, ethical approval no 2482/1/2018). More details of the spirometric measurements can be found in Farkas et al., (2019).

Patient demographics and native spirometry data of the two groups of patients are presented in Table 1. Though we have examined completely disjoint populations, the means and spread of the relevant parameters are not very different for the two groups. Although for the above reason a direct comparison of the breathing profiles cannot be performed, they reflect the known fact that Ellipta® has lower flow resistance than Turbuhaler® (Krüger et al., 2014), resulting in higher peak flow through Ellipta®.

2.2. Aerosol parameters

The amount and size distribution of the particles emitted by DPIs depend on the inhalation profile of the patient. Though there is publicly available data on the emitted dose and aerodynamic properties of the emitted particles of both drugs for different constant flow rates, obviously there is no available data corresponding exactly to the specific inhalation profiles in Fig. 1. In this study, the amount of steroid (ICS) and bronchodilator (LABA) active pharmaceutical ingredients emitted by Symbicort® Turbuhaler® and Relvar® Ellipta® and the size

Table 1
Mean value, standard deviation and range of patient demographics and native (standard, without inhaler) spirometric parameters.

	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)
Turbuhaler®	65.7±6.9	21/28	27.1±6.5	1.4 ±0.6	50.6 ±16.7	2.0±0.9	70.1±17.6	56.7±9.9	143.1±71.9	2.4 ±0.8
study	48–87		16–50.7	0.5–3.4	25–86	0.4–4.9	39–107	36.3–69.8	31.2–358.8	1.1–4.9
Ellipta®	65.5±8.9	23/36	27.8±6.1	1.6 ±0.7	60.1±25.4	2.6±0.8	72.9±21.2	79.5±16.4	153.5±80.6	2.1 ±0.7
study	45–86		17.2–51.9	0.7–3.3	16.7–117.3	1.3–4.8	36.2–118.3	34.3–108.2	68.4–268.8	1.0–4.0

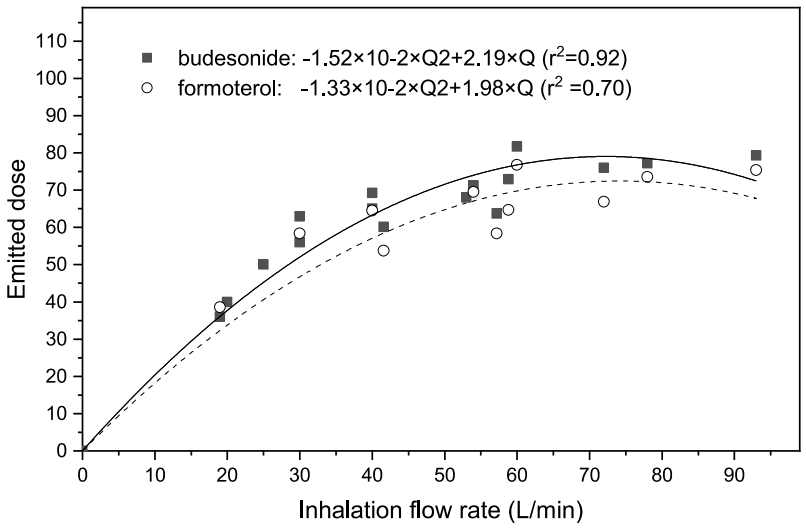

Fig. 2. Flow rate dependence of the emitted doses of budesonide and formoterol (Symbicort® Turbuhaler®) as a percent of the metered dose.

Table 2
Formulas for the determination of the emitted dose (ED), mass median aerodynamic diameter (MMAD), fine particle fraction (FPF), aerosolized fraction (AF) and emission time (t_{em}) of the steroid (ICS, inhalation corticosteroid) and bronchodilator (LABA, long-acting beta-agonist) components of Symbicort® Turbuhaler® and Relvar® Ellipta® inhalation drugs. All the quantities (except GSD and t_{em}) are expressed as a percent of the metered dose.

Symbicort® Turbuhaler®			
	ICS	LABA	Source
ED (%)	$-1.52 \times 10^{-2} \times Q^2 + 2.19 \times Q$	$-1.33 \times 10^{-2} \times Q^2 + 1.98 \times Q$	Tarsin et al., 2004 Assi et al., 2006
MMAD (μm)	$-1.30 \times 10^{-2} \times Q + 3.29$	$-1.09 \times 10^{-2} \times Q + 3.19$	Johal et al., 2013 Corradi et al, 2014
GSD	1.9	1.9	Chrystyn et al., 2015
FPF (%)	$-4.38 \times 10^{-3} \times Q^2 + 9.71 \times 10^{-1} \times Q$	$-4.07 \times 10^{-3} \times Q^2 + 8.96 \times 10^{-1} \times Q$	deBoer et al., 2015
AF (%)	Eq. 1.	Eq. 1	Buttini et al., 2016
t_{em} (s)	$69.4 \times e^{-(Q/5.4)} + 1.4 \times 10^{-1}$	$69.4 \times e^{-(Q/5.4)} + 1.4 \times 10^{-1}$	Haikarainen et al., 2017 Bagherisadeghi et al., 2017 Watz et al., 2021
Relvar® Ellipta®			
	ICS	LABA	Source
ED (%)	$-6.29 \times 10^{-3} \times Q^2 + 8.65 \times 10^{-1} \times Q + 63.34$	$-7.45 \times 10^{-3} \times Q^2 + 9.85 \times 10^{-1} \times Q + 58.70$	Lock et al., 2014; Hamilton et al., 2015; Grant et al., 2015; Saeed et al., 2018 Watz et al, 2021
MMAD (μm)	$-1.94 \times 10^{-2} \times Q + 4.80$	$-1.12 \times 10^{-2} \times Q + 2.79$	
GSD	2.1	2.3	
FPF (%)	$-4.73 \times 10^{-3} \times Q^2 + 6.76 \times 10^{-1} \times Q$	$-6.01 \times 10^{-3} \times Q^2 + Q$	
AF (%)	Eq. 1.	Eq. 1.	
t_{em} (s)	$-3.5 \times 10^{-4} \times Q + 1.5 \times 10^{-1}$	$-3.5 \times 10^{-4} \times Q + 1.5 \times 10^{-1}$	

distribution of the drug particles was obtained in three steps:

(i) Emitted doses (ED), mass median aerodynamic diameters (MMAD), geometric standard deviations (GSD), fine particle fractions (FPF) and emission times (t_{em}) of both components of the two drugs were gathered from the open literature for constant flow rates (Q);
(ii) The collected ED, MMAD, FPF and t_{em} values were plotted versus the flow rate and polynomial functions were fitted to these values to get their flow rate dependency;
(iii) EDs, MMADs and FPFs corresponding to the p50 profiles in Fig. 1 were calculated as the time integral of the fitted functions (between 0 - t_{em}).

Assuming that the size of the emitted drug particles follows a lognormal distribution, the computed MMAD and GSD values would completely define them. However, size distribution of drug particles is determined by impactor technique and only the fraction of particles deposited on the impactor stages and the final filter are considered to determine MMAD and GSD. A significant fraction (mostly large particles) of the dose can deposit also in the throat (induction port) and the pre-separator that precede the impactor. For an exact modelling of drug fate within the airways knowledge of the fraction of these particles is also needed. In this work this was accounted for as the difference between the emitted dose and the aerosolized fraction (ED-AF), where AF is the fraction of dose entering the impactor. As AF is not routinely reported in the articles from the literature, its value was determined based on theoretical considerations starting from the FPF values (which are usually provided). Assuming lognormal size distribution, the aerosolized fraction can be computed by the formula:

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

where *erf* is the error function

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

As an example, the flow rate dependency of the emitted budesonide and formoterol dose of Symbicort® Turbuhaler® is shown in Fig. 2 and the equations of all the relevant quantities are provided in Table 2 indicating the corresponding literature sources.

2.3. Deposition modelling

For the modelling of the deposition of Symbicort® Turbuhaler® and Relvar® Ellipta® inhalation drugs an analytical model (Stochastic Lung Model, SLM) has been applied. The model uses the breathing profiles (Fig. 1) and aerosol size distributions (Fig. 3) to predict the depositing amount of anti-inflammatory and bronchodilator drug components. One of the main advantages of this model is that it provides mot only regional deposition values, but airway generation specific deposition fractions as well, making the study of co-deposition possible. The basics of the model were laid down by Koblinger and Hofmann (1990) and it has been under

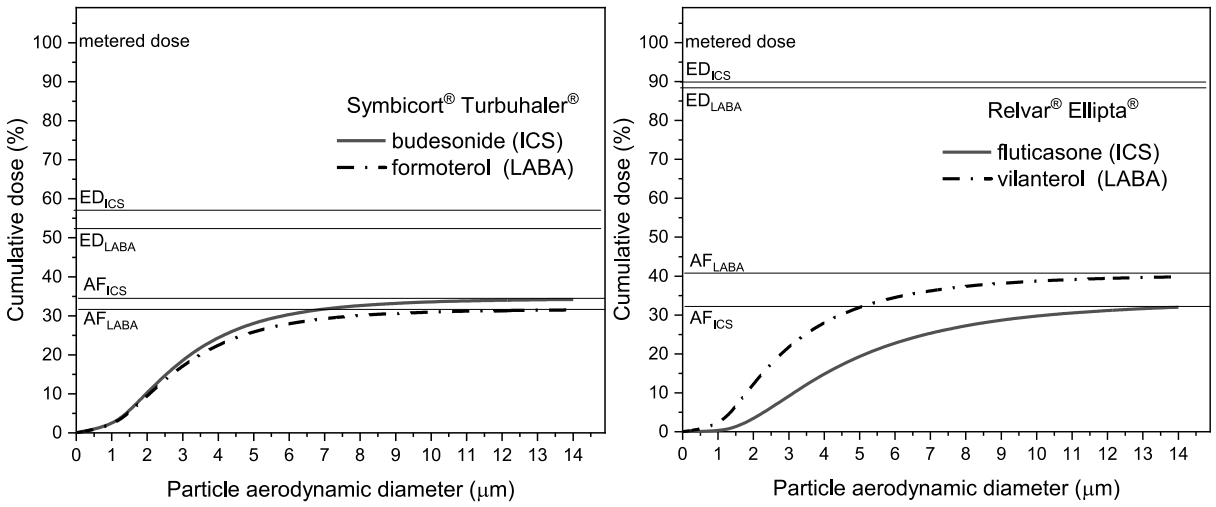

Fig. 3. Cumulative size distribution of ICS and LABA components of Symbicort® Turbuhaler® and Relvar® Ellipta®. Dose levels representing their aerosolised fraction (AF) and emitted amount (ED) are also marked. All characteristic doses are expressed as a percent of metered dose, which corresponds to 100%.

Table 3
Emitted dose (ED), mass median aerodynamic diameter (MMAD), fine particle fraction (FPF), aerosolized fraction (AF) and emission time (t_{em}) of the antiinflammatory (ICS, inhalation corticosteroid) and bronchodilator (LABA, long-acting beta-agonist) components of Symbicort® Turbuhaler® and Relvar® Ellipta® corresponding to breathing profiles in Fig. 1.

	Symbicort® Turbuhaler® ICS (budesonide)	LABA (formoterol)
ED (%)	57.1	52.2
MMAD (μm)	2.8	2.8
GSD	1.9	1.9
FPF (%)	28.1	25.9
AF (%)	34.4	31.7
t_{em} (ms)	210	210
	Relvar® Ellipta® ICS (fluticasone)	LABA (vilanterol)
ED (%)	89.9	88.3
MMAD (μm)	3.9	2.3
GSD	2.1	2.3
FPF (%)	21.2	33.4
AF (%)	33.6	40.5
t_{em} (ms)	130	130

continuous development. A more detailed description of the actual state of the model can be found in Madas et al. (2020). Its adaption to the case of aerosol drugs has been implemented and validated (Farkas et al., 2016; Farkas et al., 2019) in the last years. The model can track large numbers of inhaled particles and compute their deposition probability by impaction, sedimentation and Brownian diffusion.

3. Results

3.1. Emitted drug characteristics

The breathing profiles presented in Fig. 1 and the flow rate dependency of aerosol parameters summarised in Table 2 resulted in unique drug particle aerodynamic characteristics of each component of each drug. These data are presented in Table 3.

Assuming lognormal particle size distribution, the size spectrum of ICS and LABA components of the studied drugs can be obtained. Fig. 3 demonstrates these cumulative size distributions. On the vertical axis the cumulative mass (dose) is expressed as a percent of the metered mass (dose). As the fractionated size measurement is performed only inside the impactor, the cumulative curves have a plateau at the dose corresponding to the aerosolized fraction (AF). The rest of the emitted dose (ED) is represented by the particles that deposit in the impactor throat and the pre-separator. There is also a fraction of the metered dose which is not emitted from the DPI device (from ED to 100% in the figure). As it can be seen, ICS and LABA components of Symbicort® Turbuhaler® have similar size distribution with slightly higher amount of aerosolised ICS component. However, the aerosolised fraction of the ICS component of Relvar® Ellipta® is significantly lower than that of LABA component. In addition, the particles containing the steroid component are larger than those containing the bronchodilator (see also Table 3).

3.2. Airway deposition

The size distribution of the ICS and LABA components of the two inhalation drugs depicted in Fig. 3 corroborated with the breathing patterns in Fig. 1 were used to model the regional (upper airways, lungs) and the airway generation level deposition fractions. In this study, the deposition fraction was defined as the ratio of the mass of drug depositing in a certain airway segment to the mass of drug metered in the inhalation device.

3.3. Regional deposition

The calculated value of the deposition fraction of the ICS component of Symbicort® Turbuhaler® was 26.4% in the upper airways and 27.3% in the lungs. The same component of Relvar® Ellipta® (fluticasone) yielded 64.8% and 21.7% deposition fractions in the upper airways and in the lungs, respectively. Regarding the LABA components, formoterol had 23.9% extrathoracic and 25.1% lung deposition, while vilanterol yielded 54% upper airway and 27.4% lung deposition. However, as the p50 breathing profiles for the two inhalers refer to two different patient groups, a direct comparison between the deposition results of Symbicort® Turbuhaler® and Relvar® Ellipta® is not straightforward. Instead, in this work the comparison of co-deposition of the two different components of the same drug was in the focus. Profiting from the unique ability of our model to calculate the deposition fractions at airway generation level, the deposition of the ICS and LABA components was evaluated generation by generation.

3.4. Local distribution of the drug components

Upper panels of Fig. 4 present the airway generational deposition fraction density (fraction of the metered dose deposited in all the airways belonging to the same airway generation divided by the total area of the airways from the same generation) of ICS and LABA components

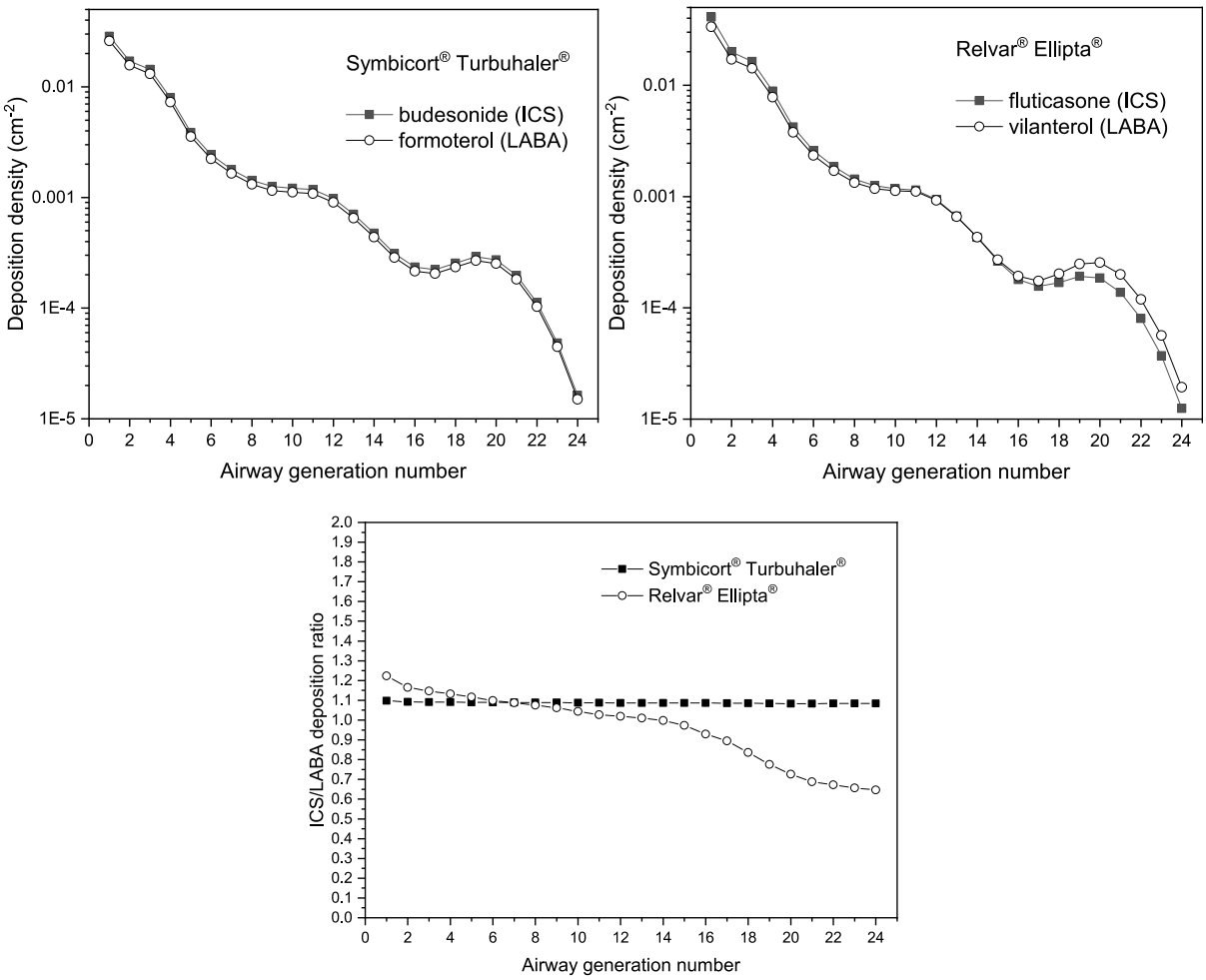

Fig. 4. Airway generation specific deposition fractions of ICS and LABA components of Symbicort® Turbuhaler® (upper left panel) and Relvar® Ellipta® (upper right panel) and ratio of deposition fractions of steroid (ICS) and bronchodilator (LABA) components (bottom panel).

of Symbicort® Turbuhaler® (left) and Relvar® Ellipta® (right).

Based on the plots, the distributions of budesonide and formoterol exhibit quite similar patterns with only slightly higher steroid deposition. According to the right upper panel of Fig. 4, the deposition density of LABA component (vilanterol) of Relvar® Ellipta® is notably lower than that of ICS (fluticasone) in the first five generations and higher in the 15–24 airway generations. As the low values of deposition density in the higher airway generations may hide the relative differences between the two components, ratios of deposition densities of steroid (ICS) and bronchodilator (LABA) components of the two drugs were also calculated. The results plotted in the lower panel of Fig. 4 clearly demonstrate that while for Symbicort® Turbuhaler® the deposition fraction of ICS is constantly about 10% higher than that of LABA, the ratio for the ICS and LABA components of Relvar® Ellipta® is monotonously decreasing towards the peripheral airways. It is obvious from these results that the initial (metered in the inhaler) dose ratio between two components of the same drug is not preserved at the level of deposited drug and it can be even a function of airway generation number (Relvar® Ellipta®). Moreover, present results refer to characteristic p50 inhalation profiles, but the ICS/LABA deposited dose ratio can be different from patient to patient. This shift in the dose ratio is not currently taken into account.

4. Discussion

Present results suggest that the two studied inhalation drugs have different co-deposition properties. One way of looking at the significance of current deposition results is to compare them with the distribution of the receptors. Almost every cell type expresses glucocorticoid receptors (receptors of ICS component), but the number of receptors per cell is the highest in the epithelial and endothelial cells (Barnes, 2004). Based on our current knowledge, the anti-inflammatory drug should be deposited throughout the whole thoracic airways. By the same token, the beta-agonist component of the drugs (LABA) relaxes precontracted human bronchi and also inhibit the release of bronchoconstrictor mediators. This component should reach the β_2-receptors (a subtype of β-adrenoceptors) which are localized to airway smooth muscle, epithelium, vascular smooth muscle and submucosal glands. Functional studies, that measure the response to specific agonists in tissue, demonstrated that β_2-receptors are equally present in smooth muscle at different airway levels (bronchial and bronchiolar). However, radioligand binding assays suggested that the density of such receptors is not uniform, but increases towards the smaller airways (Ikeda et al., 2012). Based on these considerations Haughney et al. (2010) suggested that bronchodilators should deposit mainly in the conductive airways where β_2-receptors are present in conjunction with smooth muscle, while ICS should deposit more uniformly in the whole lungs. This would also mean that the deposition distribution of different components of the fixed combination drugs should be different. It seems that this was not a leading factor driving the design of present drugs. Based on Fig. 3 the two components of Symbicort® Turbuhaler® have quite similar size distributions resulting in similar airway deposition patterns (Fig. 4). By contrast, the two components of Relvar® Ellipta® emitted from two separate strips have different aerodynamic parameters (see table 3) and different deposition fractions in some parts of the airways (Fig. 4). Since

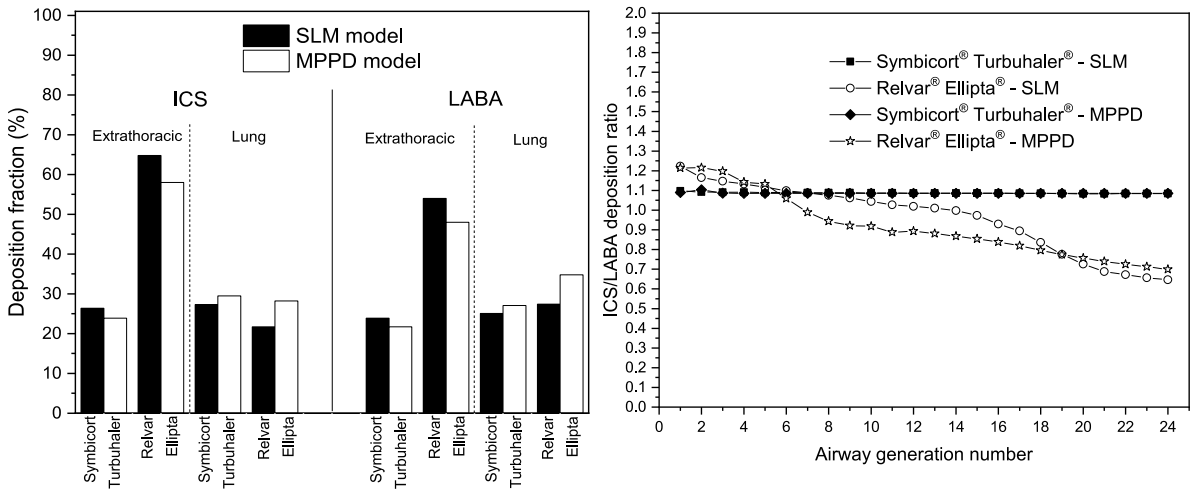

Fig. 5. Comparison of regional deposition fractions (left panel) and airway generation number specific deposition fraction ratios of ICS and LABA components (right panel) of Symbicort® Turbuhaler® and Relvar® Ellipta® obtained by SLM and MPPD models. All the deposition fractions refer to the metered dose. SLM – Stochastic Lung Model; MPPD – Multiple-Path Particle Dosimetry Model.

not the ICS, but the LABA component provides more consistent peripheral deposition, the leading cause of separate strips was hardly to follow the site specific distribution of the different receptor types. If the situation was so simple as depicted above, it would be reasonable to affirm that none of the studied drugs seems to reflect on the differences in terms of spatial distributions between the targeted receptors. However, the picture becomes more complicated if we consider the combined effects of different pharmaceutical active ingredients. It has been documented that corticosteroids increase the expression of β2-adrenoceptors and protect them against down-regulation. Conversely, β2-agonists improve the anti-inflammatory action of corticosteroids (Giembycz et al., 2008). There is also accumulating evidence that adding a LABA to an ICS results in a supra-additive, synergistic effect (Calzetta et al., 2018). These findings emphasize the significance of co-deposition of ICS and LABA components. In the present study, we could detect an overlap between the spatial deposition of the two components of both drugs, though in the case of Symbicort® Turbuhaler® this was more pronounced.

Currently, inhalation drugs are designed and formulated so that each component should have low upper airway deposition and as high as possible lung deposition without considering the inhomogeneous distribution of some types of receptors (e.g. M3 or β2). It is an open question whether it is more important to tailor the aerodynamic properties of each component of a combination drug to yield deposition distribution in accordance with the receptor distribution, or to obtain similar deposition distribution patterns of the components to benefit from the synergistic effects (or a combination of the two). If the aim is to follow the distribution of receptors, then the emission of bi-disperse aerosols (with different size distributions for the different components) would be desirable. By contrast, if a good co-deposition was the aim, similar size distribution of the components would be optimal.

Another important factor which should be taken into account when determining the "ideal" drug deposition distribution in COPD patients is the aim to ensure a more homogeneous ventilation. The maximal effects of aerosol drugs are related to improvement of dynamic hyperinflation in parallel with more exercise tolerance. Therefore, as a future direction we also need to focus on lung deposition in connection with exercise tolerance.

In case of ICS-LABA-LAMA fixed combination drugs the situation is even more complex and interesting, because the understanding of the combined effects of three active ingredient pairs (ICS-LABA, ICS-LAMA, LAMA-LABA) and one triplet (ICS-LABA-LAMA) would be required. Note that muscarinic receptor density is the highest in the large bronchial airways (Ikeda et al., 2012). Large clinical studies would be necessary in the future to decide whether co-deposition or deposition matching the receptor distribution provides better therapeutic outcomes. Based on this knowledge new challenges in the field of drug formulation and delivery would arise. Namely, the aerodynamic properties of the emitted drug components should be tuned to ensure the desired deposition pattern within the lung. Numerical modelling tools, like the one applied in this study, could also play an important role in this process by predicting the deposition of different components with similar or different aerodynamic properties.

4.1. *Limitations of the present study*

Some of the limitations of the present study were already mentioned within the paper. These include the fact that present results refer to two different patient groups limiting the possibilities of a direct comparison between the deposition of the two drugs, but also the well-known intersubject variability of airway deposition which was not considered here. In addition to these drawbacks, an important uncertainty may arise from the fact that there is variability in regional deposition predictions when one uses different models. The variability can be higher when the models belong to different classes of modelling (e.g. 3D Computation Fluid Particle Models 3D-CFPD vs 1D Equation models), but variability can be significant even amongst models within the same class. Furthermore, the differences between model predictions are particle-size dependent and typically not uniform across all particle sizes in the range 1–10 μm. In this sense, the results reported in Fig. 4 should only be understood as indicative of trends, as different models could potentially produce different distribution for each component. To check whether the conclusions of this work are universal or merely a result of model choice the deposition simulations were repeated by using a different deposition model. For this purpose, the MPPD (Multiple-Path Particle Dosimetry Model) model was chosen because to the best of our knowledge it is the only analytical 1D model (except ours) providing generation number specific deposition data. The MPPD model simulates the deposition and clearance of monodisperse and polydisperse aerosol particles in the airways for particles ranging in size from ultrafine (1 nm) to coarse (100 μm). Detailed descriptions of the model can be found in the open literature (e.g. Anjilvel and Asgharian, 1995; Miller et al., 2016) The results obtained by the two deposition models are demonstrated in Fig. 5.

The left panel of Fig. 5 demonstrates that the absolute difference between extrathoracic and lung deposition fractions obtained by the two

models varies between 2.2–7.4%. However, the columns exhibit similar trends regardless of the applied model. The comparison of the airway generation number dependent deposition fractions (right panel) demonstrated that the tendencies depicted by Fig. 4 obtained by the application of SLM model hold, though there are visible differences between the outcomes of the two models, especially regarding the deposition of Relvar® Ellipta®.

5. Conclusions

This study demonstrated that numerical modelling based on realistic input data can provide insights into the deposition and co-deposition properties of different components of fixed dose combination drugs. It has been demonstrated through the two studied aerosol drugs that deposition patterns and co-deposition properties are drug-specific. The metered dose ratio of ICS and LABA components is usually not preserved at the level of deposited doses. Better co-deposition would enhance the synergistic effects between the components, while selective deposition based on receptor distribution would lower it. As perfect co-deposition and perfect matching of receptor densities exclude each other, a third option would be some compromise between the two cases. Finding the best solution is possible only by conducting large clinical studies. Once the desired deposition distribution determined, combination drugs should be formulated to achieve it, taking into account the inter-individual variability of breathing patterns. Numerical modelling can have an important role in this process.

CRediT authorship contribution statement

Árpád Farkas: Conceptualization, Methodology, Validation, Writing – review & editing. **Alpár Horváth:** Conceptualization, Methodology, Writing – review & editing, Supervision. **Gábor Tomisa:** Conceptualization, Methodology. **Tamás Kovács:** Conceptualization, Methodology. **Renáta Marietta Böcskei:** Methodology, Data curation. **Erika Kis:** Methodology, Visualization. **János Varga:** Conceptualization, Methodology, Visualization.

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Further reading

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