Real-life budesonide and formoterol dose emission from the medium and high strength fixed dosed combinations in a Spiromax® dry powder inhaler using inhalation profiles from patients with chronic obstructive pulmonary disease

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Abstract

Dry powder inhalers (DPIs) are passive devices used to administer inhaled medication for the management of asthma and chronic obstructive pulmonary disease (COPD). DPIs require patients to generate a sufficient internal turbulent airflow force during each inhalation to deaggregate the powdered drug formulation into an emitted dose containing particles with the greatest likelihood of lung deposition. This internal force is generated by the interaction between the user's inhalation flow and the resistance of the DPI. Traditional compendial in vitro methods of measuring dose emission use a vacuum pump to simulate inhalation. We have adapted this in vitro method by replacing the square wave inhalation profile generated by a vacuum pump with the inhalation profiles of patients using an empty DPI. This method enables accurate assessment of the actual dose they would have inhaled. In the present study, real-life inhalation profiles were selected from 15 patients with COPD who inhaled through an empty placebo Spiromax® DPI. Ex vivo dose emissions were measured for the medium (emitted dose of 160 µg/4.5 µg) and high-strength (320 µg/9 µg) budesonide/formoterol formulations from the Spiromax DPI. These profiles were used to investigate the effect of the primary inhalation parameter— peak inhalation flow (PIF). Some profiles were modified to isolate other inhalation parameters (namely, inhaled volume [V_{in}] and acceleration rate of the inhalation maneuver [ACIM]). Both the medium-strength and high-strength DuoResp Spiromax displayed flow-dependent dose emission. When the PIF of a patient's inhalation maneuver increased from 26.8 L/min to 69.7 L/min, there was a significant ($p < 0.05$) effect on the dose-emission characteristics of the medium-strength and high-strength DuoResp Spiromax. At each PIF, an increase in V_{in} from approximately 500 mL to 2,000

mL had no effect on the dose-emission characteristics of either strength. However, at each V_{in} there was a significant ($p < 0.05$) effect on the dose-emission characteristics as PIF increased. The effect of ACIM on the dose-emission characteristics was small. The ex vivo methodology used in this study provides a practical approach to identify the actual dose a patient might inhale during routine real-life use of the DuoResp Spiromax.

1. Introduction

Dry powder inhalers (DPIs) are widely used for the management of asthma and chronic obstructive pulmonary disease (COPD) (Muralidharan et al 2015). DPIs are breath-actuated devices and are preferred by most patients over other pressurized devices (Lenney et al., 2000). Although DPIs are considered to be easy to use in clinical studies (Lenny et al, 2000), real-life evaluations have noted that many patients have difficulty using the correct technique and that many of these errors are clinically important (Chrystyn et al., 2017; Price et al., 2017). Using the correct inhalation maneuver when patients use a DPI is a common problem (Chrystyn & Price, 2009). Thus, it is important to determine the parameters of each inhalation maneuver that results in altered dosing during real-life use of DPIs (Chrystyn et al., 2017; Price et al., 2017).

Effective use of DPIs depends on adequate powder deaggregation to aerosolize the drug with a high fine particle fraction (FPF), which facilitates adequate deposition of the drug in the lungs (Longest et al., 2013). Deaggregation of the drug depends on many factors, including the aerodynamic particle behavior of the formulation (Longest et al., 2013) and the design of the inhaler (Muralidharan et al., 2015). Most DPIs are passive devices that require a turbulent airflow force to be generated from the patient's inhalation to deaggregate the powdered drug into an emitted dose (Chrystyn, 2003) which can be characterized by parameters such as the total emitted dose (TED), the fine-particle dose (FPD), and the mass median aerodynamic diameter (MMAD). A typical patient's inhalation generates a flow-versus-time profile that can be characterized by parameters such as the peak inhalation flow (PIF), the inhaled volume (V_{in}), and the initial acceleration of the inhalation maneuver (ACIM) (Bagherisadeghi et al., 2017).

We recently reported on the performance of the medium-strength Symbicort® Turbuhaler® (Astra Zeneca, Lund, Sweden) DPI, which dispenses a fixed-dose combination (FDC) of 200-μg

of the inhaled corticosteroid budesonide and 6-µg of the long-acting beta agonist formoterol, providing a labelled emitted dose of 160 µg/4.5 µg) (Bagherisadeghi et al., 2017). Dose-emission characteristics were measured using an ex vivo methodology based on real-life COPD patient inhalation profiles described by Azouz et al. (2015). This ex vivo methodology developed by our group (Chrystyn et al., 2015) is a modification of the mixing inlet method previously reported by Nadarassan et al. (2010) and Olsson et al. (2013). This method allows the use of the patient's real-life inhalation characteristics to identify the dose of active drug they would have inhaled, thereby providing a more realistic assessment of the performance of a DPI compared with compendial methods that use a vacuum pump to simulate an inhalation. The inhalation profiles produced by a vacuum pump are a square wave, which no human can replicate (Bagherisadeghi et al., 2017). Our previous study showed that the overall PIF markedly affected the dose-emission characteristics of the FDC of budesonide and formoterol in the medium-strength Symbicort Turbuhaler using inhalation flows just below 30 L/min and just above 60 L/min (Bagherisadeghi et al., 2017)..

The multidose DPI (MDPI) DuoResp® Spiromax® (Teva Pharmaceutical Industries, Petach Tikva, Israel) is approved in the European Union as a treatment for asthma and COPD as a generic equivalent to the Symbicort Turbuhaler (Canonica et al., 2015). The medium-strength formulation of budesonide 200 µg and formoterol 6 µg is labelled as producing an emitted dose of 160 µg/4.5 µg, while the high-strength formulation containing budesonide 400 µg and formoterol 12 µg is labelled as yielding an emitted dose of 320 µg/9 µg. The DuoResp Spiromax design resembles a pressurized metered-dose inhaler in shape and appearance, providing dose uniformity with maximum ease of use (Canonica et al., 2015).

The aim of the present study was to examine how real-life inhalation profiles obtained from 15 patients with COPD would impact the dose-emission characteristics of FDCs of the medium-strength and high-strength DuoResp Spiromax formulations. In particular, our goal was to determine the effects of PIF, V_{in}, and ACIM on dose emission.

2. Materials and methods

2.1. Chemicals and solvents

Budesonide and formoterol fumarate (analytical grade), high-performance liquid chromatography (HPLC)-grade disodium hydrogen orthophosphate, orthophosphoric acid, triethylamine (TEA), and acetonitrile were purchased commercially as described previously (Bagherisadeghi et al., 2017), and the water used for the analysis was ultra-purified for HPLC use. DuoResp Spiromax (Teva Pharmaceuticals) DPIs containing budesonide and formoterol fumarate dihydrate in medium-strength (labelled as an emitted dose of budesonide 160 µg/formoterol 4.5 µg) and high-strength (budesonide 320 µg/formoterol 9 µg) were obtained from a local supplier.

2.2. Inhalation profiles

Patients in Group A were selected from a study reported by Azouz et al. (2015) when they inhaled using an empty placebo Spiromax MDPI and additionally described by Bagherisadeghi et al. (2017). Inhalation profiles (**Figure 1A**) Profiles (1–15) were gathered from 15 patients with COPD who inhaled through an empty DuoResp Spiromax device. The mean ± standard deviation (SD) age of the patients was 67 ± 8 years, and the mean ± SD forced expiratory volume in 1 second (FEV_1) was 1.2 ± 0.5 L, corresponding to a percent predicted FEV_1 of 53 ± 10%.

The inhalation profiles of Group B (**Figure 1B)** Profiles (16–24) were designed by modifying some of the original profiles to study the effect of V_{in} on dose emission at fixed PIFs and ACIMs as described previously (Bagherisadeghi et al., 2017). The desired inhalation volumes were obtained by reducing the inhalation time (T_i) of the original profile after the time to the PIF (T_p), such that T_i was reduced while ACIM and PIF remained constant. To study the effect of V_{in}, 3 groups of profiles were designed at 3 different PIFs and ACIMs, with inhaled volumes of approximately 500 mL, 1,000 mL, and 2,000 mL. Profiles 16, 17, and 18 were obtained by modifying Profile 8; Profile 13 was the basis for Profiles (19–21); And Profiles 22, 23, and 24 were obtained by modifying Profile 15.

Group C profiles (**Figure 1C**,), which were modified from the original profiles, were used to study the effect of ACIM on the dose emission of the DuoResp Spiromax. Profile 1 was the basis for Profiles 25, 26, 35, 36, 43, and 44; Profiles 27, 36, and 45 were obtained by modifying Profile 8; Profiles 28–30, 37–39, and 46–48 were obtained by altering Profile 13; and Profiles 31–33, 40–41, and 49–51 were obtained by modifying the original Profile 8. For each fixed V_{in} and PIF, 3 different ACIM values (1, 2, and 4 L/s^2) were used. The profiles were designed in this manner so that the V_{in} remained constant while ACIM increased by approximately 1, 2, and 4 L/s^2.

2.3.   Ex vivo measurement

A schematic diagram of the sample collection device and ex vivo measurements have been described in detail previously (Bagherisadeghi et al., 2017). The emitted doses of the DuoResp Spiromax MDPI were determined using the Andersen Cascade Impactor (ACI; Copley Scientific Ltd, United Kingdom) in tandem with the Breath Simulator 3000 (BRS 3000; Copley Scientific Ltd, United Kingdom), which was used to model the patient inhalation profiles. Constant flow

through the ACI was achieved by supplementary air provided via a Mixing Inlet and a vacuum pump controlled by a dry powder flow controller (TPK 2000, Copley Scientific Ltd, United Kingdom) so that air flow through the inhaler mouthpiece was Zero. When a programmed inhalation profile was drawn from the supplementary air then this was replayed through the dose primed MDPI at the mouthpiece of an Alberta Idealised Throat (Bagherisadeghi et al., 2017). Since the vacuum pump is set to maintain a constant flow through the ACI then the inhalation flow profile is subsequently drawn through the DPI. The flow through the ACI and provided by the supplementary air source is set at either 60 or 90 L/min so that when using the appropriate ACI stages the cut-off diameters are not changed. Also, this means that an inhalation profiles with a PIF above 90 L/min cannot be used. The inhaler is connected to the induction port by means of a mouth piece adaptor which provides an airtight seal between the induction port and the inhaler under test. These stages are assembled on top of each other with orifices of decreasing size. The ACI operates on the principle of inertial impaction, therefore once the dose is discharged from the inhaler the aerosol cloud is drawn through the impactor by means of a vacuum pump connected to the outlet of the ACI using suitable tubing. Before each determination the stages of the ACI and its accessories (pre-separator, AIT) together with the mixing inlet were washed and dried in an oven and then allowed to cool to adjust to room temperature. This would also eliminate any electrostatic charge present on the inner surface of the ACI. The collection plates were cleaned with acetone to remove any organic substance and then sprayed with silicone (Pro-Power Silicone Lubricant, Premier Farnell plc, UK) to reduce any particle bouncing and allowed to dry prior to use for 30 minutes. The inside of the AIT was also coated with silicone spray.

Five diferent DuoResp Spiromax inhalers were used for each determination, and one dose was discharged from each inhaler prior to use following the product's recommended dose preparation instructions. Five doses were used for each determination to limit any influence from variable dose emissions (Tarsin et al., 2004). For each inhalation profile, 3 separate determinations were made.

After each dose emission determination using an inhalation profile the MDPI was attached to a Dose Unit Sampling Unit to determine the residual amount (RA) using an inhalation flow of 60 L/min and inhaled volume of 4 L.

A validated HPLC method was used to quantify the amount of formoterol and budesonide discharged from the inhaler and collected in the ACI as described previously (Bagherisadeghi et al., 2017). The method was linear with a correlation coefficient of 0.999 and 1 for both Budesonide and formoterol. It was accurate and precise with a relative standard deviation < 0.9 over the range of the concentration used 50 – 800 ng/mL for formoterol and 0.2 - 10μg/mL for Budesonide.

2.4. *Calculation of dose-emission characteristics*

Dose-emission characteristics for each determination were calculated using Copley Inhaler Testing Data Analysis Software (CITDAS; Copley Scientific Ltd, United Kingdom). The TED was calculated by measuring the cumulative mass of the compounds collected on the mouthpiece adapter of the collection device, the Alberta Idealised Throat induction port, and the mixing value, as well as all stages of the ACI. The FPD was calculated by measuring the total mass of the aerodynamic drug particles with a diameter of <5 micrometers. The FPF was defined as the FPD expressed as a percentage of the TED. Amounts were also expressed as a percentage of the labelled (emitted) dose (FPFlabel, TEDlabel, and TRDlabel). The MMAD was defined as the size

corresponding to half the cumulative amount deposited on the different stages of the ACI as described previously (Bagherisadeghi et al., 2017). The geometric standard deviation (GSD) It was derived from the plot of the cumulative percentage of mass less deviation (GSD): than the stated cut-off diameter versus the cut-off diameter by the equation: (D84.13% / D15.87%) $^{1/2}$.It was used to indicate the aerosol particle size variability, values of <1.2 indicate that a drug is monodisperse and a GSD of 1 indicates a monodisperse aerosol. The residual amount (RA) was recovered from the dose unit sampling apparatus (DUSA), and the total recovered dose (TRD) was calculated as TED plus RA.

2.5.   Statistical analysis

IBM SPSS Statistics software (IBM, Armonk, New York, United States) was used to determine statistical significance for FPD, TED, and MMAD. A *p*-value of less than 0.05 was considered statistically significant.

3. Results

3.1.   Aerodynamic dose emission and effect of PIF on FPD, TED, and MMAD

A summary of the aerodynamic dose-emission characteristics from all profiles for the medium-strength and high-strength DuoResp Spiromax are summarized in **Tables 1** and **2**, respectively, for budesonide and formoterol. The summary data show that emission characteristics were similar across all 3 groups for both the medium-strength and high-strength DuoResp Spiromax. The effects of PIF on FPD, TED, and MMAD for the medium-strength and high-strength DuoResp Spiromax are summarized for all profiles in **Figures 2** and **3**. These data show that, for both budesonide and formoterol, as PIF of the inhalation profiles increased from 26.8 L/min to 69.7 L/min, both FPD and TED significantly increased ($p < 0.05$), while MMAD significantly decreased ($p < 0.05$). There was a linear correlation for all 3 aerodynamic dose-emission

parameters (FPD, TED, and MMAD) with increasing PIF. **Table 1** and **Table 2** show that when TED was added to RA, the resulting TRD was equal to the labelled dose.

3.2. *Effect of V_{in} on FPD, TED, and MMAD*

The effect of V_{in} on the dose-emission characteristics was examined using Group B profiles (Figure 4). The PIFs were classified into 3 groups (low, 26.8 L/min; medium, 43.5 L/min; high, 65.6 L/min), and ACIM was fixed for each of these PIF groups while V_{in} was increased from approximately 500 mL to 2,000 mL. For medium strength DuoResp Spiromax, at each V_{in}, both FPD and TED significantly increased ($p < 0.05$), and MMAD significantly decreased, as PIF increased from 26.8 L/min to 65.6 L/min for both budesonide and formoterol (**Figure 4 A, B, and C**). Similarly, for the high-strength DuoResp Spiromax, at each V_{in} both FPD and TED increased significantly and MMAD decreased significantly ($p < 0.05$) as PIF increased for budesonide and formoterol (**Figure 4 D, E,** and **F**)

The mean and SD of FPF_{label}, TED_{label}, and TRD_{label} for both budesonide and formoterol for the medium-strength and high-strength DuoResp Spiromax are shown in **Table 3.** For the medium-strength DuoResp Spiromax in Group B at the highest PIF, FPF (% label) for budesonide increased from 22.5 to 35.0, and TED (% label) increased from 58.9 to 78.9 with increasing V_{in} for high PIF for budesonide. The results for formoterol show that for high PIF, FPF increased from 59.9 to 70.9, and TED increased from 95.5 to 106.4 with increasing V_{in}. There were no changes with low PIF. For the high-strength DuoResp Spiromax for Group B, high PIF resulted in increasing FPF and TED for budesonide and formoterol with increasing V_{in}.

3.3.   Effect of ACIM on FPD, TED, and MMAD

For both the medium-strength (**Figure 5**) and high-strength (**Figure 6**) DuoResp Spiromax, an increase in ACIM from 1 L/s^2 to 4 L/s^2 resulted in small effects on FPD and MMAD for both budesonide and formoterol, with high (69.7 L/min) PIFs on the Group C dose-emission profiles as V_{in} increased from ~1,000 mL to ~2,000 mL. No changes in TED were observed with increasing ACIM.

3.4   All profiles

The PIF of Profile 8 was 26.8 L/min with a V_{in} of 1.47 L and an ACIM of 1.8 L/sec^2, while the respective values for Profile 41 were 69.7 L/min, 1.50 L, and 2.0 L/sec^2 . These were the profiles with the slowest and fastest PIFs. **Table 4** shows the dose emission from these two profiles for the medium-strength DuoResp Spiromax.

4   Discussion

The aerosolization of dry powder drug formulations in DPIs occurs by forcing air through the loose powder (Labiris and Dolovich, 2003) in the dosing cup and inhalation channel of a DPI and creating a turbulent airflow force (Chrystyn, 2003). In the present study, the dose-emission characteristics of the DuoResp Spiromax were analyzed using an ex vivo analysis method that was programmed with inhalation profiles from different patients with COPD to model real-life doses of the drug dispensed by the DuoResp Spiromax device during inhalation by a patient. We found that when PIF was increased from 26.8 L/min to 69.7 L/min, there was a flow-dependent effect on the dose-emission characteristics of the medium-strength and high-strength DuoResp Spiromax. This effect is a classical property of DPIs (Weers and Clark, 2017). In addition to PIF, the deaggregation of the inhaled powder can be influenced by factors such as ACIM and V_{in}.

Therefore, in this study, these 3 parameters were analyzed to investigate the effect of each one on dose emission using modified COPD patient inhalation profiles for measurement of dose-emission characteristics (Bagherisadeghi et al., 2017). However, the results indicated that the effects of V_{in} and ACIM on the dose-emission characteristics were small.

Dose emission from both medium and high – strength DuoResp Spiromax increased with the inhalation flow rate (Figures 2 and 3). Suggesting both the medium-strength and high-strength DuoResp Spiromax DPIs displayed flow-dependent dose emission, which was consistent with findings reported previously by Bagherisadeghi et al. (2017) with the Symbicort Turbuhaler. However, the influence of PIF on the DuoResp Spiromax was smaller than it was for the Symbicort Turbuhaler (Bagherisadeghi et al., 2017).

Our findings regarding the effect of flow on the FPD of budesonide and formoterol were also consistent with those reported for FDCs in the NEXTHaler, Diskus, and Turbuhaler DPIs (Buttini et al., 2016). Figures 2 and 3 show that the dose-emission properties of the medium-strength and high-strength DuoResp Spiromax are similar.

It should be noted that our findings regarding the flow-dependent dose emission of the DuoResp Spiromax using the COPD inhalation profiles were similar to findings derived from a compendial method reported by Canonica et al. (2015). Moreover, it is widely accepted that the minimum flow required to deaggregate the budesonide/formoterol formulation is 30 L/min when using the Symbicort Turbuhaler or the DuoResp Spiromax (Azouz et al., 2015; Nadarassan et al., 2010). Symbicort Turbuhaler is known as a medium resistance (0.039 kPa$^{0.5}$ min/L) device and requires a minimum PIF of 30 L/min to de-aggregate the powder formulation but also to carry the drug through the long inhalation channel of the device to reach the mouthpiece (Dal Negro., 2015).

Our results also showed that both FPD and TED increased and MMAD decreased by increasing the PIF for both budesonide and formoterol. For Profile 51, at the highest PIF (69.7 L/min) with V_{in} of 2,004 mL and ACIM of 4.0 L/s^2, TED for budesonide was 165.4 µg and 313.4 µg for the medium-strength and high-strength DuoResp Spiromax DPIs, respectively. These results indicate that, like the Symbicort Turbuhaler, the dose was not completely emitted from the metering cup at these inhalation flows and volumes (Chrystyn et al., 2015).

In this study, the DuoResp Spiromax profiles were selected on the basis of comparability with the Symbicort Turbuhaler profiles. For this reason, the first 15 profiles (Group A) were selected from the study by Azouz et al. (2015). The results for both the medium-strength and high-strength DuoResp Spiromax indicated a significant effect of PIF on dose emission, as PIF increased from 26.8 L/min to 65.6 L/min, regardless of V_{in} and ACIM. As a consequence, both FPD and TED increased and MMAD decreased significantly.

Results from the dose-emission study of the medium-strength DuoResp Spiromax showed that V_{in} had a very small effect on the profiles with a medium PIF (43.5 L/min) when V_{in} increased from ~500 mL to ~1,000 mL, and there was a small effect on the profiles with a high PIF (65.6 L/min) when V_{in} increased from ~500 to ~2,000 mL.

The effect of V_{in} on the dose emission of the high-strength DuoResp Spiromax was negligible for profiles with a low PIF (26.8 L/min) and slightly greater for profiles with a high PIF (65.6 L/min) as V_{in} increased from ~500 mL to ~2,000 mL for both profiles. No change was observed for profiles with a medium PIF (43.5 L/min). This might be due to insufficient V_{in} to disperse the drug from the inhaler's channel at medium PIF. This can be confirmed by looking at the dose-emission data for Profiles 6, 10, and 14. With a PIF of ~50 L/min, ACIM ~2 L/s^2, and different V_{in} settings (970 mL, 1441 mL, and 2423 mL), small increases in FPD and TED were

observed in these profiles when V_{in} increased above 2,000 mL. The dispersion of the powder formulation primarily depends on the PIF to de-aggregate the powder and carry the dispersed powder in airstream. In the case of low PIF profile, more drug powder remains on the carrier and those detached from the carrier may remain as agglomerates. The V_{in} is not powerful enough to detach drug from the surface of the carrier, break up drug agglomerates and carry the dispersed drug in the airstream. However, at high PIF profile the drug detachment, de-agglomeration is mainly caused by the inhalation flow and the V_{in} will easily carry the dispersed drug to provide high TED, FPD and low MMAD.

For both the medium-strength and high-strength DuoResp Spiromax, the effect of V_{in} on the profiles with a high PIF was usually greater than with medium and low PIFs. Also, the impact of V_{in} on TED for the profiles with a high PIF was greater for the medium-strength DuoResp Spiromax than for the high-strength DuoResp Spiromax, which could be due to the differences in the amount of drug that is deposited into the inhaler channel. This can result in lower shear stress and viscous stress, which can occur between the particles and the inhaler's wall. Thus, particles from the medium-strength DuoResp Spiromax may be able follow the airstream more easily than those from the high-strength DuoResp Spiromax. Kamin et al. (2002) reported that V_{in} has significant effects on mass outputs but not on MMAD. In the present study and in our previous study of the medium-strength Symbicort Turbuhaler (Bagherisadeghi et al., 2017), we found that V_{in} had negligible effects on mass output and MMAD.

In profiles with high PIF, as ACIM increased from 2 L/s^2 to 4 L/s^2 (69.7 L/min), we observed only a small effect on the dose-emission characteristics of the medium-strength DuoResp Spiromax. Moreover, ACIM had no effect on the dose emission of profiles with low and medium

PIFs (26.8 L/min, 3.5 L/min); this finding may be related to the low Reynold number at these PIFs, resulting in a laminar airflow instead of a turbulent airflow inside the inhaler. These results are similar to those we found for the medium-strength Symbicort Turbuhaler (Bagherisadeghi et al., 2017).

The high-strength DuoResp Spiromax was also not substantially influenced by changes in ACIM. There was a small effect on profiles with low and high PIFs as ACIM increased from 1 L/s^2 to 4 L/s^2 and from 1 L/s^2 to 2 L/s^2, and only negligible effects were seen on profiles with a medium PIF as ACIM increased from 2 L/s^2 to 4 L/s^2. Moreover, profiles with high PIFs showed greater changes compared with those with low PIFs, and profiles with medium PIFs showed greater changes than both the low and high PIF groups.

Everard et al. (1997) and Kamin et al. (2002) showed that when acceleration was increased from a Symbicort Turbuhaler, particle deaggregation increased. Kamin et al. (2002) also reported that a faster acceleration rate results in higher FPD and smaller MMAD. In the present study, the effect of V_{in} and ACIM on the dose emission from the DuoResp Spiromax was smaller than that reported by Everard et al. (1997) and Kamin et al. (2002) with a Symbicort Turbuhaler. The difference between our findings and Everard et al. (1997) and Kamin et al. (2002) could be due to the difference in the experimental set-up.

A recent study reported significant differences in performance of the DuoResp Spiromax after shaking versus the Symbicort Turbuhaler (Janson et al., 2017). The study found that shaking the low and high strength DuoResp Spiromax resulted in 20% and 80% decreases in the delivered dose of budesonide/formoterol, respectively. These authors also found that the delivered dose from the Symbicort Turbuhaler was not different regardless of whether or not the

inhaler was shaken, except for a 10% decrease in delivered dose with the high-strength (budesonide 320 μg/formoterol 9 μg) Symbicort Turbuhaler. In both the current DuoResp Spiromax study and our previous Symbicort Turbuhaler study (Bagherisadeghi et al., 2017), the devices were not shaken prior to use, and the dose was prepared according to the instructions in the patient information leaflets.

5 Conclusions

The ex vivo methodology used in this study provides a realistic approach to quantify the dose of medication that patients actually inhale during routine use of the DuoResp Spiromax inhaler. Our findings show that PIF had a significant effect on the dose-emission characteristics of both the medium-strength and the high-strength DuoResp Spiromax when PIF increased from 26.8 L/min to 69.7 L/min. The effects of both V_{in} and ACIM were small, with V_{in} values of ~500 mL to ~2,000 mL and ACIM of 1 L/s^2 to 4 L/s^2. The effect of flow on the dose emission from the DuoResp Spiromax was not as substantial as the effect seen using similar inhalation profiles with the Symbicort Turbuhaler.

Conflict of Interest Disclosure

Acknowledgements

Figure 1   Inhalation profiles of patients in Group A (A), Group B (B), and Group C (C).

Figure 2   Effect of PIF on FPD, TED, and MMAD of each Group A profile for budesonide (A, B, and C, respectively) and formoterol (D, E, and F, respectively) for the medium-strength DuoResp Spiromax.

Figure 3   Effect of PIF on FPD, TED and MMAD for all profiles for budesonide (A, B, and C, respectively) and formoterol (D, E, and F, respectively) for the high-strength DuoResp Spiromax.

Figure 4   The effect of V_{in} on FPD (A, D), TED (B, E), and MMAD (C, F) of the medium-strength (A–C) and high-strength (D–F) DuoResp Spiromax for Group B profiles. Data are the mean of 3 determinations using 5 separate doses per determination.

Figure 5   The effect of ACIM on FPD (A, D), TED (B, E), and MMAD (C, F) of the medium-strength DuoResp Spiromax from Group C profiles. Data are the mean of 3 determinations using 5 separate doses per determination.

Figure 6   The effect of ACIM on FPD (A, D), TED (B, E), and MMAD (C, F) of the high-strength DuoResp Spiromax from Group C profiles. Data are the mean of 3 determinations using 5 separate doses per determination.

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