

Inhalation Hard Capsules – Evaluation of the Performance of Hypromellose Capsules for Dry Powder Inhaler

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Summary

One of the most crucial attributes for a Dry Powder Inhaler (DPI) products is the emitted dose (ED). With hard capsule for DPI this performance parameter is often linked to the relative humidity of the filled capsules which can have an impact on powder retention in the capsule and in the inhalation device. The emitted dose is also linked to the quality of the puncture which will allow to securely empty the capsule. The objective of this study was to evaluate the impact of various parameters believed to influence the performance of the hypromellose capsules used in conjunction with two commercial DPI devices.

Both types of hypromellose capsules (Vcaps[®] and Vcaps[®] Plus) are associated with low lactose retention in DPI applications, but prone to slightly more lactose retention under low relative humidity conditions. We speculate that lactose retention may be associated with the static charges that are not dissipated so readily under low relative humidity conditions.

Vcaps[®] and Vcaps[®] Plus capsules are shown to exhibit cleaner puncture when respectively tested with Handihaler[®] and Breezhaler[®] than hard gelatin capsule under low water content conditions.

Keywords

Inhalation hard capsules, Hypromellose capsules, powder retention, puncturing, relative humidity.

Introduction

One of the most crucial attributes for a Dry Powder Inhaler (DPI) products is the emitted dose (ED). With hard capsule for DPI this performance parameter is often linked to the relative humidity of the filled capsules which can have an impact on powder retention in the capsule and in the inhalation device. The emitted dose is also linked to the quality of the puncture which will allow to securely empty the capsule. The objective of this study was to evaluate the impact of various parameters believed to influence the performance of the hypromellose capsules used in conjunction with two commercial DPI devices.

Methods

Hypromellose capsules (Vcaps[®] & Vcaps[®] Plus, Capsugel, Colmar, France) were filled with a defined weight of lactose for inhalation (Respirose[®] ML001 from DFE Pharma), after both components were equilibrated for one week in sealed desiccators over saturated salt solutions able to maintain a Relative Humidity (%RH) of 23%, 33%, 45% or 66%.

Experiments were performed with Vcaps[®] fill weight of 5.5 mg +/- 0.1mg of lactose for inhalation in conjunction with Handihaler[®] (Boehringer Ingelheim, Ingelheim, Germany). For Vcaps[®] Plus capsules the fill weight of lactose was 25 mg +/-1 mg, and emptying tests were performed using Breezhaler[®] (Novartis, Basel, Switzerland).

Test protocol

For each test condition 20 capsules were filled. Each capsule was weighed empty, then filled with lactose and weighed again to confirm the fill weight. Capsules were then individually loaded into appropriate inhalation device and pierced according to device manufacturer's instructions, before the device was attached to the inhaler testing equipment.

The inhaler testing equipment was a Dosage Unit Sampling Apparatus (DUSA) from Copley Scientific (U.K.) coupled with a vacuum pump with a 4kP pressure drop. Air flow rate was 100L/min for a volume of 4 liters. Powder retention was determined by measuring the emptied capsules weight, and the capsule puncture was analyzed to observe the opening. Weight variation due to capsule fragments during puncturing was considered as being negligible compared to the weight of lactose.

Results

Powder retention

The amount of powder remaining in the Vcaps[®] capsules after performing the inhalation test increased under low relative humidity conditions (Table1).

Capsule storage condition % RH	Vcaps [®] capsule water content (%)*	Powder retention (mg)	Powder retention (%)
23	3,3 +/- 0,1	0,78 +/- 0,02	14,1
33	4,1 +/- 0,1	0,36 +/- 0,03	6,6
45	5,1 +/- 0,2	0,01 +/- 0,02	0,1
66	8,3 +/- 0,1	Not measurable	Not measurable

*Water content was measured by weight loss on drying in oven at 105°C after 18 hours.

Table 1: Powder retention and moisture content of Vcaps[®] capsules stored under various relative humidity conditions.

The amount of powder remaining in the Vcaps[®] Plus capsules after performing the inhalation test increased under low relative humidity conditions. (Table 2)

Capsule storage condition % RH	Vcaps [®] Plus capsule water content (%)	Powder retention (mg)	Powder retention (%)
23	2,9 +/- 0,2	0,48 +/- 0,03	1,9
33	3,9 +/- 0,1	0,33 +/- 0,03	1,3
45	4,9 +/- 0,1	0,17 +/- 0,02	0,7
66	7,4 +/- 0,2	Not measurable	Not measurable

Table 2: Powder retention and moisture content of Vcaps[®] Plus capsules stored under various relative humidity conditions.

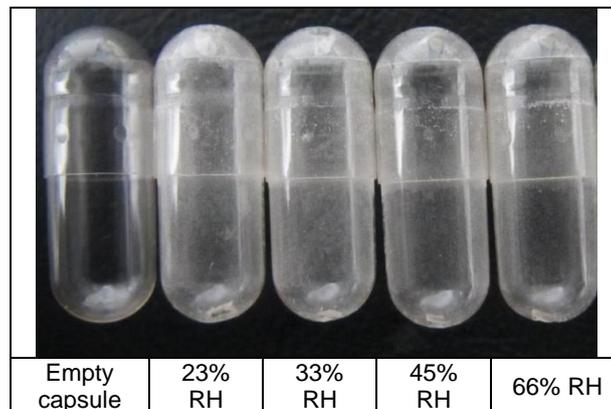


Figure 1: Vcaps[®] Plus capsules stored under various relative humidity conditions after completion of emptying test.

With both types of hypromellose capsules the slightly higher powder retention observed under low relative humidity conditions may be speculatively attributed to static electricity. Visual observation of the capsule after test confirms the above results.

Powder retention in capsules with low moisture content is proportionally higher with a low fill weight (5.5 mg) than with high fill dose (25 mg).

Capsule puncturing

For Vcaps[®] capsules:

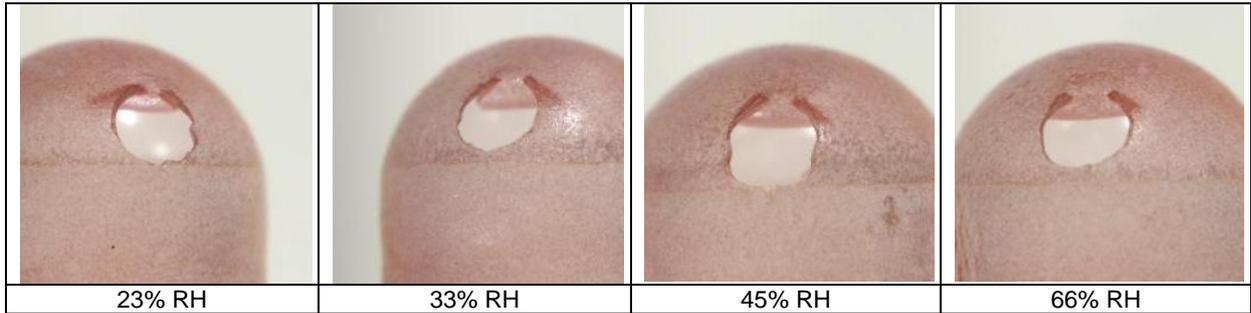


Figure 2: Vcaps[®] capsules punctured using Handihaler[®]

With Vcaps[®] Hypromellose capsules we observe that the puncturing performance remains excellent (absence of detached particle) whatever the capsules moisture content.

For Vcaps[®] Plus capsules:

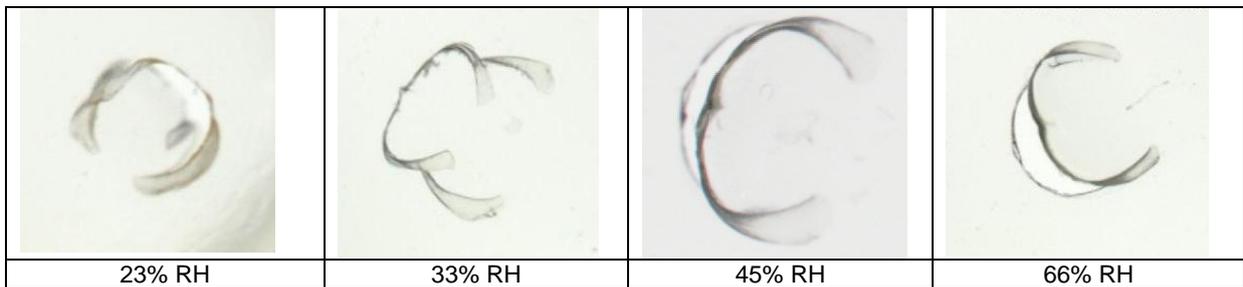


Figure 3: Vcaps[®] Plus capsule punctured using Breezhaler[®].

With Vcaps Plus[®] Hypromellose capsules we observe that the puncturing performance remains excellent (absence of detached particle) whatever the capsules moisture content.

Comparison with gelatin capsule for DPI

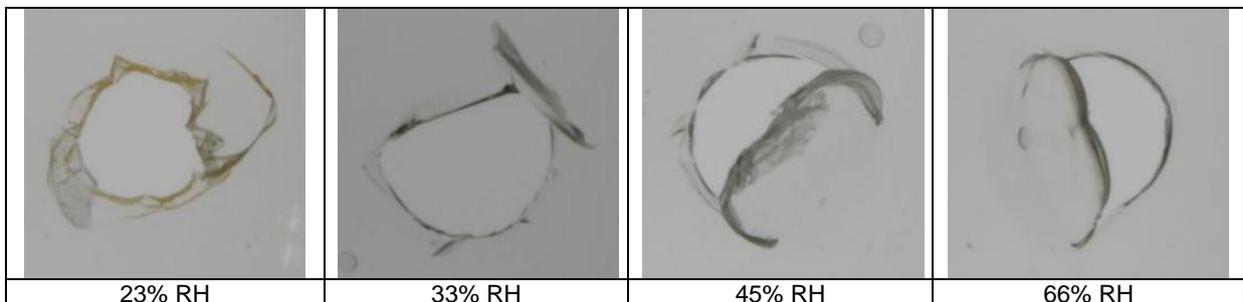


Figure 4: Gelatin hard capsules after puncturing using Breezhaler[®].

Comment

Hypromellose capsules puncturing perform better than hard gelatin capsules in terms of puncture appearance when the relative humidity is below 25 %.

Conclusions

Both types of hypromellose capsules (Vcaps[®] and Vcaps[®] Plus) are associated with low lactose retention in DPI applications, but prone to slightly more lactose retention under low relative humidity conditions. We speculate that lactose retention may be associated with the static charges that are not dissipated so readily under low relative humidity conditions.

Vcaps[®] and Vcaps[®] Plus capsules are shown to exhibit cleaner puncture when respectively tested with Handihaler[®] and Breezhaler[®] than hard gelatin capsule under low water content conditions.

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