Comparing the mechanical properties of Quali-V®-I and Quali-V®-I Extra Dry Capsules for use in Dry Powder Inhalers

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INTRODUCTION

- Hygroscopic APIs and excipients within capsule-based dry powder inhalers (DPIs) can absorb moisture from the capsule shell [1], which could reduce deagglomeration upon actuation or degrade moisture-labile APIs.
- In some cases it would be be advantageous to use capsules with a reduced moisture content.
- However reduced moisture content can increase capsule brittleness [2,3], which in turn can impact on capsule integrity (during transit or use) and/or alter mechanical performance of a capsule within a DPI that uses capsule puncturing event to facilitate release of the powdered contents (Fig 1).

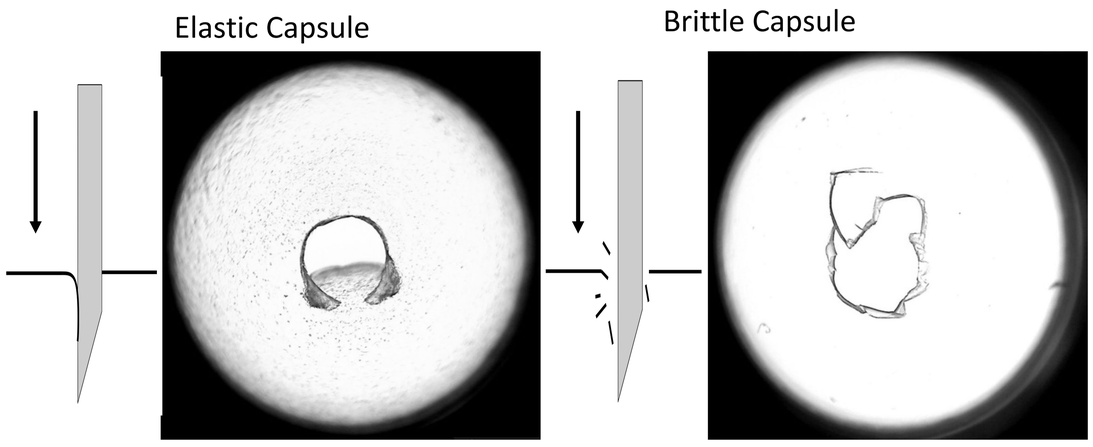


Figure 1: Exemplar puncture holes, created in an elastic or brittle capsule by a pin from a DPI, to demonstrate how moisture content can effect capsule puncture and integrity. The left capsule is a hypromellose capsule and is within its moisture content specification and the right capsule is a gelatin capsule and is significantly below its moisture content specification.

- Qualicaps have recently developed a capsule with a reduced moisture content, known as Quali-V®-I Extra Dry (XD). Quali-V®-I XD capsules have a moisture content (2-3.5% w/w), that is significantly lower than the more established commercial hypromellose capsule, Quali-V®-I (moisture content 4.5-6.5% w/w).

AIM: To determine if the lower moisture content of Quali-V®-I Extra Dry capsules has an effect on the mechanical performance and puncture properties that are associated with the established Quali-V®-I capsules.

METHODS

- Quali-V®-I and Quali-V®-I XD Size 3 empty hard-shell capsules for inhalation were supplied by Qualicaps Europe, S.A.U (Alcobendas, Spain).
- Quali-V®-I and Quali-V®-I XD capsules were conditioned at 34% Relative Humidity (RH) and 18% RH, respectively (to condition capsules to the lower boundary of the Quali-V®-I moisture content specification or within Quali-V®-I XD moisture specification).
- Loss on drying (LOD) tests were performed in triplicate at two time points in the study using both an oven (European Pharmacopoeia) and a halogen drier thermobalance method (n = 6) to determine moisture content (see Table 1).
- An established method (3) was used to test capsule puncture performance and compression using a Zwick Roell material testing machine with an XForce P 500N load cell (Herefordshire, U.K) and a test speed of 10mm/min
- Puncture tests uses an angular metal pin from a Plastiape RS01 2-pin inhaler (Plastiape S.p.A; Milan, Italy) [2, 3] and compression tests used a 25mm diameter steel platen.

RESULTS AND DISCUSSION

- Capsule conditioning produced Quali-V®-I capsules at the lower boundary of the moisture content specification range (4.5-6.5% w/w) and Quali-V®-I XD capsules within their specification range (2-3.5% w/w), as shown in Table 1. This confirmed appropriate moisture content for mechanical and puncture testing.

Table 1: The mean (± standard deviation) moisture content of Quali-V®-I and Quali-V®-I XD capsules when stored at relevant RH values for two weeks (n = 3).

Capsule	Moisture content (% w/w)	
	Oven (Ph. Eur.)	Thermobalance
Quali-V®-I stored at 34% RH	4.40 (+/-0.16)	4.39 (+/-0.18)
Quali-V®-I XD stored at 18% RH	3.52 (+/-0.38)	3.07 (+/-0.23)

- There was no significant difference ($p > 0.05$) between mean the puncture forces or mean compression forces of both Quali-V®-I and Quali-V®-I XD capsules, as shown in Figure 2.
- The shape of both puncture and compression profiles (Figures 3 and 4) were remarkably consistent between the two formulations, indicating that Quali-V®-I XD capsules remain mechanically acceptable despite the reduction in the capsule moisture content.
- The standard deviations for the mean puncture force (Quali-V®-I: ±0.57 N and Quali-V®-I ED: ±0.58 N) were low, demonstrating high reproducibility within the puncturing event for Quali-V®-I and Quali-V®-I XD capsules.
- As shown in Figure 2 and 3, the mean compression force at the point of permanent deformation (the elastic limit) was slightly higher for Quali-V®-I XD capsules, indicating a higher stiffness likely due to the lower moisture content of the formulation. This is unlikely to have any impact on the clinical and mechanical utility of the capsule.
- Quali-V®-I and Quali-V®-I XD capsules exhibited regular puncture holes (as illustrated in the left of Figure 1), with no fragmentation.
- No fragmentation occurred during compression testing for either capsule.

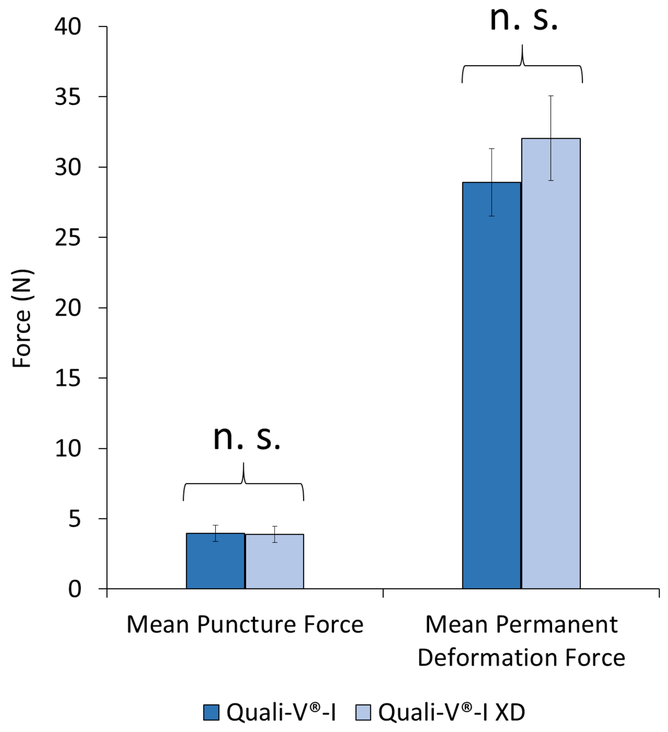
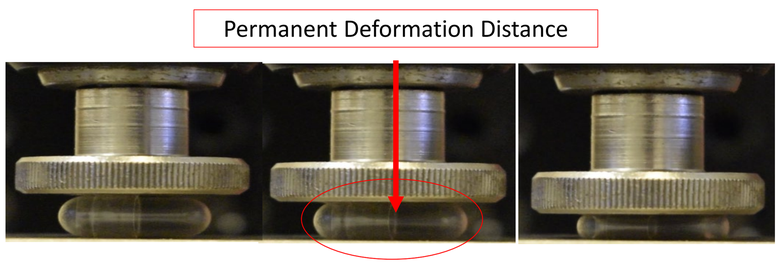


Figure 2: Mean puncture and mean permanent deformation force of Quali-V®-I (dark blue) and Quali-V®-I XD (light blue). The n.s. denotes no statistical significance (p > 0.05).



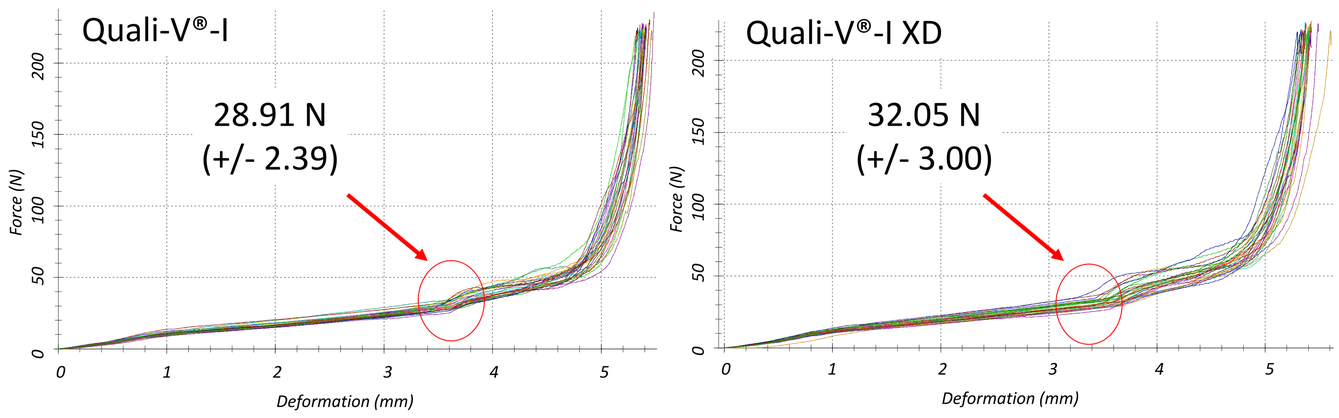


Figure 3: Force (N) vs deformation (mm) compression profiles of Quali-V®-I (left) and Quali-V®-I XD (right) capsules conditioned at their relevant relative humidity. The point of permanent deformation and its mean force (± standard deviation) is displayed on the graph. Testing ended at 5.5 mm of compression (n = 30). The images above the graphs illustrate the point at which permanent deformation begins.

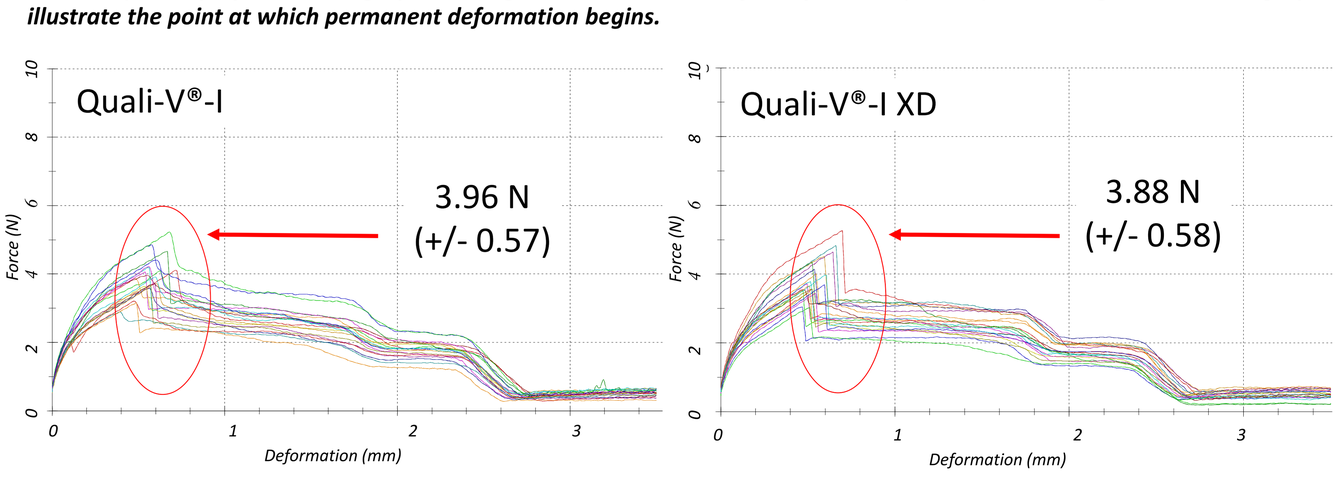


Figure 4: Force (N) vs deformation (mm) puncture profiles of Quali-V®-I (left) and Quali-V®-I XD (right) capsules conditioned at their relevant relative humidity. The point of puncture hole formation and mean puncture force (± standard deviation) is displayed on the graph. Testing ended at 3.5 mm insertion of the DPI pin (n = 20).

CONCLUSION

The mechanical properties and puncture performance of Quali-V®-I Extra Dry capsules are comparable to the more commercially established Quali-V®-I capsules, which encourages future studies to characterise pulmonary delivery from the innovative low moisture content capsule.

References: 1. Bell JH *et al.*: A moisture transfer effect in hard gelatin capsules of sodium cromoglycate. *J Pharm Pharmacol* 1973, 25: 96-103; **2.** Chong RHE *et al.*: Evaluating the sensitivity, reproducibility and flexibility of a method to test hard shell capsules intended for use in dry powder inhalers, *Int J Pharm* 2016, 500(1-2): 316-25. **3.** Torrisi BM *et al.*: The development of a sensitive methodology to characterise hard shell capsule puncture by dry powder inhaler pins. *Int J Pharm* 2013, 456(2): 545-52.
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