Optimization of formulation and process parameters for the manufacture of inhalable composite particles by spray-drying: effect of two API concentrations on the *in vitro* aerodynamic performance

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INTRODUCTION

Dry powders for inhalation are typically formulated using a carrier-based approach, However, limitations such as poor drug delivery uniformity are frequently observed. Moreover, since combination therapies are gaining momentum for the treatment of respiratory diseases, the addition of a second API further increases the complexity of the formulation. In order to overcome these challenges, the engineering of carrier-free composite particles in which the API is embedded within an excipient matrix is a suitable alternative, with spray drying (SD) being the preferred particle engineering technology.

The main goals of this work were:

1) First to optimize a composite particle formulation composition and SD process parameters in order to improve the drug delivery and;

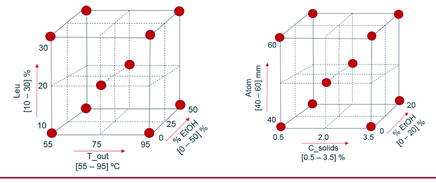
2) To assess the influence of the API concentration on the aerodynamic performance and solid state properties of the best performing composite particle formulation in a combination therapy including fluticasone propionate (FP) and salmeterol xinafoate (SX).

METHODS

1. Optimization of formulation and SD process parameters

A formulation comprising trehalose and L-leucine in water and water:ethanol mixtures was used to prepare spray dried composite particles

- **Two DoEs**



2. Influence of API concentration

Trehalose:leucine (80/20) was used as excipients at 2% (w/w) of solids content in a water:ethanol (50/50) solvent system

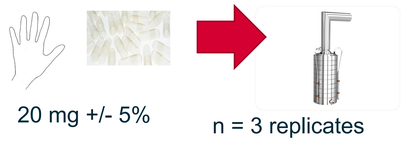
Table 1 – API dose per 20 mg of formulation

Tests	FP (µg)	SX (µg)
1	0	50
2	150	50
3	250	50
4	500	50
5	500	0

3. Analysis

- Scanning Electron Microscopy (SEM);
- PSD by laser diffraction;
- X-ray powder diffraction (XRPD);

- **Aerodynamic performance evaluation**



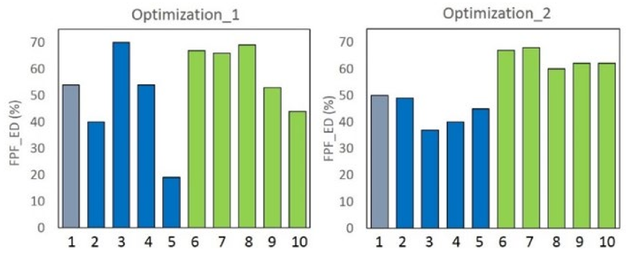
20 mg +/- 5%

n = 3 replicates

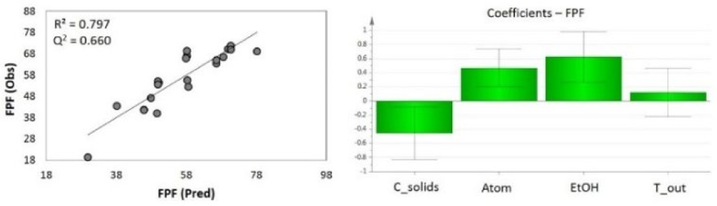
RESULTS AND DISCUSSION

1. Optimization of formulation and SD process parameters

***In-vitro* Aerodynamic performance**



Statistical Analysis – Global model



Powder solid state and aerodynamic performance evaluation

- Amorphous trehalose and peaks of crystalline leucine were detected;
- Inhalable powders with distinct PS, morphology, bulk density and aerodynamic performance were successfully produced

Statistical analysis

- The statistical analysis of the fine particle fraction (FPF, output), in relation to the formulation and process parameters input variables enabled a good prediction model for a wide range.
- In order to improve the FPF over the emitted dose ($FPF_{(ED<4.4\mu m)}$), the solids concentration should be decreased and the atomization gas flow rate, outlet temperature and ethanol percentage in the solution should be increased, the leucine fraction had no significant impact in the performance.

A trehalose/leucine system at a ratio of 80/20% w/w with a solvent mixture of water/ethanol (50/50% w/w) was selected due to its improved ($FPF_{(ED<4.4\mu m)}$). The T_out for the next trials was set at 70ºC to avoid particle fragmentation during SD

2. Influence of API concentration on the aerodynamic performance and solid state properties of single and combination inhalable composite particles

Tests	FP (%)	SX (%)	X_{50} (µm)	Span
1	2.5	0	1.3	2.0
2	0	0.25	1.2	1.9
3	0.5	0.25	1.2	1.9
4	1.25	0.25	1.2	1.9
5	2.5	0.25	1.3	1.9

Table 1: X_{50} and span of all tests.

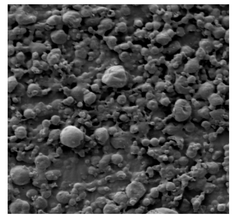


Figure 1: SEM image of Test 3.

- The SEM micrographs showed that the morphology of each powder is similar, presenting spherical and slightly shriveled particles (Figure 1), in agreement to what was previously observed with the placebo powders [4].
- All powders presented Dv50 values between 1.2 and 1.3 µm, which are in agreement with the SEM images. The PSD results seem to be independent of the FP concentration in the trehalose:leucine excipient matrix. (Table 1).

Tests	ED (%) (SD)	FP FPD (µg) (SD)	$FPF_{(ED<4.4\mu m)}$ (SD)
1	101.5 (0.6)	247.7 (11.9)	48.8 (2.6)
2	96.3 (2.2)	31.5 (1.0)	65.4 (0.7)
3	95.8 (1.6)	81.0 (2.7)	56.4 (2.5)
4	99.6 (0.9)	157.8 (9.5)	52.8 (2.7)
5	100.9 (0.4)	268.9 (2.4)	48.6 (0.6)

Table 2: ED, fluticasone propionate FPD and overall powder $FPF_{(ED<4.4\mu m)}$ of all tests.

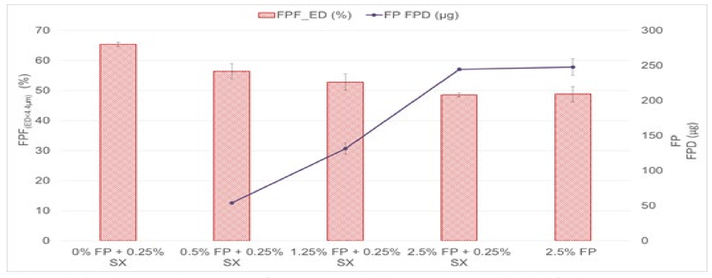


Figure 2: In vitro aerodynamic performance as $FPF_{(ED<4.4\mu m)}$ and FP FPD (µg).

- The increased addition of FP shows a decrease in the $FPF_{(ED<4.4\mu m)}$ which may be related to the interfacial properties of the powder that may be more cohesive due to the addition of APIs and/or potential differences in other particle properties that might not yet been analyzed.
- In terms of ED, all trials yielded an ED above 96%. Regarding the FP fine particle dose (FPD) a significant increase was observed as a function of the FP concentration.
- In previous work [5], in a single therapy approach similar trends were observed, namely a reduction of $FPF_{(ED<4.4\mu m)}$ with FP concentration, while still enabling higher API FPD.
- In regards to the solid state analysis, similar results to the placebo were obtained: as already described in the literature, during spray drying leucine typically precipitates and forms a crystalline shell at the particle surface, resulting in improved powder dispersibility [6].

CONCLUSIONS

Using a composite system approach for the formulation of combination therapies is beneficial in order to guarantee the homogeneity of the API in the excipient matrix and for expending dose ranging.

REFERENCES: [1] Yadav N, Lohani A: Dry powder inhalers: A review. *Indo Global Journal of Pharmaceutical Sciences* 2013, 3(2): 142-153; [2] Healy AM, Amaro MI, Paluch KJ, Tajber L: Dry powder for oral inhalation free of lactose carrier particles. *Advanced Drug Delivery Reviews* 2014, 75: 32-52; [3] Nandiyanto ABD, Okuyama K: Progress in developing spray-drying methods for the production of controlled morphology particles: From the nanometer to submicrometer size ranges. *Advanced Powder Technology* 2011, 22(1):1-19; [4] Moura C, Vicente J, Palha M, Neves F, Aguiar-Ricardo A, Costa E: Screening and optimization of formulation and process parameters for the manufacture of inhalable composite particles by spray-drying. *Drug Delivery to the Lungs* 2014: 74-77; [5] Fernando DA, Moura C, Campos S, Costa E, Neves F: Impact of the API concentration on the solid state properties and aerodynamic performance of composite particles for DPIs. *Drug Delivery to the Lungs* 2016: 135-38; [6] Feng AL, Boraey MA, Gwin MA, Finlay PR, Kuehl PJ, Vehring R: Mechanistic models facilitate efficient development of leucine containing microparticles for pulmonary drug delivery. *International Journal of Pharmaceuticals* 2011: 156-63; [7] Le VNP, Thi THH, Robins E, Flament MP: In vitro evaluation of powders for inhalation: The effect of drug concentration and particle detachment. *International Journal of Pharmaceutics* 2012: 44-49.