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Effect of inhalation profile and throat geometry on predicted lung deposition of budesonide and formoterol (BF) in COPD: An *in-vitro* comparison of Spiromax with Turbuhaler

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ABSTRACT

Successful delivery of inhalation medication to the lungs can be affected by the inhalation manoeuvre used. Conventional *in-vitro* testing of the emitted dose from a dry powder inhaler (DPI) uses a vacuum pump to simulate an inhalation. We have adapted this method by replacing the pump with patient inhalation profiles and an anatomical throat. Three anatomical throat sizes and three inhalation profiles were used. The profiles represented the 10th, 50th and 90th percentiles of peak inhalation flow and acceleration of flow from a population of 50 COPD patients inhaling through empty Spiromax and Turbuhaler devices. Combining the dose emission results for the three throat sizes, the mean (SD) budesonide fine-particle dose (FPD) from budesonide–formoterol Spiromax 320/9 μg was 78.91 (20.18), 79.91 (15.36) and 75.10 (19.91) μg and the total emitted dose (TED) of budesonide was 263.69 (40.74), 261.20 (21.65) and 261.61 (45.65) μg. Similarly, the FPD from 320/9 μg Turbuhaler was 22.45 (3.24), 52.20 (12.57) and 69.11 (75.10) μg with a TED of 143.80 (14.90), 149.50 (26.61) and 158.61 (43.04) μg. Spiromax showed greater consistency than Turbuhaler over a range of inspiratory flow profiles. The results demonstrate the value of this new method to assess the doses that patients receive during real-life use of their DPI.

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1. Introduction

When a drug is inhaled, the dose that is emitted (defined as the total emitted dose [TED]) from an inhaler is either deposited into the airways or impacts onto the oropharyngeal region and is swallowed (Chrystyn, 2000; Laube et al., 2011). Of the drug that is deposited into the airways, a small fraction is removed by normal mucociliary clearance and is swallowed. The emitted dose that is swallowed, or inhaled into the lungs, reaches the systemic circulation *via* the gastrointestinal and pulmonary routes, respectively. The drug particle size distribution, measured by *in-vitro* methodologies, provides an appreciation of the amount of drug that will impact onto the oropharyngeal region and the distribution of the inhaled fraction in the lungs. Part of this distribution is the fine-particle dose (FPD), typically defined as the quantity of drug administered as particles of diameter <5 μm (European Medicines Agency – Committee for Medicinal Products for Human Use ((CHMP), 2006). The TED is a surrogate maker for systemic delivery and hence an indicator of systemic safety, while the FPD and its distribution is an indicator of lung deposition, hence a marker for efficacy (Fernandez Tena and Casan Clara, 2012; Labiris and Dolovich, 2003).

The dose, and its particle size distribution, emitted from a dry powder inhaler (DPI), is determined by the inhalation manoeuvre performed by the patient, the inhaler and the formulation. There are differences between devices in the extent to which inhalation

Abbreviations: ACC, acceleration at the beginning of inhalation; BF, budesonide plus formoterol; COPD, chronic obstructive pulmonary disease; DPI, dry powder inhaler; FDC, fixed-dose combination; FPD, fine-particle dose; GSD, geometric standard deviation; HPLC, high-performance liquid chromatography; ICS, inhaled corticosteroid; IV, inhaled volume; LABA, long-acting beta2-agonist; LOQ, limit of quantitation; MMAD, mass median aerodynamic diameter; MVIC, Medicon Valley Inhalation Consortium; NGI, next generation impactor; PIF, peak inspiratory flow; TED, total emitted dose.

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profile parameters (*e.g.* acceleration at the beginning of inhalation [ACC], peak inspiratory flow (PIF) and the total inhaled volume [IV]) affect the delivered dose from a DPI (Atkins, 2005; Virchow et al., 2008). The inhalation manoeuvre is affected by a wide variety of factors such as the user's inspiratory effort and flow, the inhaled volume and throat geometry (Dolovich and Dhand, 2011; Zhou et al., 2011). The need for correct inhalation technique is clear; different patients may find some inhalers easier to use, and easier for them to master the required inhalation technique. However, published data suggest that a large proportion of patients use a suboptimal technique when using DPIs (Lavorini et al., 2008; Molimard, 2005; Thomas and Williams, 2005).

Traditionally, the *in-vitro* TED and its particle size distribution *via* a DPI, which includes the FPD, is measured using standard pharmacopoeial methods (Council of Europe, 2014; United States Pharmacopeia, 2014) and is widely accepted by the regulatory authorities. The method involves simulating an inhalation profile through a DPI using a vacuum pump to emit a dose and collect it into a cascade impactor. The measured particle size distributions represent particle deposition into different zones of the lungs. Humans cannot replicate the square wave generated by a vacuum pump; nor can the majority of patients achieve the pharmacopoeia-recommended inhalation parameters for the change in the pressure inside the inhalation channel of the inhaler or the inhaled volume (Azouz et al., 2015).

More recently, a method has been proposed that replaces the vacuum pump used in pharmacopoeial methods with an inhalation profile measured during real-life use when an individual uses an inhaler (Olsson et al., 2013). The method is an extension of that described using a mixing inlet (Nadarassan et al., 2010) which enables zero flow through the inhaler *in-situ* attached to the cascade impactor by providing supplementary air into the cascade impactor at the same flow as the vacuum that is drawn through the impactor. Replaying an inhalation profile from the supplementary air supply means that the vacuum pump forcing the flow through the cascade impactor causes the inhalation profile to be replayed through the inhaler *in-situ* (Olsson et al., 2013). This *ex-vivo* method, using a patient inhalation profile instead of the vacuum pump, provides information on the TED and particle size distribution (which includes the mass median aerodynamic diameter [MMAD] and the geometric standard deviation [GSD]) that the patient would have inhaled.

We have collected inhalation profiles from patients when they inhaled using empty versions of a Symbicort® Turbuhaler® (AstraZeneca, UK) and DuoResp® Spiromax® (Teva Pharmaceuticals, Israel) and, using an adaption of the *ex-vivo* method described by (Olsson et al., 2013), we have measured the emitted dose characteristics that the patients would have inhaled. Both these DPIs contained budesonide plus formoterol (BF). DuoResp (BF) Spiromax DPI was recently developed as an alternative to Symbicort® (BF) Turbuhaler® DPI and is approved in the European Union for use in adult patients (≥18 years old) with asthma or chronic obstructive pulmonary disease (COPD) where an inhaled corticosteroid (ICS)/long-acting beta2-agonist (LABA) is indicated. The intention when developing the Spiromax device was to maximise ease of use, potentially leading to improvements in treatment adherence and eventual clinical outcomes (Barrons et al., 2011; Lareau and Yawn, 2010; Rand, 2005). Instructions for using Spiromax, as described in the summary of product characteristics, describe 'three simple steps': open, breathe, close (Teva Pharma BV, 2014). The device provides patients with confirmation by taste (lactose) that a dose has been successfully administered, and a single-increment dose counter provides further means of monitoring therapy. Comparative studies have demonstrated pharmacokinetic equivalence of BF Spiromax to BF Turbuhaler (Weisfeld et al., 2013a, 2013b). Further studies have shown the delivered dose of BF *via* Spiromax to be consistent in a variety of simulated real-world conditions (Arp et al., 2013).

2. Materials and methods

2.1. Overview

Methodology for characterising the emitted dose from a DPI using the Next Generation Impactor (NGI) replacing the vacuum pump with a patient's inhalation profile has been described previously by Olsson et al. (Olsson et al., 2013). The current *in-vitro* study used similar methods to those described by Olsson et al., and was carried out by Emmace Consulting AB and the Medicon Valley Inhalation Consortium (MVIC); it was funded by a research grant from Teva Pharmaceuticals.

2.2. Inhalers

BF Spiromax inhalers (DuoResp, Teva Phamaceuticals, Israel) used in this study contained high-strength budesonide and formoterol (labelled, emitted ['delivered'] dose of 320/9 μg; lot MD9001) in fixed-dose combination (FDC) and were provided to MVIC and Emmace by Teva Pharmaceuticals. BF Turbuhalers (Symbicort, AstraZeneca, UK) containing BF (labelled dose of 320 to 9 μg; lot PASZ) were commercially purchased and also supplied by Teva Pharmaceuticals.

2.3. Throat geometry models (small, medium, large)

To replicate respiratory tract geometry from a variety of patients, three anatomically accurate models with small, medium and large throat dimensions (Olsson et al., 2013) were used.

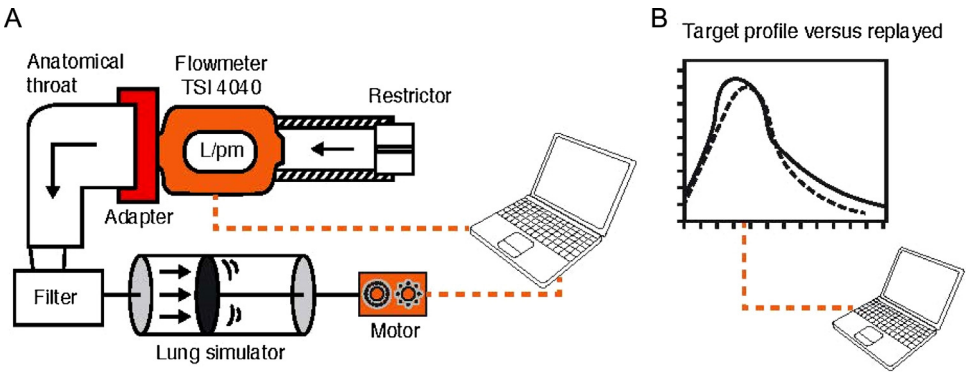

Fig. 1. (A) Experimental setup for generating and replaying inhalation profiles. (B) The restrictor was equivalent to the air flow resistance of the inhaler device. The generated (replayed) profile was recorded and compared with the target profile.

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