

# HPMC Capsules for Moisture Sensitive and Hygroscopic Products

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**Abstract:** *Background:* Moisture content varies in capsules made from different materials. Gelatin capsules contain 13-16% moisture. HPMC (Hydroxypropyl methyl cellulose or Hypromellose) capsules may contain moisture 2- 8%. Usual HPMC capsules have inherently low moisture content which allows for the encapsulation of ingredients that are sensitive to moisture and are hygroscopic in nature. This has greatly broadened the scope of capsules in drug delivery. Moisture content of HPMC capsules can be reduced as low as 2%. HPMC capsules lower moisture content is better for moisture sensitive and hygroscopic products. *Objective:* Low moisture content of HPMC capsules help to improve stability of moisture sensitive active pharmaceutical and active nutraceutical active ingredients. This is illustrated with examples. Different properties of HPMC capsules helps targeted delivery. It offers some special advantages for nutraceutical products. It also helps to improve physical stability of capsules. Liquid filled hard capsules provide many options and are commonly used for nutraceutical products.

**Keywords:** HPMC Capsules, Moisture Sensitive Products, Hygroscopic Products, Liquid-filled Hard Capsules

## 1. Introduction

Higher moisture content in some capsules may affect potency or strength, chemical degradation, change in polymorph forms and capsules characteristics for moisture sensitive and hygroscopic APIs (Active Pharmaceutical Ingredients) and excipients. Moisture content of commonly used capsules is given in Table 1.

Table 1. Moisture content of hard capsules.

Gelatin	Gelatin PEG	HPMC	Low moisture HPMC
13-16%	10-12%	3-8%	2-3.5%

Usual HPMC (Hydroxypropyl methyl cellulose or Hypromellose) capsules have inherently low moisture content which allows for the encapsulation of ingredients that are sensitive to moisture and are hygroscopic in nature. This has greatly broadened the scope of capsules in drug delivery. Due to their manifold advantages, HPMC capsules are gradually gaining popularity among pharmaceutical and nutraceutical manufacturers [1]. HPMC capsules can be dried to low moisture HPMC capsules by drying in low humidity. Such dried capsules should be packed in airtight aluminum

lined bags. HPMC capsules maintain physical characteristics and present very low brittleness at low RH as compared to gelatin capsules. Besides there is no cross-linking risk and does not affect dissolution profile. HPMC capsules provide higher bioavailability for poorly soluble APIs. The commercially available HPMC capsules range from conventional powder-fill to liquid-fill capsules, sprinkle capsules, dry powder inhalation capsules and much more, offering greater formulation flexibility for product development [1, 2].

## 2. Dry Powder Inhalers

Capsule-based dry powder inhalers (cDPIs) are widely utilized in the delivery of pharmaceutical powders to the lungs. The encapsulation of hygroscopic drugs in hard gelatin capsules may result in increased water loss from the capsule and subsequently changes in the powder properties (e.g., increased agglomeration) as well as brittleness of the capsule. Both may result in reductions in the fine particles fraction (FPF) and deep lung deposition of the drug. In general, HPMC capsule shells seem to be less sensitive to moisture transfer and low water content [3].

### 3. Hygroscopic/Moisture Sensitive APIs

Dabigartan, Enalapril, Lansoprazole, Losartan, Omeprazole, Pancreatine, Ranitidine, Tiotropium (inhalable powder) are some of the examples hygroscopic / moisture

sensitive APIs. HPMC capsules for dry powder inhalers (DPI) minimize agglomeration, inconsistent delivery and hygroscopicity issues. Table 2 gives details of some marketed products where HPMC capsules are used [4].

*Table 2. Some products where HPMC capsules are used.*

Active	Brand name	Company
Dabigartan Etexilate	Pradaxa	Boehringer Ingelheim
Dexlansoprazole	Kapidex/Dexilant	Takeda Pharmaceuticals
Dutasteride and Tamsulosin	Jalyn Combodart/Duodart	Catalent/Rottendorf GlaxoSmithKline
Pancrelipase DR	Creon Ultresa	AbbVie Adare Pharmaceuticals
Glkycopyrronium bromide	Seebri Breezhaler	Novartis
Indacaterol and Glycopyrronium bromide	Ultibro Breezhaler	Novartis
Tobramycin	Tobi Podhaler	Novartis

### 4. Hygroscopic Excipients

Amines, Ammonium sulfate, Calcium chloride, Citric acid, Glycerin, fatty acid esters, Croscarmellose sodium, Maltodextrin, Microcrystalline cellulose (MCC), medium chain fatty acid triglycerides, low molecular weight Polyethylene glycols (PEGs), Polyvinyl pyrrolidone (PVP), Sodium chloride, Sodium sulphate, Sorbitol are some of the examples of hygroscopic excipients.

PEG is the most common solvent used for liquid fill capsules. Lower molecular weight PEG exhibit better solubility for most poorly soluble actives. PEGs below MW 4000 are not compatible with gelatin hard capsules. However, PEG 1000 is compatible with HPMC hard capsules. Liquid filled hard capsules can help to improve bioavailability by dissolving poorly soluble APIs.

### 5. Different Aspects of HPMC Capsules

Dissolution controls the release and exposure of the drug formulation into the dissolution media. Dissolution of gelatin capsules is not affected by the pH of dissolution media. However HPMC capsules exhibit difference in dissolution profile at different pH level. At certain pH levels, the dissolution profile may not meet the expectations of the pharmaceutical applications. Earlier, to an extent, this was considered as one of the limitations in using HPMC capsules for certain formulations at specific biological pH media. However, advancement in technology has now enabled the next generation of HPMC capsules to meet the expected dissolution requirements of pharmaceutical formulations at all biological pH media. A study conducted using ACG's next-gen HPMC capsules shows a dissolution profile, which is comparable to gelatin capsules, over 80% release is reached at 15 min. [5]. However, in order to match disintegration time with fast disintegrating tablets, there is need to develop capsules which can disintegrate within a minute. This could be probably done by incorporating disintegrating agents in the capsules shell.

HPMC capsules prepared using hot process not requiring gelling agent are preferred for pharmaceutical applications.

These meet dissolution requirements across all biological pH. HPMC capsules prepared by cold process using gelling and co-gelling agents are preferred in nutraceuticals / dietary supplements.

There is an additional way to optimize the process from encapsulation to packaging, maintaining the desired bacterial counts. After filling, HPMC capsules can be stored at low RH. Once a satisfied equilibrium is obtained, the probiotic capsule can be blister packaged. This ensures a reduction in the moisture content that will be maintained at a low level from the initial encapsulation value. If the storing conditions are 20°C and 11% RH, the final moisture content is around 1%. There is no brittleness risk to the capsules at these low levels. Furthermore, in HPMC capsules, water does not act as plasticizer, like in gelatin where brittleness could be observed.

### 6. Facilitates Targeted Delivery

Apart from protection against moisture, HPMC capsules are excellent targeted delivery systems for gastric acid-sensitive nutraceuticals, including probiotics. The gastro-resistant properties of HPMC capsules, owing to the presence of a suitable gelling agent, allows them to protect the formulations, which are susceptible to degradation in stomach acid and deliver to the targeted absorption site such as intestine and colon.

### 7. Nutraceuticals

Better acceptance in nutraceuticals and customer demand is driving pharmaceutical companies to use HPMC capsules [4]. Moisture content plays a vital role in stability amino acids (acetyl-L-carnitine HCl, L-arginine base), vitamins (Vitamin C, Thiamin, Vitamin B12, Pantothenic acid), enzymes and coenzymes (NADH), certain minerals and their salt forms (Copper, Iron, Zinc, Magnesium chloride) and certain herbal preparations. For these formulations where moisture significantly affects the activity of the product, HPMC capsules offer an apt alternative owing to its low inherent moisture content.

## 8. Promise of Stability

Product stability is a particularly important concern in nutraceutical industry because it affects the overall appeal and aesthetic of the product. The elegant appearance of the product has a profound impact on consumer minds. In such a scenario, a visually discolored product can create a wrong perception about the brand and its quality. This challenge is overcome by HPMC capsules as these capsules, being devoid of plasticizer and low in moisture content, do not undergo cross-linking or react with ANI (Active Nutritional Ingredient) [6].

For example, Ascorbic acid (vitamin C) was found to be discolored (brown colored) in gelatin capsules. However, it was found to be perfectly stable in HPMC capsules even at accelerated storage conditions such as 40°C and 75% RH for 2 months [7] In another study, bacterial strain *Lactobacillus fermentum* CECT 5716 when encapsulated in gelatin and HPMC capsules and stored at RT as well as at 4°C, it was found that the best viability of the probiotic was observed in HPMC capsules (109 CFU/capsule) at both the temperatures [8].

Some examples of marketed dietary supplements using HPMC capsules are given in table 3 [9, 10].

**Table 3.** Some marketed dietary supplements using HPMC capsules.

Dietary supplement	Company
DHA Liquid Filled Hard Capsules	Vantage Nutrition, India
Damiana Herb 300 mg	Bio-Health Ltd., UK
Thera Vedas's Ajay-Allergy support formula	Organix South, USA
Natren Life Start 2	Natren, Inc., USA
Coloclear	Higher Nature Ltd., UK
Jarro-Dophilus EPS	Jarro Formulas, USA
Culurelle Hs Capsules	Kirkman Labs, USA
Align Daily Probiotic Supplement capsules	Procter & Gamble, USA
Sportlegs Supplement	Sportlegs, USA
Planetary Herbals Cinnamon	Planetary Herbals, USA
Ex-Tx II	Progressive Labs, USA

## 9. Conclusion

HPMC capsules are well suited for moisture sensitive and hygroscopic products to improve stability. Low moisture HPMC capsules retain physical characteristics/does not turn brittle and dissolution is not affected even when stored at low humidity. Improvement in stability is useful for APIs for pharma as well as nutraceutical products industry as illustrated by examples. Different aspects of HPMC capsules should be considered while selecting capsules. It also helps for dry powder inhalers, and targeted drug delivery. Dissolution of poorly soluble APIs can improve bioavailability. Liquid filled hard capsules are commonly used for dietary supplements.

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