Tablets & Capsules
Solid Dose Digest

Insights, advice, and industry news about formulating, manufacturing, and packaging solid dosage forms brought to you by Tablets & Capsules magazine

Ask an Expert

Properties of HPMC capsules

Q: Can you fill HPMC capsules with hygroscopic formulations?

Brian Jones, Brian Jones Associates says:

Many of the early papers that addressed capsules made from hydroxypropyl methylcellulose (HPMC), or hypromellose, included comments about their moisture content, indicating that they did not lose their mechanical properties with a reduction in moisture content [1-3]. In contrast, gelatin capsules become brittle when their moisture content—which typically is 13 to 16 percent—falls below 10 percent. The problem becomes evident when patients store their medicines incorrectly, and breakage occurs during subsequent handling, i.e., during de-blistering or when used in dry powder inhalers.

In 1998, Ogura et al. of Shionogi Qualicaps published the results of the first study that described the use of HPMC capsules. The researchers made a statement in their conclusions that an HPMC capsule "maintains mechanical integrity under extremely low moisture conditions, such as created by the addition of excipients that absorb water" [1].

Jones first described the ability of HPMC capsules to retain their integrity when filled with "materials that are sufficiently hygroscopic to remove enough moisture from gelatin capsules to cause them to break and split" [3]. At that time, the integrity of the HPMC capsules was important because of the industry's interest in filling hard capsules with liquid, semisolid matrix formulation that could include excipients with a degree of hygroscopicity.

The literature since that time includes many references to HPMC capsules being useful when filling capsules with hygroscopic formulations. It is possible, however, to interpret that statement about usefulness in two ways. It could mean that the capsules retain their integrity when filled with hygroscopic formulations and exposed to varying conditions. Or it could mean that HPMC capsules filled with hygroscopic substances retain their properties when placed in pharmaceutical packaging as per the standard procedures for stability testing.

Two studies that applied the first interpretation in setting up their protocols were published in 2015. In the first study, Al-Tabakha et al. carried out a hygroscopicity and stress test by filling capsules with polyvinylpyrrolidone (PVP), a hygroscopic excipient, and exposing them to a range of relative humidity (RH) levels—15, 45, 70, and 90 percent [4]. The researchers compared one type of gelatin capsule and two types of HPMC capsules—one with a gelling system of carrageenan and potassium chloride and the other with no added gelling agents that was made using a hot-mold process. At the highest RH, the PVP in the gelatin capsules liquefied and leaked out. The

HPMC capsules had a slower rate of uptake than the gelatin capsules, and none of the capsule types protected their contents from moisture. Based on their findings, the authors questioned the claim that HPMC capsules are suitable for hygroscopic formulations.

The second study, by Braham et al., included a similar series of tests [5]. The researchers compared gelatin capsules with HPMC capsules produced by the hot-mold process. They filled samples of both capsule types with spray-dried lactose, which they characterized by scanning electron microscopy, differential scanning calorimetry, and particle size analysis. They compared the moisture uptake of empty and filled capsules by using dynamic vapor sorption. The gelatin capsules showed a stronger attraction for moisture than the HPMC capsules and had a different mechanism of water absorption. A saturated monolayer formed on the gelatin capsules at 20 percent RH, whereas the monolayer on the HPMC capsules increased slowly at levels up to 70 percent RH. The capsule shells swelled during the process. The thickness of the HPMC capsules increased up to 40 percent RH and then decreased up to 70 percent RH. On the other hand, the gelatin capsules increased in thickness up to 40 percent RH and then did not change up to 70 percent RH. The lactose in both types of capsule showed signs of crystallization as the RH increased from 50 to 70 percent. The authors concluded that the moisture properties of the capsules were different, and based upon the changes in the lactose form, neither capsule type adequately protected its contents.

Both studies were perfectly correct in their conclusions, but in applying a literal rather than a qualified interpretation, they misunderstood the claims of the capsule manufacturers, i.e., that HPMC capsules provide a degree of protection from hygroscopic materials when the filled capsules are packaged in sealed containers (blisters or bottles) and are not exposed to the ranges of RH used in the two studies. Pharmaceutical manufacturers can use desiccants in the packaging to maintain a low RH, if required, with no risk of embrittlement of the shells, as would happen with gelatin capsules. The hygroscopic fills would embrittle the gelatin worse than the HPMC even when stored properly.

Pradaxa, a drug product marketed by Boehringer Ingelheim, is a very good example of a filled HPMC capsule that was chosen for its low moisture content to protect the active pharmaceutical ingredient [6]. I hope that this article corrects any misunderstanding about the relationship between HPMC capsules and hygroscopic formulations. The article will enable the correct design of stability experiments in future studies to assess the performance of HPMC capsules.

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