IMPACT OF CAPSULE TYPE ON THE AERODYNAMIC PERFORMANCES OF A FLUTICASONE PROPIONATE-BASED DRY POWDER UNDER OPTIMAL AND SUBOPTIMAL INHALATION FLOW RATES

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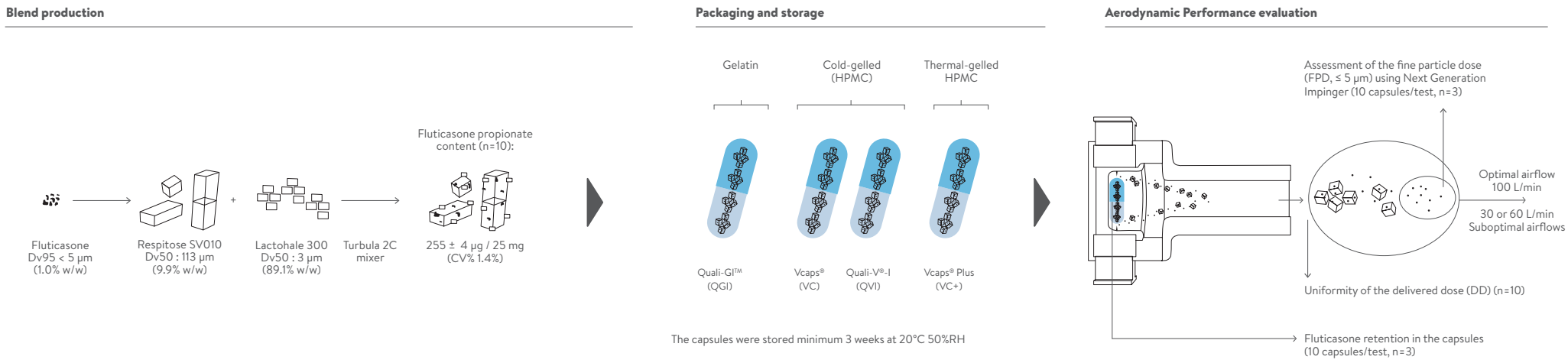
INTRODUCTION

In the case of capsule-based DPIs, the capsule is an important parameter, not only in the packaging of the formulation, but also in the powder aerosolisation and the dispersion of the micronized drug from the carrier during inhalation [1]. We performing studies on low drug-dosage dry powders (i.e. a binary blend with coarse lactose and a ternary blend with coarse and fine lactose) using formoterol fumurate dihydrate (12 µg/24 mg) [2,3,4]. The results showed better aerodynamic performances at optimal inhalation flow rate (i.e. 100 L/min through Axahaler® DPI) with cold-gelled hypromellose (HPMC) capsules (Quali-V®-I and Vcaps®) in comparison with gelatin capsules (Quali-G™ or hard gelatin capsules for DPI from Capsugel®) and thermal-gelled HPMC capsules (Vcaps® Plus). Moreover, in suboptimal conditions, cold-gelled HPMC capsules have shown no significant differences in fine particle dose (FPD) between 60 and 100 L/min, contrary to gelatin capsules (thermal-gelled HPMC capsules were not tested). After exposure to a hot/humid environment, the FPD drastically decreased for each capsule type tested (cold-gelled HPMC and gelatin capsules).
The **aim of this work** was to evaluate the capsule impact in **a higher drug-dosage** dry powder using **fluticasone propionate (250 µg/25 mg)**, using different capsules in optimal and in the most relevant suboptimal use conditions *(i.e. suboptimal inhalation flow rates).*
The work evaluated **different capsules used in the inhalation field: *Quali-G™–I*** and ***Quali-V®-I*** from ***Qualicaps®*** for gelatin and cold-gelled HPMC capsules, respectively, and ***hard gelatin capsules for DPIs*** (HCG), ***Vcaps®*** and ***Vcaps® Plus*** from Capsugel® for gelatin, cold-gelled HPMC and thermal-gelled HPMC capsules, respectively. To evaluate only the impact of the capsule type, a ternary blend based on the same coarse and fine lactose used for the formoterol study was made. It was then packaged in the different capsule types under the same conditions, and the capsules were evaluated the same day by the same technician.

EXPERIMENTAL METHODS



RESULTS AND DISCUSSION

Under optimal airflow (i.e. 100 L/min)
DDs **Fig. 1A** and FPDs **Fig. 1B** were significantly lower with gelatin capsules than with cold and thermal-gelled HPMC capsules ($p < 0.05$, one-way ANOVA), with non-significant differences between HPMC capsules ($p > 0.05$, one-way ANOVA). However, thermal-gelled HPMC capsules showed a significantly higher fluticasone propionate retention in the capsules than gelatin and cold-gelled HPMC capsules ($p < 0.05$, one-way ANOVA), without significant differences between them ($p > 0.05$, one-way ANOVA) **Fig. 1C.**

Under suboptimal airflows (i.e. 30 and 60 L/min)
There were very high significant differences ($p < 0.001$, ANOVA) compared to the optimal airflow (i.e. 100 L/min) in terms of DDs **Fig. 2A** and FPDs **Fig. 2B** for each capsule. At a suboptimal airflow mainly performed by asthma and COPD patients i.e. between 60 and 89 L/min (21/53 and 13/29, respectively) in a similar low-resistance device [5]. We observed no or low significant differences for FPDs from the cold-gelled HPMC capsules ($p > 0.05$ for Vcaps® and $p < 0.05$ but $p > 0.01$ for Quali-V®-I between 60 and 100 L/min) **Fig. 2B**. In terms of capsule retention **Fig. 2C**, there were no significant differences for each capsule at suboptimal airflows in comparison to 100 L/min, except for Vcaps® and Vcaps® Plus at 30 L/min.

Figure 1 *Aerodynamic performances at optimal airflow (i.e. 100 L/min) of fluticasone propionate dry powder, packaged in different capsules: gelatin Quali-G™-I (QGI); cold-gelled HPMC Quali-V®-I (QVI) and Vcaps® (VC); thermal-gelled HPMC Vcaps Plus (VC+). The tests were performed using the Axahaler capsule-based DPI at the optimal airflow recommended by the European Pharmacopeia (i.e. 100 L/min for 2.4 sec). NS = non-significant differences ($p > 0.05$, ANOVA); $p < 0.05$ = significant differences (ANOVA).*

Figure 2 *Aerodynamic performances at suboptimal airflows in comparison to optimal airflow of fluticasone propionate dry powder, packazged in different capsules: gelatin Quali-G™-I (QGI); cold-gelled HPMC Quali-V®-I (QVI) and Vcaps® (VC); and thermal-gelled HPMC Vcaps Plus® (VC+). The tests were performed using the Axahaler capsule-based DPI at suboptimal airflows (i.e. 60 L/min for 4 sec and 30 L/min for 8 sec) in comparison to 100 L/min for 2.4 sec. NS = non-significant differences ($p > 0.05$, ANOVA); * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ = significant, very significant and extremely significant differences, respectively (ANOVA).*

Figure 1A UNIFORMITY OF DELIVERED DOSE

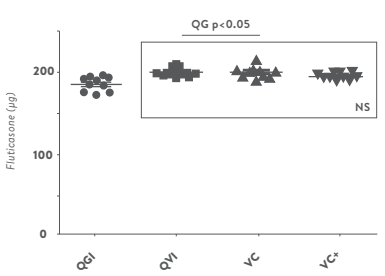


Figure 2A UNIFORMITY OF DELIVERED DOSE

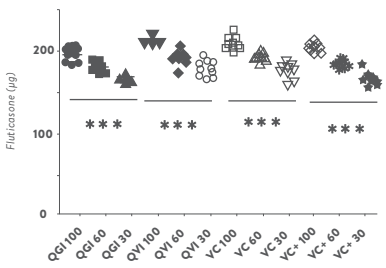


Figure 1B FINE PARTICLE DOSE

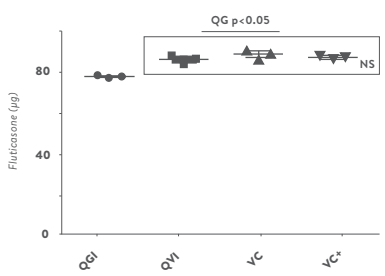


Figure 2B FINE PARTICLE DOSE

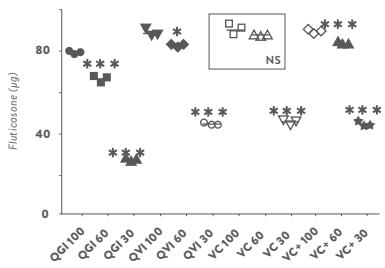


Figure 1C CAPSULE RETENTION

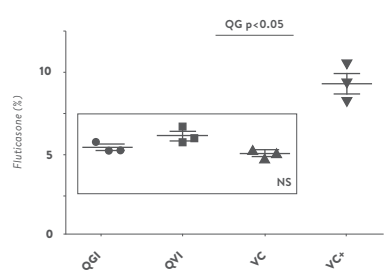
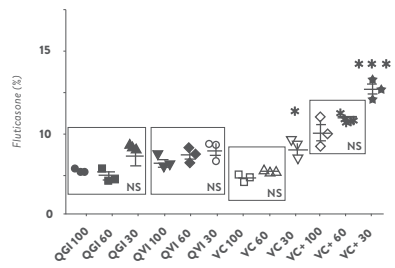


Figure 2C CAPSULE RETENTION



CONCLUSIONS

Cold-gelled HPMC capsules (Quali-V®-I and Vcaps®) showed the best results in terms of DD, FPD and capsule retention at optimal airflow in comparison to gelatin and thermal-gelled HPMC capsules in the cases of a low drug dosage dry powders using formoterol fumurate dihydrate and a higher drug dosage dry powder using Fluticasone propionate. Moreover cold-gelled HPMC capsules showed less impact on FPD at the suboptimal airflow usually performed by asthma and COPD patients in a similar low-resistance device (i.e. 100 and 60 L/min, respectively), in comparison to gelatin (as previously shown with low drug dosage) but also in comparison to thermal-gelled HPMC capsules.

REFERENCES

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