International Journal of Pharmaceutics: X 1 (2019) 100018

Contents lists available at ScienceDirect

International Journal of Pharmaceutics: X

journal homepage: www.journals.elsevier.com/international-journal-of-pharmaceutics-x

Biophysical model to predict lung delivery from a dual bronchodilator dry-powder inhaler

Myrna B. Dolovich[a], Andreas Kuttler[b], Thomas J. Dimke[b], Omar S. Usmani[c,*]

[a] Department of Medicine, Division of Respirology, Faculty of Health Sciences, McMaster University, Hamilton, Ontario, Canada
[b] Novartis Pharma AG, Basel, Switzerland
[c] National Heart and Lung Institute, Imperial College London, London, UK

ARTICLE INFO

Keywords:
Inhaler devices
Lung deposition
Computational fluid dynamics
Chronic obstructive pulmonary disease
Dry powder inhaler

ABSTRACT

A biophysical lung model was designed to predict inhaled drug deposition in patients with obstructive airway disease, and quantitatively investigate sources of deposition variability. Different mouth-throat anatomies at varying simulated inhalation flows were used to calculate the lung dose of indacaterol/glycopyrronium [IND/GLY] 110/50 µg (QVA149) from the dry-powder inhaler Breezhaler®. Sources of variability in lung dose were studied using computational fluid dynamics, supported by aerosol particle sizing measurements, particle image velocimetry and computed tomography. Anatomical differences in mouth-throat geometries were identified as a major source of inter-subject variability in lung deposition. Lung dose was similar across inhalation flows of 30–120 L/min with a slight drop in calculated delivery at high inspiratory flows. Delivery was relatively unaffected by inhaler inclination angle. The delivered lung dose of the fixed-dose combination IND/GLY matched well with corresponding monotherapy doses. This biophysical model indicates low extra-thoracic drug loss and consistent lung delivery of IND/GLY, independent of inhalation flows. This is an important finding for patients across various ages and lung disease severities. The model provides a quantitative, mechanistic simulation of inhaled therapies that could provide a test system for estimating drug delivery to the lung and complement traditional clinical studies.

1. Introduction

The inhaled route of administration is the preferred method for delivering therapeutic aerosols to the respiratory tract (Global Initiative for Chronic Obstructive Lung Disease, 2018). The efficacy of an inhaled therapy depends primarily on the quantity of drug deposited in the lung (Chow et al., 2007). To improve the effectiveness of inhalation therapies for asthma and chronic obstructive pulmonary disease (COPD), novel formulations and devices have been developed that produce particles with the defined size distribution and characteristics required to target lung delivery (Colthorpe et al., 2013; Lavorini et al., 2014; Wedzicha et al., 2016). However, there is inherent variability in the dose reaching the lungs, determined by formulation, device and patient characteristics (Chapman et al., 2011; Colthorpe et al., 2013; Dolovich and Dhand, 2011; Islam and Cleary, 2012; Lavorini et al., 2014).

In the clinic, lung dose variability is recognised as a factor affecting patient response to inhaled therapy (Usmani et al., 2005). With an ever-increasing number of inhaler devices providing a variety of therapies, device characteristics and formulation may be as important as the drug pharmacology in determining clinical response. Healthcare professionals and patients need confidence that the prescribed inhaler drug/device can provide reproducible dosing, especially once the patient leaves the clinic. Pressurised metered dose inhalers (pMDIs) may aerosolise the drug faster than the patient can inhale, necessitating coordination between device actuation and inhalation; this source of error may contribute to variability in lung delivery (Chapman et al., 2011). In contrast, dry powder inhalers (DPIs) usually require minimum coordination between inhalation and actuation, although most rely on a patient's rapid inspiratory flow rate (IFR) to provide the force to aerosolise a powder medication for effective lung delivery (Islam and

Abbreviations: AIT, Alberta idealised throat; APSD, aerodynamic particle size distribution; CFD, computational fluid dynamics; COPD, chronic obstructive pulmonary disease; CT, computed tomography; DPI, dry powder inhaler; FDC, fixed-dose combination; GLY, glycopyrronium; HRCT, high-resolution computed tomography; IFR, inspiratory flow rate; IND, indacaterol; MMAD, mass median aerodynamic diameter; NGI, Next Generation Impactor; PIV, particle image velocimetry; pMDI, pressurised metered dose inhaler; USP/Ph. Eur, European Union Pharmacopoeias

* Corresponding author at: National Heart and Lung Institute, Imperial College London & Royal Brompton Hospital, London SW3 6LY, UK.
E-mail address: o.usmani@imperial.ac.uk (O.S. Usmani).

https://doi.org/10.1016/j.ijpx.2019.100018
Received 6 February 2019; Received in revised form 24 May 2019; Accepted 27 May 2019
Available online 30 May 2019

Cleary, 2012). However, a rapid IFR can result in increased oropharyngeal (mouth-throat) drug deposition, potentially reducing lung delivery and as a consequence, worsening patient outcomes (Chow et al., 2007; Coates et al., 2005). Furthermore, variability in patients' day-to-day inhalation effort is expected, given differences in airflow limitation of patients with COPD (Global Initiative for Chronic Obstructive Lung Disease, 2018). While improvement in COPD treatment is usually credited to innovative drugs, successful treatment of the diverse patient population is not possible without an inhalation device that a patient will be able to handle well and consistently engage with and, a well-optimised powder formulation in an efficient device (Donovan et al., 2012; Molimard et al., 2017; Usmani et al., 2018).

Since the delivery technology of inhaled therapies can be difficult to assess using clinical studies alone, we established an innovative experimental/computational framework to assess clinically relevant aspects of the whole causal chain of the inhaled drug delivery process. Using a fixed-dose combination (FDC) of a long-acting β_2-agonist (indacaterol [IND]) and a long-acting muscarinic antagonist (glycopyrronium [GLY]; [IND/GLY]), delivered via the Breezhaler® DPI (Ultibro® Breezhaler®, Novartis Pharma AG, Basel, Switzerland), we assessed performance of the device including flow characteristics of the inhaler mouthpiece, powder emptying (i.e., the efficiency by which the powder is released from the capsule after inhalation) and detachment (i.e., the detachment of the active substance particles from the surface of the carrier particles), and physiological parameters such as inhalation rate and airway anatomy (Fig. 1). The aim was to use this biophysical model to predict inhaled drug deposition in patients with COPD, and quantitatively investigate sources of variability in the delivery of inhaled IND/GLY.

2. Materials and methods

2.1. Study design

A biophysical lung model was developed that integrated computational fluid dynamics (CFD) in combination with *in vitro* aerosol and *in vivo* lung measurements, namely; particle size determination using the Next Generation Impactor (NGI; Copley Scientific, UK), flow field characterisation using particle image velocimetry (PIV; Envision Pharma R&D system, Oxford Lasers Ltd., UK), and high-resolution computed tomography (HRCT) lung scans of patients with COPD. The biophysical model was used to quantify lung delivery of inhalation powder from hypromellose capsules of IND/GLY 110/50 µg. The monotherapies IND 150 µg and GLY 50 µg were also tested for comparison, delivering the drug from hard gelatin capsules and hypromellose capsules, respectively. All powders were delivered via the Breezhaler® DPI.

Variability in inhalation flow rate, mouth-throat anatomy, inhaler inclination angle and formulation batch were investigated, as well as the rationale for dose scaling for the FDC of IND/GLY versus the monotherapy components. To compute the aerodynamic particle size distribution (APSD) and the drug dose delivered into the patient's lungs, 3D computational models of the human oropharynx were used with the inhaler mouthpieces attached (Fig. 2).

2.2. Study materials

Ultibro® Breezhaler® inhalers were used to deliver the drugs from hypromellose capsules containing a fixed combination of 143 µg of

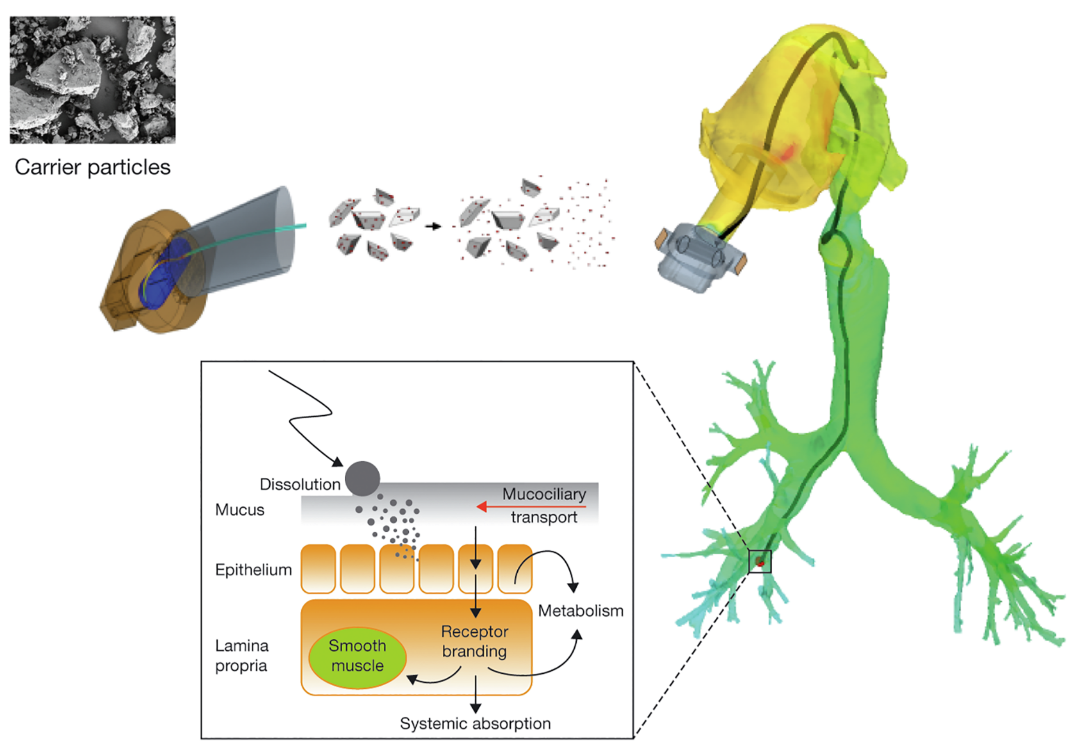

Fig. 1. From device to effect: integrated biophysical modelling strategy to link drug effect and its lung delivery with device, formulation, and patient characteristics. This illustration shows the context of the mouth-throat simulation presented in the study (see Fig. 2). The experimentally investigated powder release and dispersion performance as well as the flow field characteristics at the inhaler mouthpiece have been used to inform the inlet boundary conditions of the mouth-throat model shown in Fig. 2. Only the total lung dose and the particle size spectrum transitioning beyond the trachea were investigated in this study.

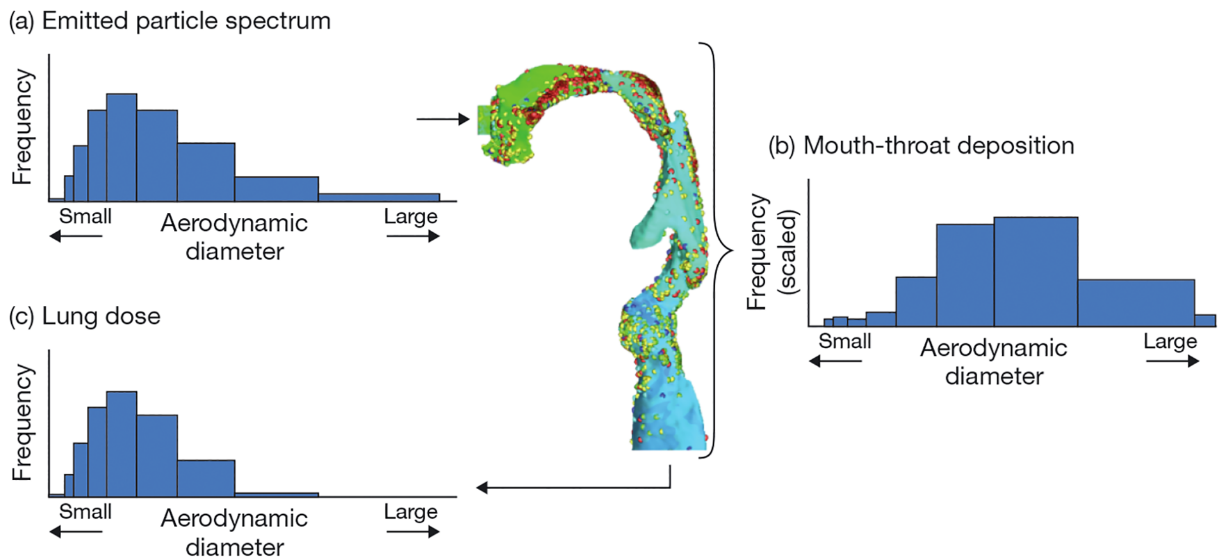

Fig. 2. Mouth-throat deposition and lung delivery simulation input and results. (a) Emitted aerodynamic particle size distribution of detached particles from the device (determined by NGI measurements), (b) losses in the mouth-throat region (determined by biophysical simulation) and (c) aerodynamic particle size distribution delivered into the lungs (determined by biophysical simulation), at a constant flow rate of 90 L/min. The particle dynamics were calculated by Lagrangian particle tracking of approximately 66,000 particles between 1 and 14 µm (aerodynamic diameter; determined by NGI measurements). An aerodynamic diameter of 1.0 µm was considered small; 8.0 µm was considered large. NGI, Next Generation Impactor.

indacaterol maleate (corresponding to 110 µg of IND) and 63 µg of glycopyrronium bromide (corresponding to 50 µg of GLY), with the delivered dose (the dose that leaves the mouthpiece of the inhaler) containing 110 µg of indacaterol maleate equivalent to 85 µg of IND and 54 µg of glycopyrronium bromide equivalent to 43 µg of GLY. Onbrez® Breezhaler® and Seebri® Breezhaler® (Novartis Pharma AG, Basel, Switzerland), respectively, were used to deliver the monotherapies IND 150 µg using hard gelatin capsules and GLY 50 µg using hypromellose capsules (Supplementary Table 1 shows the product specifications for nominal and delivered dose). During the development of the Ultibro® Breezhaler®, the dose of 110 µg IND was chosen to provide exposures similar to that seen with 150 µg IND in Onbrez® Breezhaler® by ensuring a similar fine particle mass (FPM) in both formulations. No dose adjustment was necessary for glycopyrronium bromide. The carrier molecule for all active substances was lactose (European Medicines Agency, 2013).

2.3. In vitro measurements

In vitro measurements of the release conditions of the drug from the inhaler were determined using PIV (for flow conditions, i.e. velocity and turbulence) and the NGI for particle size measurements. These data (cross-sectional flow velocities, turbulence intensity and particle size distribution) were integrated into the model as flow and particle release conditions (see Section 2.4, Inhaler characteristics).

2.4. Anatomical models

Drug losses in the mouth-throat region are a potential source of variability for inhaled drug delivery to the lungs (Fig. 2) (Stahlhofen et al., 1989). To investigate flow rate dependency and batch variability, as well as the comparison between combination and monotherapy formulations, an anatomic mouth-throat model of an averaged adult anatomy was used. This model, referred to as the 'Alberta mouth-throat model' or the Alberta idealised throat (AIT) model' (Stapleton et al., 2000), is a design based on 10 computed tomography (CT) oropharyngeal scans, direct observations from five living subjects and characteristic parameters from the literature, and is presumed to represent an averaged adult mouth-throat geometry. This geometry was additionally used to compare and verify our computational results with published laboratory data (DeHaan and Finlay, 2001; Stapleton et al., 2000). Good agreement between the experimental and computational results for lung doses of mono- and poly-dispersed APSDs were obtained (see further details in the Supplementary Methods).

To explore the variability of drug losses from individual mouth-throat geometries, CT oropharyngeal scans from three COPD patients were selected from an existing bank of 20 low radiation scans. These anatomical models (stereolithography format) of COPD patients (two with Global Initiative for Chronic Obstructive Lung Disease [GOLD] stage III COPD aged 60 and 76 years; one with GOLD stage IV aged 58 years) were selected based on preliminary deposition results using CFD analysis with simplified inhaler release conditions to represent a wide range of possible oropharyngeal deposition values (Table 1).

2.5. Inhaler characteristics

Since inhaler geometry was only partially (last 8 mm of the mouthpiece) included into the simulation, flow profiles and turbulence levels were determined by PIV (Adrian, 2005) for constant inhalation flows of 30, 60, 90 and 120 L/min, the typical range of operation for low-medium resistance devices such as the Breezhaler® DPI. NGI measurements (ambient temperature: 23 ± 2 °C; and humidity: 55 ± 5% RH) were performed using three batches of the drug combination product and the monotherapy components, with five replicates per batch (combination and monotherapy). Using the NGI, the APSDs were determined over a range of 30–100 L/min operating flows. The data at the maximal available test flow rate served as the best approximation for the particle size distribution at high flow rates and were used in the lung delivery simulations with 120 L/min inhalation rates.

2.6. Computational model

CFD software (see Supplementary Methods) was used to determine the fluid flow driven by inhalation conditions (specified by PIV measurements as explained above). For an accurate representation of the transition flow effect in these flow regimes, the CFD model consisted of 3–4 million elements. Large eddy simulation methods were used to

Table 1
Characteristics of the three out of 20 anatomical models of COPD patients to assess differences in pulmonary delivery from individual airway in addition to the results generated from the averaged mouth-throat geometry. The selection was based on a preliminary, product independent deposition simulation and aimed to cover a large range of different mouth-throat anatomies (see first estimation of lung delivery). The selected anatomies and the simulation results did in no way influence the specification of the additionally used averaged adult anatomy which is purely based on the previously published mouth-throat geometry: the Alberta-throat (Stapleton et al., 2000).

	GOLD stage	Age (years)	Mouth-throat anatomy	First estimation of lung delivery (product independent particle spectrum)	Final results for lung delivery of GLY and IND in QVA149 (from Fig. 5)
Patient A	IV	58		45%	36%, 30%
Patient B	III	60		80%	42%, 35%
Patient C	III	76		6%	14%, 13%

COPD, chronic obstructive pulmonary disease; GLY, glycopyrronium; GOLD, Global initiative for chronic Obstructive Lung Disease; IND, indacaterol.

resolve the transient turbulence situation. The particle dynamics were calculated by Lagrangian particle tracking of approximately 66,000 particles between 1 and 14 µm (aerodynamic parameter) determined by NGI measurements. The release was spread over six different time points to average out variable flow conditions in the unsteady fluctuating fluid flow.

2.7. Analysis

The primary outcome of the integrated simulations was the amount and particle size distribution of drug (IND or GLY) delivered into the lung (Fig. 2c) for a given flow rate (90 L/min for all cases and 30, 60, 90 and 120 L/min for the averaged mouth-throat model, namely, the Alberta Throat model). The delivered lung dose for each case was determined by adding up the drug mass from all the representative bins of the APSD spectrum (Fig. 2c). The same procedure was used to determine the amount of carrier-detached drug deposited in the mouth-throat region during inhalation (Fig. 2b).

In addition to these losses, all drug particles not separated from their carrier during the de-agglomeration process and found in the induction port and the pre-separator of the NGI impactor, were assumed to deposit in the mouth-throat. Thus, the reported mouth-throat losses were the sum of detached drug particles deposited in the mouth-throat cavity obtained from the biophysical simulation and those particles which had not been detached from the carrier, measured by the NGI.

3. Results

3.1. Lung delivery of IND/GLY determined computationally using an averaged adult mouth-throat model

The effect of anatomy-independent factors on lung delivery of IND/GLY was investigated using a computational averaged adult mouth-throat model, namely the Alberta Throat model.

3.1.1. Flow rate

Applying constant inhalation flows between 30 and 120 L/min, the overall lung delivery of IND/GLY 110/50 µg ranged between 32 and 42% for IND and 38–54% for GLY. A relatively constant lung delivery was observed for flow rates between 30 and 90 L/min, with a slight decrease in delivered dose for 120 L/min (Fig. 3a). The results in percentage of the experimentally recovered dose [the sum of inhaler losses (capsule and device), material found in the induction port and pre-separator as well as the material from stage cups 1–7 and the micro-orifice collector recovered during the NGI measurements] are provided in the Supplementary Material. The efficiency of emptying the capsule of powder, as well as fine particle mass at the mouthpiece outlet, increased with flow rate (Fig. 4), similar to data published previously by Pavkov et al. (2010). The lung dose remained almost unchanged over the range of inhalation rates due to increased mouth-throat deposition (Figs. 3 and 4).

3.1.2. Formulation/dose selection

The dose selection for the FDC of IND/GLY 110/50 µg was established from *in vitro* formulation performance data and *in vivo* pharmacokinetic studies. Using the biophysical model, we investigated if there was any difference in inhaled drug deposition between the FDC and the approved monotherapies (IND 150 µg and GLY 50 µg). With a dose reduction from 150 to 110 µg for IND and no change for GLY, the simulations showed that the delivered lung doses of the corresponding therapies were within 10% of an acceptable range for inhaled therapies (Fig. 3c and 3d) (Lu et al., 2015). The data also showed that for IND in the FDC versus the monotherapy (tested at a flow rate of 90 L/min), delivery performance of the device was improved (19 versus 29 µg retained in the capsule and device), and a reduction in mouth-throat deposition from 80 to 46 µg was achieved (Fig. 3c and d). Mean lung delivery of IND and GLY was 44 and 22 µg, respectively, when given as monotherapy and 43 and 24 µg when given as a FDC (Fig. 3c and 3d).

3.1.3. Product/manufacturing variability

Lung delivery of IND/GLY 110/50 µg was consistent across various drug batches at a flow rate of 90 L/min (Table 2). The comparison of the APSD of detached drug particles entering the lungs with the APSD emitted from the inhaler showed a predominant filtering of particles larger than the mass median aerodynamic diameter (MMAD) by the mouth-throat cavity (Fig. 4). The results show filtering of particles ranging from 0.5 µm to 7.0 µm. These particle size distributions do not include the drug particles which have not been released from the lactose carriers. The sizes of these particles have not been characterised in the experiments, but the total amount is known from induction port and pre-separator measurements. This drug amount was added to the data shown for mouth-throat deposition to calculate the total drug mass lost in the mouth-throat.

3.2. Lung delivery of IND/GLY in individual anatomic patient scans

3.2.1. Mouth-throat anatomy

Mouth-throat geometries of three patients with severe COPD are shown in Table 1. At a constant flow rate of 90 L/min and an inhaler

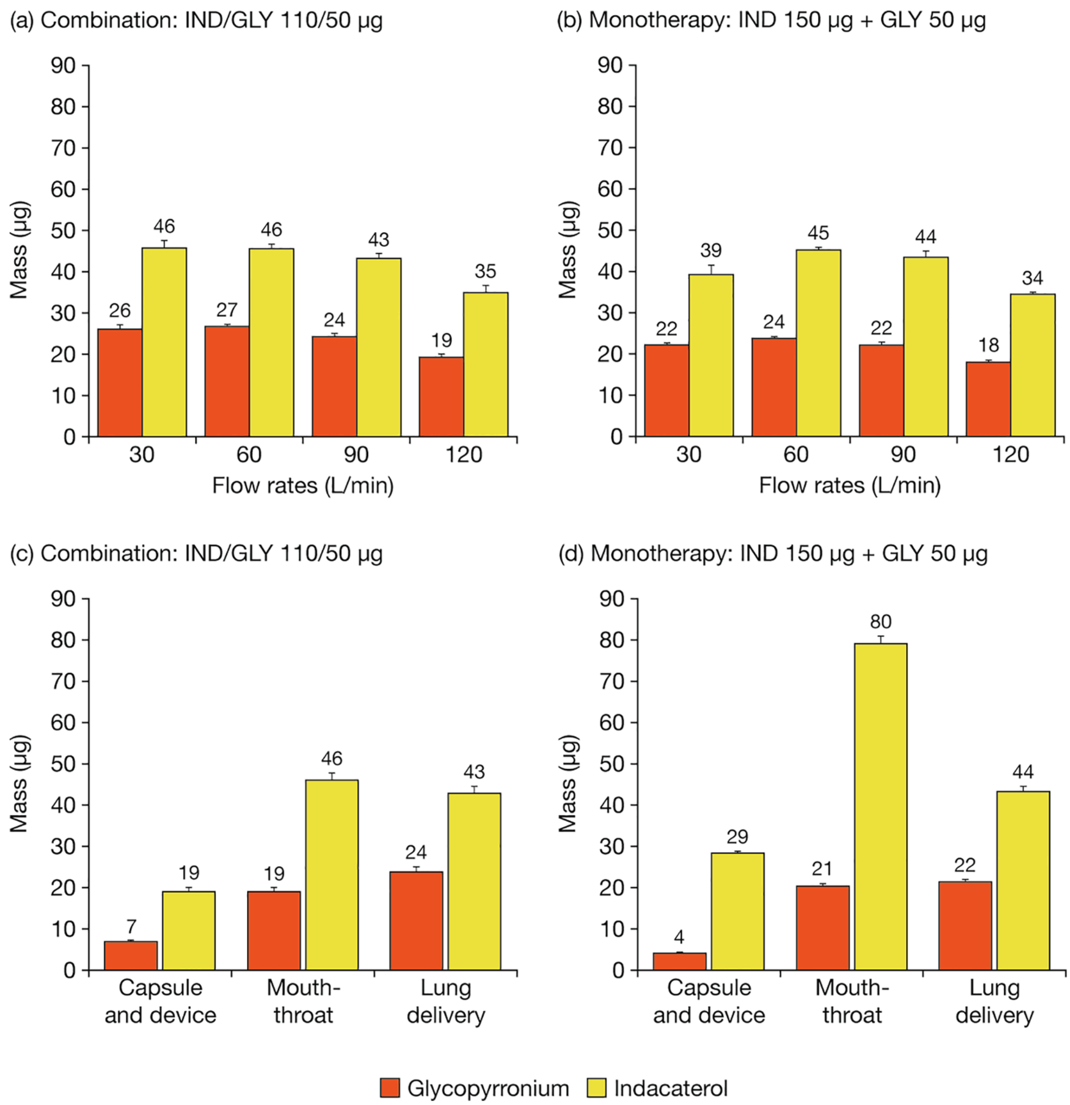

Fig. 3. (a) Mean lung delivery of IND/GLY 110/50 µg and (b) IND 150 µg and GLY 50 µg monotherapies at different flow rates via the Breezhaler® DPI. (c) Drug loss in capsule and device, and in mouth-throat region, and mean lung delivery of IND/GLY 110/50 µg and (d) IND 150 µg and GLY 50 µg monotherapies at a constant flow rate of 90 L/min, all via the Breezhaler® DPI. Data are mean ± standard deviation (Alberta mouth-throat model) and based on three batches with five replicates (n = 15), except for indacaterol monotherapy which was one batch with five replicates (n = 5). DPI, dry powder inhaler; GLY, glycopyrronium; IND, indacaterol; GSD, geometric standard deviation.

inclination angle of 25°, the total amount of drug delivered below the trachea was strongly influenced by the patients' airway geometry and the resulting local flow velocities (Fig. 5a and b). In the simulation, lung delivery of IND and GLY ranged from 13% and 14%, respectively, in Patient C, to 35% and 42%, respectively, in Patient B. These deposition data are correlated with the maximal observed flow velocity in the middle section of the geometry, indicating that reduced airway cross-section and high local velocities can result in increased particle deposition in the mouth-throat region, resulting in reduced drug delivery beyond the trachea. The differences observed in flow velocities are due to different local cross-section areas of airways at the flow rate of 90 L/min for each model.

3.2.2. Inhaler inclination angle

Investigations in an individual CT-based mouth-throat geometry at a constant flow rate of 90 L/min revealed that inhaler inclination angle had little effect on total delivered lung dose of IND/GLY. In the simulation, lung delivery for IND and GLY was 29% and 36%, respectively, with a 25° inhaler inclination angle and 28% and 34%, respectively, with a 0° (horizontal) inhaler inclination angle.

4. Discussion

Accurate biophysical lung modelling can contribute to the development of inhaled formulations and inhaler devices providing a test system for estimating drug delivery to the lung and complement traditional clinical studies.

In this study, an innovative integrated *in vitro-in vivo* biophysical model was designed to predict one of the key determinants of inhaled drug efficacy; namely, inhaled drug deposition. This biophysical model demonstrated consistent delivery of IND/GLY to the lung from the Breezhaler® DPI, irrespective of inspiratory flows of up to 90 L/min, inhaler inclination angle and drug batch. The model also estimated low drug loss due to mouth-throat deposition (approximately 40% versus for example 54.7% for Genuair (Newman et al., 2009)), which may have contributed to reducing the variability of the delivered dose to the lung. This observation is supported by the clinically observed absolute bioavailability of 47–66% for IND, when a 25% absorption from the gastrointestinal tract is taken into account (European Medicines Agency, 2013). Although predicting regional/targeted lung delivery was not a major topic of the current investigation, comparison of the

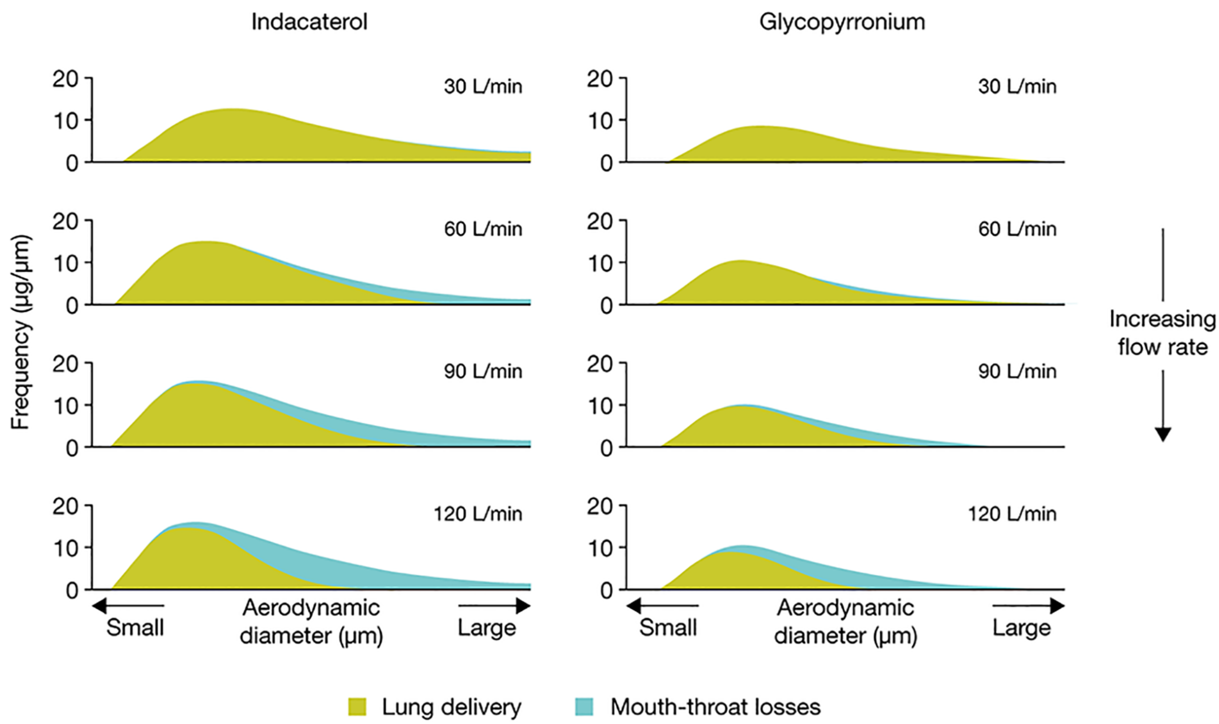

Fig. 4. Fraction of lung dose (green) and mouth-throat losses (blue) in the emitted particle spectrum (both areas combined) of IND/GLY compounds (IND 110 μg and GLY 50 μg), for increasing flow rates from top to bottom (detached drug particle fraction only is shown). Emitted dose derived from a log-normal distribution of the emitted dose based on MMAD and GSD calculated from NGI measurements. Lung dose and mouth-throat losses are derived from biophysical simulation. An aerodynamic diameter of 0.5 μm was considered small; 7.0 μm was considered large. IND/GLY, indacaterol/glycopyrronium; MMAD, mass median aerodynamic diameter; NGI, Next Generation Impactor.

Table 2
Mean lung delivery of IND/GLY 110/50 μg at a constant flow rate of 90 L/min via the Breezhaler® DPI interfaced to the Alberta throat model.

Treatment	Relative lung dose*, % (SD)		
	Batch 1	Batch 2	Batch 3
Indacaterol 110 μg	39.7 (0.99)	38.9 (1.06)	40.5 (0.41)
Glycopyrronium 50 μg	49.6 (1.07)	47.9 (1.28)	47.5 (0.33)

DPI, dry powder inhaler; IND/GLY, indacaterol/glycopyrronium; SD, standard deviation.

* Lung dose relative to capsule content (based on percentage of the recovered dose from particle sizing measurements at the specified sampling flow rate).

APSD of detached drug particles entering the lungs with the APSD emitted from the inhaler showed filtering of particles ranging from 0.5 μm to 7.0 μm.

The lack of effect of the inhaler inclination angle on mouth-throat deposition losses may be explained by the relatively large effective cross-section of the Breezhaler® DPI mouthpiece and the resulting low flow velocities on inspiration (Coates et al., 2004). Notably, this observation cannot be generalised for all DPIs since the effective mouthpiece diameter (D) of the model and the resulting jet of powder released into the oral cavity varies substantially between different DPIs (Breezhaler® D = 10.6 mm; Handihaler®: D = 5.3 mm (Ung et al., 2014); Novolizer®: D = 6.0 mm (Delvadia et al., 2013)). Our findings are consistent with the observations by Delvadia et al. (2013).

Importantly, differences in mouth-throat anatomy between patients were identified to be the major reason for inter-patient variability in drug delivery and provide one explanation for the low signal-to-noise ratio in clinical studies for inhaled therapies (Borgström et al., 2006). We selected three mouth-throat anatomies that represented a wide range of oropharyngeal deposition (based on preliminary deposition *in vitro* results) and found that lung deposition correlated with maximal observed flow velocity in the middle section of the mouth-throat geometry, indicating that local maximum velocity is a good indicator for deposition efficiency.

In vitro investigations have shown that device performance parameters (including emitted dose, fine particle mass and APSD) can improve with increasing flow rates when measured directly at the inhaler outlet (de Boer et al., 1996; Kamin et al., 2002; Pavkov et al., 2010). However, when accounting for delivery losses in the mouth-throat region with the biophysical model, the calculated lung dose shows a different result. For both compounds in the FDC IND/GLY therapy, lung delivery was similar for inhalation rates between 30 and 90 L/min. While the model showed a slight decrease in the calculated lung dose at the high inhalation rate (120 L/min, at 90 L/min), the model predicted a lung dose of 40% and 48% for IND and GLY, respectively. These results are in line with previous in-vitro and in-vivo investigations of GLY delivery via Breezhaler® and compare favourably with other DPI products (e.g. 30.1% for Genuair or 18.0% for Handihaler) (Chodosh et al., 2001; Newman et al., 2009; Palander et al., 2000; Prakash et al., 2015). This is an important outcome, as age and disease severity impact the inspiratory flow rates that patients with COPD can achieve through current DPIs (Janssens et al., 2008; Pavkov et al., 2010).

The Alberta mouth-throat model was selected for use in these experiments as an established model with a highly reproducible, human-like geometry (Stapleton et al., 2000; Zhang et al., 2007). An alternative model used for cascade impaction measurements, the United States and European Union Pharmacopoeias (USP/Ph. Eur) induction port has a tendency to underestimate mouth-throat medication losses compared with *in vivo* measurement and the Alberta mouth-throat model (Grgic et al., 2004; Zhou et al., 2011). However, it should be noted that the CT scans used for the development of the Alberta mouth-throat model were conducted over 10 years ago (Stapleton et al., 2000). It is therefore likely that the resolution of these scans is lower than what would be possible with current CT technology. Furthermore,

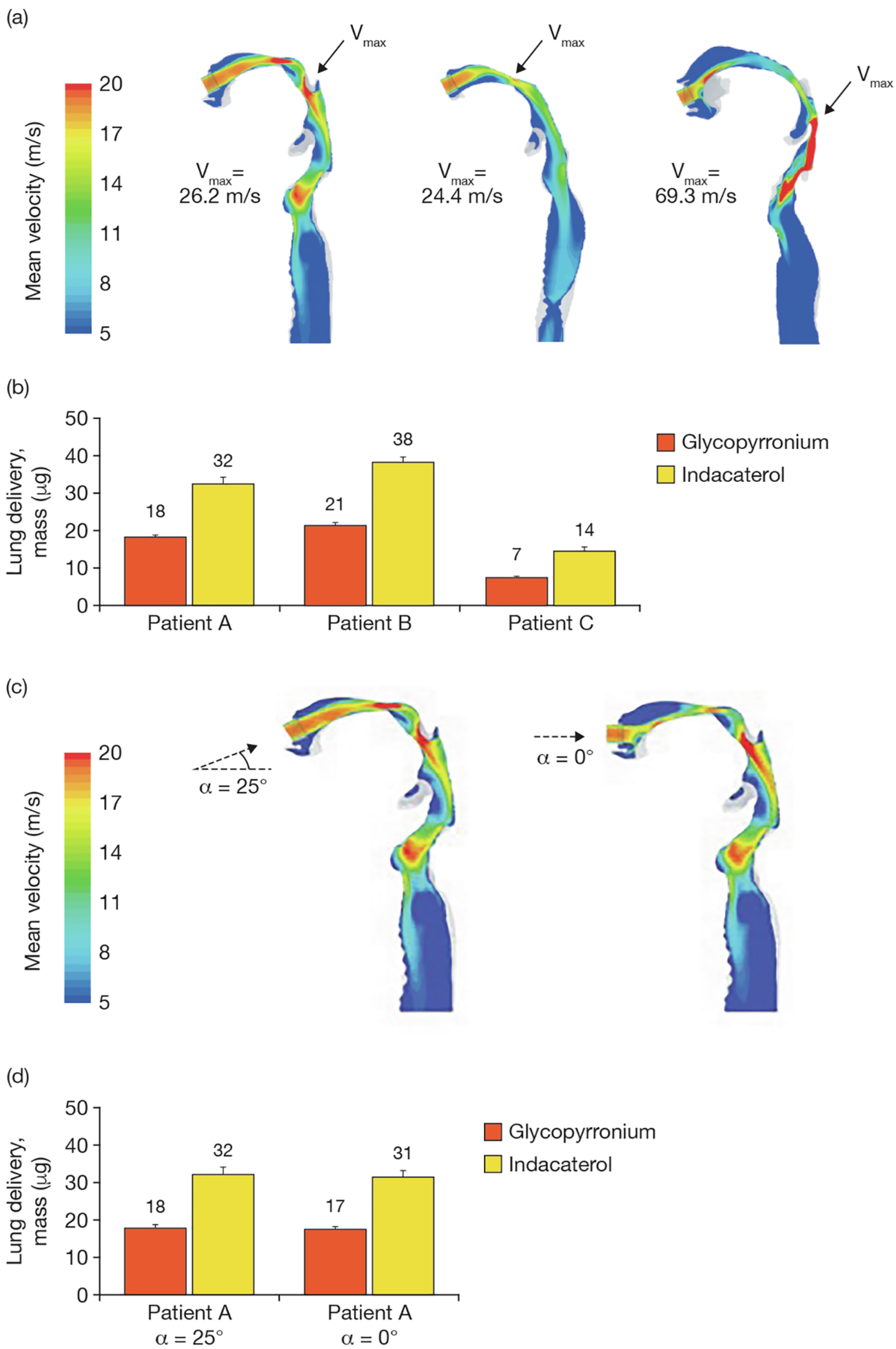

Fig. 5. (a) Velocity representations in the mid-section of CT-based mouth-throat models for 25° and (b) mean lung delivery of IND/GLY 110/50 µg from the Breezhaler® DPI in three patients with different airway geometries at a constant flow rate of 90 L/min. (c) Velocity representations in the mid-section of CT-based mouth-throat models for 25° (left) and horizontal (right) inhaler inclination angle at a constant flow rate of 90 L/min and V_{max} of 26.2 m/s via the Breezhaler® DPI for Patient A. (d) Mean lung delivery of IND/GLY 110/50 µg for 25° (left) and horizontal (right) inhaler inclination angle at a constant flow rate of 90 L/min via the Breezhaler® DPI. Images were taken during breath-hold. Data are mean ± standard deviation. CT, computed tomography; DPI, dry powder inhaler; IND/GLY, indacaterol/glycopyrronium; NGI, Next Generation Impactor.

the current use of mouth-throat models based on magnetic resonance imaging may be a better approach. Nevertheless, our results show that lung delivery of IND/GLY in a population-averaged patient anatomy (mouth-throat model) was higher than in individual anatomic patient scans from CTs. One possible explanation could be the lack of a trachea in the Alberta Throat model, thus reducing the path length for drug particles exiting the AIT model. A comparison of the Alberta-Throat geometry with other established physiological throat models is currently ongoing.

The Breezhaler® inhalation platform and optimised lactose-carrier formulation are important factors for the clinical success of the IND/GLY FDC in a heterogeneous patient population (Frampton, 2014; Wedzicha et al., 2016), since delivery of IND/GLY to the lung is consistent, irrespective of flow rate and inhaler inclination angle. Our results showed a reduction in mouth-throat deposition of IND from 80 to 46 µg for the FDC compared with the monotherapy, which approximated the 40 µg used for the dose scaling from monotherapy to combination therapy. Retrospectively, the dose scaling during the change to FDC therapy for IND was necessary to maintain equivalent lung dose and systemic exposure, and the findings from this study support the dose scaling approach (Bateman et al., 2013).

There is a lack of methods for correlating *in vivo* and *in vitro* results for pulmonary products, due to the complex delivery process and limitations in experimental and computational standard procedures, such as the difficulty involved in resolving flow dynamics, the large inter-individual variability seen in real-life patients and the effect of geometry simplifications on modelling accuracy (Daley-Yates et al., 2009; de Matas et al., 2010). Based on biophysical modelling, it is possible to determine the delivery of various particle spectrums at different flow rates prior to any pre-clinical or clinical investigation, and potentially correlate lung deposition with dose and outcomes. This technology, therefore, is an essential tool in the development of inhaled formulations and their devices, which saves time/cost and ensures high-quality standards. Although the methodology presented here is applicable to all types of inhalation devices and formulations, the results and conclusions from our analysis are only applicable to IND/GLY delivered via the Breezhaler® DPI. The complex interaction of fluid dynamic forces on the drug particle detachment process and the influence of velocity jet/turbulence of the inhaler mouthpiece on deposition in the oral cavity are two of the reasons why the findings presented may not be generalised to other DPIs. To avoid late phase failures and inadequate dosing, a biophysical modelling approach could be designed and applied to each inhaler/formulation separately in order to computationally investigate its predicted *in vivo* performance prior to clinical trials (European Medicines Agency, 2013).

In summary, this innovative respiratory model provides a quantitative, mechanistic simulation of inhaled therapies, which may ultimately help to plan better clinical investigations, improve inhaler design and promote effective pulmonary drug delivery to patients with obstructive lung diseases.

Declaration of Competing Interest

Myrna B. Dolovich has no competing interests. Andreas Kuttler and Thomas J. Dimke are employees of Novartis Pharma AG. Omar Usmani has received consultancy fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Napp, MundiPharma, Sandoz, Cipla, Takeda, Zentiva and Trudell Medical; has received grant support from AstraZeneca, Boehringer Ingelheim, Chiesi, and Edmond Pharma; pyaments for lectures (including service on speaker bureas) from Boehringer Ingelheim, Chiesi, Cipla, Napp, MundiPharma, Sandoz and Aerocrine.

Acknowledgements

The authors were assisted in the preparation of the manuscript by professional medical writers contracted to CircleScience (an Ashfield Company, part of UDG Healthcare plc) who were funded by Novartis, Pharma AG.

Funding

This study was funded by Novartis Pharma AG, Basel, Switzerland.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijpx.2019.100018.

References

Adrian, R.J., 2005. Twenty years of particle image velocimetry. Exper. Fluids. 39, 159–169. https://doi.org/10.1007/s00348-005-0991-7.

Bateman, E.D., Ferguson, G.T., Barnes, N., Gallagher, N., Green, Y., Henley, M., Banerji, D., 2013. Dual bronchodilation with QVA149 versus single bronchodilator therapy: the SHINE study. Eur. Respir. J. 42, 1484–1494. https://doi.org/10.1183/09031936.00200212.

Borgström, L., Olsson, B., Thorsson, L., 2006. Degree of throat deposition can explain the variability in lung deposition of inhaled drugs. J. Aerosol. Med. 19, 473–483. https://doi.org/10.1089/jam.2006.19.473.

Chapman, K.R., Fogarty, C.M., Peckitt, C., Lassen, C., Jadayel, D., Dederichs, J., Dalvi, M., Kramer, B., 2011. Delivery characteristics and patients' handling of two single-dose dry-powder inhalers used in COPD. Int. J. Chron. Obstruct. Pulmon. Dis. 6, 353–363. https://doi.org/10.2147/COPD.S18529.

Chodosh, S., Flanders, J.S., Kesten, S., Serby, C.W., Hochrainer, D., Witek Jr., T.J., 2001. Effective delivery of particles with the HandiHaler dry powder inhalation system over a range of chronic obstructive pulmonary disease severity. J. Aerosol. Med. 14, 309–315. https://doi.org/10.1089/089426801316970268.

Chow, A.H., Tong, H.H., Chattopadhyay, P., Shekunov, B.Y., 2007. Particle engineering for pulmonary drug delivery. Pharm. Res. 24, 411–437. https://doi.org/10.1007/s11095-006-9174-3.

Coates, M.S., Chan, H.K., Fletcher, D.F., Raper, J.A., 2005. Influence of air flow on the performance of a dry powder inhaler using computational and experimental analyses. Pharm. Res. 22, 1445–1453. https://doi.org/10.1007/s11095-005-6155-x.

Coates, M.S., Fletcher, D.F., Chan, H.K., Raper, J.A., 2004. Effect of design on the performance of a dry powder inhaler using computational fluid dynamics. Part 1: grid structure and mouthpiece length. J. Pharm. Sci. 93, 2863–2876. https://doi.org/10.1002/jps.20201.

Colthorpe, P., Voshaar, T., Kiekbusch, T., Cuoghi, E., Jauernig, J., 2013. Delivery characteristics of a low-resistance dry-powder inhaler used to deliver the long-acting muscarinic antagonist glycopyrronium. J. Drug. Assess. 2, 11–16. https://doi.org/10.3109/21556660.2013.766197.

Daley-Yates, P.T., Parkins, D.A., Thomas, M.J., Gillett, B., House, K.W., Ortega, H.G., 2009. Pharmacokinetic, pharmacodynamic, efficacy, and safety data from two randomized, double-blind studies in patients with asthma and an in vitro study comparing two dry-powder inhalers delivering a combination of salmeterol 50 microg and fluticasone propionate 250 microg: implications for establishing bioequivalence of inhaled products. Clin. Ther. 31, 370–385. https://doi.org/10.1016/j.clinthera.2009.02.007.

de Boer, A.H., Gjaltema, D., Hagedoorn, P., 1996. Inhalation characteristics and their effects on in vitro drug delivery from dry powder inhalers Part 2: Effect of peak flow rate (PIFR) and inspiration time on the in vitro drug release from three different types of commercial dry powder inhalers. Int. J. Pharmaceut. 138, 45–56. https://doi.org/10.1016/0378-5173(96)04526-7.

de Matas, M., Shao, Q., Biddiscombe, M.F., Meah, S., Chrystyn, H., Usmani, O.S., 2010. Predicting the clinical effect of a short acting bronchodilator in individual patients using artificial neural networks. Eur. J. Pharm. Sci. 41, 707–715. https://doi.org/10.1016/j.ejps.2010.09.018.

DeHaan, W.H., Finlay, W.H., 2001. In vitro monodisperse aerosol deposition in a mouth and throat with six different inhalation devices. J. Aerosol. Med. 14, 361–367. https://doi.org/10.1089/089426801316970321.

Delvadia, R.R., Longest, P.W., Hindle, M., Byron, P.R., 2013. In vitro tests for aerosol deposition. III: effect of inhaler insertion angle on aerosol deposition. J. Aerosol. Med. Pulm. Drug. Deliv. 26, 145–156. https://doi.org/10.1089/jamp.2012.0989.

Dolovich, M.B., Dhand, R., 2011. Aerosol drug delivery: developments in device design and clinical use. Lancet 377, 1032–1045. https://doi.org/10.1016/S0140-6736(10)60926-9.

Donovan, M.J., Kim, S.H., Raman, V., Smyth, H.D., 2012. Dry powder inhaler device influence on carrier particle performance. J. Pharm. Sci. 101, 1097–1107. https://doi.org/10.1002/jps.22824.

European Medicines Agency (EMA), 2013. Committee for Medicinal Products for Human Use (CHMP) Assessment report. Ultibro Breezhaler. International non-proprietary name: indacaterol/glycopyrronium bromide. Procedure No. EMEA/H/C/002679/0000. 25 July 2013. EMA/CHMP/296722/2013. [WWW Document]. URL http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002679/WC500151257.pdf (accessed 25 March 2015).

Frampton, J.E., 2014. QVA149 (indacaterol/glycopyrronium fixed-dose combination): a review of its use in patients with chronic obstructive pulmonary disease. Drugs 74, 465–488. https://doi.org/10.1007/s40265-014-0194-8.

Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2018. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. 2018 Report [WWW Document]. URL http://goldcopd.org/gold-reports/ (accessed 28.11.17.).

Grgic, B., Finlay, W.H., Heenan, A.F., 2004. Regional aerosol deposition and flow measurements in an idealized mouth and throat. J. Aerosol. Sci. 35, 21–32. https://doi.org/10.1016/S0021-8502(03)00387-2.

Islam, N., Cleary, M.J., 2012. Developing an efficient and reliable dry powder inhaler for pulmonary drug delivery–a review for multidisciplinary researchers. Med. Eng. Phys. 34, 409–427. https://doi.org/10.1016/j.medengphy.2011.12.025.

Janssens, W., VandenBrande, P., Hardeman, E., De Langhe, E., Philps, T., Troosters, T., Decramer, M., 2008. Inspiratory flow rates at different levels of resistance in elderly COPD patients. Eur. Respir. J. 31, 78–83. https://doi.org/10.1183/09031936.00024807.

Kamin, W.E., Genz, T., Roeder, S., Scheuch, G., Trammer, T., Juenemann, R., Cloes, R.M., 2002. Mass output and particle size distribution of glucocorticosteroids emitted from different inhalation devices depending on various inspiratory parameters. J. Aerosol. Med. 15, 65–73. https://doi.org/10.1089/08942680252908593.

Lavorini, F., Fontana, G.A., Usmani, O.S., 2014. New inhaler devices - the good, the bad and the ugly. Respiration 88, 3–15. https://doi.org/10.1159/000363390.

Lu, D., Lee, S.L., Lionberger, R.A., Choi, S., Adams, W., Caramenico, H.N., Chowdhury, B.A., Conner, D.P., Katial, R., Limb, S., Peters, J.R., Yu, L., Seymour, S., Li, B.V., 2015. International guidelines for bioequivalence of locally acting orally inhaled drug products: similarities and differences. AAPS. J. 17, 546–557. https://doi.org/10.1208/s12248-015-9733-9.

Molimard, M., Raherison, C., Lignot-Maleyran, S., Balestra, A., Lamarque, S., Chartier, A., Droz-Perroteau, C., Lassalle, R., Moore, N., Girodet, P.O., 2017. Chronic obstructive pulmonary disease exacerbation and inhaler device handling: real-life assessment of 2935 patients. Eur. Respir. J. 49. https://doi.org/10.1183/13993003.01794-2016.

Newman, S.P., Sutton, D.J., Segarra, R., Lamarca, R., de Miquel, G., 2009. Lung deposition of aclidinium bromide from Genuair, a multidose dry powder inhaler. Respiration 78, 322–328. https://doi.org/10.1159/000219676.

Palander, A., Mattila, T., Mika, K., Muttonen, E., 2000. In vitro comparison of three salbutamol-containing multidose dry powder inhalers Buventol Easyhaler®, Inspiryl

Turbuhaler® and Ventoline Diskus®. Clin. Drug Investig. 20, 25–33. https://doi.org/10.2165/00044011-200020010-00004.

Pavkov, R., Mueller, S., Fiebich, K., Singh, D., Stowasser, F., Pignatelli, G., Walter, B., Ziegler, D., Dalvi, M., Dederichs, J., Rietveld, I., 2010. Characteristics of a capsule based dry powder inhaler for the delivery of indacaterol. Curr. Med. Res. Opin. 26, 2527–2533. https://doi.org/10.1185/03007995.2010.518916.

Prakash, A., Babu, K.S., Morjaria, J.B., 2015. Profile of inhaled glycopyrronium bromide as monotherapy and in fixed-dose combination with indacaterol maleate for the treatment of COPD. Int. J. Chron. Obstruct. Pulmon. Dis. 10, 111–123. https://doi.org/10.2147/COPD.S67758.

Stahlhofen, W., Rudolf, G., James, A.C., 1989. Intercomparison of experimental regional aerosol deposition data. J. Aerosol. Med. 2, 285–308. https://doi.org/10.1089/jam.1989.2.285.

Stapleton, K.W., Guntsch, E., Hoskinson, M.K., Finlay, W.H., 2000. On the suitability of k-w turbulence modeling for aerosol deposition in the mouth and throat: a comparison with experiment. J. Aerosol. Sci. 31, 739–749. https://doi.org/10.1016/S0021-8502(99)00547-9.

Ung, K.T., Rao, N., Weers, J.G., Clark, A., Chan, H.K., 2014. In vitro assessment of dose delivery performance of dry powders for inhalation. Aerosol. Sci. Technol. 48, 1099–1110. https://doi.org/10.1080/02786826.2014.962685.

Usmani, O.S., Biddiscombe, M.F., Barnes, P.J., 2005. Regional lung deposition and bronchodilator response as a function of beta2-agonist particle size. Am. J. Respir. Crit. Care. Med. 172, 1497–1504. https://doi.org/10.1164/rccm.200410-1414OC.

Usmani, O.S., Lavorini, F., Marshall, J., Dunlop, W.C.N., Heron, L., Farrington, E., Dekhuijzen, R., 2018. Critical inhaler errors in asthma and COPD: a systematic review of impact on health outcomes. Respir. Res. 19, 10. https://doi.org/10.1186/s12931-017-0710-y.

Wedzicha, J.A., Banerji, D., Chapman, K.R., Vestbo, J., Roche, N., Ayers, R.T., Thach, C., Fogel, R., Patalano, F., Vogelmeier, C., 2016. Indacaterol-glycopyrronium versus salmeterol-fluticasone for COPD. N. Engl. J. Med. 374, 2222–2234. https://doi.org/10.1056/NEJMoa1516385.

Zhang, Y., Gilbertson, K., Finlay, W.H., 2007. In vivo-in vitro comparison of deposition in three mouth-throat models with Qvar and Turbuhaler inhalers. J. Aerosol. Med. 20, 227–235. https://doi.org/10.1089/jam.2007.0584.

Zhou, Y., Sun, J., Cheng, Y.S., 2011. Comparison of deposition in the USP and physical mouth-throat models with solid and liquid particles. J. Aerosol. Med. Pulm. Drug. Deliv. 24, 277–284. https://doi.org/10.1089/jamp.2011.0882.