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Impact of capsule selection on formulation stability in dry powder inhalers (DPIs)

An examination of differences between gelatin and HPMC capsules and their respective contributions to DPI formulations

Matt Richardson
Capsugel

With the growing number of dry powder inhalers, it has been well recognized that a unique set of requirements related to these formulations exist separately from traditional, solid-dose, oral formulations. These requirements have implications for devices, containers and manufacturing equipment, such that a successful product will ultimately be the partnership of these. This article will discuss the unique qualities associated with a dry powder inhaler formulation and ways to streamline DPI formulation efforts by the choice of capsule.

Introduction

Many diseases and disorders of the lungs, such as chronic obstructive pulmonary disease (COPD) and asthma, have been successfully treated through the use of inhalation-based formulations due to the localized delivery/action of active pharmaceutical ingredients (APIs) to the lungs. In recent years, there has been a growing interest in the development of inhalation therapy to address other disease states given the avoidance of first-pass metabolism via delivery to the lungs that the inhalation route affords. A few examples within the literature list antibiotics, diabetes and cystic fibrosis.[1] Of particular interest have been those drugs that are protein-based or use peptide therapeutics which, to date, have primarily been available via injection.

The delivery of inhalation-based formulations is achieved by devices that fall into three segments: nebulizers, metered dose inhalers (MDIs), and dry powder inhalers (DPIs).[2] There is much discussion about which device is most appropriate, though that discussion is well beyond the scope of this article. It is of note however, that MDIs and DPIs have been shown to function equally well when patients were treated with acute systems of COPD.[3] DPIs seem to be a popular choice among patients who can better coordinate dosing with their personal breathing pattern.[4] They tend to be both less complex and less expensive to manufacture than MDIs, especially those DPIs that use two-piece capsules as the container for the dose.

Dry powder inhalers: the sum of the parts

While less complex than their MDI counterparts, capsule based DPIs still require a successful combination of elements to be effective. The formulation, its container and the device must all work in concert to effec-

tively deliver the dose to the patient. Interaction of the formulation and the container must be limited. In some cases, the container can act to protect the formulation. Likewise, the container must be compatible with the device, be easily pierced without shattering and have properties to retain shape for optimal interaction with the device. Even the container and formulation must be compatible such that the formulation is easily delivered to the patient without being trapped in the device.

Formulations for DPIs are especially attractive due to their simplicity, as the formulation usually consists of the API alone or the micronized API and an inert carrier like lactose or mannitol. The amount of formulation is typically less than 40 mg and the trend is for even lower fill weights to be used. As the formulation needs to be quickly and easily evacuated from both container and device, it is important that it remain free-flowing from the point of manufacture to the point of inhalation by the patient. This particular property will sometimes require additional attention, as DPI formulations tend to have a hygroscopic nature and the absorption of moisture can quickly cause a change in powder flow properties.

Polymer implications for dry powder formulations

For these factors, interplay between the formulation and the container become very important and the properties of the capsule come into play. There are two choices in capsule polymers that can be used for DPI formulations: hard gelatin capsules or hydroxypropyl methylcellulose (HPMC) capsules. Hard gelatin capsules have been successfully used in DPIs for more than 30 years, making them a standard choice for DPI development, given the wealth of data available on their use. HPMC capsules, like Capsugel Vcaps capsules, while certainly newer to the market than hard gelatin capsules, have also demonstrated excellent properties for use in DPI applications. The two polymers are quite different with respect to their chemical and physical attributes and the choice between the materials is ultimately based on the least amount of interaction between formulation and material. One substantial difference between the two polymers is the amount of moisture in the capsule. Figure 1 shows the differences in moisture between the two polymers across a range of relative humidities (RH).

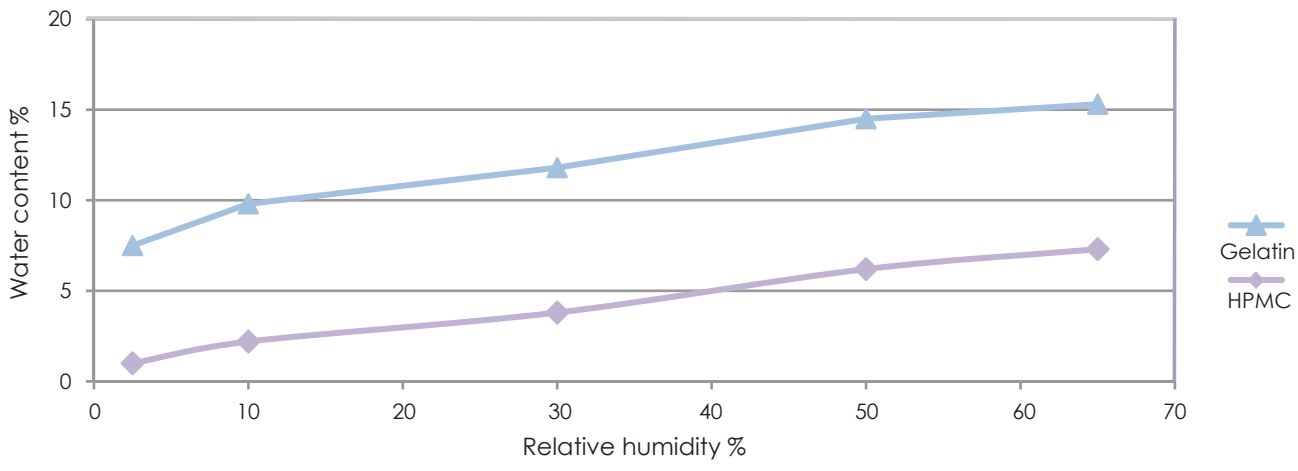
For formulations that are moisture sensitive, the difference in water content can be quite significant, especially given the small fill amount within the capsule. For such a case, the choice of HPMC as the capsule becomes quite important. Studies with both polymer capsules containing the highly moisture sensitive salicyclic acid as a reference demonstrate this effect (Figure 2).

Another point of difference between hard gelatin and HPMC capsules is the potential for build-up of static charge (triboelectrification), which can attract the API or formulation to the interior of the capsule, thereby not releasing the full dose to the patient. Hard gelatin capsules have been shown to have a higher potential for triboelectrification than HPMC capsules[5] and the possibility of this occurrence must be examined during formulation.

While these factors would seem to indicate that HPMC is better choice for DPI considerations, other factors might make hard gelatin capsules a better choice. One factor is the higher potential for oxidation in HPMC capsules than hard gelatin. Hard gelatin capsules have demonstrated excellent protection against oxygen permeability while HPMC capsules offer less protection.

Figure 1

Water content differences between gelatin and HPMC hard capsules



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Standard Mocon testing on 100 mm thick films of hard gelatin and HPMC demonstrate this readily (Figure 3).

Though this is an inherent property of HPMC films, the formulator has fewer concerns with a powder formulation in this regard than, for example, a liquid formulation, where the use of antioxidants as a preventative measure is often considered. Further, the formulator has an additional safeguard in the proper choice of packaging to easily overcome the issue.

For either polymer chosen, it is always recommended that chemical compatibility between the API, excipients and the capsule be established as a first step in ensuring a successful formulation.

Compatibility between capsule and DPI device

Properties of the capsule also need to be compatible with the device. Perhaps the most important attribute when considering these properties is the ability of the capsule to be punctured easily (or cut, depending on the device) without producing fragments that could be inhaled. Hard gelatin capsules have proved to be quite robust in this respect when kept at recommended storage conditions of 15-25 °C and 35-65% RH.[6] Gelatin has a natural tendency to equilibrate its moisture level with the surrounding environment. It has been demonstrated that when hard gelatin capsules are stored at low humidity conditions, they lose moisture. Water acts as a plasticizer for gelatin, keeping it flexible at normal ranges, but when removed, hard gelatin capsules can become brittle to the point that a capsule can shatter into many fragments quite readily. Consequently, care must be taken to ensure that a brittle capsule is not introduced into a DPI device.

A few strategies have been developed to reduce the possibility of brittleness. Perhaps the most commonly used is packaging. Suitable packaging for the hard gelatin capsule can provide ample protection from the environment for the capsule containing the dose until

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Figure 2

Rate of degradation of packaged salicylic acid in gelatin vs. HPMC capsules

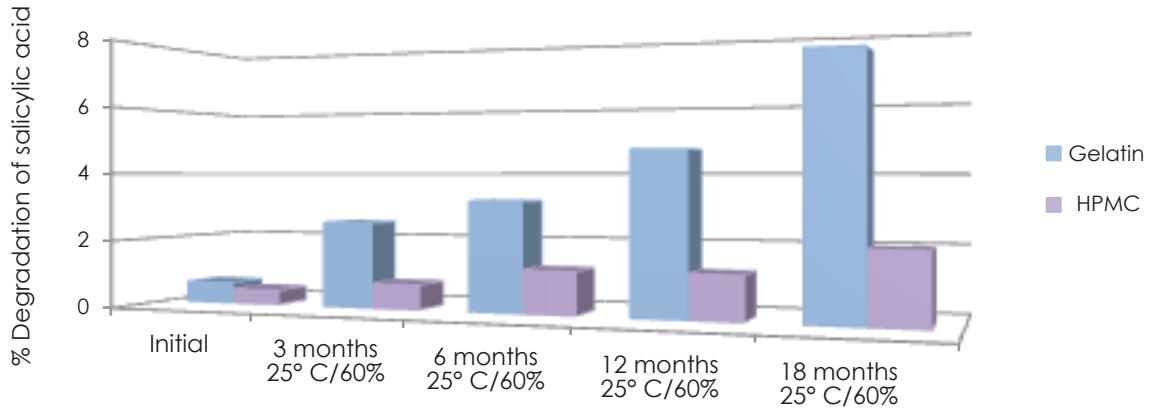
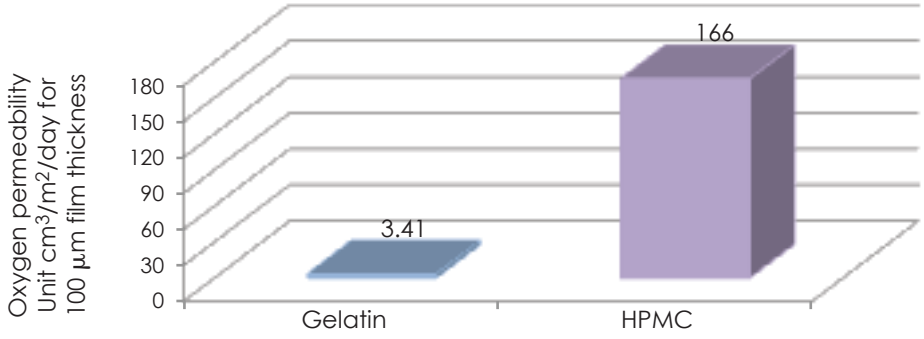


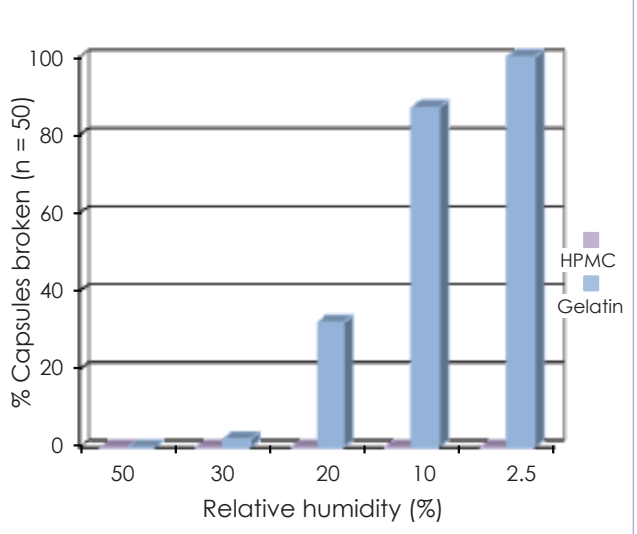
Figure 3

Standard ASTM D-3985 measurement of oxygen permeation



used in the DPI device. Another strategy is the use of a modified gelatin polymer, like PEG gelatin, which extends its flexibility to the capsule further than a traditional hard gelatin could withstand. The last, and perhaps fastest growing trend, is to develop the formulation in an HPMC capsule instead of gelatin. Unlike gelatin, HPMC does not require water to remain flexible. Therefore even at low humidity, whether environmental or when a dessicant is employed, the HPMC capsule remains very resistant to breakage. (Figure 4 and Figures 5 a-d). Since HPMC capsules contain overall lower moisture than hard gelatin, as discussed above, there is also less potential to shrink when stored under low humidity conditions, which minimizes issues with size interplay between the DPI device and capsule.[7]

Figure 4



Capsule filling equipment: R&D to manufacturing scale

As the capsule has been focused on as the primary container in this article, it would also be appropriate to discuss the role of the capsule filling equipment. Traditionally, capsules are used to deliver oral medications. The formulations filled in them substantially exceed the weight of the capsule and the filling operation can be checked by measuring the gross weight of filled products. For DPI formulations, however, it is typical for the capsule weight to be about equal or more than the formulation contained within. Technology of filling machines has evolved to compensate for what amounts to a fundamental shift in the filling process. Several filling machines are now capable of weighing the capsule, both pre- and post-fill, to ensure proper dose weights. Technology has also enabled smaller fill amounts to be dosed accurately to the capsule. Dosators and vacuum dosators can dose reliably at the ≥ 10 mg range, tamp filling based machines can dose reliably at the ≥ 25 mg range and some vacuum drum fill based machines can dose down to 1 mg. These innovations have led to the ability to fill low dose DPI formulations in capsules at manufacturing speeds.[4]

While filling machines have evolved to produce DPI capsules in the manufacturing environment, they still rely on significant amounts of formulation in order to produce capsules efficiently. For early development, when only small quantities of the drug product are available, the ability to use these filling machines may be limited, as many of them rely on a powder bed for dosing. This can also be said of the similar small scale equipment which utilize powder beds for dosing. A more recent innovation in filling machines, one based on a tapping motion to dispense powder such as the Xcelodose 600, sold by Capsugel, has been demonstrated to be quite efficient at the laboratory scale. These systems utilize a dispensing head which holds the powder formulation. A tapping motion allows powder to flow from the dispensing head to the capsule directly for filling and, with real-time weight monitoring, allows for dosing in the milligram and microgram range with very low relative standard deviation.

Conclusion

Two-piece capsules have proven to be excellent containers to hold powder formulations for DPI applications. By treating the capsule as an excipient of the formulation itself, formulators can take advantage of the properties of various polymers to enhance and protect the formulation held inside. Similarly, understanding those properties can further minimize interaction between the capsule and the DPI device used. New technologies in powder filling allow for capsules to be filled with precision in the earliest of trials while filling machines have evolved to provide high speed production of products at a manufacturing scale. From discovery to marketing, technology is well in hand to make new DPI applications a success.

References

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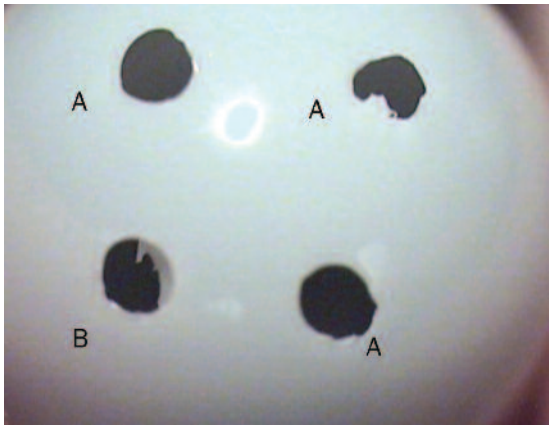
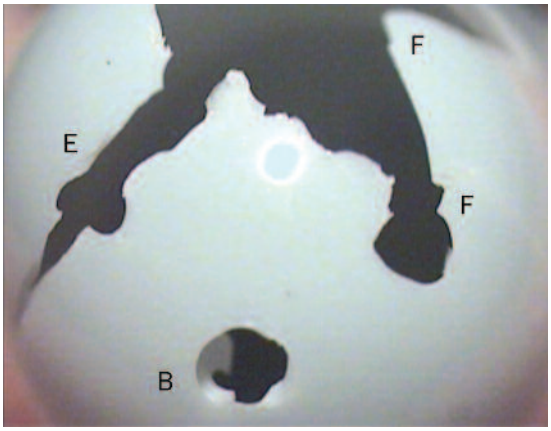
Figure 5

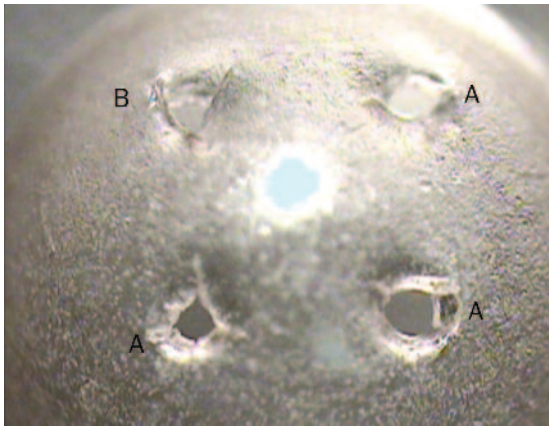
Photos of standard and dry capsules after piercing tests in a DPI device



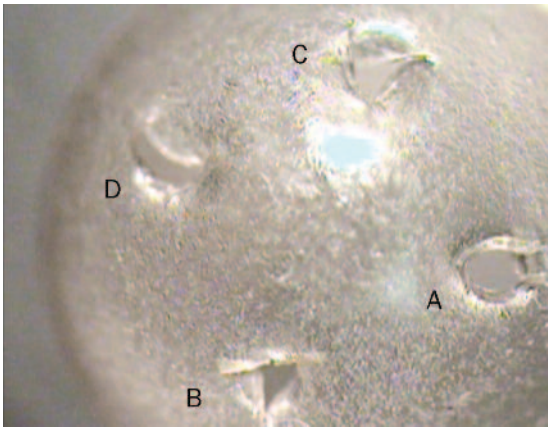
(a) Standard gelatin capsule at 50% RH punctured in a Novartis Aerolizer DPI device



(b) Standard gelatin capsule at 10% RH punctured in a Novartis Aerolizer DPI device



(c) Standard Vcaps HPMC capsule at 50% RH punctured in a Novartis Aerolyzer DPI device



(d) Standard Vcaps HPMC capsule at 10% RH punctured in a Novartis Aerolizer DPI device

Photographs and photo legend courtesy of Cirrus Pharmaceuticals, Inc.

Legend:	
A: Clean puncture	D: Fissure
B: Puncture with flap	E: Fracture, between holes
C: Puncture with small diameter hole	F: Shatter with large diameter hole and fragments

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Matt Richardson, Ph.D. is Manager of Pharmaceutical Business Development at Capsugel, 535 N. Emerald Road, Greenwood, SC, 29662, US. Tel: +1 800 845-6973. Matt.Richardson@pfizer.com. Website: www.capsugel.com.