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INFLUENCE OF FLOW RATE AND USAGE IN DRASTIC CONDITION ON THE AERODYNAMIC PERFORMANCE OF A FORMOTEROL DRY POWDER FORMULATION USING DIFFERENT KINDS OF CAPSULE

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PURPOSE

The **capsule** is an important part of capsule-based dry powder inhalers (DPIs) because 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 [1]. However, there are few studies focusing on the impact of capsule type on the aerodynamic performance.

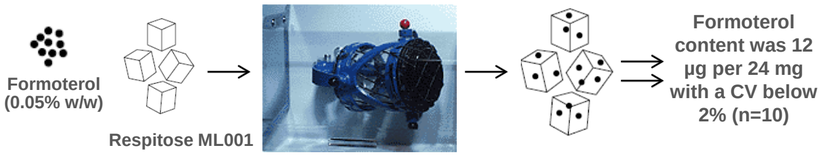
In addition, **inspiratory flow rate** and **humidity** are important parameters that can impact the aerodynamic performance.

The **aim of this study** was to evaluate the **aerodynamic performance** of a conventional formoterol-based dry powder formulation using 2 *types of capsules* (hypromellose and gelatin) from 2 *manufacturers (Qualicaps® and Capsugel®):*

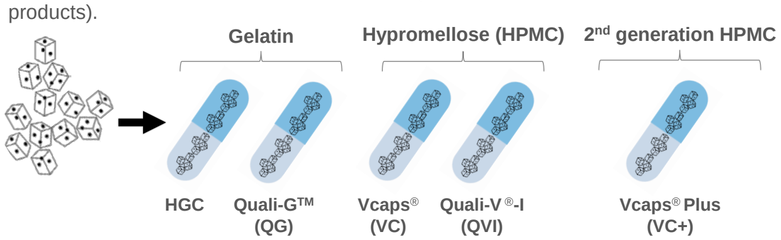
(i) using different flow rates (i.e. 30, 60 and 100 L/min) and
(ii) in drastic conditions (i.e. 4 h at 40°C 75% RH) to simulate misuse (e.g. exhalation) or inappropriate storage in a warm humid environment.

METHOD

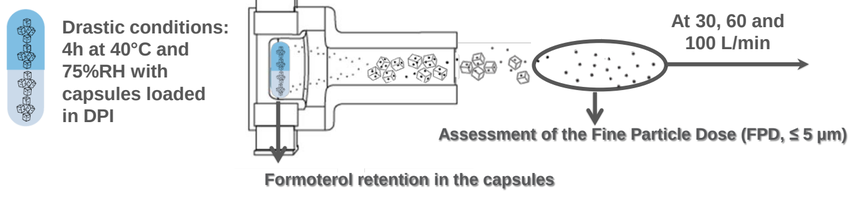
Blending using a laboratory-scale three dimensional motion mixer, the Turbula 2C (Bachofen AG, Switzerland)



Capsule filling: 24 ± 1 mg of powder blend was weighed in different types of size 3 capsules: hard gelatin for DPI (HGC), Vcaps® and Vcaps® Plus from Capsugel® and Quali-G™ and Quali-V®-I from Qualicaps®. All the filled capsules were conditioned for minimum 1 week at 20°C and 50%RH (usual environmental conditions for inhalation products).



Aerodynamic assessment was made using a Next Generation Impactor (NGI; apparatus 5) connected to the low-resistance Axahaler® DPI filled successively with 10 pre-filled and pre-conditioned capsules with an optimal air flow rate of 100L/min for 2.4 sec (n=3).



RESULTS

AERODYNAMIC PERFORMANCE AND CAPSULE RETENTION

At optimal flow rate (100 L/min), significantly higher FPD ($p < 0.05$, One Way ANOVA) and lower drug retention were observed for HPMC capsules (Quali-V®-I and Vcaps®) than for gelatin capsules (Quali-G™ and HGC) and 2nd generation HPMC capsules (Vcaps® Plus).

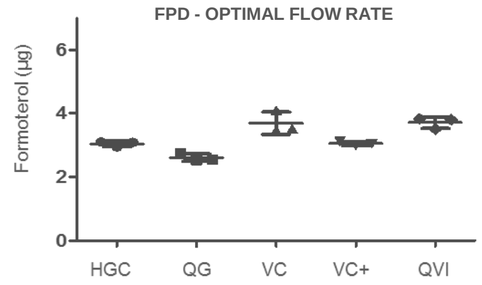


Figure 1. Fine Particle Dose (FPD) (µg) determined using the NGI (100L/min for 2.4 s, n=3).

Table1. Formoterol capsule retention (% per capsule) determined using the NGI connected to the Axahaler® at different flow rates and capsule storage conditions. < LOQ: lower than the Limit Of Quantitation

FORMOTEROL RETENTION IN CAPSULE (%)

Capsule	Gelatin		HPMC	
	HGC	Quali-G™	Vcaps®	Quali-V®-I
30 L/min	1.9 ± 0.4	0.4 ± 0.6	1.1 ± 0.2	< LOQ
60 L/min	2.1 ± 0.2	1.0 ± 1.0	1.1 ± 0.3	< LOQ
100 L/min	2.3 ± 0.5	1.4 ± 0.3	< LOQ	< LOQ
20°C 50%RH	2.3 ± 0.6	0.5 ± 0.8	< LOQ	< LOQ
40°C 75%RH	2.1 ± 0.4	< LOQ	2.5 ± 0.3	2.9 ± 0.1

At different flow rates corresponding to 30 L/min (0.38 kPa), 60L/min (1.32 kPa) and 100 L/min (3.60 kPa), only Quali-V®-I and Vcaps® (i.e. HPMC capsules) presented no significant differences ($p > 0.05$, One Way ANOVA) between 60 and 100 L/min for their FPD. In addition, only Quali-V®-I showed the lowest capsule retention at the different flow rates (below the limit of quantification for all of them).

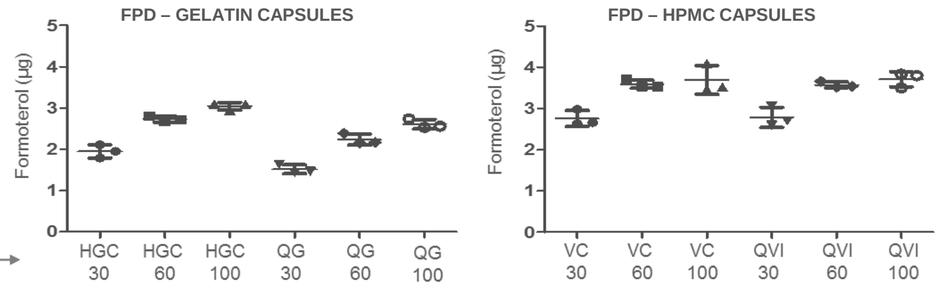
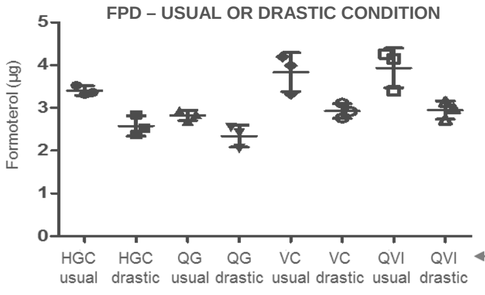


Figure 2. FPD (µg) determined on gelatin or HPMC capsules at different flow rates (30L/min for 8s, 60L/min for 4s or 100 L/min for 2,4 s; n=3).



In drastic conditions (4h at 40°C and 75%RH), the FPD was affected significantly ($p < 0.001$, three-way ANOVA) by the capsule type. However, the FPD was not affected significantly ($p > 0.05$, three-way ANOVA) by the manufacturer and there was no significant interfactorial interaction. The highest FPD was obtained with the HPMC capsules (Quali-V®-I and Vcaps®) unexposed vs drastic conditions. The exposure of filled capsules for a short time (4 h) to drastic conditions decreased significantly the FPD, approximately 25% for both HPMC and gelatin capsules. In terms of capsule retention, the drastic conditions increased by about 2-3% the capsule retention of formoterol in Quali-V®-I and Vcaps® and decreased at most 0.5% the capsule retention of formoterol in Quali-G™ and HGC, being the Qualicaps® gelatin capsules retention below the LOQ.

Figure. 3. Fine particle dose (FPD) (µg) determined using the NGI (100L/min 2.4 s, n=3) connected to the Axahaler®, filled successively with 10 capsules pre-filled and pre-stored either in normal conditions (20°C 50%RH) or in drastic conditions (4h at 40°C 75%RH).

CONCLUSIONS

The HPMC capsules evaluated, Quali-V®-I and Vcaps®, seem to be the best capsule type for inhalation in terms of aerodynamic performance, with lower dependency on airflow (between 60 and 100 L/min). In addition, Quali-V®-I showed the lowest formoterol retention in capsules at different flow rates for a dry powder blend composed of micronized formoterol and lactose carrier with a broad distribution. However, it is very important to avoid exposing the capsules to drastic conditions, which could affect significantly the aerodynamic performance of dry powder inhalers, independently of the type of capsule used.

REFERENCE

[1] Coates MS, Fletcher DF, Chan HK, Raper JA, *Pharm Res* 2005, 22(6):923-32

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