



FORMULATION SOLUTION FOR MOISTURE-SENSITIVE DRUGS

In this article, Laura Canalejas, Scientific Business Development Manager at Qualicaps Europe, outlines the benefits of Quali-V® Extra Dry – a hypromellose capsule designed for moisture-sensitive formulations.

It is well known that moisture affects the performance of some drug products, presenting a fierce challenge in the formulation of oral dosage forms. Moisture may have a significant impact on a wide range of chemical, physical and microbial properties of the finished pharmaceutical product, leading to a degradation of the API and a subsequent loss of potency and reduced shelf life.

The interaction of moisture with pharmaceutical solids is essential to an understanding of water-based processes, for example, manufacturing processes or prediction of the stability of solid dosage forms. Furthermore, both the API and excipients have different moisture sorption properties that can result in unexpected processing-induced phase transitions.¹

Dosage forms are exposed to moisture from many sources – including bulk drug, excipients, manufacturing processes, environmental conditions, etc.² In terms of excipients, using hard capsules could contribute to minimising the potential moisture effect on the formulation since they act as a container and therefore as a physical barrier to protect the filling content.

Back in the 1990s, Qualicaps introduced the first vegetal capsule based on hypromellose (HPMC) into the pharmaceutical market, branded as Quali-V®. This plant-based capsule made it possible to overcome stability issues that had emerged in gelatin capsules and were prevailing in the two-piece capsules market from the 19th century.

Despite the low moisture content present in HPMC capsules (three times reduced versus gelatin capsules), there are still some APIs (e.g. pancreatin, omeprazole,

ranitidine, dabigatran and tiotropium) and excipients (polyethylene glycols, acid glycerol esters and acid triglycerides) whose hygroscopicity and sensitivity to moisture may alter the properties of the product.

Such hygroscopic and moisture-sensitive compounds could be challenging for formulators and may involve extra investment due to the need to apply different pathways to protect the API – i.e. galenic forms such as pellets or capsule-in-capsule technology, a final additional drying process after filling or the use of moisture-protective packaging materials. The possibility of drying the filled capsule to reduce the water content as much as possible exposes the whole filling to harsh drying conditions. Furthermore, adding an additional step in the process after the filling involves extra resources in terms of capabilities (with dedicated equipment, room, human resources and conditions) and timing, extending the process up to 12–14 hours and thus decreasing the overall yield.

Quali-V® Extra Dry, the HPMC Capsule Designed for Moisture-Sensitive Formulations

Qualicaps, the pioneer hard capsule manufacturer, which developed the

“The production process for Quali-V® Extra Dry was adapted to incorporate an extra drying phase by using unique equipment developed by Qualicaps Europe.”



Laura Canalejas
Scientific Business
Development Manager
E: lcanalejas@qualicaps.com

Qualicaps Europe
Avenida Monte Valdelatas, 4
28108 Alcobendas
Madrid
Spain

www.qualicaps.com

“In HPMC capsules, water does not act as a plasticiser – hence the moisture content can be decreased whilst the mechanical strength remains.”

first HPMC capsule, has launched a novel HPMC capsule that resolves the aforementioned undesirable effects and additional costly countermeasures caused by moisture. Quali-V® Extra Dry is a capsule with an extremely reduced moisture content (2.0%–3.5%), half that of the standard HPMC capsules on the market.

In order to obtain such a low moisture value, the production process for Quali-V® Extra Dry was adapted to incorporate an extra drying phase by using unique equipment developed by Qualicaps Europe, with funding awarded by the European Union through the Centre for the Development of Industrial Technology.

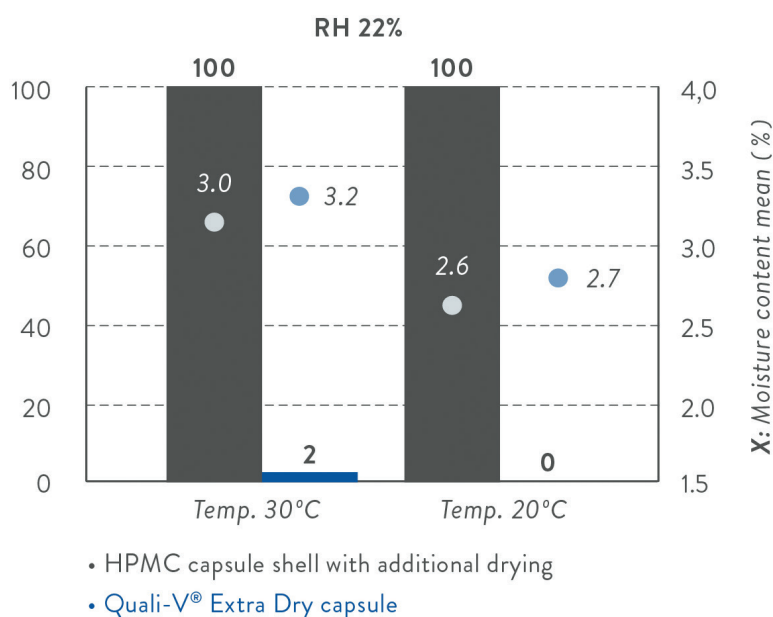


Figure 1: Capsule brittleness/impact test (empty capsule; n=50) (Qualicaps Japan).

HPMC Extra Dry Capsule				
Parameter	Description			
Moisture content	2.0%–3.5%			
Dissolution	USP and Eur.Ph dissolution profile at pH 1.2 and pH 6.8			
Brittleness	Minimal			
Runnability	Tested in automatic high-speed filling machines:			
	MG2 Planeta 100	Bosch GKF-1400	IMA MATIC-120	IMA Adapta 100
Storage conditions	15°C–30°C in heat-sealed aluminium liners			
Handling conditions	Temperature: 20°C–30°C (set point 25°C ± 2) RH: 15%–25% (set point 20% ± 2)			
Shelf Life	Capsule: 18–24* months Final drug product: 2–3 years			

* Stability studies carried out at ICH accelerated and long-term conditions meeting the specifications after 6 months. Shelf life depends on the size of the capsule.

Table 1: Description of the Quali-V® Extra Dry capsule properties.

Nevertheless, this special drying process does not compromise the capsule's physical or mechanical properties. The innovative

capsule maintains the advantages of the standard Quali-V® – i.e. without preservatives, pharmaceutical grade, plant-based suitability for certain dietary and religious restrictions and chemically inert with the absence of crosslinking phenomena. Some Quali-V® Extra Dry properties are described hereafter and listed in Table 1.

Brittleness is a critical aspect when capsules come into play. Water in gelatin capsules functions as a plasticiser and, when this level falls below the specification limits, the capsules become brittle and crack on handling. However, in HPMC capsules, water does not act as a plasticiser – hence the moisture content can be decreased whilst the mechanical strength remains.^{3,4,5}

An impact test, by dropping a weight of 50 g from 10 cm above the capsule, was performed to evaluate how fragile Quali-V® Extra Dry could be at low relative humidity environmental conditions: minimal brittleness has been observed, as shown in Figure 1.

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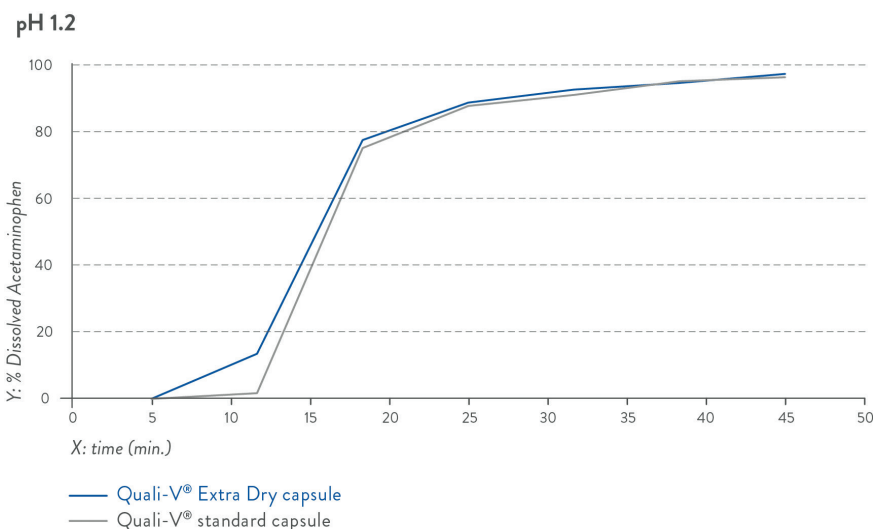


Figure 2: Dissolution profile for pH 2.1 capsule fill formulation – acetaminophen.

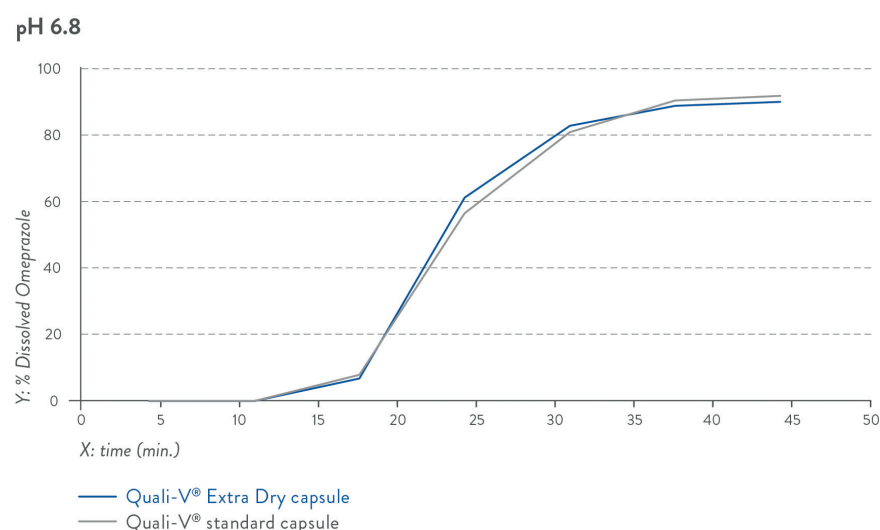


Figure 3: Dissolution profile for pH 6.8 capsule fill formulation – omeprazole pellets.

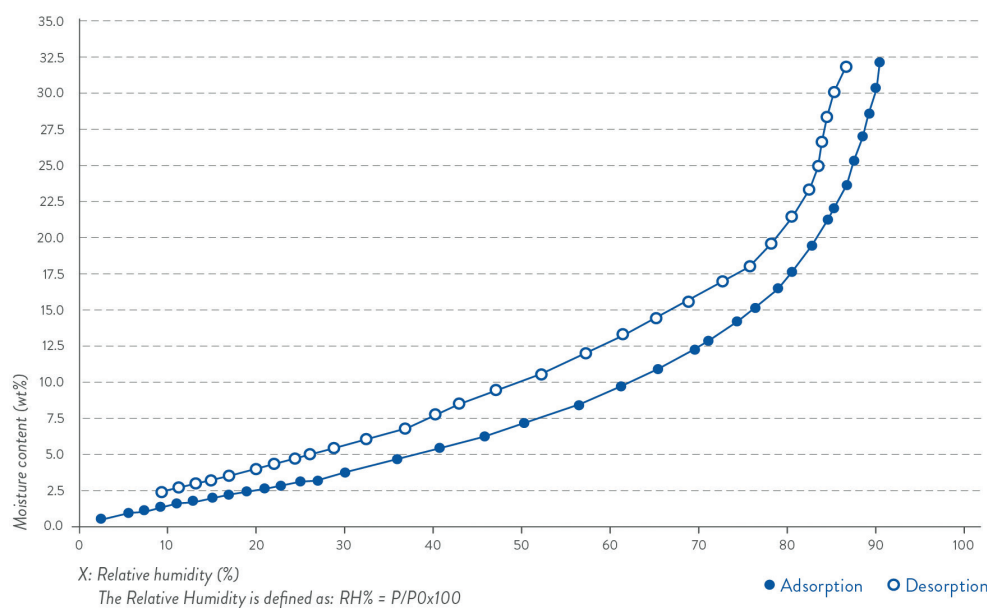
The dissolution profile of this novel capsule is equivalent to the one of standard HPMC capsules, complying with both USP and Eur Ph dissolution profiles at either pH 1.2 or pH 6.8 (Figures 2 and 3).

It is important to highlight that Quali-V® Extra Dry requires specific handling and storage conditions in order to retain the moisture content within the specification and thus secure its quality properties. Since Quali-V® Extra Dry is provided in heat-sealed and moisture-proof aluminium liners, only the temperature needs to be controlled between 15°C and 30°C when storing these capsules.

Once the bag is opened, the following handling and filling conditions are highly recommended: a temperature between 20°C and 30°C as well as a relative humidity in the range of 15%–25%. Such handling conditions have been defined by performing an absorption and desorption study with a volumetric method (Figure 4).

The present data are obtained by means of a volumetric method, as per USP41<1241>, EP9.02.9.39.

“The Quali-V® Extra Dry capsule, with a guaranteed extremely low moisture content, provides enormous benefits when formulating moisture-sensitive drugs.”



RH (%)	wt/%
14.94	1.9771
16.90	2.1951
18.92	2.4111
20.95	2.6282
22.96	2.8464
24.91	3.067
26.74	3.286
30.11	3.7131
36.02	4.5543

The present data are obtained by means of a volumetric method as per USP41<1241>, EP9.0 2.9.39.

Figure 4: Water vapour absorption/desorption isotherm curve (25°C) (Qualicaps Japan).

CONCLUSION

In summary, the Quali-V® Extra Dry capsule, with a guaranteed extremely low moisture content, provides enormous benefits when formulating moisture-sensitive drugs. It has a number of advantages over standard HPMC capsules – such as superior chemical inertness, stability results by avoiding compatibility issues and brittleness when environmental conditions are out of the standard range – and the Extra Dry capsule makes it possible to maximise those benefits even when formulating moisture-sensitive drugs. Furthermore, the Quali-V® Extra Dry capsule may limit or even avoid the need for other measures to control moisture, such as adding a drying step in the filling process, thus improving the manufacturing yield.

ABOUT THE COMPANY

Qualicaps, a Mitsubishi Chemical Holding Corporation company, has more than 120 years of experience as a company dedicated to manufacturing capsules. It delivers pharmaceutical-grade, hard, two-

piece capsules to the pharmaceutical and consumer healthcare industries, together with a comprehensive service along the product life cycle through a global team of commercial, scientific and technical experts. Qualicaps is a responsible company that takes pride in producing each capsule with the aim of offering specific and optimal solutions for drug delivery and overall health and wellbeing challenges.

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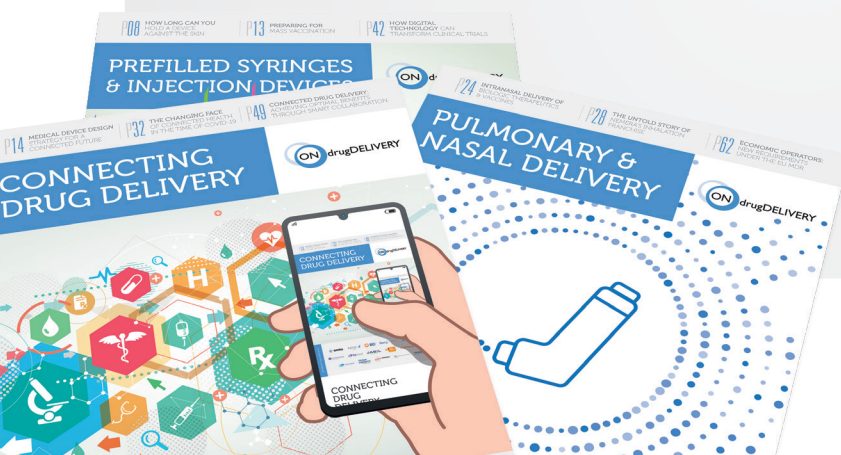
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ABOUT THE AUTHOR

Laura Canalejas is Scientific Business Development Manager at Qualicaps Europe. She holds a bachelor's degree in Biotechnology and an MSc in Pharmaceutical Industry. Her main work mission in Qualicaps is to continuously assess and provide formulation support throughout the whole life cycle of products in hard capsule dosage form, especially during the development of NMEs. Ms Canalejas also takes an active role in promoting collaborations with third parties, focusing on the application of state-of-the-art capsule technologies.



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Qualicaps®, the company responsible for several milestones in the history of hard capsule development within the pharmaceutical industry, continues to innovate by presenting an extra dry cellulose capsule that will enable the development and production of moisture-sensitive and hygroscopic drugs.

Quali-V® Extra Dry, the cellulose capsule with an extremely low moisture content ideal for moisture-sensitive and hygroscopic pharmaceutical drugs.



Pharmaceutical
Grade



100%
Vegetal Origin



Preservative
Free



Standard HPMC
Equivalent
Dissolution Profile



Minimal
Brittleness



Lower Moisture
Content
(2.0%-3.5%)

 **Qualicaps**

