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Research paper

Experimental and computational study of the effect of breath-actuated mechanism built in the NEXThaler® dry powder inhaler

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ABSTRACT

The breath-actuated mechanism (BAM) is a mechanical unit included in NEXThaler® with the role of delaying the emission of the drug until the inhalation flow rate of the patient is sufficiently high to detach the drug particles from their carriers.

The main objective of this work was to analyse the effect of the presence of BAM on the size distribution of the emitted drug and its airway deposition efficiency and distribution. Study of the hygroscopic growth of the emitted drug particles and its effect on the deposition was another goal of this study.

Size distributions of Foster® NEXThaler® drug particles emitted by dry powder inhalers with and without BAM have been measured by a Next Generation Impactor. Three characteristic inhalation profiles of asthmatic patients (low, moderate and high flow rates) were used for both experimental and modelling purposes. Particle hygroscopic growth was determined by a new method, where experimental measurements are combined with simulations. Upper airway and lung deposition fractions were computed assuming 5 s and 10 s breath-hold times.

By the inclusion of BAM the fine particle fraction of the steroid component increased from 24 to 30% to 47–51%, while that of bronchodilator from 25–34% to 52–55%. The predicted upper airway steroid and bronchodilator doses decreased from about 60% to 35–40% due to BAM. At the same time, predicted lung doses increased from about 20%–35% (steroid) and from 22% to 38% (bronchodilator) for the moderate flow profile and from about 25% to 40% (steroid) and from 29% to 47% (bronchodilator) for the high inhalation flow profile. Although BDP and FF upper airway doses decreased by a factor of about two when BAM was present, lung doses of both components were about the same in the BAM and no-BAM configurations at the weakest flow profile. However, lung dose increased by 2–3% even for this profile when hygroscopic growth was taken into account.

In conclusion, the NEXThaler® BAM mechanism is a unique feature enabling high emitted fine particle fraction and enhanced drug delivery to the lungs.

1. Introduction

Foster® NEXThaler® is an ICS + LABA (inhaled corticosteroid and long-acting β2-agonist) fixed combination aerosol drug used in current COPD and asthma therapy (Crisafulli et al., 2016). According to the SPC (summary of product characteristics) of Foster® NEXThaler® each metered dose of 10 mg powder contains 100 micrograms of beclometasone dipropionate anhydrous (BDP) and 6 micrograms of formoterol fumarate dihydrate (FF). As excipients, Foster® NEXThaler® contains lactose monohydrate (about 9.9 mg, which contains small amounts of milk protein), and magnesium stearate.

Based on the experimental measurements of several investigators

Abbreviations: ACI, Andersen Cascade Impactor; ACN, acetonitrile; BAM, breath-actuated mechanism; BDP, beclomethasone dipropionate; BH, breath-hold time; CK-EDB, comparative kinetic electrodynamic balance; DD, delivered dose; DPI, dry powder inhaler; DUSA, dosing unit sampling apparatus; EPF, extrafine particle fraction; FF, formoterol fumarate; FPF, fine particle fraction; GF, growth factor; ICS, inhaled corticosteroid; LABA, long-acting β2-agonist; MMAD, mass median aerodynamic diameter; MOC, micro-orifice collector; NGI, Next Generation Impactor; p10, p50 p90 10th 50th and 90th percentile inhalation curves; PIF, peak inspiratory flow; PIL, patient information leaflet; RH, relative humidity; SPC, summary of product characteristics; UPLC, ultra performance liquid chromatography

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(e.g. De Boer et al., 2015) the NEXThaler® inhaler is a DPI (dry powder inhaler) device delivering an almost pressure-drop independent dose of BDP and FF. It has also been demonstrated that Foster® NEXThaler® emits a high fraction of fine (diameter < 5 μm) and extrafine (diameter < 2 μm) particles (Buttini et al., 2016) with high lung deposition efficiency and a more uniform deposition distribution (Mariotti et al., 2011). The special internal design and structure of the inhaler is considered to contribute to the above characteristics of the drug (Scichilone et al., 2013). The most innovative feature of the device is the built in BAM (breath-actuated mechanism). The BAM is a mechanical unit integrated into the NEXThaler® with the aim of delaying the emission of the drug until the flow rate of the patient is sufficiently high (about 35 L/min). This level flow rate causes high turbulence intensity inside the cyclone chamber, resulting in efficient detachment of drug particles from the carriers. The detachment is promoted also by the strong collisions between the particles with high kinetic energy and between the particles and the walls of the device (Corradi et al., 2014). While qualitatively the above reasoning seems to be logical and correct, a systematic quantitative analysis of the effect of the inclusion of BAM is still missing in the literature. A number of investigators have analysed by both Andersen Cascade Impactor (ACI) and Next Generation Impactor (NGI) the size distribution of drug particles emitted by NEXThaler® and proved that fine and extrafine particle fractions (FPF and EPF, that is, fractions of particles with aerodynamic diameter smaller than 5 μm and 2 μm, respectively, expressed as per cents of metered dose/label claim) are indeed high compared to the corresponding values of other DPI drugs in the market. Based on Table 1, which is a summary of the measurement results gathered from the open literature, the FPF is between 42.5% and 59.4% for BDP and between 43.3% and 56.7% for FF while the EPF is between 32% and 52.7% for BDP and between 22.5% and 48.9% for FF, depending on the flow rate of the impactor. The corresponding mass median aerodynamic diameter (MMAD) values were systematically low (between 1.1 μm and 1.7 μm).

However, it has not been analysed so far to what extent the advantageous aerodynamic characteristics of the emitted particles are due to the BAM. By the same token, the high number of the resulting fine and extrafine drug particles should lead to lower deposited upper airway doses and higher lung doses. To the best of our knowledge, an analysis on the effect of the presence of BAM on the amount of drug deposited in different regions of the airways is also missing. One way of studying the effect of BAM is to compute and compare the airway deposition distributions of the drugs emitted by the inhalers with BAM included and lacking it. Carefully validated numerical models proved to be a powerful tool in the quantification of total respiratory tract, regional and local deposition distributions of different drugs (e.g. Jókay et al., 2016; Horváth et al.,2017). However, most of the numerical models do not consider the growth of the inhaled particles due to the humid environment within the airways. Aerodynamic properties of the emitted aerosol drugs, like the parameters in Table 1, are also determined under certain humidity and temperature conditions. Knowledge of growth dynamics may be important also in the perspective of drug development. If drug particles are sufficiently small to enter the lungs and their hygroscopic growth is significant within particle residence time, then chances of exhalation decrease and lung deposition will be higher.

The main objective of this study is to apply experimental techniques to analyse the effect of the inclusion of BAM on the main aerodynamic characteristics of the emitted particles. Another aim is to use the measured values as inputs of numerical models to characterize the deposition distribution of the drugs in different anatomical regions of the airways and analyse the effect of BAM on the deposition of Foster® NEXThaler® drug. Finally, this study proposes to measure the hygroscopic growth of the drug particles emitted by NEXThaler® and to analyse the possible effect of their hygroscopic behaviour on the deposited drug dose distributions within the airways.

2. Methods

In this study both experimental techniques and numerical modelling tools were applied. Experimental measurements were performed to analyse the effect of BAM on the aerodynamic properties of the emitted particles. The results of these measurements were then used as inputs of the numerical airway deposition model. Extended hygroscopicity measurements of ICS and LABA drug components were also completed. Realistic breathing profiles of asthmatic patients through the NEXThaler® were used for both measurement and modelling purposes. The original inhalation profiles were acquired by Scuri et al. (2013) on 41 asthmatic patients with varying levels of disease control while they inhaled through the inhaler by using acoustic monitoring equipment. Casaro et al. (2014) then processed these profiles and calculated the p10, p50 and p90 representative profiles, which were adopted in our study. The p10, p50 and p90 curves were generated by calculating the 10th, 50th and 90th percentile cohort values at each recorded time interval (0.01 s). The p10, p50 and p90 inhalation profiles are characterised by 1.0 s, 1.9 s and 3.4 s inhalation times, and 45 L/min, 60 L/min and 100 L/min peak inspiratory flow (PIF) values, respectively. The three inhalation flow curves are plotted in Fig. 1.

We now present the experimental and numerical techniques used in this study.

2.1. Experimental method for the characterization of the emitted particles

The aim of experimental work was to measure and compare the particle characteristics emitted by NEXThaler® DPI inhalers with and

Table 1
Summary of the measured fine (< 5 μm) and extrafine (< 2 μm) particle fractions of the two drug components of Foster® NEXThaler® with different impactors at different flow rates retrieved in the open literature. FPF − fine particle fraction; EPF − extrafine particle fraction.

Impactor type	Flow rate (L/min)	FPF (% of label claim)		EPF (% of label claim)		Author
		BDP	FF	BDP	FF	
ACI	60	49.9	52.2	32.0	34.5	Zanker et al. (2011)
NGI	41.7	42.5	48.8	–	–	De Boer et al. (2015)
NGI	59	45.5	50.3	–	–	De Boer et al. (2015)
NGI	72.3	47.3	53.1	–	–	De Boer et al. (2015)
NGI	30	48.2	43.3	34.5	22.5	Buttini et al. (2016)
NGI	40	49.2	48.3	34.7	25.3	Buttini et al. (2016)
NGI	60	58.4	56.7	41.3	28.4	Buttini et al. (2016)
ACI	60	59.4	52.5	52.7	48.9	Buttini et al. (2016)
NGI	90	57.9	56.7	43.4	34.9	Buttini et al. (2016)
NGI	realistic profile, p10	45.9	45.3	36.4	30.8	Casaro et al. (2014)
NGI	realistic profile, p50	48.8	48.3	38.9	32.7	Casaro et al. (2014)
NGI	realistic profile, p90	47.4	44.5	36.8	28.8	Casaro et al. (2014)