

Assessment of the Effect of Fluticasone Furoate Morphology on the *In Vitro* Performance of a Dual Blister Dry Powder Inhaler

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Summary

Microstructural equivalence is required for local acting products that are qualitatively and quantitatively the same as the reference listed drug in terms of their active (API) and inactive pharmaceutical materials. In this study we have assessed the influence on the aerosolisation performance and *in vitro* dissolution of fluticasone furoate (FF) API batches engineered with a similar particle size distribution, but different morphology (prismatic-shape crystals vs needle-shape crystals). FF-lactose blends were prepared by high shear mixing, filled into blister strips and coiled into a dual blister strip device. Different drug morphology resulted in different specific surface area (SSA) which influenced the *in vitro* dissolution profile. Lower SSA determined a higher ISM and FPD for the prismatic-shape API but slowed down drug dissolution. The investigation of the FF agglomeration state in the ISM will additionally clarify the differences observed in the *in vitro* performance of formulations prepared with API with different morphology. Nevertheless, this study shows how understanding and controlling API's physico-chemical properties and their effect on product performance is fundamental in DPI development. Further optimisation of FF morphology will be performed to expand the design space of the formulation, such that the *in vitro* performance can be fine-tuned based on bioequivalence requirements.

Key Message

Microstructural equivalence is one of the FDA requirements for generics development. In this study we have assessed the influence of fluticasone furoate morphology on the *in vitro* aerodynamic and dissolution performance of a dual blister DPI. Prismatic-shape drug showed higher FPD but slowed down dissolution when compared to needle-shape crystals.

Introduction

When developing a generic dry powder inhaler (DPI), it is important to keep in mind that the Food and Drug Administration (FDA) have recommended qualitative (Q1) and quantitative (Q2) formulation sameness between the test and the reference listed drug. More recently FDA has introduced the concept of microstructural equivalence (Q3) for local acting products. The microstructural differences in the arrangement of matter and state of aggregation within formulated and aerosolized forms of DPIs are dependent on the physicochemical properties of active and inactive materials, device characteristics, and processing history [1].

Morphology plays a huge role in adhesive blends of carrier and active pharmaceutical ingredient (API) controlling the detachment of the API particles from the surface of the carrier by regulating the arrangement and level of attachment of the API particles on the carrier surface [2]. By modifying the drug morphology through particle engineering techniques, it is possible to reduce the relative contact area between drug and carrier, thus reducing adhesion and promoting drug liberation during the aerosolisation process [3].

Differences in Q3 at both a microscopic and macroscopic scale can be characterized using a combination of orthogonal *in vitro* based techniques, such as morphology and surface mapping through Raman spectroscopy and *in vitro* dissolution [1]. Those in conjunction with more realistic aerodynamic particle size distribution testing can allow for a deeper characterization and prediction of differences and similarities between RLD and test product before enrolling in clinical studies.

In this study we have assessed the influence on the aerosolisation performance and *in vitro* dissolution of the same fluticasone furoate formulation prepared with two API batches with different morphology and delivered employing a dual blister strip device.

Materials and Methods

Two batches of fluticasone furoate (FF) were provided by Sterling (IT) applying particle engineering to obtain crystals with similar particle size distribution (PSD), but two different morphology (Figure 1). The solid-state of the two API batches was characterized for PSD wet analysis employing a Malvern 2000 (Malvern Panalytical, UK), specific surface area (SSA) by BET (ACS Material, CA, USA), crystals morphology by scanning electron microscopy (SEM; Leo 1525, Zeiss, CH), water content by Karl Fisher (Mettler Toledo, DE), X-Ray powder diffraction (XRPD) using instrument D2 Phaser (Bruker, USA) equipped with Cu K α radiation source and, finally, amorphous content by differential scanning calorimetry (DSC 4000, Perkin Elmer, USA) or solution calorimetry (TAM IV, TA Instruments, USA).

The two FF batches (0.8% w/w) were then separately blended by high shear mixing with the same batch of customized lactose provided by DFE Pharma (DE) with a volume diameter of the 10% percentile of the particles population < 5 μm and percentage of particles with a size < 30 μm (Q30) of 40%. The two formulations were filled into a blister strip employing the SSP2 (Harro Höfliger, DE), targeting 12.5 mg $\pm$ 5% as pocket fill weight. The Slitting TT (Harro Höfliger, DE) was then used to manually cut the double blister produced into a single blister strip with the right length (~32.5 cm) for it to be inserted into a Relvar® Ellipta device, sourced from the market (GSK, DE; batch W83A). The test FF strip was loaded into the device together with the originator Vilanterol strip employing the Coiling TT (Harro Höfliger, DE), as previously described [4].

Traditional aerodynamic particle size distribution (APSD) and realistic aerodynamic particle size distribution (rAPSD) were carried out employing a next generation impactor (NGI) at 60 L/min coupled with a USP throat for APSD and instead an OPC-medium size throat (Emmace, SE) for rAPSD. Impactor sized mass (ISM), Fine Particle Dose (FPD) < 5 μm , Mass Median Aerodynamic Diameter (MMAD), Geometric Standard Deviation (GSD) and Fine Particle Fraction (FPF) calculated on the emitted dose were assessed for both techniques.

Finally, *in vitro* dissolution of the FF ISM of both formulations was performed employing a USP Apparatus II. Briefly, the ISM was collected on a paper filter employing the NGI and dissolution was carried out using 250 mL of phosphate buffer at pH 7.4 with 0.2% v/v of sodium dodecyl phosphate as medium.

Results and Discussion

The two batches of FF presented the same polymorph (Form I), similar PSD (D_{v50} < 2.5 μm), water content (0.1% w/w) and amorphous content (1.5-1.8%) but very different morphologies (Figure 1) and, consequently, SSA (6.3 and 4.6 m²/g for the needle-shape and prismatic-shape API, respectively).

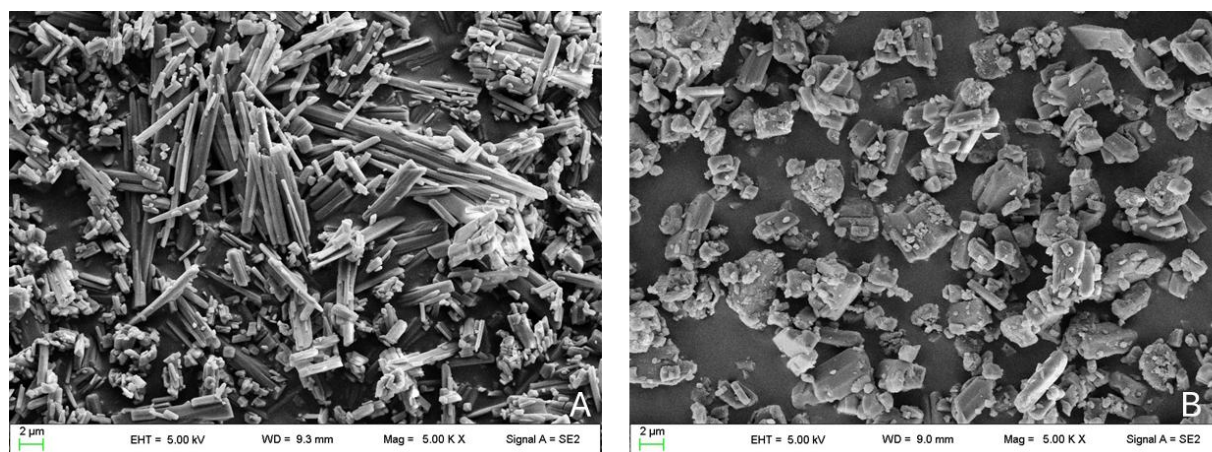


Figure 1 - SEM image of the two morphologically different FF batches employed in this study: (A) needle-shape and (B) prismatic-shape.

The two APIs were then blended with the same lactose batch and filled into blister strips, as previously described [4]. Analysis of blend uniformity and pocket content uniformity was around 100% for both powders, indicating homogeneity of the products obtained. APSD and rAPSD were then tested delivering the powder with an Relvar® Ellipta device (Figure 2) pre-loaded with the originator Vilanterol formulation. Whereas no differences in ISM were observed between the two analytical techniques for both blends (Table 1), the rAPSD resulted for both formulations in a higher deposition in the induction

port, as expected employing a more anatomically relevant throat, instead of the preseparator where more API was collected when traditional APSD was performed.

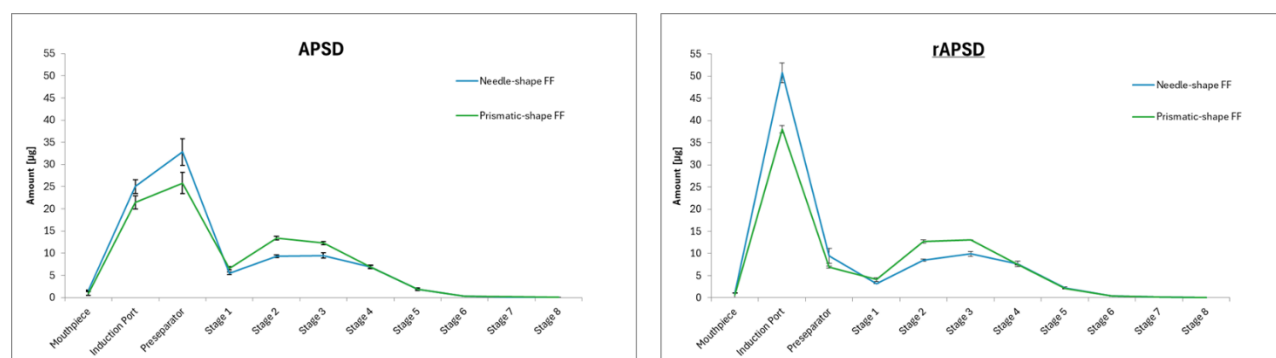


Figure 2 - APSD (on the left) and rAPSD (on the right) analysis of the two blends prepared with FF APIs with different morphology (n=6, mean value with bars representing standard deviation).

Moreover, with both techniques the prismatic-shape FF showed a statistically significant higher ISM (32-34 µg vs 40-42 µg for needle-shape vs prismatic-shape, respectively) and FPD (21-22 µg vs 25-26 µg for needle-shape vs prismatic-shape, respectively) due to a higher deposition on Stages 2 and 3 of the NGI (Figure 2 and Table 1).

Table 1. APSD and rAPSD parameters obtained for the two blends prepared with FF APIs with different morphology (n=6, mean value with standard deviation in parenthesis).

FF Formulation	APSD					rAPSD				
	ISM (µg)	FPD (µg)	MMAD (µm)	GSD	FPF (%)	ISM (µg)	FPD (µg)	MMAD (µm)	GSD	FPF (%)
Needle-shape	33.59 (1.58)	20.87 (1.16)	4.07 (0.05)	1.87 (0.07)	22.41 (0.67)	32.09 (1.54)	22.48 (1.46)	3.66 (0.07)	1.85 (0.01)	24.08 (1.33)
Prismatic-shape	41.61 (1.24)	24.61 (0.95)	4.34 (0.08)	1.83 (0.03)	27.46 (1.84)	40.11 (1.20)	26.46 (0.98)	4.00 (0.07)	1.73 (0.01)	30.89 (0.75)

Even though MMAD was similar for the two formulations, FPF was higher for the powder prepared with the prismatic-shape FF, as shows by both techniques (Table 1).

On the contrary, the dissolution analysis showed a slower kinetic for this API morphology which may be attributed to its lower SSA. Differences in surface properties modulate particle interactions which can influence API-lactose agglomeration upon actuation and, consequently, *in vitro* aerodynamic behaviour, as observed for FF needle-shape [6]. Moreover, it is known that SSA influences dissolution rate which, in turn, might affect bioavailability [7]. An increase in SSA generally accelerates the dissolution rate, often in a linear manner, however this effect can be negatively influenced by API aggregation that can occur for lipophilic drugs with a very narrow particle size during formulation manufacturing process [7].

Further studies focused on the assessment of FF agglomeration state in the two formulations could additionally clarify the behaviour observed [8]. The use of orthogonal techniques to dissolution, such as morphologically directed raman spectroscopy, will help understanding the effect of drug morphology on powder structure (e.g. API-API and API/lactose interactions and agglomeration behaviour) and, consequently, on dissolution.

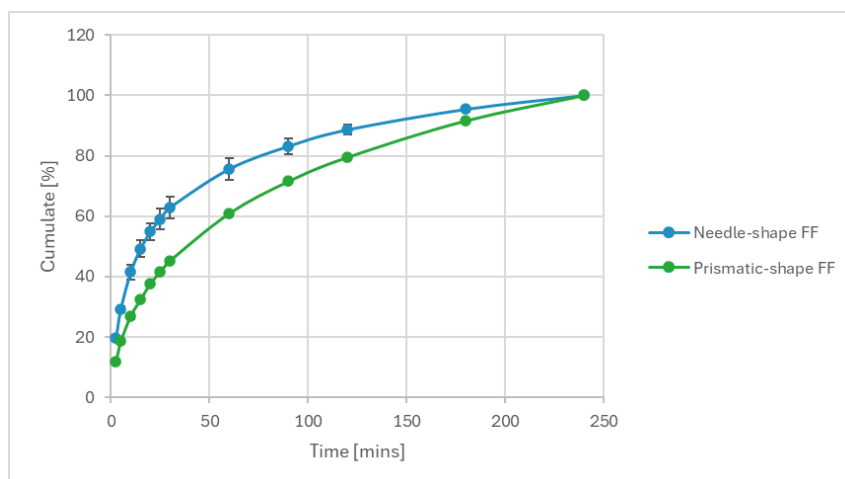


Figure 3 - *In vitro* dissolution profile as cumulative (%) of the ISM of the two blends prepared with FF APIs with different morphology.

Conclusions

In this study we have assessed the influence of API morphology on the *in vitro* performance of an FF blend delivered by a dual blister device. Different drug morphology resulted in different SSA which influenced the *in vitro* aerodynamic behaviour and dissolution profile. Lower SSA determined a higher ISM and FPD for the prismatic-shape API but slowed down drug dissolution. The investigation of the FF agglomeration state in the ISM will additionally clarify the differences observed in the *in vitro* performance of formulations prepared with API with different morphology. Nevertheless, this study shows how understanding and controlling API's physico-chemical properties and their effect on product performance is fundamental in DPI development. Further optimisation of FF morphology will be performed to expand the design space of the formulation, such that the *in vitro* performance can be fine-tuned based on bioequivalence requirements.

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