In Vitro and In Silico Comparison of Indacaterol and Glycopyrrolate Pulmonary Deposition between a Single-Unit Dose and a Multi-Unit Dry Powder Inhaler

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is one of the major causes of morbidity and mortality worldwide; with around three million deaths annually [1]. Due to the high rate of morbidity, the COPD pharmaceutical market is $32 billion with an additional indirect cost of $20.4 billion, principally related to COPD exacerbations [1]. Ultibro® Breezhaler® (Novartis, CH), fixed dose combination of indacaterol maleate and glycopyrronium bromide, is intended to reduce exacerbations in patients with COPD through once daily maintenance treatment [2]. However, the use of a capsule based single-unit low resistance dry powder inhaler (DPI) presents many disadvantages [3], such as capsule handling and device loading problems for young and elderly, and the relatively large amount of inspiratory flow required to extract the formulation, which can reduce therapeutic efficacy and patients' adherence and compliance [4].

In this study, *in vitro* and in silico pulmonary delivery performance of a reference capsule based DPI was compared to a multi-unit dose DPI. The objective of the study was to evaluate the interchangeability of these devices in terms of being bioequivalent.

METHODS

Each blister pocket of a Wixela™ Inhub™ device (Mylan, USA) was manually filled with 12.5 mg of reclaimed Ultibro® (85 µg of indacaterol maleate/43 µg of glycopyrronium bromide, Novartis, CH) formulation. However, to deliver the same amount of drugs, one Ultibro® capsule (25 mg) corresponded to two pockets to make an equivalent 25 mg fill. In-line particle size distribution (PSD) measurements (n=3) were carried out using a Spraytec (Malvern Panalytical Ltd, UK),

which was set up with a coated (brij-35: glycerol: ethanol: Milli-Q water, 1.7: 38: 54: 6.3% v/v) medium sized anatomical throat (AT; oropharyngeal consortium, OPC, Emmace Consulting, SE) attached to the inhalation cell (Figure 1). Breezhaler and Wixela Inhub were actuated at 90 L/min for 2.7 seconds and 60 L/min for four seconds, respectively to achieve a 4 KPa pressure drop across the respective devices.

Aerodynamic particle size distribution (APSD) measurements (n=5) were performed with a coated medium sized OPC AT [5] attached to a next generation impactor (NGI, Copley Scientific, UK), which was connected to a critical flow controller and a vacuum pump (Copley Scientific, UK). The flow rate and time of the devices actuation were set to the same values employed for the PSD measurement. The amount of each drug collected was quantified by HPLC and data statistically analysed using Microsoft Excel.

Regional deposition modelling of the APSD data was undertaken using The National Council on Radiation Protection and Measurements (NCRP) deposition model implemented within Mimetikos PreludiumTM [6]. The tidal volume was set to 3300 mL, inspiratory and expiratory flow rates to 60 L/min and 90 L/min for Breezhaler and Wixela Inhub, respectively and a breath hold time of five seconds. The bolus volume was estimated using the laser obscuration data measured via the Spraytec. These bolus volumes were 1146.6 mL and 180.4 mL for the Breezhaler and Wixela Inhub, respectively. The regional deposition of the aerosolised dose from the DPI devices was modelled for the tracheobronchial region (BB), defined as generation 0–8 of the Weibel lung A model; the bronchiolar region (bb), generation 9–15; the alveolar-interstitial region (AL), generation 16–23 and the exhaled (EX) dose. The extrathoracic (ET) dose was taken from the recovered dose within the anatomical throat.

RESULTS AND DISCUSSION

Spraytec PSD measurements of the aerosol emitted from the two devices tested were comparable (Figure 1), although the median volume diameter ($D_{v,50}$) was lower for the Breezhaler® (Table 1). All PSDs presented a multimodal distribution, characterized by two populations: APIs and fine lactose ($D_{v,50}$ about 4 µm), and carrier coarse fraction ($D_{v,50}$ > 100 µm).

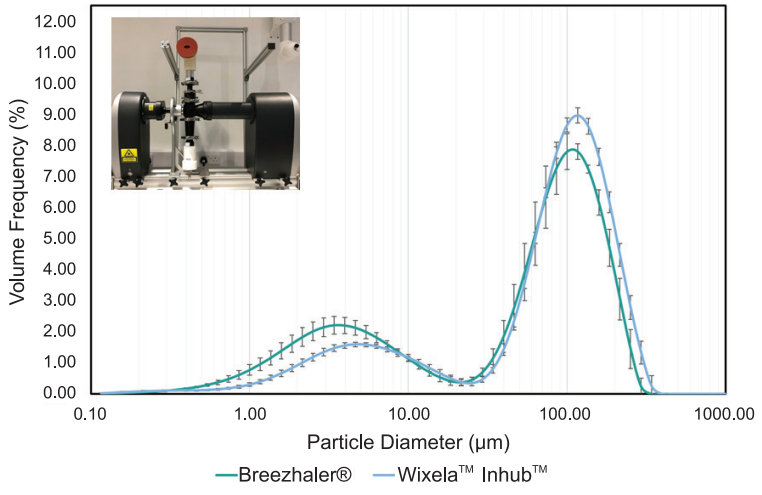

Figure 1. Particle size distribution of the aerosol emitted from the two devices tested (n=3).

The general aerodynamic performance of the two devices (Table 1) was not significantly different ($p > 0.05$) in terms of Mass Median Aerodynamic Diameter (MMAD), Geometrical Standard Deviation (GSD) and Fine Particle Mass (FPM) <5 μm. Furthermore, there was no significant difference in the emitted dose (ED) from the two DPI devices. Despite the total amount of the two drugs collected within the AT being higher when the formulation was aerosolized with Wixela Inhub (Total Lung Deposition, TLD, lower), APIs *in vitro* aerodynamic deposition in the impactor were similar.

Table 1.

Aerodynamic performance and particle size distribution for the two devices studied (n=5, mean values ± standard deviation).

	Indacaterol					Glycopyrrolate					PSD			
	MMAD (μm)	GSD	FPM (μg)	ED (μg)	TLD (μg)	MMAD (μm)	GSD	FPM (μg)	ED (μg)	TLD (μg)	Span	$D_{v,10}$ (μm)	$D_{v,50}$ (μm)	$D_{v,90}$ (μm)
Breezhaler®	2.41 ± 0.08	1.99 ± 0.05	43.82 ± 1.93	85.99 ± 1.86	57.17 ± 1.52	2.67 ± 0.02	1.89 ± 0.07	21.67 ± 1.19	39.91 ± 1.73	27.51 ± 1.26	2.31 ± 0.13	2.12 ± 0.26	66.54 ± 0.83	156.03 ± 9.40
Wixela™ Inhub™	2.50 ± 0.09	1.82 ± 0.04	36.69 ± 1.47	90.53 ± 2.39	47.31 ± 1.01	2.74 ± 0.05	1.72 ± 0.04	17.49 ± 1.04	41.08 ± 1.75	22.29 ± 1.41	2.09 ± 0.04	3.70 ± 0.37	83.96 ± 3.91	178.90 ± 7.45

The in silico regional deposition modelling (RDM) of the local deposition of the two APIs are shown in Table 2. The AL deposition is a relatively good indication of systemic exposure of the APIs which may impact clinical pharmacokinetic studies of bioequivalence. The AL deposition of both indacaterol and glycopyrrolate between the two devices are very similar differing only by 1.22% and 2.22%, respectively. The therapeutic targets of these APIs however, are in the shallower regions of the lung (represented by the BB and bb regions), where the thicker epithelium results in slower permeation into blood vessels reducing the rate of systemic exposure [7]. The total BB and bb deposition of both indacaterol and glycopyrrolate between the two devices are similar differing by 1.87% and 2.88%, respectively.

Table 2.

Regional deposition of the aerosolised dose of the two APIs with the single-unit and multi-unit device.

	Indacaterol (μg)					Glycopyrrolate (μg)				
	ET	BB	bb	AL	EX	ET	BB	bb	AL	EX
Breezhaler®	41.963	4.910	0.181	0.053	0.004	18.091	2.533	0.110	0.035	0.002
Wixela™ Inhub™	53.241	4.153	0.122	0.033	0.001	23.350	2.151	0.073	0.020	0.001

CONCLUSIONS

In conclusion, pulmonary delivery performance of the two devices were comparable. There was no significant difference in the *in vitro* aerodynamic distribution the single-unit and the multi-unit DPI ($p > 0.05$). These data supported the similar in silico regional deposition modelling of the fate of the respirable dose. These preliminary results support the possibility of achieving clinical bioequivalence between these single-unit dose and multi-unit dose DPIs, and thus opening the door to a possible switch to a more patient friendly and efficient multi-unit device.

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