IMPACT OF DIFFERENT CAPSULES FOR DRY POWDER INHALERS ON THE AERODYNAMIC PERFORMANCES OF FORMOTEROL-BASED BINARY AND TERNARY BLENDS

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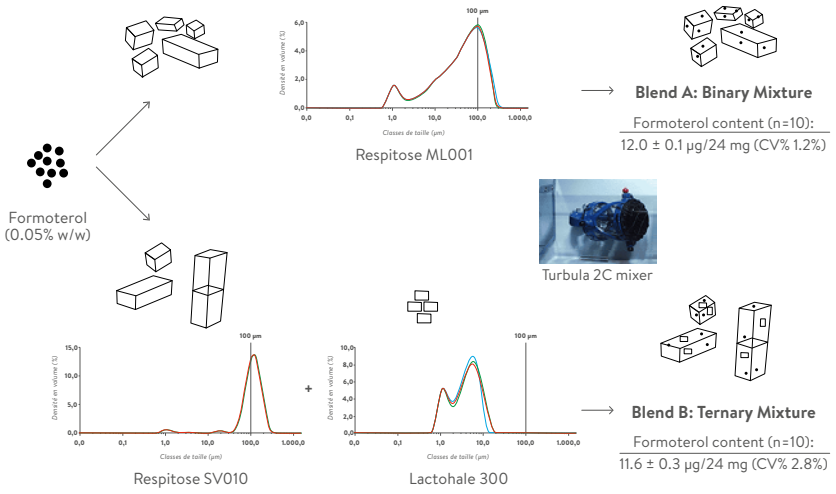
INTRODUCTION

In the case of capsule-based DPIs, the capsule plays a role not only in the packaging of the formulation, but also in powder aerosolization and the dispersion of the micronized drug from the carrier during inhalation [1]. Therefore, the choice of the capsule could be an important parameter in the performance of dry powder inhalers. However, few studies have been conducted on the impact of the kind of capsule on dry powder aerodynamic performance.

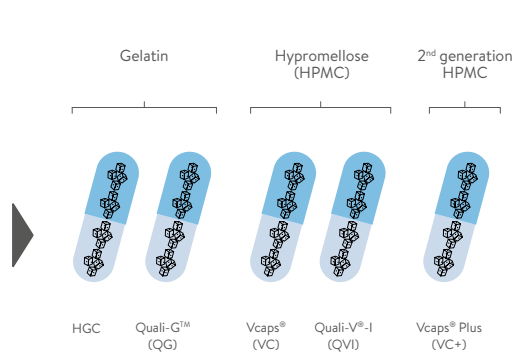
The aim of this work was to evaluate the impact on the aerodynamic performance of two dry powder formulations for inhalation based on formoterol by using different capsules in the Axahaler® capsule-based DPI. The study evaluated **different capsules used in, though not necessarily marketed for, the inhalation delivery**: ***Quali-G™*** and ***Quali-V®-I*** from Qualicaps® for gelatin and hypromellose (HPMC) capsules, respectively, and ***hard gelatin capsules*** (HGC), ***Vcaps®*** and ***Vcaps® Plus*** from Capsugel® for gelatin, HPMC and second-generation HPMC capsules, respectively. To be representative of the kind of dry powder found in the market for low-content drug formulations [2], **two dry powder formulations for inhalation** were produced using the same micronized formoterol, but with different lactoses for inhalation: milled lactose presenting a broad particle size distribution (PSD) to be used in a ***binary mixture***, and sieved lactose presenting a narrow PSD with the addition of 10% of fine lactose to be used in a ***ternary mixture***.

EXPERIMENTAL METHODS

Blend production

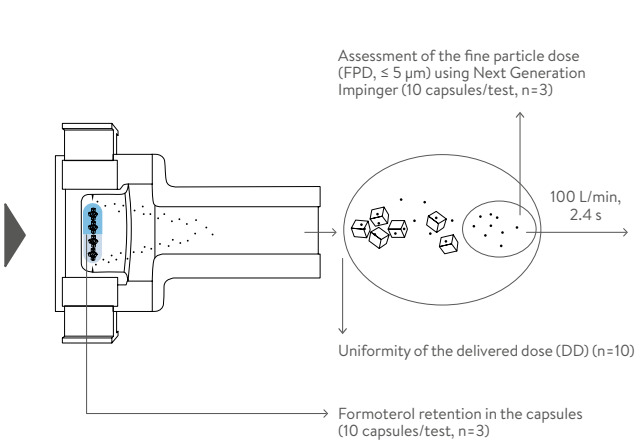


Packaging and storage



The capsules were stored minimum 3 weeks at 20°C 50%RH (usual environmental conditions used by Pharma companies for the production of dry powders for inhalation)

Aerodynamic Performance evaluation



RESULTS AND DISCUSSION

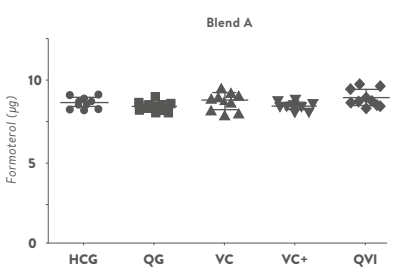
Similar trends were observed for the DD, FPD and formoterol capsule retention for both dry powders packaged in the different capsules. **The highest DD and FPD and the lowest formoterol capsule retention were observed with HPMC capsules such as Quali-V®-I and Vcaps®, without significant differences between these HPMC capsules (p > 0.05, one-way ANOVA with Newman-Keuls post-hoc test) for both dry powders.**

More specifically for **Blend A**, significantly higher FPDs ($p < 0.01$, one-way ANOVA with Newman-Keuls post-hoc test) and lower capsule retentions ($p < 0.001$, one-way ANOVA with Newman-Keuls post-hoc test) were observed for HPMC capsules (Quali-V®-I, Vcaps®) in comparison with gelatin capsules (Quali-G™ and HGC DPI) and second-generation HPMC (Vcaps® Plus).

Blend B showed higher FPDs than those observed for Blend A (5.15 ± 0.33 µg to 4.15 ± 0.1 µg vs. 3.71 ± 0.2 µg to 2.6 ± 0.1 µg, respectively). It was also less sensitive to the type of capsule used (less significant differences among the different kind of capsules than observed for Blend A). However, the formoterol capsule retention was higher with the Blend B than with Blend A 4.3 ± 1.2% to 1.1 ± 0.2% vs. 2.0 ± 0.5% to < LOQ, respectively). This higher capsule retention did not impact the FPDs or the DDs, which were slightly higher than those from Blend A (DDs of 9.5 ± 0.5 µg to 8.8 ± 0.6 µg vs. 9.0 ± 0.5 µg to 8.4 ± 0.2 µg, respectively).

***Figure A**. Uniformity of dose (µg), **B**. Fine particle dose (µg) or **C**. Formoterol retention (%) in the capsule for Blends A (binary mixture) and B (ternary mixture), packaged in different capsules: hard gelatin capsules for DPI (HGC), Quali-G™ (QG), Vcaps® (VC), Vcaps® Plus (VC+) or Quali-V®-I (QVI). The tests were performed using the Axahaler® capsule-based DPI at 100 L/min for 2.4 sec.*

Figure A UNIFORMITY OF DELIVERED DOSE



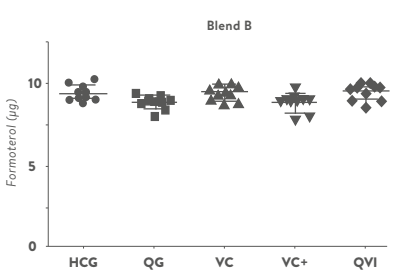
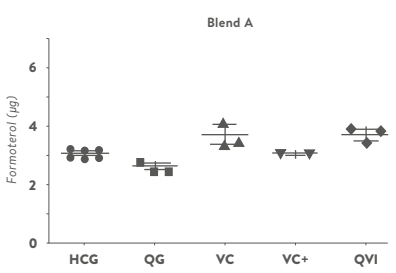


Figure B FINE PARTICLE DOSE



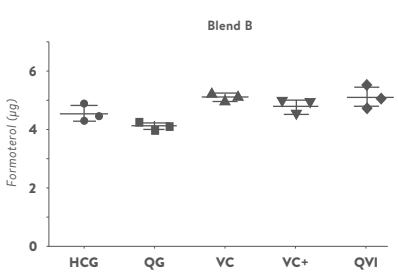
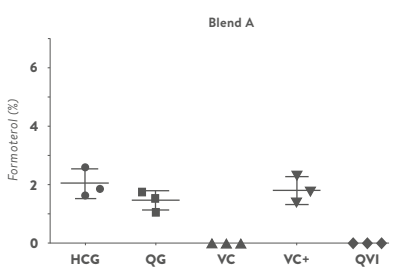
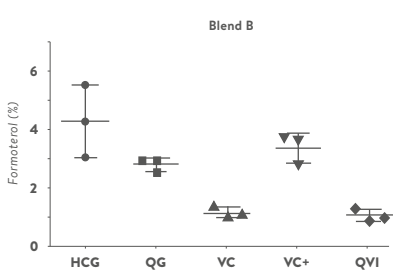


Figure C CAPSULE RETENTION





CONCLUSIONS

Although similar trends were observed for the DD, the FPD and formoterol capsule retention for both the binary and ternary dry powder mixtures packaged in the different capsules, the best results were obtained with HPMC (Quali-V®-I and Vcaps®). Therefore, the choice of the kind of capsule used to package the dry powder formulations has an influence on the DDs and FPDs, key parameters in the evaluation of dry powder aerodynamic performance. Further investigations are needed to better understand the varying aerodynamic performances observed among the different capsules.

REFERENCES

[1] Wauthoz N et al. RDD2015 Congress, France, 2015; 2: pp 453-458
[2] Coates M S et al. Pharm Res 2005; 22: pp 923-932
[3] Pilcer G et al. Adv Drug Deliv Rev 2012; 64: pp 233-256

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