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, which is associated with increased risk of physical defects, such as fragmentation during handling or clinical use.

**“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. In 2019, an HPMC...
“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.”

The mechanical properties of DPI capsules can be examined using a range of test methods, both published8–9 and unpublished (bespoke in-house methods). These include a puncture performance test,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-Ⅴⅰⅰ-I
- Quali-Ⅴⅰⅰ-Ⅰ XD
- Quali-Gⅳⅳⅳ-I
- Quali-Gⅳⅳⅳ-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 calcium chloride (CaCl2) or lithium iodide (LiI) to store over saturated salt solutions of either calcium chloride (CaCl2) or lithium iodide (LiI) for at least two weeks.

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Table 1: The mean moisture contents (%w/w) of Quali-Ⅴⅰⅰ-I, Quali-Ⅴⅰⅰ-Ⅰ XD, Quali-Gⅳⅳⅳ-I and Quali-Gⅳⅳⅳ-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

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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%. 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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4. Encinas JL, Ecenarro S, "Quali-V Extra Dry: A Novel Capsule For Delivering Hygroscopic Pharmaceutical Drugs".


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.
ONE CUSTOMER, ONE CAPSULE

Capsules are the very essence of Qualicaps®

As a company dedicated to capsules we have a unique perspective on how to contribute to health.

Qualicaps® delivers pharmaceutical-grade capsules together with a comprehensive service along the drug product life cycle through our global team of commercial, scientific and technical services.

Quali-V®-I capsules for inhaled drug delivery.

- Strict Microbiological Control
- Better Aerosolization
- Inner Surface Control
- Reduced Powder Adhesion
- Superior Puncturing Properties

Quali-V®-I Extra Dry, when a minimum moisture content level is required

Lower moisture content (2.0 - 3.5%)