EVALUATING THE MECHANICAL PROPERTIES OF "EXTRA DRY" HARD-SHELL CAPSULES

Here, Sion Coulman, PhD, Senior Lecturer, Siamac Parker, PhD Student, and Prof James Birchall, PHD, Professor of Pharmaceutical Sciences, of Cardiff University, alongside Susana Ecenarro, Director of Scientific Business Development, and Mahmoud Farag, Scientific Business Development Manager, of Qualicaps Europe, discuss new developments in low moisture content capsule technology for hygroscopic and very moisture-labile APIs.

Dry powder inhalers (DPIs) are breath-actuated devices used to deliver drugs to the lung for local or systemic therapy. A DPI consists of two principal components, the inhaler device and a reservoir containing the micronised dry powder formulation. Hard-shell capsules are one such type of reservoir. These are inserted into the DPI and then punctured or cut *in situ* immediately prior to inhalation. One of the core functions of the capsule is to maintain the physical and chemical stability of the powdered formulation during storage. Increasing interest in the pulmonary delivery of biologics and potentially hygroscopic or very moisture-labile APIs has stimulated demand for capsules that are functional at lower moisture contents than current market-established capsules.

The moisture content of capsules at ambient relative humidity, which for pharmaceutical manufacturing is typically in the region of 40–60%, is determined by the inherent properties of the capsule material. Traditional gelatin capsules have a standard moisture specification of 13–16% under typical manufacturing conditions. The water within the capsule shell acts as a plasticiser, helping to maintain the flexibility required for capsule handling and functionality. Reducing the moisture content of the capsule therefore causes an accompanying increase in the brittleness of the material,[1] which is associated with increased risk of physical defects, such as fragmentation during handling or clinical use.[2]

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"EXTRA DRY" CAPSULES

Hydroxypropylmethylcellulose (HPMC) capsules have lower moisture contents (4.5–6.5% at 35–55% relative humidity). They do not require water to act as a plasticiser, which prevents brittleness and fragmentation when the capsule moisture content is reduced through exposure to low relative humidity.[3] In 2019, an HPMC

Dr Sion Coulman
Senior Lecturer
T: +44 2920 876418
E: coulmansa@cardiff.ac.uk

Cardiff University
Redwood Building
King Edward VII Avenue
Cardiff
CF10 3NB
United Kingdom

www.cardiff.ac.uk

Mahmoud Farag
Scientific Business Development Manager
E: mfarag@qualicaps.es

Qualicaps Europe
Avenida Monte Valdelatas, 4
28108 Alcobendas
Madrid
Spain

www.qualicaps.com

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capsule formulation (Quali-V®-I XD) with a reduced standard moisture content specification of 2.0–3.5% was developed with the aim of exploiting this property.[4] These "extra dry" (XD) HPMC capsules are intended to provide an appropriate reservoir for hygroscopic and especially moisture-labile DPI formulations.

This new HPMC capsule has been accompanied by the development of an XD gelatin capsule (Quali-G™-I XD; moisture content of 9.0–10.5%), which contains an additional plasticiser that aims to maintain the flexibility of the capsule material at lower moisture content. Polyethylene glycol (PEG) has previously been proposed as a plasticiser in capsules, with the addition of 4% w/w PEG 4000, for example, conferring a reduction in the brittleness of gelatin capsules with low moisture content.[5]

Whilst the development of XD capsules may provide the pharmaceutical industry with new opportunities for the encapsulation of particularly challenging DPI formulations, it will be important to ensure that this does not come at the expense of the mechanical properties of the capsule. DPI capsules are subject to various mechanical stresses during pharmaceutical processing (i.e. capsule filling, handling, packaging and transport) and when a DPI is used, where capsules are typically de-blistered, inserted into the DPI, punctured or cut and then subjected to the forces within the inhaler that enable aerosolisation of the powdered contents. A significant increase in brittleness at the lower moisture contents of XD capsules could result in a loss of capsule integrity at any of these stages and compromise product manufacture or performance in the hands of the end user, e.g. during de-blistering.

Capsule Formulation (saturated salt)	% Moisture Content of Capsule (+/- standard deviation)
Quali-V®-I (CaCl2)	4.36 (+/- 0.12)
Quali-V®-I XD (LiI)	3.24 (+/- 0.21)
Quali-G™-I (CaCl2)	13.62 (+/- 0.39)
Quali-G™-I XD (LiI)	9.31 (+/- 0.91)

Table 1: The mean moisture contents (%w/w) of Quali-V®-I, Quali-V®-I XD, Quali-G™-I and Quali-G™-I XD formulations, as determined by LOD tests (N=3), after storage over saturated salt solutions of either calcium chloride (CaCl2)or lithium iodide (LiI) for at least two weeks.

TESTING DPI CAPSULES

The mechanical properties of DPI capsules can be examined using a range of test methods, both published[6–9] and unpublished (bespoke in-house methods). These include a puncture performance test,[7,8,9] which uses a material testing machine to characterise the mechanical behaviour of capsule materials upon controlled puncture with a DPI pin. This particular test has been used for various capsules, stored at a range of relative humidities and temperatures.[8]

Whilst the puncture performance test is directly relevant to the clinical use of capsules in a DPI, more traditional compression testing methods, which provide an indication of the behaviour of the capsule under a crushing load, provide valuable information related to the behaviour of capsules in response to the forces they may experience during manufacture, handling, transport and storage. These testing methods can be used to determine the impact of the reduced moisture content of XD capsules on their elastic (reversible) and plastic (permanent) deformation under known compression forces, as well as the potential for complete loss of capsule integrity, i.e. capsule failure (the ultimate compressive strength).

DPI Capsule Test Case Study

The following describes a compression test that has been developed to evaluate the mechanical strength of different capsules that, together with a published puncture performance test,[9] was used to compare XD capsules with their more established higher moisture content counterparts. The capsules under investigation were:

- Quali-V®-I
- Quali-V®-I XD
- Quali-G™-I
- Quali-G™-I XD (containing PEG).

Prior to testing, all hard-shell capsules under investigation were conditioned for at least two weeks within glass desiccators containing saturated salt solutions of either lithium iodide (for XD capsules) or calcium chloride (for "standard" capsules stored at the lower boundary of their specification range), producing a relative humidity of 18% and 34%, respectively. The moisture content of each capsule type was then measured using an oven-based loss on drying (LOD) test (Table 1).[10] Capsule puncture tests were conducted using a previously published and established methodology.[8,9] Briefly, an angular pin from an RS01 DPI (Plastiape, Osnago, Italy) was mounted in a material testing machine and used to puncture the central section of the capsule dome. This event was measured quantitatively, using a force-displacement curve, and qualitatively by visual inspection under a light microscope.

A bespoke compression test was developed using a flat platen, with a diameter greater than the contact surface of the capsule, mounted in a Zwick material testing machine (ZwickRoell, Ulm, Germany). Capsules were mounted on the rig in a horizontal orientation and compression occurred at quasi-static speeds to negate the force of inertia and ensure deformation of the structure at a low strain rate. The test was completed with a detected force of 230 N.

Whilst the force-displacement puncture profile of capsules is well established (Figure 1A),[9] the compression profile for a hard-shell capsule is less well understood.[6] Capsule compression occurs in three stages (Figure 1B).

Stage I of the force displacement curve is indicative of the initial contact event between the platen and the capsule body, followed by a negligible observed reduction in capsule diameter prior to elastic deformation.

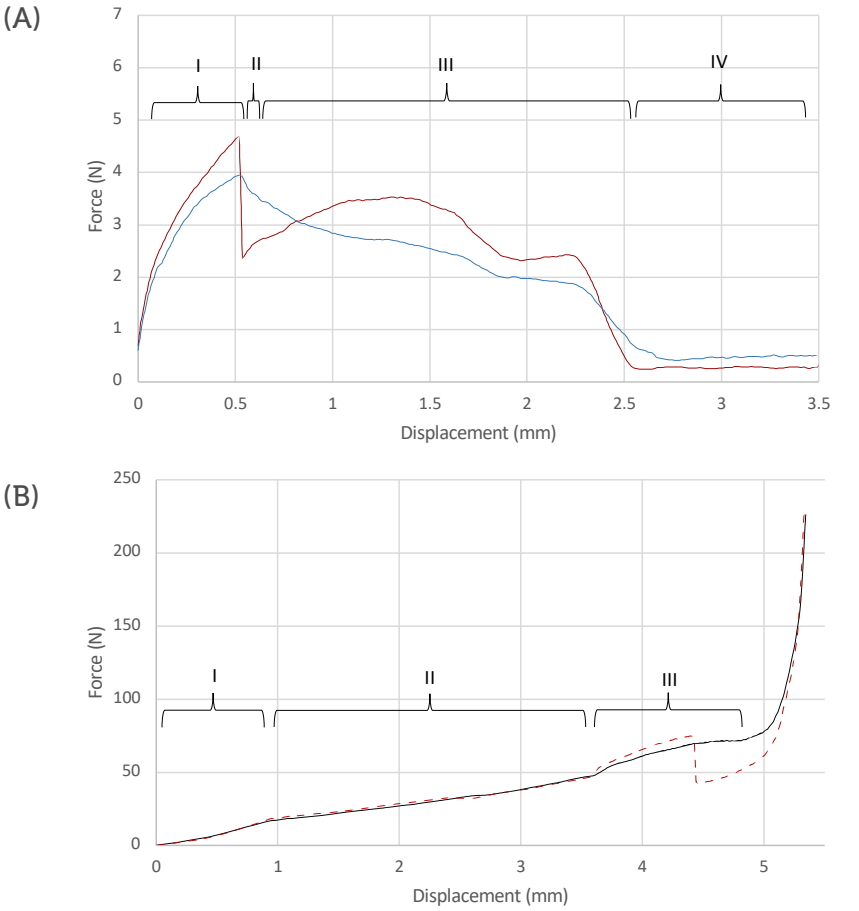

Figure 1: (A) Puncture profiles for a Quali-G™-I (red line) and Quali-V®-I (blue line) capsule formulation. (B) Compression profile from a capsule that remained intact (solid line) and one that failed (red dotted line) during a compression test. (C) Visualisation of a capsule at each stage of compression.

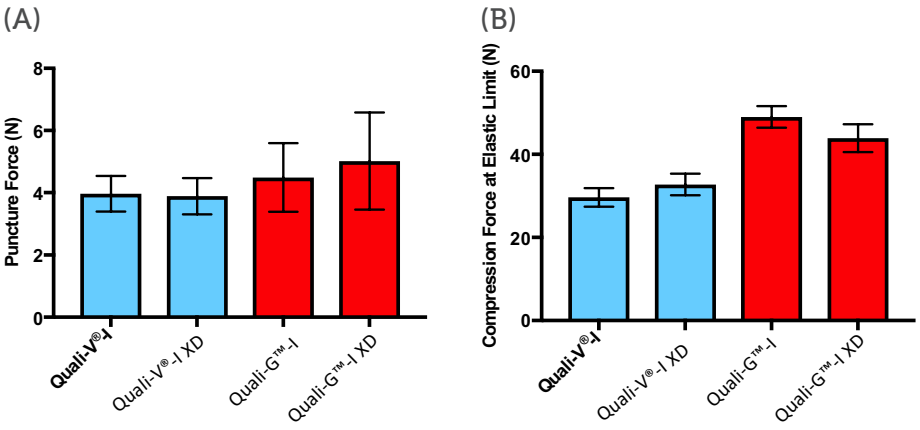

Figure 2: (A) Force required to puncture the capsule dome (n=20) and (B) the compression force required to initiate permanent deformation to the capsule shell (n=30) of capsules conditioned over saturated solutions of calcium chloride (Quali-V®-I, Quali-G™-I) or lithium iodide (Quali-V®-I XD, Quali-G™-I XD). Values represent the mean average and error bars are the standard deviation.

Stage II of the curve characterises elastic deformation of the capsule. If the compression test were paused at this stage and the load removed, the capsule would revert to its original shape. A small but discernible increase in the gradient of the force-displacement curve between 3 mm and 4 mm signifies the limit of the elastic phase for the capsule. This is the maximum extent to which a capsule can be compressed without permanent alteration to its size and shape. In this study we refer to this as the "elastic limit".

Compression of the capsule beyond its elastic limit results in plastic deformation, the third stage of capsule compression. Plastic deformation results in a permanent structural change to the capsule shell; the shoulders of the cap and the body begin to buckle under the compressive force that is applied. At this point the capsule is considered to be unacceptable for use. Within Stage III, complete capsule failure may also occur (i.e. fragmentation of the capsule shell), which is detected by a substantial vertical displacement in the force-displacement curve.

The mean puncture forces recorded for Quali-V®-I capsules (3.96 +/- 0.57 N) conditioned over saturated salts of calcium chloride (to create a relative humidity of 34%) were not significantly different from those recorded for the XD capsules (3.88 +/- 0.58 N). Compression tests also indicated comparable performance (Figure 2B) of Quali-V®-I and Quali-V®-I XD capsules. A marginal increase in the compression force (29.7N to 32.7N) at the elastic limit of the XD HPMC capsules suggests a minor decrease in capsule flexibility upon reduction of moisture content. Taken together, however, these data suggest that the reduced moisture content of the Quali-V®-I XD formulation, compared with its more established Quali-V®-I counterparts, is unlikely to have a detrimental practical impact on the flexibility of the HPMC capsule formulation.

Quali-G™-I and Quali-G™-I XD also performed comparably in terms of both the puncturing event (Figure 2A) and the compression test (Figure 2B). Both tests therefore indicate that the PEG excipient in Quali-G™-I XD capsules is able to mitigate the notable decrease in flexibility and increased brittleness, even at a moisture content of less than 10%.[5] Most remarkably, the compression data (Figure 2B) suggests that the XD gelatin capsule, stored at 18% relative humidity, may even be more

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flexible than the standard gelatin alternative stored at a relative humidity of 34%. This exemplifies and reinforces the value of PEG as a capsule excipient.[5]

However, whilst these studies indicate that a plasticiser is able to maintain the flexibility of a gelatin capsule at reduced moisture contents, it does not transform the mechanical performance of a gelatin capsule to a point where it is comparable to its HPMC counterparts. It was notable that two of the 20 Quali-G™-I and one of the 20 Quali-G™-I XD capsules fractured during compression tests, as indicated by a vertical displacement in the force-displacement curve (Figure 1) and visible fragmentation of the capsule shell. No fractures were detected in either HPMC capsule used in this study (Quali-V®-I and Quali-V®-I XD) and both require lower forces for puncture and compression than gelatin capsules (Figure 2), which indicates greater flexibility.

CONCLUSION

The development of capsules with reduced moisture contents and moisture transfer properties will assist with the development of capsule-based DPI products for hygroscopic and very moisture-labile APIs. However, a reduction in capsule moisture content is typically associated with increased capsule brittleness and the risk of physical capsule defects or failure during manufacture of the product or its clinical use. Understanding the mechanical properties of innovative XD capsules is therefore key to determining their commercial and clinical potential.

In the study covered in this article, an established puncture test[9] and a bespoke compression test method were used to characterise XD capsules and compare them with more clinically and commercially established capsules with a higher moisture content. The study indicated that the reduced moisture content of the XD capsules does not have a significant impact on their mechanical performance. This encourages further evaluation of these low moisture content capsules for the aerosolisation of dry powder formulations to be used in DPIs.

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ABOUT THE ORGANISATIONS

Cardiff University is a member of the Russell Group of research-intensive universities (ranked 5th overall by the Research Excellence Framework 2014) and has been recognised as a leader in translational science (2nd overall in impact by the Research Excellence Framework 2014). The School of Pharmacy and Pharmaceutical Sciences was ranked the joint top School of Pharmacy in the UK on the basis of its publications, research environment and impact and 12th in the world by the Shanghai World Rankings. The department's research is highly interdisciplinary, spanning the full translational pathway associated with pharmaceutical medicine.

Qualicaps, a Mitsubishi Chemical Holding Corporation company, has over 120 years of experience in manufacturing hard capsules and a strong record of pioneering new forms of drug administration. Qualicaps is responsible for several milestones in the history of hard capsule development, introducing features so widely accepted and trusted that they have since become industry standards. The company takes pride in producing each capsule with the aim of offering specific and optimal solutions for drug delivery and overall health and wellbeing challenges. By way of Qualicaps' rich history, knowledge, capabilities, global presence and kaiteki values, the company is leading the way for the next-generation capsule.

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ABOUT THE AUTHORS

Sion Coulman completed his PhD in 2005, studying microneedle-mediated intradermal gene delivery to human skin. He is a Senior Lecturer at Cardiff University with an interest in pulmonary and dermal drug delivery and works at the interface of pharmaceutical science and engineering. Dr Coulman has specific expertise in the design and performance of drug delivery devices, both in the laboratory and clinical practice, and also has active research interests in bioprinting technology and tissue engineering. His research is funded by a diverse selection of national and international funding bodies, charities and commercial partners from the pharmaceutical industry.

Mahmoud Farag is a Scientific Business Development Manager at Qualicaps Europe, where he plays an important role in supporting pharmaceutical R&D departments with solid oral dosage developments, as well as capsule-based DPIs. He also leads the Qualicaps participation in different research programmes in collaboration with a number of research centres and universities to further study the properties and performance of inhalation capsules. Mr Farag holds an MSc degree from Uppsala University, Sweden.

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