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Improving the Aerodynamic Performance of Fluticasone Propionate Powders by Tuning Particle Size through Wet Polishing

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INTRODUCTION

The aerodynamic performance of a carrier-based inhalation powder is determined by the API physicochemical properties, formulation composition and process, device type and environmental variables, amongst other factors. The particle engineering technologies are used to target a defined particle size (PS) within the inhalation range, which can lead to different physicochemical properties that may impact the API formulation and product performance [1]. In order to overcome some of the challenges observed in the jet milling (JM) approach [2,3], a new technology that has been gaining momentum as a pharmaceutical engineering technology was used: Wet Polishing (WP) [4]. This technology comprises the size-reduction of the API in a suspension followed by spray drying (SD) – **Figure 1.**

The **purpose** of this work was to investigate the influence of the PS on the physical properties and aerodynamic performance of two fluticasone propionate (FP) powders size reduced by WP.

MATERIALS & METHODS

- **A) API Engineering**
  - FP size reduced by WP → a) Dv50 = 2 µm (FP2) b) Dv50 = 3 µm (FP3)

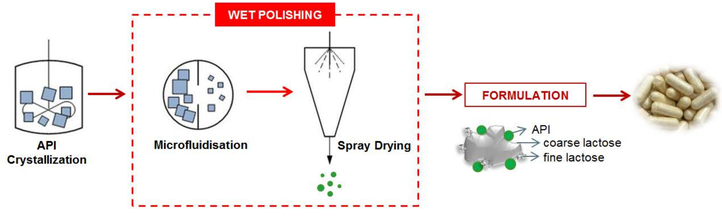


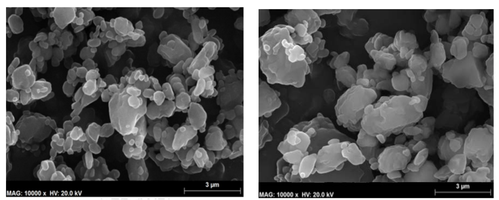
Figure 1. Schematic representation of the Wet Polishing (WP) technology.

- **B) API Characterization**
  - PSD by LD; SEM; mDSC; XRPD; mercury intrusion; BET; Karl Fischer; GC.
- **C) Blending & Formulation Characterization**
  - 2 blends were performed with:
    0.4 % (w/w) of FP2 and FP3 + 4% Lactohale 300 + 95.6% Respitose ML001
  - Cohesion-adhesion balance (CAB) by atomic force microscopy (AFM)
- **D) Performance**
  - NGI using Plastiape (60L/min; 4 kPa, 4L) with HPMC#3 capsules, 12.5 mg of formulation.

RESULTS & DISCUSSION

- **API Engineering and Characterization**

FP2 and FP3 presented similar physicochemical properties (**Table 1**), regardless of the differences in PS. The FP3 particles had higher rugosity, which was supported by SEM – **Figure 2**. According to the XRPD and mDSC data, both FP maintained the polymorphic Form I.



a) FP2 **b) FP3**

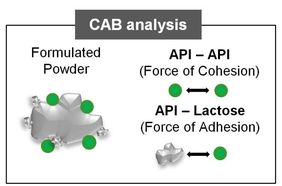
Figure 2. SEM micrographs of two FP samples (10000x).

Table 1. Physicochemical characterization of two FP samples.

	FP2	FP3
Median particle size (µm)	2.0	3.0
Specific Surface area by BET[α] (m^2/g)	4.85	4.81
Rugosity factor	1.5	2.1
Skeletal density (g/mL)	0.82	0.84
Bulk density (g/mL)*	0.31	0.32
Porosity (%)	62	62
Moisture (% w/w)	0.06	0.06
Solvents Content (ppm)[¶]	680	681

* at 3.4 kPa; [¶]Total residual solvents as determined by GC
[α] Brunauer-Emmett-Teller method

- **Formulation Characterization**



The CAB ratio was similar for both powders, although slightly lower for FP3, which might be related to the higher rugosity / number of API-lactose contact points **(Figure 3).**

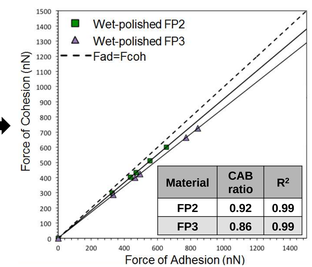


Figure 3. Cohesive-adhesive balance of FP2 and FP3 relative to lactose monohydrate.

- **Performance**

The aerodynamic performance (AP) results obtained for both formulations (containing FP2 and FP3) showed that, the formulated FP3 powder yielded a FPF_{ED}(%) (< 5 µm) about 10 percentage points higher than that of FP2 – **Figure 4** – not what would be expected from a formulation with a higher MMAD. The deposition of FP3 particles was mainly observed in stages 2, 3 and 4, probably due to the higher PS and lower particle cohesion.

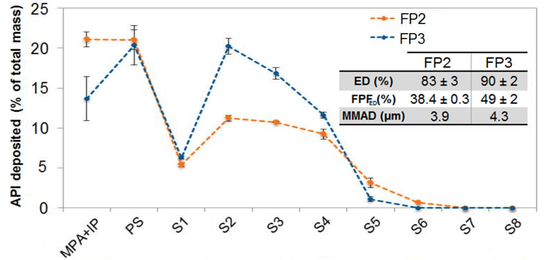


Figure 4. NGI aerodynamic deposition of FP2 and FP3 where ED, FPF, MMAD, MPA, IP, PS and S1 stand for emitted dose, fine particle fraction, mass median aerodynamic diameter, mouthpiece adaptor, induction port, pre-separator and stage 1 respectively.

CONCLUSIONS

Both FP powders presented similar physicochemical properties and CAB-ratios, hence similar AP was expected. However, distinct aerodynamic profiles were observed, resulting in a higher FPF_{ED}(%) for the FP3 possibly due to an increase in PS which also caused a reduction in the powder cohesion.

Although a small PS is required for a deep lung deposition (typically < 5 µm), in some cases, a small increase in PS benefits the overall amount of drug delivered. According to this work, it is clear that obtaining particle size distributions with a high degree of precision is a pre-requisite to studies investigating changes in deposition performance. The data also indicates that WP enables the production of different PS without impacting the remaining physicochemical properties.

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