INVESTIGATION OF DRY POWDER INHALATION AEROSOLISATION PERFORMANCE AT DIFFERENT FLOW RATES FROM A CONVENTIONAL CAPSULE-BASED INHALER DEVICE

Imran Y Saleem[1], Rajith KR Rajoli[1], Brian E Jones[2], Fernando Diez[2]

[1]School of Pharmacy & Biomolecular Sciences, Liverpool John Moores University, Byrom Street, Liverpool L3 3AF, UK.
[2]Qualicaps Europe, S.A.U., Avda. Monte Valdelatas, 4, 28108 Alcobendas, Madrid, Spain

INTRODUCTION

- Dry powder inhalers (DPIs) have become increasingly common in the treatment of respiratory diseases [1,2].
- Passive devices have involved the use of inhalation grade Hypromellose (hydroxypropyl methylcellulose [HPMC]) capsules.
- DPIs are generally required to be used at a flow rate of 60 L/min for effective pulmonary deposition, which may not be appropriate for those with lung diseases.
- In addition, capsule-based DPI are intended for treatment over a 4-week period and storage conditions can influence the interaction of powder with the capsule affecting the aerosolisation drug deposition and hence reproducibility of inhalation dose and treatment outcome.

AIM

- **To investigate the aerosolisation properties of dry powder formulations composing of inhalation grade lactose and micronized salbutamol, in HPMC (size 3) capsules (Qualicaps®) using a standard resistance 2-pin inhaler device at different flow rates (30 and 60 L/min).**

METHODS

Preparation of inhalation grade lactose & powder mix:

- Inhalation grade lactose (DFE Pharma, The Netherlands) was collected on 90 µm sieve, at amplitude 40 for 10 minutes, and mixed with micronized salbutamol (Lusochimica, Spain) (50:1 w/w) using a Turbula® orbital mixer (Glen Mills, Clifton, New Jersey) for 30 min at 46 rpm [3,4]
- 20 ± 1 mg of blended powder was loaded into HPMC size 3 capsules and stored at 22 °C and 40 % RH over 4 weeks (n=6).

In vitro drug deposition:

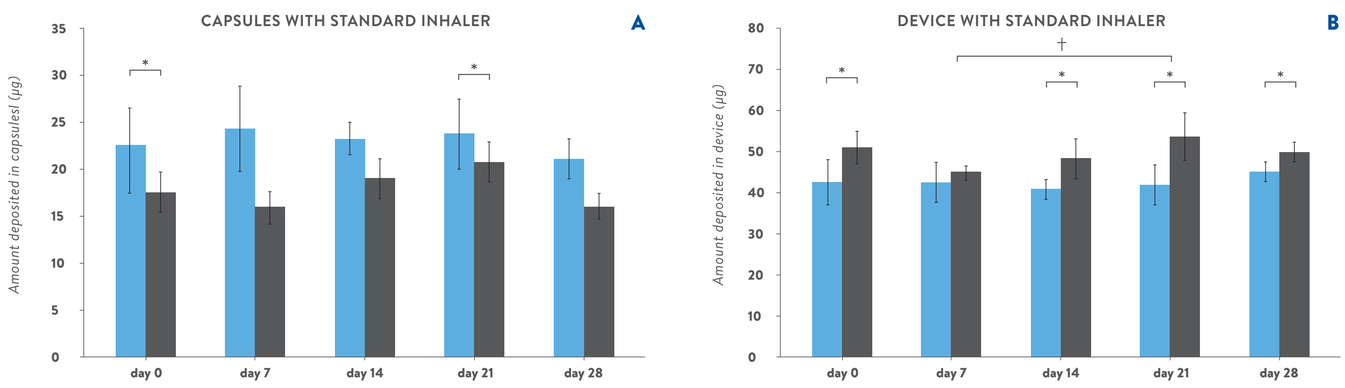
- The capsules were dispersed through a 2-pin DPI inhaler (Plastiape S.p.a Italy) into a NGI cascade impactor (MSP Corporation, Shoreview, MN) at flow rates of 30 & 60 L/min (n=6). Repeated at weekly intervals for 4 weeks.
- Mass of drug remaining in capsule/device, Emitted Dose (ED), Fine Particle Dose (FPD), Fine Particle Fraction (FPF) and the Mass Mean Aerodynamic Diameter (MMAD) were measured.

Analysis of Salbutamol Sulphate:

- HPLC (Agilent) using a Zorbax® 5 µm Eclipse-XDB-C18 (phenomenex, UK).
- The mobile phase: 0.25% (w/v) 1-heptane sulphonic acid sodium salt and methanol. The flow rate: 1 mL/min, inj. Vol.: 10 µL, temp: 25 °C and wavelength 215 nm, retention time: 3.7 min.

RESULTS & DISCUSSION

Figure 1

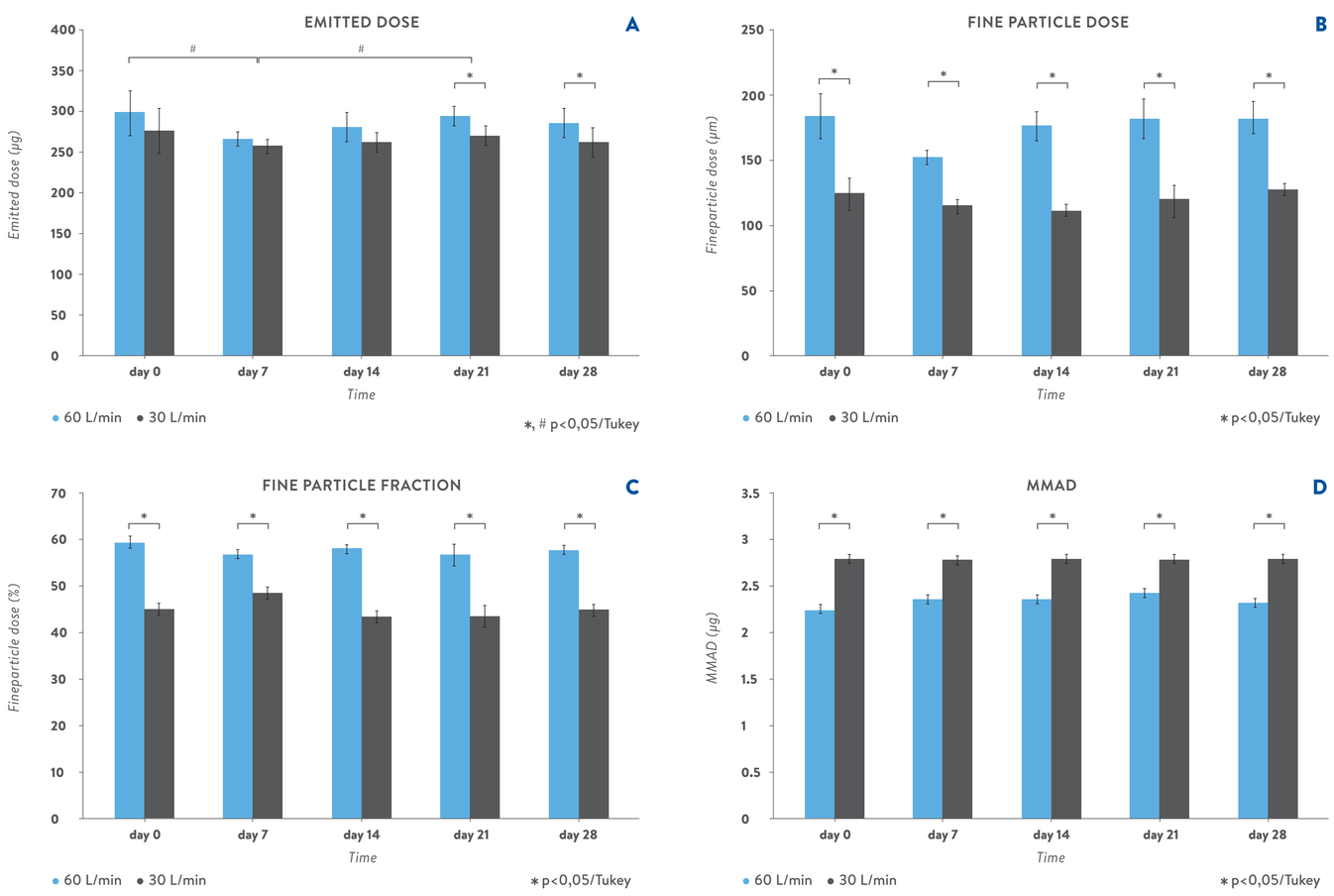


COMPARING CAPSULES AND DEVICE

- Less deposition of the drug was observed in capsules with 30 L/min compared to 60 L/min (**Figure 1A**).
- Neither a significant increase nor decrease can be observed at both the flow rates with time.
- A significant difference in the deposition of salbutamol in the standard inhaler was observed between the flow rates (**Figure 1B**).
- There is no change in deposition with time except on day 7 and 21 for 30 L/min.

Figure 1: *Deposition of salbutamol sulphate remaining in capsules (A) and device (B) following aerosolisation at 60 L/min and 30 L/min from a 2-pin standard inhaler (Mean ± SD, n=6) * - indicates significance between 30 and 60 L/min. # - indicates significance between different time points at 60 L/min. † - indicates significance between different time points at 30 L/min.*

Figure 2



COMPARING EMITTED DOSE, FINE PARTICLE DOSE, FINE PARTICLE FRACTION & MMAD

- There was no significant difference in the deposition of salbutamol across different weeks of analysis (**Figure 2**).
- Except for the ED day 0 to day 7 and day 7 to day 21 at 60 L/min (**Figure 2A**).
- However there seems to be a significant difference between the different flow rates used – 30 and 60 L/min for ED, FPD, FPF and MMAD (**Figure 2A-D**).
- A higher flow rate (60 L/min) indicated more FPD and FPF with lower MMAD when compared with the lower flow rate (30 L/min) (**Figure 2B-D**).
- There is no change in deposition with time except on day 7 and 21 for 30 L/min.

Figure 2: *Emitted dose (µg) (A), Fine particle dose (µg) (B), Fine particle fraction (%) (C), MMAD (µm) (D) of salbutamol sulphate at 30 and 60 L/min from a 2-pin standard inhaler (Mean ± SD, n=6). * - indicates significance between 30 and 60 L/min. # - indicates significance between different time points at 60 L/min.*

CONCLUSIONS

- **The results indicate significant differences in powder retention with higher deposition at 60 L/min within capsules and 30 L/min in the device.**
- **In addition, the ED, FPD, FPF was significantly greater at 60 L/min compared to 30 L/min at each time point.**
- **This demonstrates the important relationship between inhalation, therapeutic dose and lung deposition.**
- **However, despite these differences there was very little significant variability when comparing each flow rate over time. Hence, there is very good dose reproducibility which is important for ensuring equivalent doses are administered during the treatment cycle.**

REFERENCES

[1] Smith IJ et al. J Aerosol Med Pulm Drug Deliv 2010; 23: S25-37.
[2] Chan HK. J Aerosol Med 2006; 19: 21-27.
[3] Saleem IY et al. Int J Pharm 2015; 492: 258-63
[4] Saleem I et al. Drug Dev Ind Pharm 2008; 34: 1002-10.

ACKNOWLEDGEMENTS

Dr Imran Saleem would like to acknowledge Qualicaps Europe S.A.U., Spain for funding this work.