Designing a Model Dry Powder Formulation for Aptar Prohaler®: The Influence of Fine Lactose and Force Control Agent

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INTRODUCTION

A major challenge in dry powder inhaler (DPI) design is the balance between inhaler resistance and flow rate. The DPI can be divided in high, low and medium resistance based on their resistance to inhaled airflow [1] with patients inhaling faster through low-resistance devices and slower through high-resistance devices, so to generate similar pressure drops [2].

Generally, DPI devices fall into three categories, single-unit dose devices, multi-dose reservoir devices and multiple-unit dose devices [1]. High resistance multi-dose inhaler devices are usually prescribed to Chronic Obstructive Pulmonary Disease (COPD) and asthma patients regardless of the severity of their disease, due to their easier handling and the lower peak inhalation flow (PIF) required for their operation [3].

When developing a formulation for a DPI, it is important to remember that fluidization, de-aggregation and aerodynamic particle size distribution (APSD) of the emitted dose (ED) are controlled by the complex relationship between the design of the inhaler device and the physicochemical properties of the powder formulation [4]. In addition drug particles interaction, due to formulation/device combination, influences powder dissolution and, consequently, drug bioavailability [5].

In this study, the influence of the concentration of fine lactose and the presence of a force control agent (FCA) to decrease inter-particulate interactions of micron-sized drug particles was assessed in designing a model formulation for Aptar Prohaler® (Aptar Pharma, FR), a novel high resistance multi-dose inhaler. Moreover, the correlation between formulation composition and dissolution rate after aerosolization was studied *in vitro*.

METHODS

Dry powder blend formulations were produced employing Fluticasone Propionate (FP) as model drug. FP was blended (0.8% w/w) with coarse lactose ($Dv_{,50}$ 74 μm) to manufacture eight different formulations comprising of different percentages (0, 2.5%, 5% and 10% w/w) of fine lactose ($Dv_{,50}$ 3 μm) and/or a FCA (magnesium stearate) at fixed concentration of 1% w/w. Formulations were blended using Turbula mixer (WAB, Switzerland). The blends were then loaded into strips comprising of 5 mg of powder (RSD 1–2.8%) per pocket using an Omnidose TT (Harro Höfliger, Germany). Strips were subsequently loaded into the Aptar Prohaler® for evaluation.

Aerodynamic particle size distribution (APSD) was tested using a Next Generation Impactor (NGI, Copley Scientific, UK) connected to a critical flow controller and a vacuum pump (Copley Scientific, UK). In order to achieve a pressure drop of 4 kPa across the inhaler, flow rate was set at 39 $L \cdot min^{-1}$ for 6.2 seconds set using a flow meter and flow controller (Copley Scientific, UK).

Dissolution measurements were carried out on the impactor stage mass (ISM) of three formulations containing the FCA and increasing percentages of fine lactose, collected through an aerosol dose collection system designed by Nanopharm [6]. An adapted USP Apparatus V, also known as Paddle over Disk, filled with 300 mL of phosphate buffer and 0.2% w/v sodium dodecyl phosphate media at 37°C with a stirring speed of 75 rpm was employed. Aliquots of 3 mL were withdrawn at 2.5, 5, 10, 15, 20, 25, 30, 60, 120, 180, and 240 min time intervals.

Drug collected was analysed by high performance liquid chromatography and data analysis was performed using R statistical software. Tukey's multiple comparison test using *post-hoc* analysis of variance was employed and for p-value ≤0.05 differences were considered statistically significant.

RESULTS AND DISCUSSION

All formulations manufactured presented an active pharmaceutical ingredient content >90% of the expected value and were homogenous.

Table 1 shows the results obtained from the APSD analysis. Emitted Dose (ED) was higher when the FCA was present. The lowest Mass Median Aerodynamic Diameter (MMAD) was reported by formulation #3, whereas the highest Fine Particle Mass (FPM) was shown by #4. Both these blends comprised the FCA. MMAD and FPM statistically changed when FCA was present.

The general deposition of FP aerosolized with Aptar Prohaler® in presence of the FCA was higher in stages 3 to 5 of the NGI compared to the amount observed in presence of only fine lactose. However, the APSD analysis highlighted how, for the formulations without FCA (#1, 6, 7 and 8), increasing the percentage of fine lactose increased the deposition in stages 3 to 5 of the NGI and decreased the FP deposition in the pre-separator. This was presumably due to reduced inter-particulate interactions between lactose and micronized FP. This effect of the fine lactose significantly increased the FPM only in the formulations without FCA [7].

Table 1.

Aerodynamic performance parameters for the eight formulations manufactured (n=3, mean values and standard deviation in parenthesis).

Formulation # (Fine lactose, FCA % w/w)	MMAD (µm)	GSD	FPM <5 µm (µg)	ED (µg)	ISM (µg)
1 (0%, 0%)	2.92 (0.24)	2.20 (0.05)	5.50 (0.88)	26.94 (3.41)	6.78 (1.13)
2 (0%, 1%)	2.32 (0.03)	2.31 (0.25)	10.97 (1.28)	31.17 (1.70)	12.60 (1.33)
3 (2.5%, 1%)	2.10 (0.15)	2.02 (0.01)	12.97 (1.08)	29.77 (2.67)	14.01 (1.13)
4 (5%, 1%)	2.40 (0.11)	2.02 (0.08)	14.05 (0.80)	32.86 (1.52)	15.85 (0.41)
5 (10%, 1%)	2.78 (0.03)	1.97 (0.01)	13.83 (1.36)	30.86 (2.12)	16.50 (1.55)
6 (2.5%, 0%)	2.74 (0.01)	2.11 (0.01)	8.79 (1.16)	30.21 (2.11)	10.54 (1.35)
7 (5%, 0%)	2.61 (0.14)	2.08 (0.05)	9.46 (0.28)	27.32 (1.13)	11.08 (0.29)
8 (10%, 0%)	2.76 (0.06)	1.99 (0.04)	9.99 (0.86)	27.06 (1.49)	11.87 (1.07)

Whereas the four formulations with FCA showed the best performance (fine particle fraction up to 45%) in comparison to formulations without FCA, no significant difference was observed within the FCA formulations. Dissolution profiles of the ISM of formulation #2, 4 and 5 (Figure 1) were perfectly overlaid showing how these formulations were following the same dissolution kinetics. Therefore, no effect could be observed for fine lactose in presence of the FCA.

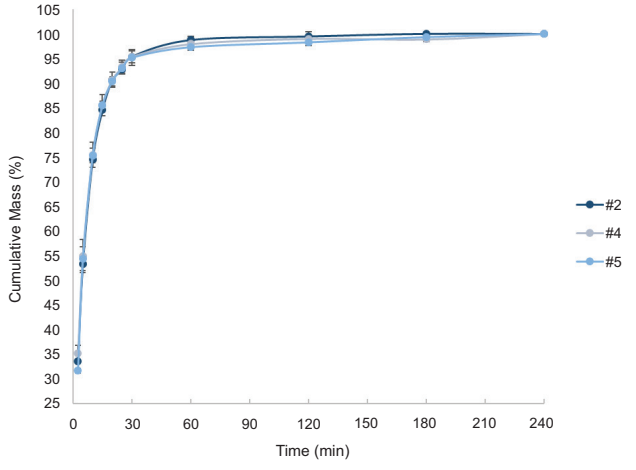

Figure 1. **Cumulative mass (%) for dissolution profiles of three formulations comprising the FCA and increasing percentages of fine lactose (n=3, mean values and bars represent standard deviation).**

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CONCLUSIONS

This study highlighted that the use of a FCA, in a model blend formulation aerosolized with Aptar Prohaler®, positively increased the FPM and determined a lower MMAD. Moreover, no differences were observed between the blends with the FCA even increasing the fine lactose content, whereas a higher amount of fines determined higher FPM when the FCA was not present.

In conclusion, the presence of a FCA proved to be fundamental in positively influencing the aerodynamic performance and it should be taken into consideration when developing a blend formulation for Aptar Prohaler®.

REFERENCES

1. Ibrahim M *et al.*: Inhalation drug delivery devices: technology update. *Med Dev Evid Res* 2015, 8: 131–139.

2. Clark A *et al.*: The confusing world of dry powder inhalers: It is all about inspiratory pressures, not inspiratory flow rates. *J Aerosol Med Pulm Drug Deliv* 2020, 33(1): 1–11.

3. Chrystyn H *et al.*: The dry powder inhaler features of the Easyhaler that benefit the management of patients. *Expert Rev Respir Med* 2020, 14(4): 345–351.

4. Shur J *et al.*: Effect of device design and formulation on the *in vitro* comparability for multi-unit dose dry powder inhalers. *AAPS J* 2015, 17(5): 1105–1116.

5. Bäckman P *et al.*: Advances in inhaled technologies: Understanding the therapeutic challenge, predicting clinical performance, and designing the optimal inhaled product. *Clin Pharm Ther* 2014, 95(5): 509–520.

6. Price R *et al.*: Development of an aerosol dose collection apparatus for *in vitro* dissolution measurements of orally inhaled drug products. *AAPS J* 2020, 22(47): 47–56.

7. Kinnunen H *et al.*: An investigation into the effect of fine lactose particles on the fluidization behaviour and aerosolization performance of carrier-based dry powder inhaler formulations. *AAPS J* 2014, 15(4): 898–909.