Predicting the Regional Deposition and Systemic Exposure of Albuterol Sulfate Formulated with Low Global Warming Potential Propellants

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INTRODUCTION

Since adoption of the Kyoto Protocol in 1997 [1] and the Europe F-Gas regulation in 2015 [2], further amendments to the Montreal Protocol have been proposed. These amendments aim to gradually phase-down the production of hydrofluorocarbons (HFCs) over the next 20 years due to their high global warming potential (GWP), which creates a need to develop pressurized metered dose inhalers (pMDIs) with lower GWP propellants.

Short-acting beta agonists account for half of global inhaled medications (by number of doses prescribed) with much of this volume attributed albuterol sulphate pMDIs [3]. Switching existing albuterol sulphate pMDIs formulated with HFA 134a (GWP=1,300) [3] to inhalers based on lower GWP propellants would preserve this important albuterol sulfate drug product, but in order to be found bioequivalent these 'greener alternatives' may be required to demonstrate similar regional deposition and clearance from the lung.

In this study, we manufactured a suspension-only formulation containing albuterol sulfate (AS) and 1,1-Difluroethane (HFA-152a, GWP=138) and used realistic aerodynamic particle size analysis of the sprayed product to predict the regional deposition of the albuterol using a one-dimensional model. In addition, drug absorption was predicted using a physiologically-based pharmacokinetic (PB-PK) model.

METHODS

Micronized albuterol sulfate (salbutamol sulfate, Neuland, India, d50: 2.2 μm, 90% below 5 μm) was formulated with HFA-152a (Koura, UK) in uncoated 19 mL aluminum canisters (Presspart, UK) crimped with 50 μL metering valves (Aptar, France). Similarly, canisters were prepared in transparent PET vials (Merxin, UK) to permit evaluation of sedimentation behavior using the Turbiscan system (Turbiscan Lab, Formulation, France). This experimental product is referred to as the 'albuterol HFA-152a formulation'.

The aerodynamic particle size distribution (APSD) of the albuterol HFA-152a formulation and a commercial HFA-134a based Ventolin pMDI (GSK, USA, B/N: 8ZP8132) were evaluated (one cannister per product, five sprays per canister) downstream of a medium oropharyngeal consortium (OPC) throat model (Emmace, Sweden) coated with glycerol and operated with at 30 L/min. The resulting realistic APSD measured by cascade impaction (Next Generation Impactor, Copley Scientific, UK) was used to estimate the regional deposition pattern in the Weibel A lung model using the National Council on Radiation Protection and Measurements (NCRP) regional deposition model [5] combined with a realistic breathing profile. The model was used to estimate the fractional deposition of albuterol in the tracheobronchial region (BB, generations 0–8), the bronchiolar region (bb, generations 9–15), and the alveolar-interstitial region (AL, generations 16–23). Mouth–throat deposition (ET = extrathoracic) was based on deposition in the OPC realistic throat model. The mass that did not deposit in any region was exhaled (EX).

A mathematical simulation of albuterol plasma concentration versus time based on each product's predicted regional deposition was undertaken assuming a two systemic compartment PK model with absorption from multiple regions in the lung and mucociliary clearance from the BB and bb regions [6, 7].

RESULTS AND DISCUSSION

The suspension stability assessment of AS in liquefied HFA-152a suggested that the average floc particle size was approximately 2.0 μm and that the sedimentation time was 1.6 mins. Sedimentation time was defined as the time taken for changes in light transmission to cease after agitation of the cannister. Previous studies have reported that sedimentation time of albuterol sulfate in HFA-134a was less than 30 s [4]. The emitted dose of the Ventolin and albuterol HFA-152a formulation measured using cascade impaction was 111 μg and 105 μg, respectively. The mean MMAD and their standard deviations of the Ventolin and albuterol HFA-152a formulation measured using cascade impaction was 2.22 ± 0.10 μm and 2.13 ± 0.11 μm, respectively showing similar delivery and aerodynamic behavior.

The predicted regional deposition of Ventolin and the albuterol HFA-152a formulation are shown in Table 1. These data suggested that whilst the central lung regional deposition was similar between both products, the extrathoracic deposition of Ventolin was lower than the albuterol HFA-152a formulation. Figure 1 shows the simulated systemic exposure of albuterol sulfate from both products. The predicted peak plasma concentration was lower for the albuterol HFA-152a formulation than the Ventolin product which we attribute to the lower predicted peripheral deposition of albuterol for the HFA-152a formulation compared to Ventolin.

Table 1.

Summary of modeled regional deposition expressed as a percentage of the delivered dose of albuterol for Ventolin and albuterol HFA-152a formulation (n=1 based on mean APSD data).

Product	% Deposition				
	ET	BB	bb	AL	EX
Ventolin	70.1	1.1	2.1	24.0	2.7
Albuterol HFA-152a	74.1	1.3	1.5	20.9	2.2

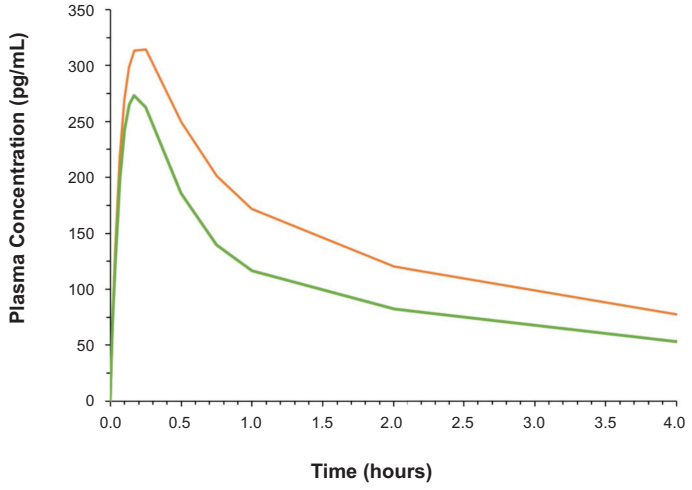

Figure 1. **Simulated albuterol PK profile for Ventolin (orange) and albuterol HFA-152a (green) formulation following inhalation.**

CONCLUSIONS

We have demonstrated the potential feasibility of developing an albuterol sulfate pMDI formulation containing only the drug and HFA-152a pending further *in vitro* characterization. Our data suggested that the HFA-152a formulation had good suspension stability. Moreover, through regional deposition modelling we expect that the HFA-152a formulation will exhibit similar central deposition as Ventolin. Further optimization of the extrathoracic and peripheral dose deposition of the albuterol HFA-152a formulation is required to enable matching of the pharmacokinetic exposure to that of Ventolin.

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