DETERMINING THE PUNCTURE PERFORMANCE OF QUALI-V®-I HYDROXYPROPYLMETHYLCELLULOSE CAPSULES AT VERY LOW MOISTURE CONTENTS

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INTRODUCTION

- Hygroscopic active pharmaceutical ingredients (APIs) and excipients may be able to draw moisture from hard shell capsules [1].
- If such capsule formulations are subsequently used in monodose dry powder inhalers (DPIs), this could influence effective deagglomeration of the encapsulated drug-carrier formulation upon actuation.
- Therefore for some formulations hard shell capsules with reduced water transfer properties may be advantageous.
- Reducing the moisture content of capsules changes their mechanical behavior and their puncture performance by a DPI pin [2, 3].
- Gelatin capsules become brittle at moisture contents lower than their standard specification (moisture content of 13-16% w/w) and therefore storage at a low relative humidity (RH) e.g. 11% RH, increases the force required by a DPI pin to puncture the capsule shell and may result in unwanted fragmentation [3].
- Hydroxypropylmethylcellulose (HPMC) capsules have a lower standard moisture content (4.5-6.5% w/w for HPMC inhalation grade capsules) and maintain their puncture performance at 11% RH (resulting in a moisture content of 3.2% w/w) [3]. However, little is known about the mechanical performance of these capsules at even lower moisture contents.

The aim of this study was to characterise the puncture properties of HPMC capsules that have been stored at a RH close to 0%.

METHODS

- Size 3 empty hard shell capsules for inhalation (Quali-V®-I) were supplied by Qualicaps Europe, S.A.U.
- Capsules were stored in glass desiccators for at least 2 weeks at three different relative humidities, created by a saturated solution of magnesium nitrate (54% RH), calcium chloride (34% RH), or lithium chloride (11% RH) to produce capsules towards the upper end of their normal moisture specification range (4.5-6.5% w/w for HPMC inhalation grade capsules), at the lower end or below it, respectively (*Fig 1*).
- Phosphorous pentoxide powder was used to condition capsules at 0.5% RH for at least one week.
- Loss on drying (LOD) tests were used to determine the moisture content of capsules (n=3).
- A published method using a ZwickRoell 0.5TS materials testing machine (*Fig 1*) and an XForceP 500N load cell was used to to conduct quasi-static (10mm/min) puncture tests on pre-conditioned hard shell capsules (n=30 per capsule condition) using a DPI pin from a Plastiape RS01 2 pin inhaler (Plastiape S.p.A; Milan, Italy) [3].

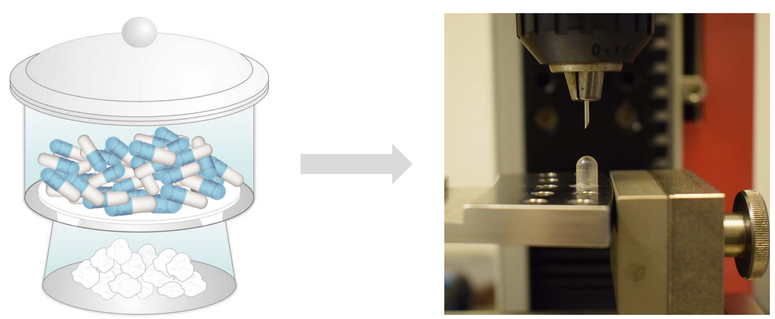

Figure 1. Capsules are stored in desiccators at a controlled temperature and relative humidity before being punctured using a materials testing machine

RESULTS & DISCUSSION

- Conditioning at 11%, 34% and 54% RH produced capsules with moisture contents below, within and just above the specification range.
- Capsules stored over phosphorous pentoxide (0.5% RH) had a moisture content of 1.3% w/w (calculated by LOD), which is significantly below the moisture specification range (4.5-6.5% w/w) for HPMC inhalation grade capsules.
- The puncturing event for capsules stored at 34% and 54% RH was highly reproducible (*Fig 2*).
- At the lower storage RH values, the force displacement curves were more variable; however, the shape of the curves remained remarkably consistent, even at 0.5% RH. This variability may be attributable to changes in the dimension of the capsules at low RH and resulting challenges in the puncture force testing methodology.
- At lower capsules moisture contents the forces required to puncture capsules (*Fig 3*) increase due to increased capsule stiffness.
- However, the small increase in puncture force required (an increase from 3.75N to 4.54N for capsules stored at 34% RH and 0.5% RH) is unlikely to affect the clinical utility of the capsule.
- There were no notable differences in the appearance of punctured capsules stored at 0.5% RH (*Fig 4*) and therefore the mechanical properties of these HPMC capsules (moisture content of 1-2%) are retained to enable effective puncture in a DPI without fragmentation.
- Further work is needed to determine how this very low moisture content effects other physical and mechanical properties of the capsule, which may be important during handling, filling, storage, transport and use. A greater understanding of the interaction of a powdered pharmaceutical formulation with a very low moisture capsule and the subsequent aerosolization performance of that powder is also required and work is ongoing in these areas.

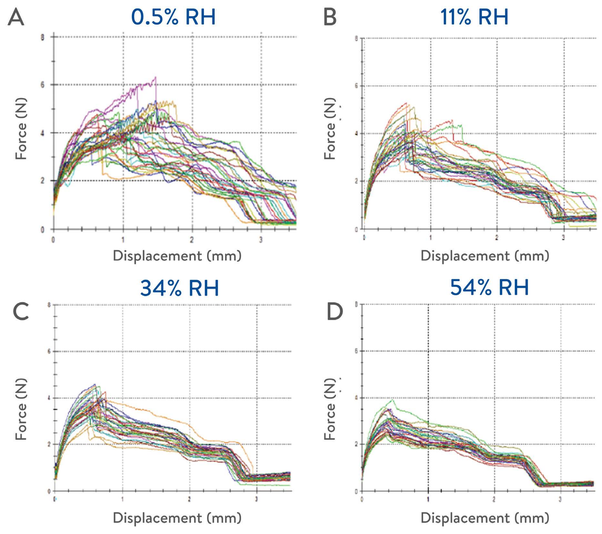

Figure 2. Single pin puncture curves for HPMC capsule formulations stored in desiccators at A) 0.5%, B) 11%, C) 34%, and D) 54% RH (N = 30).

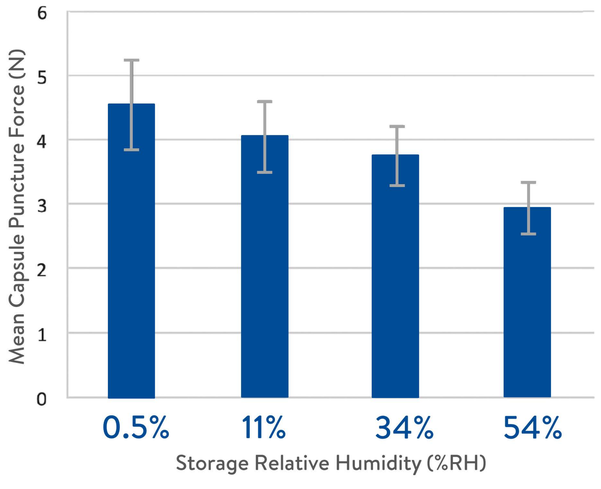

Figure 3. The mean (±SD) puncture force recorded for HPMC capsule formulations stored in desiccators at 0.5%, 11%, 34%, and 54% RH (N = 30).

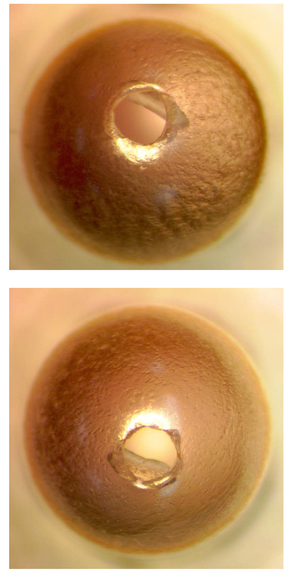

Figure 4. Light microscope images of punctured HPMC capsules stored at 0.5% RH.

CONCLUSION

HPMC capsules conditioned at an extremely low RH (close to 0%) have a moisture content below 2%. At this very low moisture content the capsules require a slightly greater force for puncture by a DPI pin but remain intact following the puncturing event and possess a puncture profile that is comparable to capsules maintained within the normal moisture content specification.

REFERENCES

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