Technology selection in capsule-based inhalation product development

Developers must carefully evaluate the device, formulation and capsule, as well as the interactions among them

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Introduction

A key motivation in pharmaceutical development is getting a product to patients quickly. There are various dry powder inhaler (DPI) types (i.e., reservoir-, blister- and capsule-based) but when developing a new DPI product, using capsule-based inhalers may optimize speed to clinic and market. Unless a company already has manufacturing capabilities for reservoir- or blister-based DPIs, capsule-based inhalers may be the first choice in DPI technology for several reasons. Off-the-shelf, capsule-based devices are readily available, capsules may be easily filled during feasibility studies using standard capsule-filling equipment and early phase clinical trials can be pursued with extemporaneous preparation if encapsulation equipment is not available. After feasibility and phase I studies, formulators can choose to continue using a capsule-based inhaler or move forward with one of the other DPI types.

Because DPIs are a drug/device combination product, there are three critical components within the overall product that developers must select and evaluate: the device, the formulation and (when using a capsule-based inhaler) the capsule itself. These components form what may be called "the DPI interaction triangle." Using a risk-based approach that ensures the appropriate technologies are selected for the three components can be the best path to success.

The DPI interaction triangle and target product profile (TPP)

During product development, research and development (R&D) should evaluate each component of the finished drug product, then relate the results to the quality target product profile (QTPP) and critical quality attributes (CQA), as part of the design control requirements (in the United States) or the medical devices directive (in the European Union) for a combination product. While the inhaler device and formulation are important aspects separately, R&D should also evaluate interactions among the three components—device, formulation and capsule—which form the DPI interaction triangle.

The pharmaceutical product development process starts with defining the target product profile (TPP) to outline the desired outcomes and performance of the drug product. For inhalation, this includes the mechanism of action, location for deposition, permeability and absorption properties of the drug substance[1] as well as the dose being delivered. The TPP assists in defining the critical quality attributes, including particle size distribution (to target the deposition site), particle morphology (which may impact aerodynamic particle size), physical form and state (which may impact uptake kinetics depending whether it is crystalline, amorphous or a combination of the two). In addition, considerations for chemical and physical stability should be made (such as propensity of moisture uptake and the potential for degradant formation). Rheological properties (such as powder flow and packing) may not typically be defined early on but would impact the handling properties during processing.

Capsule-based inhalation device selection

Once the target product profile is established, formulators must consider the device. In addition to ensuring

that the selected device can deliver the formulation to the patient, inhalation drug developers must consider the human factors involved in using the inhalation device, such as device resistance and improper patient handling, which may inhibit the target patient population from successfully operating the inhaler and complying with recommended use. Still, innovations in inhalation devices have provided solutions to these human factors. Capsule-based connected devices, for example, have the ability to gather and monitor key data on patient compliance and behaviors.[2]

There are now many capsule-based inhalers available for use,[3] so selection of a capsule-based inhalation device may depend on other parameters, including powder retention (primarily related to device geometry) and cost (depending mainly on the number of device pieces). Another consideration is the capsule-opening mechanism, of which there are three main aspects: puncturing of the capsule, cutting of the capsule and opening of the capsule (separating the body from the cap).

Formulation technology selection

The next component is the formulation of the drug, where the selected technology enables effective delivery of the drug through the inhalation device. There are various particle engineering approaches for developing an inhalable dry powder formulation, including micronizing the drug substance to a respirable particle size, spray drying, spray freeze drying, thin-film freezing[4] or micro-molding engineered particles.[5] Irrespective of the particle engineering technique, the goal is to produce a formulation that can consistently be dispersed and delivered into the respiratory tract and to the target site. The majority of the techniques listed would be able to address the critical attributes, depending on the drug substance properties. Given that, what is the most appropriate particle engineering option to consider?

From a practical perspective, access to a jet mill or a spray dryer is relatively common compared to more novel particle engineering approaches. Access to such specialized approaches is likely to be restricted by intellectual property owners, unless there is a partnership in place. Micronization and subsequent formulation with the use of carriers is the typical path for inhalation product development due to existing precedents and a large body of supporting research. Depending on the drug substance, the active pharmaceutical ingredient (API) may be soft or plastic, where jet milling may not have adequate energy to micronize the API to the appropriate particle size[6] and cryo-milling may be required. Due to the high energy involved in the comminution process, the potential for surface amorphization of the API and the impact on particle size distribution (PSD) need to be assessed over time. Once the particle size is rendered to be within respirable range, the dispersion properties would be evaluated to determine if additional formulation development work with carrier blends and a short-term accelerated study are required. The uses of force control agents and blending with a combination of coarse and fine carriers are well-studied and can successfully optimize formulations to improve aerosol performance and stability.

If the micronization path is not feasible, an alternative approach is spray drying. Similar to micronization, spray drying is commonly used for particle engineering. In addition to the formulation's drug substance, additional excipients may be used to improve dispersibility and product stability. Spray drying may be evaluated in place of micronization for early feasibility if there are concerns about the drug substance being exposed to shear or attrition. Spray drying may also be tested if a drug substance is a large molecule in a solution or suspension, where the goal is to increase stabilization and reduce cold chaining when possible.

Within the spray drying approach, one particle engineering method is isolating the formulation as a dry powder by preparing particles in a suspension that then undergo spray drying. Controlled precipitation of the drug substance can be achieved using antisolvent precipitation with high intensity mixing to generate particles[7] or by reactive means where the subsequent drug substance precipitates due to low solubility.[8] Nanomilling is another method for producing nanosuspensions prior to spray drying,[9] where excipients may be used to both stabilize the suspension and improve aerosol performance after drying.

As there are multiple options available, there is a risk of over-engineering and over-complicating the formulation's manufacturability. One such case might be the use of multiple excipients to provide multiple benefits, such as improving dispersibility while protecting the drug substance from moisture, with a glassy matrix. However, the excipients may interact with each other and form a hybrid phase that could cause them to behave differently than expected.

Capsule selection

For DPI capsule selection, there are various parameters to consider with respect to both the formulation and the device, as summarized in Table 1. In addition, the microbiological quality for inhalation dosage forms has a tighter specification than for oral applications.[10, 11] Inhalation dosage forms require capsules that have less than 100 colony-forming units per gram (cfu/g) total aerobic microbial count and less than 10 cfu/g each of yeasts, molds and specified microorganisms.

Currently, the most common capsule size for inhalation is size 3 due to their use in earlier inhaler designs. However, larger capsule sizes may be required and could be considered for newer drug substances that require higher doses. For capsule polymer types ideal for inhalation products, there are two capsule families: gelatin and hydroxypropyl methylcellulose (HPMC). Of the two, the HPMC polymer type is more widely used for inhalation products due to the various advantages it provides.

Table 1

Impact of various capsule factors on formulation and device

Parameters	Considerations
Dimensions/Size	Size 3 capsules are the standard size for asthma/COPD applications. However, for cystic fibrosis and other applications, a larger dose may be needed, which could require Size 2 to Size 00 capsules.
Polymer Type/ Loss on Drying (LOD)	Several options are available, ranging from gelatin and gelatin/PEG to HPMC capsules, with or without a gelling agent. LOD customization is possible for HPMC-based capsules to ensure optimal stability of the finished product.
Powder Retention	Powder retention is driven by multiple factors including the capsule polymer, capsule LOD, lubricant content residual, formulation characteristics and filling conditions.
Color, Print and Transparency	Transparency may be required to allow the patient to confirm that the powder has been correctly inhaled. Specific color and print combinations can facilitate brand recognition and may improve patient adherence.
Individual Capsule Weight Specifications	For the low doses typically used in the asthma/COPD market, weight of the empty capsule is often much lower than the weight of the formulation to be filled. Specifications for individual, empty capsule weights may be reduced to help ensure accurate dosing.

Powder retention is also critical. There are various parameters that impact powder retention in the capsule, such as capsule moisture, roughness of the capsule's internal surface and lubricant content residual.

Moisture content in capsules is dependent on the polymer type. Gelatin capsules have higher water content than HPMC capsules across a wider humidity range (Figure 1). Capsule water content should be defined carefully, as moisture content that is too low or too high can lead to ineffective drug delivery.

Dry capsules with low moisture content can have higher powder retention, a performance indicator of ineffective delivery. In one study, HPMC capsules (Capsugel® Vcaps® Plus DPI; Colmar, France) containing 150 mesh lactose (25 mg fill weight) were evaluated after the formulation was released from capsules that had different levels of water content. It was observed that powder retention increased with lower moisture content. Up to 12.6% retention occurred with a capsule water content of 1.9%, compared with 0.1% retention with a capsule water content of 5% (Lonza internal data). In this case, powder retention was mainly driven by static charge build-up inside the capsules.

To ensure optimal product stability while minimizing powder retention inside the capsule, one method involves defining the optimal loss on drying (LOD) value of the capsule. This can be done by measuring the specific water activity of the formulation and customizing the capsule's LOD to match that value. Inhalation powder capsule-filling operations are then conducted in dry-box conditions of less than 30% relative humidity to maintain the low LOD. In this way, there is no water exchange between the capsule shell and the capsule fill while the system remains stable.

Another cause of powder retention is the use of lubricants. During capsule manufacturing, lubricants are typically used to assist in the demolding of capsules off the pins. While this method improves manufacturing performance and maintains the capsules' mechanical properties, it can cause powder retention—in which the formulation adheres to the residual lubricant left on the internal surface of the capsule. To improve the emitted dose, less lubricant should be used in DPI capsules than in standard capsules intended for oral use. To illustrate the direct correlation between residual lubricant and increased powder retention, Figure 2 illustrates how a dry powder formulation (a placebo/lactose blend) coats the inner surface of HPMC capsules manufactured with a standard amount of lubricant (Capsugel Vcaps Plus) compared to capsules manufactured with a reduced amount of lubricant (Capsugel Vcaps Plus DPI).

Figure 1

Water vapor sorption curves for gelatin and HPMC capsules

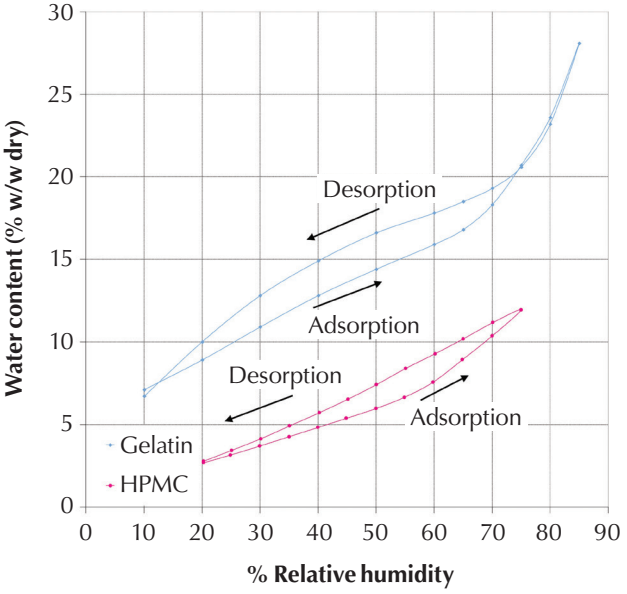
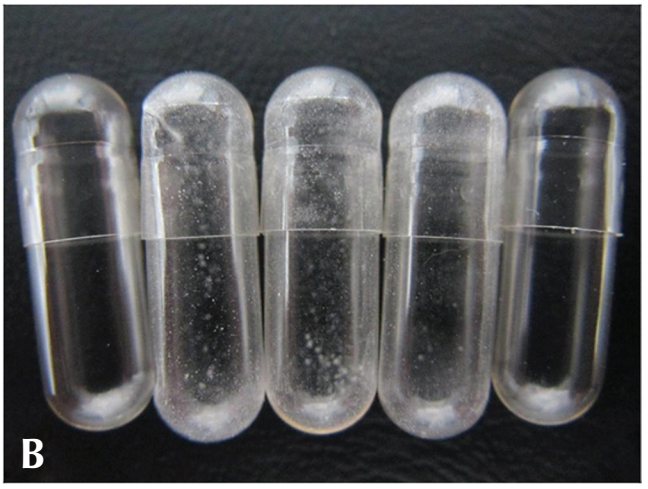


Figure 2

HPMC capsules (Capsugel Vcaps Plus) coated with (A) a standard amount of lubricant and (B) a reduced amount of lubricant. For reference, empty capsules are shown at both sides of each photo.



If gelatin capsules are combined with a water-sensitive or hygroscopic formulation, the chemical stability of the end product may be impacted, which can lead to brittleness issues. For hygroscopic or water-sensitive formulations, the use of HPMC-based capsules is recommended over gelatin-based DPI capsules. The advantage of using HPMC capsules is that their water content can be customized to accommodate water-sensitive formulations. A study compared gelatin and HPMC capsules conditioned at different relative humidities to determine the percentage of capsule breakage. In less than 10% relative humidity, the gelatin capsules became extremely brittle and were therefore unsuitable for inhalation applications, while the mechanical performance of HPMC capsules was unaffected by the low-humidity conditions (Figure 3).

If the device uses a mechanism that pierces the capsule or separates the capsule body from the cap, brittle capsules can generate fragments of the capsule, potentially raising safety concerns for patients. Again, in cases where a formulation requires low humidity to protect the drug substance and formulation, HPMC-based capsules may be preferred over gelatin capsules, which could turn brittle and lead to unsafe delivery.

External design and manufacturing partners can help drug developers ensure they are making optimal decisions regarding technology selection for DPI products. Also, contract design and manufacturing organizations (CDMOs) may help drug developers overcome challenges and nuances in DPI product development and enable consistent and optimal release performance for inhalation drugs.

Conclusions

Capsule-based dry powder inhalers are combination products in which the various interactions between the inhalation device, formulation and capsule need to be evaluated alongside individual primary attributes, including the target product profile. As briefly described in this article, there are specific considerations for each component and the ways they interact. A risk-based approach can help ensure the appropriate technologies are selected for the three components. Close cooperation with potential suppliers or partners (CDMOs, device suppliers and capsule suppliers) can help ensure critical parameters are well defined and eventually customized to facilitate optimal performance of the finished dosage form.

Figure 3

Evaluation of mechanical properties (including breakage) for gelatin and HPMC capsules under various storage conditions (relative humidities)