INFLUENCE OF DIFFERENT CAPSULES FOR INHALATION ON THE AERODYNAMIC PERFORMANCE OF FORMOTEROL DRY POWDER FORMULATION AT DIFFERENT FLOW RATES

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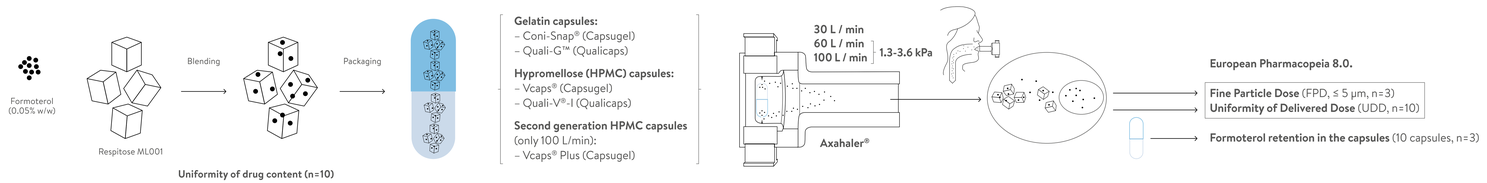
INTRODUCTION

An ideal inhalation medicine has to deliver an accurate delivered dose (DD) and fine particle dose (FPD) with low dependency on the patient's inspiratory airflows [1].

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 [2]. However, there are few studies focusing on the impact of capsule type on the aerodynamic performance.

AIM OF THE STUDY

Storage time at 20°C 50% RH (> 3 weeks) was applied on filled capsules before analyses. All capsule types were analyzed at the same time to evaluate only the capsule influence.



RESULTS AND DISCUSSION

FORMOTEROL BLEND

The blend composed of 0.05% formoterol w/w with coarse lactose (Respitose® ML001, DFE pharma) using the Turbula 2C (Bacholen AG) mixer presented a drug content of 12.0 ± 0.1 µg per 24 mg of blend (dosage unit) and was homogenous with a coefficient of variation (CV) of 1.2%.

UNIFORMITY OF DELIVERED DOSES

The blend tested with the different types of size 3 capsules (gelatin and HPMC) at different flow rates (30, 60, 100 L/min) or 2nd generation HPMC at 100 L/min complies with the test of UDD. The CV% was between 2-6% and therefore no more than one individual content was outside the limits of 75-125% of the average content and none was outside the limits of 65-135%.

ASSESSMENT OF FINE PARTICLE DOSES AND DRUG RETENTION IN THE CAPSULE

FPD (≤ 5 µm) and drug retention in the different types of size 3 capsules were assessed using a low resistance device (Axahaler®, SMB) that was connected to a Next Generation Impactor (NGI, Copley Scientific Limited) including the pre-separator and uncoated plates. Ten capsules were used for each test and three independent tests were performed for each capsule type. The airflow was applied for time lengths that able to generate 4L through the device (8 sec for 30 L/min, 4 sec for 60 L/min and 2.4 sec for 100 L/min).

FINE PARTICLE DOSES AT THE OPTIMAL FLOW RATE (100 L/MIN)

At 100 L/min, FPD was significantly ($p < 0.05$, One-way ANOVA) higher for HPMC capsules (Quali-V® -I and Vcaps®) in relation to:

– gelatin capsules (Quali-G™ and Coni-Snap®)

– 2nd generation HPMC capsules (Vcaps® Plus)

Figure A

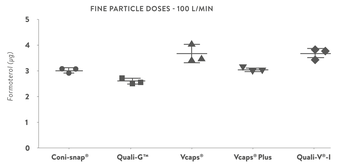


Figure A. *FPD (µg) determined using the NGI (100L/min 2.4 s, n=3) connected to the Axahaler®, filled successively with 10 capsules pre-filled and pre-stored.*

FINE PARTICLE DOSES AT DIFFERENT FLOW RATES (30, 60 AND 100 L/MIN)

At the different flow rates corresponding to 30 L/min (0.38 kPa), 60 L/min (1.32 kPa) and 100 L/min (3.60 kPa), only the HPMC capsules (Quali-V®-I and Vcaps®) presented no significant differences ($p > 0.05$, One-way ANOVA) between 60 and 100 L/min. Therefore, more robust performances were observed with HPMC versus gelatin capsules that could be explained by the higher moisture content inherent in gelatin capsules (13-16% vs 2-6% for gelatin and HPMC capsules, respectively).

Figure B

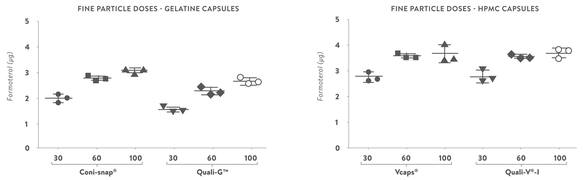


Figure B. *FPD (µg) determined using the NGI (30 L/min 8 s, 60 L/min 4 s, 100L/min 2.4 s, n=3) connected to the Axahaler®, filled successively with 10 capsules pre-filled and pre-stored.*

DRUG RETENTION IN THE CAPSULES

At 100 L/min, drug retention was significantly ($p < 0.001$, One-way ANOVA) lower in HPMC capsules (Quali-V®-I and Vcaps®) than in:

– gelatin capsules (Quali-G™ and Coni-Snap®)

– 2nd generation HPMC capsules (Vcaps® Plus)

Moreover, Quali-V®-I showed the lowest formoterol retention in the capsule at the different flow rates (< LOQ for all of them)

FORMOTEROL CAPSULE RETENTION (µG / CAPSULE)

Table. *Capsule retention of formoterol (µg per capsule) determined using the NGI at different flow rates (30 L/min 8 s, 60 L/min 4 s, 100L/min 2.4 s, n=3) connected to the Axahaler®, filled successively with 10 capsules pre-filled and pre-stored. < LOQ inferior to the limit of quantitation, N.A. not applicable.*

Flow rate	Coni-Snap®	Quali-G™	Vcaps®	Vcaps® Plus	Quali-V®-I
100 L/min	0.24 ± 0.06	0.17 ± 0.04	< LOQ	0.21 ± 0.06	< LOQ
60 L/min	0.26 ± 0.03	0.11 ± 0.12	0.26 ± 0.03	N.A.	< LOQ
30 L/min	0.23 ± 0.05	0.04 ± 0.07	0.13 ± 0.02	N.A.	< LOQ

CONCLUSIONS

It is well known that the patient can generate different flow rates through his/her device relating to its resistance. Therefore, it is important that the combination of the dry powder for inhalation and its capsules presents high FPD with low dependency on a flow rate corresponding to a pressure drop comprised between 2 and 3 kPa and low capsule retention. HPMC capsules showed higher and more robust FPD at this flow rate range than gelatin capsules. Moreover, Quali-V®-I showed the lowest capsule retention at all tested flow rates.

REFERENCES

[1] Chrystyn H, Int J Clin Pract 2007, 61(6):1022-36
[2] Coates MS et al., Pharm Res 2005, 22(6): 923-932