EVALUATION OF THE AERODYNAMIC PERFORMANCE OF FORMOTEROL DRY POWDER USING DIFFERENT CAPSULES FOR INHALATION: HYPROMELLOSE VERSUS GELATIN FROM QUALICAPS® AND CAPSUGEL®

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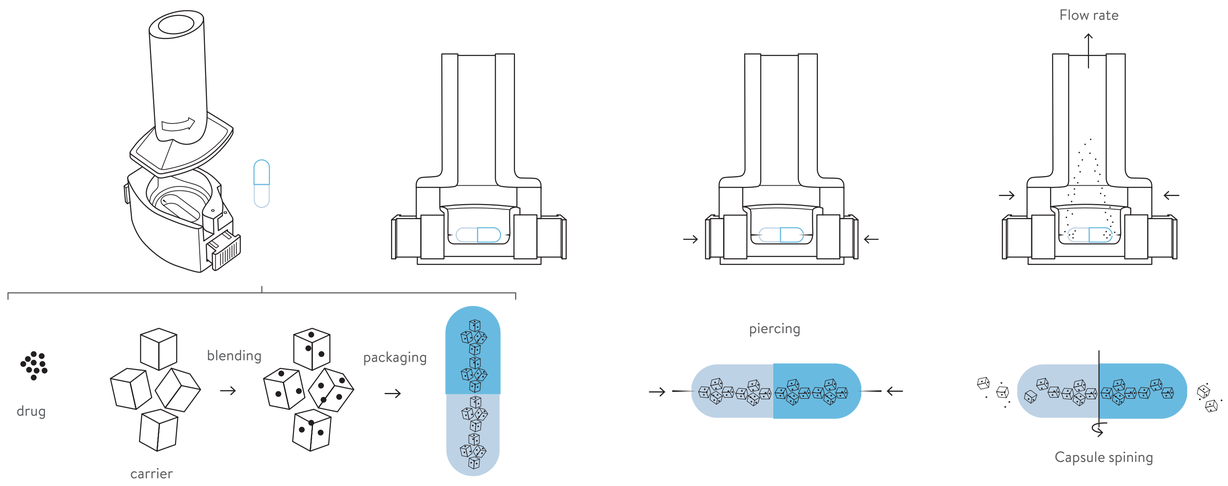
INTRODUCTION

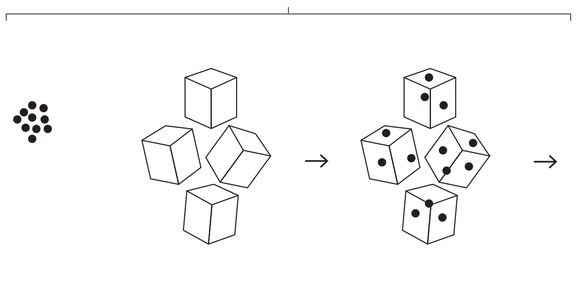
The **capsule** is an important part of the functioning of capsule-based dry powder inhalers (DPIs): it participates in the packaging of the formulation, the aerosolization of the powder and the dispersion of the micronized drug from the carrier after the patient has pierced the capsule and inhaled through the DPI to usually spin the capsule [1,2]. Moreover, **humidity** is an important parameter that can impact the adhesive forces (e.g. capillary forces) between the micronized drug and the carrier and therefore the aerodynamic performance [3].

The aim of this work was to evaluate the impact on the **aerodynamic performance** of a dry powder based on formoterol and milled lactose with a broad size distribution, using the Axahaler® DPI and using different kinds of capsules for inhalation (gelatin or hypromellose, HPMC), from different suppliers (Capsugel® and Qualicaps®) at different storage conditions (usual: 20°C 50% Relative Humidity (RH) or drastic: 40°C 75% RH to simulate a misuse in extreme environmental conditions).



EXPERIMENTAL METHODS

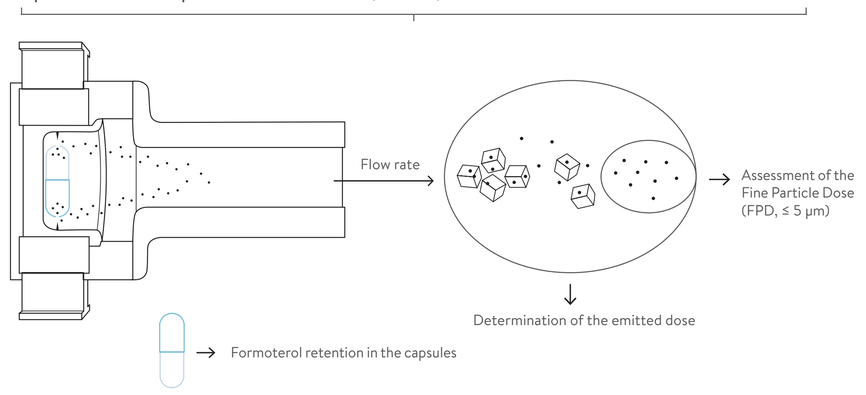
Blending using a laboratory-scale three dimensional motion mixer, the Turbula 2C (Bachofen AG, Switzerland)



Packaging: 24 ± 1 mg of powder blend was weighted in 100 capsules of size N°3 capsules for inhalation: hard gelatin and HPMC from Capsugel® and Qualicaps®, respectively.

Storage: minimum 1 week at 20°C 50%RH and then either at 20°C 50%RH (usual environmental conditions) or at 40°C 75%RH for 4h (to simulate a misuse in extreme environmental conditions).

Inhalation through the Next Generation Impactor (NGI; apparatus E) connected to the Axahaler® DPI filled successively with 10 pre-filled and pre-stored capsules (100 L/min, 2.4 s, n=3).



RESULTS AND DISCUSSION

UNIFORMITY OF DRUG CONTENT

The blend complied with the test for uniformity of content of single-dose preparations (Test B) from European Pharmacopeia 8.0. This was tested on 10 dosage units as no more than one individual content was outside the limits of 85% and 115% of the average content and none was outside the limits of 75% and 125% of the average content.
The drug content was 11.7 ± 0.2 µg formoterol per 24.3 ± 0.7 mg of the powder blend, with a CV% of 1.5%.

The blend was considered homogeneous as it complied with the Test B and the CV% was below 6% [3].

AERODYNAMIC PERFORMANCE

FPD, as reported in the **Figure A**, was affected significantly by the kind of capsules and by the storage conditions ($p < 0.001$, three-way ANOVA). However, there was no significant effect from the supplier ($p > 0.05$, three-way ANOVA) and no significant interfactorial interaction.

The highest FPD was obtained with the HPMC capsules at usual storage conditions (20°C 50% RH) in comparison to the gelatin capsules.

HPMC capsules contained lower moisture content than gelatin capsules, which could explain the FPD differences. Gelatin capsules require a higher moisture content that acts as a plasticizer to avoid capsule brittleness. Therefore, too low humidity induce that the gelatin capsule become brittle, which impact the operations of capsule piercing, powder aerosolization and drug dispersion. The exposure of the formulation during a short time to high humidity and temperature conditions affected the FPD significantly.

There was a significant decrease in the FPD of ~25% for both hypromellose and gelatin capsules after drastic storage condition simulating a misuse in extreme environmental conditions in comparison to the usual storage condition of 20°C 50% RH.

A significant difference was revealed ($p < 0.01$, Kruskal Wallis) for formoterol retention in the different kind of capsules from the different suppliers stored in different conditions, as shown in the **Figure B**. For **hypromellose capsules**, a higher retention was observed after drastic storage, with ~2-3 % of the nominal dose retained in the capsules, in comparison to none detected (i.e. below the limit of quantification) for usual storage. For **gelatin capsules**, lower formoterol retention was observed for gelatin capsules from Qualicaps® in comparison to those from Capsugel®. Moreover, exposure to drastic storage slightly decreased the formoterol retention for gelatin capsules, which was consistent with the significant increase ($p < 0.001$, three-way ANOVA) in the emitted dose (94.8 ± 0.8 vs 95 ± 2 and 90.6 ± 0.9 vs 91 ± 1 for Capsugel® and Qualicaps® gelatin capsules, respectively). Moreover, there was significant interaction with the kind of capsules and the storage conditions ($p < 0.05$, three-way ANOVA).

Figure A

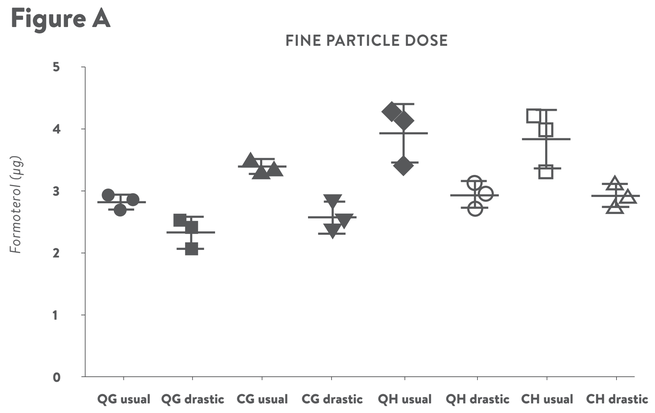
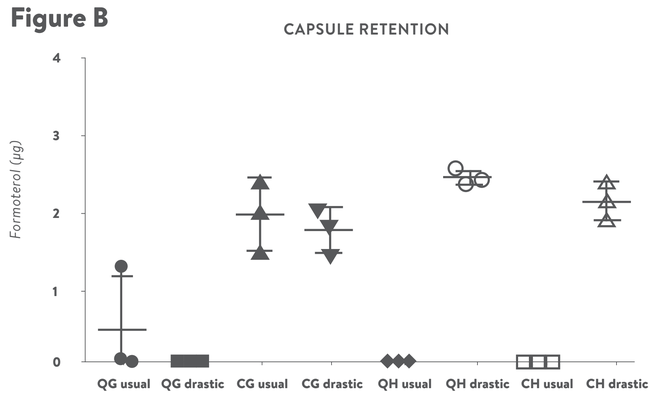


Figure B



Prolonged contact with drastic environmental condition increased the formoterol retention in the HPMC capsules (maximum 2-3%) and increased the emitted dose from the gelatin capsules (about 4%).

Figure A. *Fine particle dose (FPD) (µg),* ***B.*** *Formoterol retention (%) in the capsule, determined using the Next Generation Impactor (100L/min 2.4 s, n=3) connected to the Axahaler®, filled successively with 10 capsules pre-filled and pre-stored.*

CONCLUSIONS

HPMC capsules seemed to be the best capsules for inhalation in terms of aerodynamic performance and drug retention in the capsule for a micronized formoterol and milled lactose carrier blend presenting a broad particle size distribution. Controlled storage conditions at low temperature and humidity of 20°C 50% RH showed better FPDs than 40°C 75% RH, which decreased drastically the FPDs (~25%). This decrease was not due to the increase in formoterol retention by the capsules or to a decrease in the emitted dose. It was certainly due to the increase of moisture content in the formulation increasing the capillary forces between micronized formoterol and the lactose carrier. This increase of adhesive forces decreases drastically the dispersion of micronized drug from the carrier, and/or the deagglomeration of micronized drug and the fine lactose during the inhalation procedure and therefore its deposition in the latest stages of the NGI.

REFERENCES

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[3] Pilcer G et al. Adv Drug Deliv Rev 2012; 64: pp 233-256.

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