Selection of the Best Capsule Type to Maximize the Performance of a Model Carrier-Based Dry Powder Inhalation Formulation

Lonza
Capsules & Health Ingredients

Camille Dumont[1], Sandrine Picco[1], Beatriz Noriega-Fernandes[2], Molly Gallagher[2], Christopher Bock[2], Pierre Verlhac[1], Vincent Jannin[1]

[1]Capsugel France – Lonza, Innovaform® Accelerator, Colmar, France
[2]Lonza, Bend, OR, United States of America

Keywords : Capsule, Dry Powder Inhalation, Micronization, Aerodynamic performance, Capsule selection

Introduction

The rising prevalence of respiratory diseases has driven a growing demand for effective inhalation therapies. Capsule-based Dry Powder Inhaler (cDPI) represent a prominent solution in this domain, offering accuracy, portability and ease of use, with a projected CAGR of 7.7% by 2034 [1].

While the critical roles of formulation, device, and capsule in cDPI performance are widely acknowledged, limited research has specifically explored the influence of capsule type.

Goal: This study aims to bridge this gap by evaluating the impact of different capsule types – Hard Gelatin Capsules, PEG-modified HGC, and a range of HPMC-based capsules (Vcaps® and Vcaps® Plus capsules) – on the inhalation performance of a model formulation containing micronized phenytoin. Utilizing a standard inhalation device and *in vitro* assessment, the study seeks to **highlight the critical role of capsule selection in optimizing the delivery of DPI** and provide valuable insights for the development of improved inhalation therapies.

Material and methods

Formulation

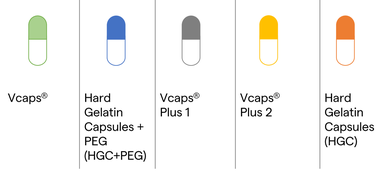
Coarse lactose - 79.5% (w/w)
Respitose® SV003

Fine lactose - 15% (w/w)
Lactohale® L230

Micronized Phenytoin – 5.5% (w/w)
MC50 spiral jet mill
Dv50=1.8 µm / Dv90=3.3 µm

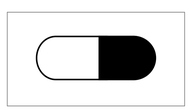
Blending process: 120 min Low-shear mixing in 1-quart Patterson-Kelley blender (Buflovak)

Capsule filling



- Capsugel® Zephyr® capsules
- 10 days equilibration 45%RH prior filling
- 25 mg formulation / capsule (1.38 mg phenytoin)

Aerodynamic behavior


Filled capsules


RS01 DPI device– Berry


Next Generation Impactor (Copley Scientific) with pre-separator and coated cups

Phenytoin quantification via HLPC

Emitted Fraction (EF)
Fraction of the nominal dose released from capsule and device

Capsule retention
nominal phenytoin content in capsule

Fine Particle Fraction (FPF)
Fraction of phenytoin with particles sizes below 5 µm recovered in NGI

Very Fine Particle Dose (vFPD)
Fraction of the emitted dose with particle sizes below 2 µm

Test conditions:
- 60 L/min flow rate (4 kPa pressure drop)
- n=3

Results

	Vcaps®		HGC		HGC+PEG		Vcaps® Plus 1		Vcaps® Plus 2	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
MMAD (µm)	3.28	0.07	3.48	0.13	3.42	0.06	3.39	0.13	3.35	0.06
Capsule retention (%)	3.4	0.9	13.8	1.1	12.7	1.2	9.8	0.7	6.3	0.2
Emitted fraction (%)	86.5	0.9	74.8	1.1	74.2	2.8	76.7	2.8	80.8	1.8

Table 1. MMAD, capsule retention and emitted fraction values of the model phenytoin formulation encapsulated in various Capsugel® Zephyr® capsule types

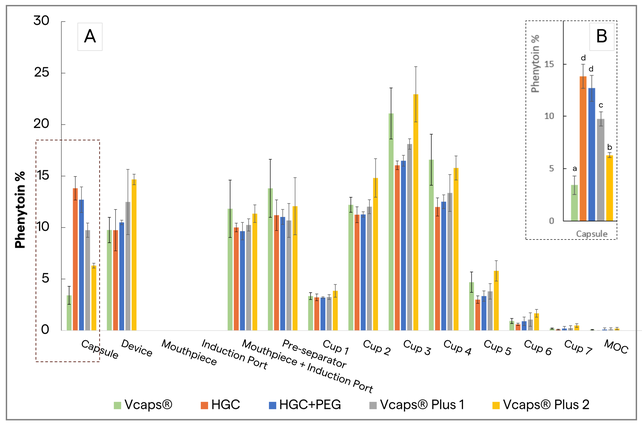


Figure 1: (A) NGI deposition profile of model formulation in Capsugel® Zephyr® capsules: Vcaps® (green), HGC (orange), HGC+PEG (blue), Vcaps® Plus 1 (grey) and Vcaps® Plus 2 (yellow) and (B) Phenytoin retained in capsules, no statistical difference was observed between groups represented by the same letter ($p<0.05$)

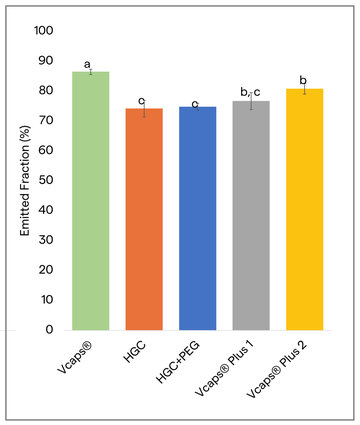


Figure 2: Phenytoin emitted fraction from RS01 device as a function of Capsugel® Zephyr® capsule type, no statistical difference was observed between groups represented by the same letter ($p<0.05$)

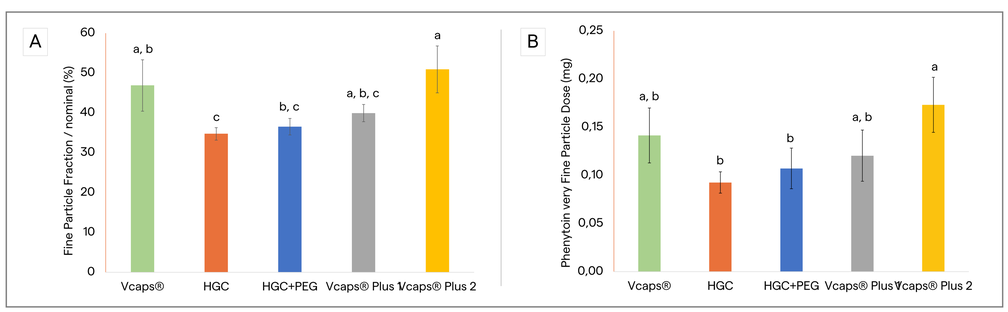


Figure 3: Phenytoin FPD divided by the nominal dose (A) and vFPD (B) from RS01 device as a function of Capsugel® Zephyr® capsule type, no statistical difference was observed between groups represented by the same letter ($p<0.05$)

No significant differences were observed in the MMAD values across the different capsule types, indicating that the **formulation's aerodynamic properties remained consistent**.

Capsule retention varied significantly among the capsule types with the lowest values obtained with Vcaps®. The highest retention were measured with gelatin-based capsules, Figure 1.

Vcaps® exhibited the highest emitted fraction. no significant differences were found between gelatin-based capsules, while statistical differences were evidenced among all HPMC capsule types, Figure 2.

Emitted fraction was not statistically different between Vcaps® Plus 2 and Vcaps® Plus 1, despite slight variations in their manufacturing processes.

HPMC-based capsules consistently demonstrated significantly higher FPD compared to gelatin-based capsules, Figure 3 (A). Vcaps® Plus 2 exhibited the highest performance, followed by Vcaps®.

Similar trends were observed with phenytoin vFPD, Figure 3 (B).

Several parameters could explain the differences between capsule performances such as capsule free water content, differences in capsule shell roughness, shell brittleness upon capsule puncturing or electrostatic charges [2–7].

Conclusion

This study unequivocally demonstrates the critical importance of capsule selection in the development of optimal cDPI products.

Aerodynamic performance comparisons at an early stage of product development can guide the selection of the most suitable capsule for a specific formulation and device.

In the case of the model phenytoin/lactose ternary blend tested with the RS01 device, **HPMC-based capsules, particularly Vcaps® Plus 2, consistently exhibited superior cDPI performance.**

Acknowledgements and disclosures

CD, SP, PV and VJ are employees of Capsugel France SAS which manufactures the capsules tested in the study. BNF, BG and NC are employees of Lonza Small Molecules which manufacture DPI drug products.

References

1. Dry Powder Inhaler Market Size and Share | Statistics - 2034 [Internet]. [cited 2024 Dec 9]. Available from: https://www.factmr.com/report/dry-powder-inhaler-market
2. Wauthoz N, Hennia I, Ecenarro S, Amighi K. Impact of capsule type on aerodynamic performance of inhalation products: A case study using a formoterol-lactose binary or ternary blend. International Journal of Pharmaceutics. 2018;553:47–56.
3. Barham AS, Tewes F, Healy AM. Moisture diffusion and permeability characteristics of hydroxypropylmethylcellulose and hard gelatin capsules. International Journal of Pharmaceutics. 2015;478:796–803.
4. Ding L, Brunaugh AD, Thakkar R, Lee C, Zhao QJ, Kalafat J, et al. Comparison of HPMC Inhalation-Grade Capsules and Their Effect on Aerosol Performance Using Budesonide and Rifampicin DPI Formulations. AAPS PharmSciTech. 2022;23:52.
5. Ding L, Brunaugh AD, Stegemann S, Jermain SV, Herpin MJ, Kalafat J, et al. A Quality by Design Framework for Capsule-Based Dry Powder Inhalers. Pharmaceutics. 2021;13:1213.
6. Tan SB, Newton JM. Influence of capsule dosator wall texture and powder properties on the angle of wall friction and powder-wall adhesion. International Journal of Pharmaceutics. 1990;64:227–34.
7. Pilcer G, Wauthoz N, Amighi K. Lactose characteristics and the generation of the aerosol. Advanced Drug Delivery Reviews. 2012;64:233–56.