Microstructural Mapping of Dry Powder Inhalers (DPIs) using Morphologically Directed Raman Spectroscopy (MDRS): A Novel Analytical Tool for DPI Characterization

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INTRODUCTION

Dry Powder Inhalers (DPIs) are complex drug-device combination products in which the drug constituent is a locally acting powder blend formulation and the device constituent is a portable oral inhaler. DPI formulations typically consist of fine micronized drug particles blended with coarse carrier particles. The inspiratory effort by patients generates air flow through the device, which creates an environment for de-agglomeration of drug particles from drug-drug and drug-carrier agglomerates (1). The extent of drug particle de-agglomeration depends on the magnitude of complex cohesive and adhesive inter-particulate interactions, which contributes to drug delivery to the sites of action in the lung. Particles with aerodynamic diameter between 1-5 µm are likely to deposit in the lung and hence are generally considered clinically relevant. For product development and quality control purposes, cascade impactors are commonly used to characterize the aerodynamic particle size distribution of DPIs, but they provide no insight on the microstructure of the aerodynamically classified particle populations. Furthermore, the microstructure of aerosolized fraction from DPIs, along with their aerodynamic size distribution, may also affect their dissolution performance. Morphologically Directed Raman Spectroscopy (MDRS) is a novel *in vitro* technology for elucidation of morphological and chemical features of drugs and excipients (2). For example, the FDA has recognized the potential of MDRS to provide supportive information on equivalence in drug particle size between test and reference nasal spray suspension products (3). This microstructural analysis is assisting development of alternative approaches to evaluating bioequivalence at the site of action within the respiratory tract. Current recommendations for generic dry powder inhalation drug products still include comparative clinical endpoint bioequivalence studies (which are often not sensitive to formulation differences) because of residual uncertainties from in vitro methods regarding the in vitro to in vivo correlation. This study explores the use of MDRS, in conjunction with in vitro dissolution, to gain deeper understanding of the microstructure of aerosolized fraction from DPI drug products, which may help identify formulation differences among products.

METHODS

Product Selection: Advair® Diskus® [fluticasone propionate and salmeterol xinafoate (FP/SX)] at three different strengths (i.e., FP/SX;100/50 µg, FP/SX; 250/50 µg, FP/SX; 500/50 µg), Seretide® Accuhaler® (FP/SX;100/50 µg), Flovent® Diskus® (FP;100 µg), and Flixotide® Accuhaler® (FP;100 µg), all manufactured by the same pharmaceutical company, were the commercial DPI products selected for the study.

Aerosolized Fraction Collection: The aerosolized fraction (or impactor-sized mass; ISM) of each commercial DPI was collected into the Unidose® aerosol collection system (4) via a USP inlet port at a fixed flow rate of 60 L/min for 4.0 seconds. The ISM was collected onto 47mm Pall A/E type glass fiber filters (Copley Scientific, Nottingham, UK) housed at stage 2 of an Next Generation Impactor (NGI), which was then used for MDRS and *in vitro* dissolution studies.

Morphologically Directed Raman Spectroscopy (MDRS): The filter substrate with ISM from one actuation was mounted on to the sample stage of a Morphologi G3-ID automated image analysis and Raman Chemical Imaging system (Malvern Instruments, Malvern, UK). A 50x objective lens was used for analysis. Reference spectra of fluticasone propionate, salmeterol xinafoate, and lactose were used to identify the chemical composition of the particles collected. Identification was performed by comparing the entire spectrum for the analyzed particles to the library spectra of fluticasone propionate, salmeterol xinafoate and lactose. The scan area was set to 4.5 mm x 4.5 mm and a total of 4,000 particles were analyzed for each drug product. The X-Y coordinates of the particles recorded during morphological analysis were also used to locate the center of the particles, where the Raman spectrum was acquired.

***In vitro* Dissolution:** Conducted in a modified USP Apparatus V using 300 mL pH 7.4 PBS containing 0.2 %w/v sodium dodecyl sulfate (SDS) dissolution medium maintained at 37°C with a stirring speed of 75 rpm (Erweka GmbH, DT 126, Heusenstamm, Germany) (5). The USP disk assembly membrane holder was adapted to enable 47 mm glass fiber filters to be housed. Three mL aliquots were withdrawn at 2.5, 5, 10, 15, 29, 25, 30, 60, 120, 180, and 240 minute time intervals and filtered directly into HPLC vials. To maintain a constant volume in the dissolution vessel, the sampling volume was replaced with pre-warmed dissolution media. The percentage of the drug dissolved at each time point was determined by dividing the amount of drug by the total mass loading. The studies were carried out using the ISM collected from one actuation of Advair® Diskus® (500/50 µg), two actuations of Advair® Diskus® (250/50 µg) and five actuations of each Advair® Diskus® (100/50 µg), Seretide® Accuhaler® (100/50 µg), Flovent® Diskus® (100) and Flixotide® Accuhaler® (100 µg).

RESULTS

The MDRS data of different strengths of Advair® Diskus® (FP/SX; 100/50 , 250/50 and 500/50 µg) showed considerable differences in the fraction of drug-drug and drug-carrier agglomerates. The most notable difference was observed in the fraction of FP and FP-lactose. The fraction of FP increased, while the fraction of FP-lactose decreased with increasing of FP strength in the Advair® Diskus® products (Figure 1).

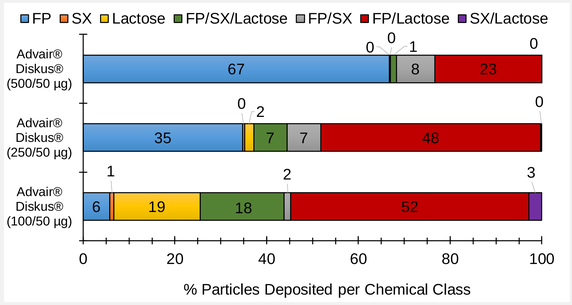

Figure 1: Particles deposited per chemical class (%) of the ISM of Advair® Diskus® (FP/SX; 100/50 µg), Advair® Diskus® (FP/SX; 250/50 µg), and Advair® Diskus® (FP/SX; 500/50 µg). These are presented as mean ± standard deviation (n=5).

As noted in Figure 2, at 2.5 minutes, the FP dissolved (%) appeared to decrease with increasing FP strength in Advair® Diskus® products (Advair® Diskus® (FP/SX; 500/50 µg) < Advair® Diskus® (FP/SX; 250/50 µg) < Advair® Diskus® (FP/SX; 100/50 µg)). For Advair® Diskus® products, the fraction of FP increased, while the fraction of FP-lactose decreased with increasing FP strength in Advair® Diskus® products. Therefore, it is proposed that the highly soluble lactose particles dissolve rapidly from FP-lactose agglomerates, exposing the surfaces of FP particles to the dissolution media enabling rapid dissolution. However, these mechanisms may not operate in the case of FP-FP agglomerates. To investigate this hypothesis, the MDRS and *in vitro* dissolution data of Advair® Diskus® (FP/SX; 100/50 µg) were compared with other similar commercial DPI products with the same FP strength (i.e., Seretide® Accuhaler® (FP/SX;100/50 µg), Flovent® Diskus® (FP;100 µg) and Flixotide® Accuhaler® (FP;100 µg).

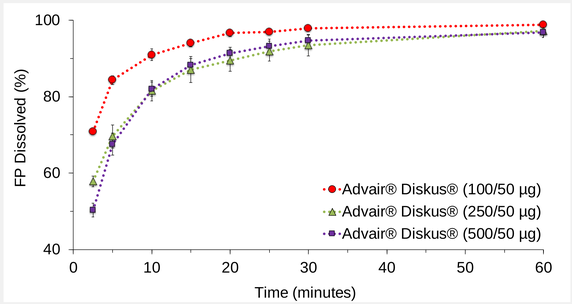

Figure 2: FP dissolved (%) from the ISM of Advair® Diskus® (100/50 µg) as Red Circle, Advair® Diskus® (250/50 µg) as Green Triangle, and Advair® Diskus® (500/50 µg) as Purple Square. These are presented as mean ± standard deviation (n=2).

Figure 3 shows the "Free" FP and FP agglomerated for Advair® Diskus® (FP/SX; 100/50 µg), Flixotide® Accuhaler® (FP; 100 µg), Flovent® Diskus® (FP; 100 µg), and Seretide® Accuhaler® (FP/SX; 100/50 µg), where "Free" FP represents the fraction of individual FP particles or FP-FP agglomerates, and FP agglomerates represents the fraction of FP particles agglomerated with lactose and/or SX. The MDRS data showed that the fractions of "Free" FP and FP agglomerated in Advair® Diskus® (FP/SX; 100/50 µg) were considerably different from that of Seretide® Accuhaler® (FP/SX;100/50 µg), Flovent® Diskus® (FP; 100 µg), and Flixotide® Accuhaler® (FP; 100 µg). The fraction of "Free" FP was lower, while that of FP agglomerated was higher for Advair® Diskus® (FP/SX; 100/50 µg) compared with that of Seretide® Accuhaler® (FP/SX;100/50 µg), Flovent® Diskus® (FP;100 µg), and Flixotide® Accuhaler® (FP; 100 µg).

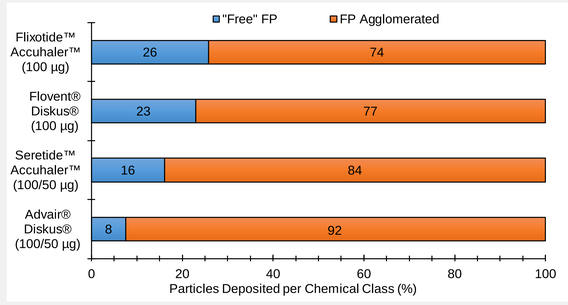

Figure 3: Particles deposited per chemical class (%) of the ISM of Advair® Diskus® (FP/SX; 100/50 µg), Flixotide® Accuhaler® (FP; 100 µg), Flovent® Diskus® (FP; 100 µg), and Seretide® Accuhaler® (FP/SX; 100/50 µg). These are presented as mean ± standard deviation (n=5).

Figure 4 shows that the FP dissolved (%) was higher for Advair® Diskus® (100/50 µg), compared with that of Seretide® Accuhaler® (FP/SX; 100/50 µg), Flovent® Diskus® (FP; 100 µg), and Flixotide® Accuhaler® (FP; 100 µg). In addition, the FP dissolved (%) at 2.5 minutes (the first timepoint, highly discriminatory as dissolution progresses) also was found to increase linearly with increasing FP agglomerated (Figure 5). This is consistent with our hypothesis that when FP is agglomerated (with lactose and/or SX, which are highly water-soluble materials), its dissolution is faster as compared to when it is present as "Free" FP (individual FP particles or agglomerated to other FP particles, relatively less water-soluble materials). This indicates that the microstructure may substantially affect the dissolution of aerosolized fraction from DPI products.

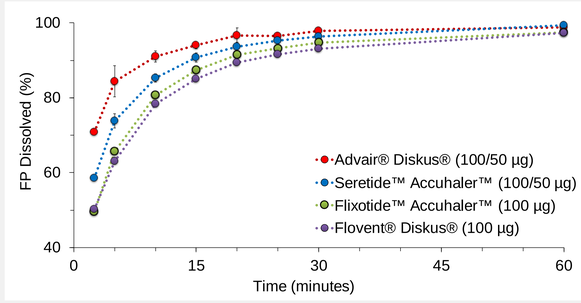

Figure 4: FP dissolved (%) from the ISM of Advair® Diskus® (100/50 µg), Flixotide® Accuhaler® (100 µg), Flovent® Diskus® (100 µg), and Seretide® Accuhaler® (100/50 µg). These are presented as mean ± standard deviation (n=2).

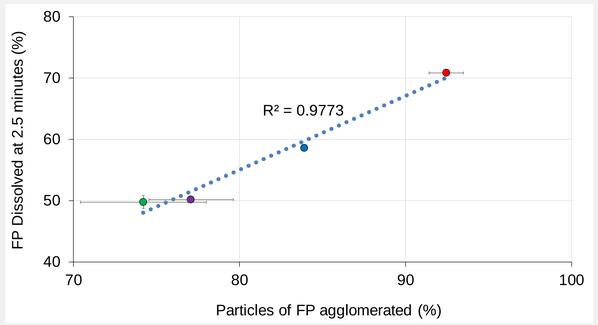

Figure 5: FP dissolved at 2.5 minutes (%) as a function of FP-lactose agglomerates (%) for Advair® Diskus® (100/50 µg, red circle); Flixotide® Accuhaler® (100 µg, green circle); Flovent® Diskus® (100 µg, purple circle); and Seretide® Accuhaler® (100/50 µg, blue circle).

CONCLUSION

The collected aerosolized fraction of DPI products were analyzed using MDRS and found to have different microstructures, which may help to explain differences in dissolution performance. Therefore, the MDRS has the potential to serve as a new analytical tool to provide information on formulation differences among DPI products, which may improve the development of generic DPI drug products.

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