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Customized Resistance of a Capsule-based Dry Powder Inhaler

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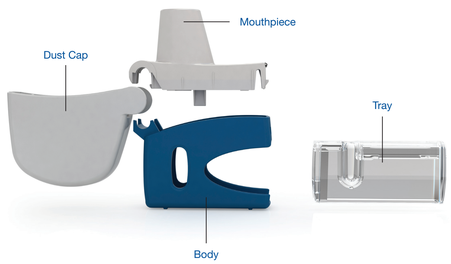
INTRODUCTION

Dry powder inhalers (DPIs) are combination products in which the device and formulation together comprise a delivery system intended to ensure the drug(s) reaches the lungs following oral inhalation. There are different schools of thought regarding which device resistance (high, low or something in-between) is most appropriate for ensuring the optimal inspiratory air flow rate [1,2].

The simplicity of the device design and its resulting handling characteristics influence patient adherence [3]. Further, regulatory recommendations in most countries emphasize that generic DPI products should have similar handling characteristics, resistance, and performance to the innovator product [4] .In this study, the currently marketed PowdAir Plus DPI device (H&T Presspart, Figure 1) was modified to achieve a medium resistance (corresponding to a flow rate of ~ 72 lpm at a pressure drop of 4 kPa across the device) and a low resistance (corresponding to a flow rate of ~ 100 lpm at 4 kPa across the device) and the aerosol performance was compared to the current device. A modular design approach was taken to enable modifications to the individual components to understand the influence of changes in dimensions on the air flow rate (resistance) and turbulence created within the device.

Figure 1: PowdAir Plus device



METHODS

Two sets of experiments were performed using marketed samples of (i) salbutamol (albuterol, 200 mcg Asthalin Rotacaps, Cipla Ltd, India), and (ii) budesonide (200 mcg, Budecort 200 Rotacaps, Cipla Ltd, India). The blends were manually transferred into size 3 HPMC capsules (Capsugel,France) at the H&T Presspart Inhalation Product Technology Center in the UK. To achieve the target air flow resistances, modified modular PowdAir Plus DPI prototypes were manufactured using 3D printing at the H&T Presspart New Product Development Center in Spain. A modular prototype (Nominal, Figure 2) of the marketed PowdAir Plus DPI was also 3D printed and tested with salbutamol 200 mcg capsules to establish equivalence. The prototypes were manufactured according to a design of experiments matrix

The flow rate corresponding to 4kPa pressure drop across each modular prototype inhaler and powder evacuation were tested using a critical flow controller and flow meter (TPK 100i-R and DFM200, respectively, Copley Scientific, UK) and the APSD was tested using Next Generation Impactor (Copley Scientific, UK) .

Figure 2:
Nominal prototype

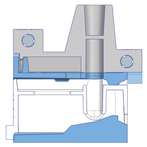


Figure 3:
Prototype 1 with lateral slits in capsule chamber

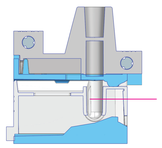
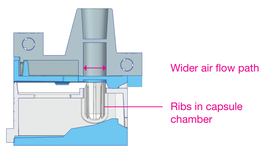


Figure 4:
Prototype 2 with modified mouthpiece and capsule chamber



RESULTS AND DISCUSSION

Two different approaches were selected to achieve medium and low resistance versions. Modifications were made to ensure the capsule remains in the capsule chamber and does not enter the mouthpiece. Lateral slits were introduced in the capsule chamber to increase turbulence and air flow to achieve the medium resistance prototype (Prototype 1). Capsule chamber diameter was increased (lateral ribs were introduced in the capsule chamber to maintain the capsule position)and mesh, mouthpiece and capsule chamber configuration were optimized to achieve the low resistance prototype (Prototype 2).

Table 1 – Flow Rate and Capsule Evacuation at 4 kPa Pressure Drop

Device	Air Flow Rate (n=5)		Evacuation (n=5)	
	lpm	SD	%	SD
PowdAir Plus	55	3.6	87	0.06
PowdAir Plus Prototype (Nominal)	55	4.3	76	0.05
Prototype 1 (Medium Resistance)	72	0.9	79	0.07
Prototype 2 (Low Resistance)	100	4.7	86	0.05

Table 2 – APSD at an Air Flow Rate Corresponding to 4kPa Pressure Drop

Device	Salbutamol (n=3)			Budesonide (n=3)		
	% FPF (SD)	% Mass Balance (SD)	MMAD (SD)	% FPF (SD)	% Mass Balance (SD)	MMAD (SD)
PowdAir Plus	26.6 (1.2)	79.4 (0.4)	3.3 (0.1)	22.2 (1.4)	85.4 (3.1)	3.8 (0.1)
Prototype Nominal	29.1 (1.3)	77.4 (2.0)	3.2 (0.01)	Unavailable		
Medium Resistance	37.3 (1.1)	75.0 (0.8)	2.7 (0.1)	28.6 (1.2)	82.7 (1.1)	3.3 (0.1)
Prototype 2 Low Resistance	36.5 (0.9)	77.8 (1.6)	2.9 (0.1)	27.7 (0.9)	79.9 (3.3)	3.3 (0.04)

FPF (Fine Particle Fraction): is calculated as mass of particles less than 5 microns, divided by the Mass Balance, expressed as %.

Mass Balance: Sum of the drug deposited from Induction port to MOC (Filter) stages in the NGI, expressed as % of the capsule's labelled drug content.

MMAD: Mass Median Aerodynamic Diameter.

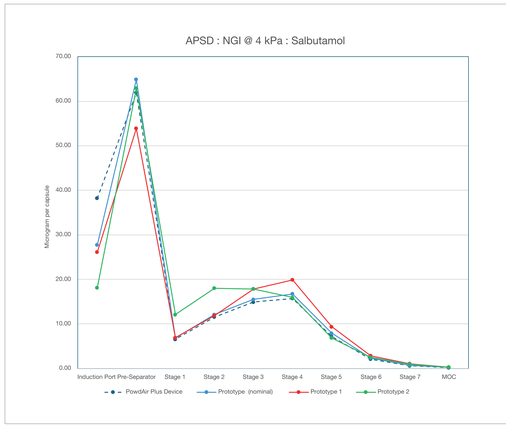


Figure 5: APSD Salbutamol

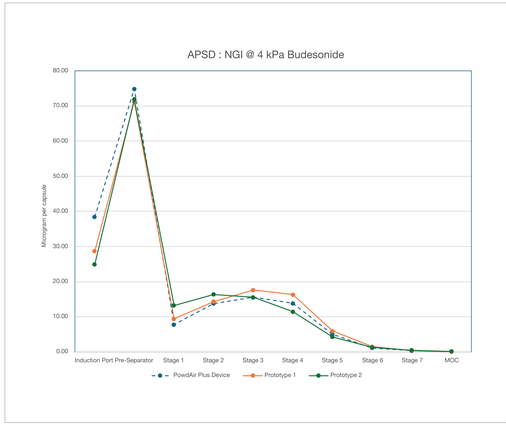


Figure 6: APSD Budesonide

The effect of the design changes in Prototypes 1 and 2 can be seen in their significantly improved aerosol deaggregation, students T-test, $p<0.05$ (Figure 5 and Figure 6) as measured by increased % FPM and MMAD compared to the PowdAir Plus device.

CONCLUSIONS

Understanding the influence of specific variables is crucial in inhalation device development. These variables can be investigated using 3D printed modular device prototypes. The configuration of the air flow path through the device and the turbulence this creates significantly influences device resistance and the ability of the inhaler to deaggregate powder formulations and achieve efficient pulmonary drug delivery. The study demonstrated that the resistance and performance of inhaler design can be significantly ($p<0.05$) changed to meet the needs of specific drug products.

References

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