INTRODUCTION

Combination therapies for the treatment of chronic obstructive pulmonary disease (COPD) have long been used to provide improved disease management. Current therapies aim to provide bronchodilation and most of them are based on beta-agonists or anticholinergics/ muscarinics (1).

A widely used combination is an inhaled corticosteroid (ICS) plus a long-acting β-agonist (LABA), which have shown additive improvement in lung function (2). However, for inhalation combination products, the most significant pharmaceutical challenge is to maintain a constant ratio of drug components during various stages of drug formulation and drug delivery. This implies that, when the drug product with high content uniformity is formulated, it should further maintain the ratio of actives upon re-dispersion and inhalation.

Drug delivery to lungs with a consistent and pre-designed ratio of co-associated active components can help to maximise the chance of synergistic action. Currently, marketed products are predominantly manufactured by the jet milling micronization process. This high energy process causes poor chemical and physical stability of drug components. In turn, the formation of amorphous domains, unwanted changes in surface free energy and polymorph transition. Collectively, these deleterious effects bring about variation and limitations in performance (3, 4).

Newer particle engineering led approaches, such as those offered by Prosonix Ltd, can help to solve these problems by designing improved medicines that can help to achieve consistent localised delivery and enable efficent, free drug, only MDI formulations. These engineered medicines have the potential to enhance the efficiency of the molecular and cellular level, and can further help to achieve acceptable efficacy at reduced dose, thus improving topical delivery due to enhanced safety and mutual synergistic approach.

METHODS

Particle preparation, formulation and aerosolization: Highly crystalline inhalable size combination particles of budesonide (BDS) and formoterol fumarate dihydrate (FFD), BDS-FFD, in a pre-defined ratio, were manufactured by the UMAX™ (Ultrasuond Mediated Amorphous to Crystalline transition) technology (5). The aerolization efficiency of the combination particles were evaluated in excipient free, drug only pressurised metered dose inhalation (pMDI) formulations using HFA134a propellant. The blend strength of BDS-FFD combination formulation equated to 125 µg BDS and 7.5 µg FFD giving ratio of 16.7 for BDS:FFD. Aerodynamic assessment was carried out using an Anderson Cascade Impactor (ACI), calibrated at 28.5 L/min flow rate. The mass of drug deposited on each part of the ACI was determined by HPLC and the mass median aerodynamic diameter (MMAD), and fine particle fraction (FPF) was determined.

Characterization by Raman Microscopy: Raman Chemical Imaging was performed using a ChemImage Falcon II™ Raman Imaging System (ChemImage, Pittsburgh, USA) to investigate relative distribution of actives (6).

RESULTS AND DISCUSSION

Multicomponent products are difficult to prepare and have been reported to exhibit significant delivery variability (7). This can further lead to increased safety concerns, especially with inhalation combination products containing highly potent LABA molecules (8, 9). The recent study details the benefit of using a particle-engineering approach in order to overcome these issues. Scanning electron micrograph and particle size distribution profiles of UMAX engineered combination drug particles of BDS-FFD are shown in figure 1, which indicates particles with high morphological uniformity.

The aerosol dispersion performance and uniformity of delivery across the stages of impactor were evaluated for the drug only pMDI formulation of UMAX 100(BDS:FFD), in order to provide an indication of the potential benefit of processing the actives in a single particle in terms of dose delivery and content uniformity. For the initial time point data, only one canister was tested from the batch and only one ACI assay was performed per can. Figure 2 shows the comparison of ACI profile in %target for the two compounds. This data suggests that following aerosolization of the engineered BDS-FFD particles, both actives were delivered consistently together across various stages of the impactor, with an average ratio of 16.2 ± 0.8 for BDS:FFD.

Raman Microscopy: Reference spectra for the dry powder samples of pure components were collected using ChemImage Falcon II™ with 532 nm laser wavelength (figure 3, left). A significant spectral difference between FFD and BDS was observed in the spectral region from 1270 to 1700 cm⁻¹ and was selected for the Raman imaging studies. Spectral analysis indicated that the active pharmaceutical ingredients contain characteristic Raman peaks distinguishing them from each other (1310 cm⁻¹ for FFD and 1660 cm⁻¹ for BDS). Raman analysis of the dry powder sample, within the region of interest (ROI) indicates that the material is well mixed (figure 3, right) with repeat traces of Raman spectra of the engineered BDS-FFD sample showing high homogeneity and reproducibility. No stand-alone FFD particle is detected; rather the FFD Raman signal is co-registered in the ROI with the BDS signal.

ACKNOWLEDGEMENTS: Prosonix daily acknowledges the assistance, analytical expertise and guidance of Tracey Safan, Okiana Olkhovoy and Ryan Priore of the Gateway Analytical, LLC, 3136 William Flynn Highway, Gibsonia, PA 15044.

CONCLUSIONS

The effective production and delivery of combination medicines in a consistent, stable and co-localised manner are lacking due to inefficiencies in current manufacturing and formulation processes. This paper highlights the potential of engineered multi-component particles to develop superior drug formulations, offering more accurate dosing and enabling the use of simple, cost-effective drug only pMDI formulations.

Whilst physical mixture combination products offer a solution to achieve the desired and targeted material mix, the co-deposition of actives occurs randomly when derived from the same aerolized cloud and, as a result, there is inconsistency in the ratio of deposition in various regions of the lung, despite the use of a precise formulation mass ratio of the actives.

Particle engineering techniques involving the use of ultrasound can be used to manufacture micromerite dual component particles for inhalation drug delivery with high homogeneity, and in particular particles consisting of an ICS and a LABA, as in this investigation. In turn these particles should facilitate optimal and concurrent delivery of both drugs to the lung.

The UMAX sonocrystalization process used for manufacture of such particles circumvents the use of mechanical milling and in turn avoids the use of poor and variable performance, and the effects of comminution on sensitive organic crystals. These engineered particles have optimal performance attributes for inhalation products designed for asthma and COPD.

Particles of BDS-FFD have been engineered and formulated as excipient free drug only pMDI. Furthermore, aerosol performance has been assessed by ACI to identify co-deposition of individual drug particles within the impactor. The results to date have shown that these combination particle formulations are very consistent with respect to the delivery of each active ingredient at each stage of the impactor, and presented excellent content uniformity. These improved medicines could help to achieve acceptable efficacy at reduced dose, thus improving topical delivery due to enhanced safety and mutual synergistic approach.

REFERENCES


