AN ADVANCED CUSTOMISABLE COMPREHENSIVE DPI CAPSULE PORTFOLIO OFFERING

Here, Frédérique Bordes-Picard, Business Development Manager for Innovative Products, and Julien Lamps, Product Manager, both of Lonza Capsules and Health Ingredients, discuss the factors driving development in the area of capsule-based dry powder inhalers, and how the company's Capsugel® Zephyr™ portfolio offering is perfectly positioned to meet and exceed industry's growing and evolving requirements.

Drug developers looking to deliver drugs via the inhalation route can generally choose from a variety of different technology platforms. These include:

- Pressurised metered dose inhalers (pMDIs), which are designed to use compressed propellants
- Dry powder inhalers (DPIs), which are kinetic, mechanical, dry powder counterparts of pMDIs
- Nebulisers and soft mist inhalers.

Within these segments there is a range of device types, varying from simple and inexpensive to highly sophisticated, more expensive options such as e-devices to improve patient compliance. In practice, drug development is segmenting along these device lines, for example, drug developers are tending to choose pMDI systems primarily for emergency medications like the bronchodilator albuterol.[1]

When considering DPI technology, there are three further subdivisions based on how the powder is stored and dosed – capsule, reservoir and blister:

- Capsule-based DPIs (cDPIs) meter each dose by containing it in an individual hard capsule and then placing in the aerosolisation chamber for delivery
- Reservoir devices hold a more substantial quantity of the formulation within the device and generally use a relatively complex mechanisation to meter the dose
- Blister-type devices employ a "magazine-fed" approach with each dose presented in its individual blister for aerosolisation.

A variety of attributes make DPIs appealing for the delivery of inhalable oral solid doses (OSDs), but cDPIs in particular provide a very strong value proposition from factory to patient. These attributes include manufacturing economies from a cost-of-goods (CoGs) and supply chain perspective, as well as the innate patient-friendly ease-of-use, portability and better dose compliance of the delivery method.

Central to the value proposition of cDPIs are the economies and efficiencies related to encapsulating any drug. Along with compressed tablets, capsules are among the most manufactured and best understood dosage forms in existence – and DPIs that use

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them only expand upon their intrinsic value.

The current prevalence of respiratory diseases is driving a renewed interest in cDPIs. Asthma and chronic obstructive pulmonary disease (COPD) are currently the two leading respiratory conditions globally; according to estimates from the WHO, COPD will become the third leading cause of death worldwide by 2030.[2] In response, pharmaceutical development pipelines are focusing on creating effective inhalable compounds that are better at treating asthma and COPD than the current market offering. One of the key considerations for this development is the cost of the compound, as WHO data shows that over 90% of COPD deaths are in low- and middle-income countries.[3]

Preference for cDPIs In Emerging Markets

In emerging markets, there remains a clear preference for the capsule approach, due to the fact that cDPIs generally provide a means of making certain therapies more accessible.[4] Asthma and COPD have been underserviced for a long time in these regions. There is significant opportunity to improve the lives of patients by leveraging developments in generic COPD medications and the advantages offered by cDPI-based delivery.

For most developers and manufacturers, capsules are a familiar delivery form with readily available, well-established processes and manufacturing lines. Compared with blister and reservoir platforms, where more dedicated lines are needed and there is a significant leap required in technical knowledge and capital expenditure, capsules offer a simpler, more cost-effective route into new markets.

A CAPSULE PORTFOLIO OFFERING TAILORED TO INHALATION

Capsules presented as a portfolio allow developers and manufacturers to achieve optimal and consistent performance by customising polymer formulations by adjusting key design parameters including: capsule size and design; polymer/gelling agents; moisture content; lubricant levels; and weight tolerances.

Lonza's Capsugel® Zephyr™ portfolio comprises customised capsules, in both gelatin and hypromellose, optimised to provide impeccable performance and compatibility between the capsule/device and capsule/formulation (Figure 1).

> "Reliably consistent emitted doses need to be quickly and thoroughly evacuated from both capsule and device, meaning it is important that the capsule contents remain free flowing – from the point of manufacture to the point of inhalation by the patient."

Key advantages of Capsugel® Zephyr™ capsules include:

- Consistent powder release
- Customised approach to optimise performance of the end product
- Compatible with a large selection of device principles and opening systems
- Ideal puncturing and cutting performance
- Available in gelatin (Coni-Snap® Gelatin or Coni-Snap® Gelatin-PEG) and HPMC (Vcaps® or Vcaps® Plus) capsules.

Support and Value-Added Service

Lonza leverages its vast experience and know-how in all aspects of cDPI capsule development to offer its customers a comprehensive range of value-added services as part of its Zephyr™ offering. These include R&D services such as water activity testing; device compatibility testing; powder retention with standard lactose blend; and investigation of the impact of storage conditions on performance. Additionally, on-site technical support is offered for first trial fillings through to scale-up and filling process optimisation. Finally, Lonza provides quality assurance and regulatory support with answering questions from agencies and compiling the required statements for dossier filings.

Device Compatibility

There are many "off-the-shelf" cDPI devices with different levels of sophistication. Some consist of only three to four pieces, which makes them very cost effective, and many can be customised in resistance, colour and shapes. The way in which a given device opens a capsule can also vary; some devices use one or several needles to pierce the capsule on the side or on the top, while others have blades that slice open the capsule on the side, and some simply separate the body and cap of the capsule. Ultimately, the compatibility between the device and the capsule is a critical factor when choosing the best capsule materials and designs with which to work.

The capsule's structural integrity is of paramount importance. First, the capsule must withstand sudden piercing without shattering. Second, the capsule must be sufficiently robust to take this blow without being crushed – thus preventing distortion or other factors that would inhibit the full dispersion of the capsule's entire contents. Structural integrity is therefore a key consideration for developers looking to ensure downstream patient centricity and support patient compliance efforts with their products.

Figure 1: The Capsugel® Zephyr™ DPI Capsule Portfolio offers options in gelatin and HPMC.

Capsugel® Zephyr™ capsules comfortably meet these requirements and are compatible with a large variety of DPI device principles and opening systems.

Direct feedback from patients suggests that they are comfortable with loading a device with the medication dose, inhaling and then checking the emptied capsule to ensure the full dose has been taken.

Tuneable for Optimal Formulation-Capsule Compatibility

Reliably consistent emitted doses need to be quickly and thoroughly evacuated from both capsule and device, meaning it is important that the capsule contents remain free flowing – from the point of manufacture to the point of inhalation by the patient. Ensuring the complete and uninterrupted exit of the capsule's contents is an aspect of cDPIs that requires focused attention in development.

Many existing and in-development DPI formulations tend to be hygroscopic in nature, and as such cause changes in flow properties of the powder. Interactions between the formulation and the capsule are therefore critical. The properties of capsule materials and the specific characteristics of its polymers can either enhance or diminish the performance of the formulation's flow characteristics.

The customisable range of materials and design options offered by Capsugel® Zephyr™ means that the portfolio caters for a wide range of dry powder formulations with widely variable properties, including those containing standard and engineered particles. With the rise of combination products, capsules still present the simplest way of formulating, filling and delivering said products.

Capsule Polymers

There are several choices in capsule type using different polymers suitable for encapsulating cDPI formulations. The most popular include:

- Hard gelatin capsules (HGCs)
- Modified HGCs
- Hypromellose capsules (HPMCs).

The technology and the material science behind capsule and formulation are well understood and capsule manufacturers are offering a number of solutions for cDPI applications. For example, the Capsugel® Zephyr™ DPI portfolio contains four different varieties of capsule, each customisable. They are:

- Coni-Snap® Gelatin DPI, the standard gelatin component of the Capsugel® Zephyr™ portfolio
- Coni-Snap® Gelatin-PEG DPI, the robust gelatin component of the Capsugel® Zephyr™ portfolio
- Capsugel® Vcaps® DPI HPMC, a plant-based solution within the Capsugel® Zephyr™ portfolio
- Capsugel® VCaps® Plus DPI HPMC, a plant-based solution within the Capsugel® Zephyr™ portfolio, without gelling agent.

Controlling water content is a particular consideration for many due to the trend towards hygroscopic formulations. Often, capsule loss on drying (LOD) has to be adapted to specific formulation filling properties and stability requirements. Water activity measures can be performed in-house to find out the best range. Zephyr™ DPI portfolio offers LOD range customisation (see Figure 2).

Figure 2: Zephyr™ offers LOD range customisation.

HGCs have been successfully used in cDPIs for more than 30 years, during which time they have proved their viability across a broad range of cDPI applications. HPMC capsules, on the other hand, demonstrate excellent properties that address the challenges of some of the newest APIs and formulations, especially towards hygroscopic or water-sensitive formulations that need to be filled under dry environmental conditions.

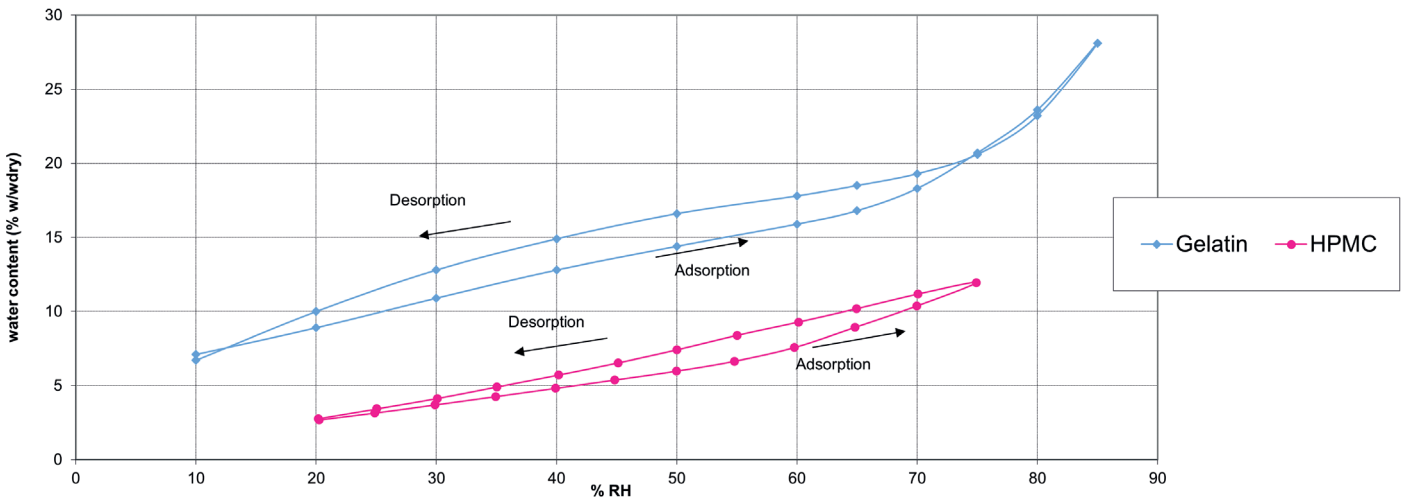

Figure 3: Water vapour adsorption-desorption of gelatin and HPMC capsules at 25˚C.

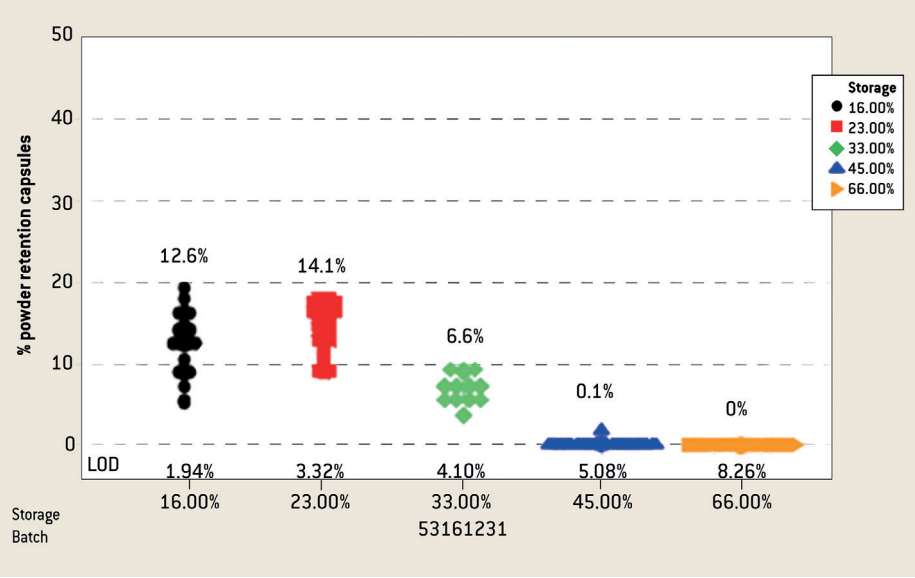

Figure 4: Individual value plot of percentage powder retention in Capsugel® Vcaps® DPI HPMC capsules under different storage conditions.

"Lonza is creating breakthroughs in capsule and encapsulation technologies that are changing the functional role of capsules in medical research, drug formulation and drug delivery."

The two polymers are quite different with respect to both chemical and physical attributes and the choice between the materials is ultimately based on which has the least impact on the formulation. One substantial difference between the two polymers is the amount of moisture in the capsule. Figure 3 shows the results of an internal Lonza study which looked at the differences in water content between two capsule types equilibrated across a range of relative humidities (RHs).

Because many dry powder formulations are hygroscopic or water sensitive, it is not surprising that HPMC capsules have taken a foothold in the cDPI market, given their relative lower moisture content compared with HGC capsules. However, this must be balanced with the triboelectric (electrostatic) properties of the formulation and capsule interface. A dry capsule will exhibit a reduction in dry powder release (i.e. a higher powder retention inside the capsule) primarily due to static charges (Figure 4).

Although dry conditions may be required during filling, as well as within the capsule, to ensure the stability of the API or the formulation, it is important to find the right balance to ensure stability while not excessively impacting the emitted dose. According to the results of an internal study by Lonza, water activity measurements of the formulation can help identify the optimal LOD target for the capsule.

Regardless of the polymer chosen, best practice recommends that compatibility between the capsule, formulation and device is well established as a first step in a successful DPI formulation drug strategy. It is a necessary step and the earlier that this analysis occurs in development the better.

BROADER APPLICATIONS ON THE HORIZON

By combining polymer science, engineering and formulation know-how within its Capsugel® Zephyr™ DPI portfolio, Lonza is creating breakthroughs in capsule and encapsulation technologies that are changing the functional role of capsules in medical research, drug formulation and drug delivery.

Capsules are a highly adaptable form, offering a range of customisation options to ensure formulation suitability and flexibility in size, catering for higher dosing requirements. As a result, there is increasing interest in expanding cDPI delivery beyond respiratory indications to inhalable therapeutics for diseases such as Parkinson's and Alzheimer's through systemic delivery. There is also notable interest in developing inhalable compounds for nasal/sinus membrane routes of administration for conditions affecting the central nervous system (CNS).[5]

CONCLUSION

As well as for their cost efficiency, cDPIs are recognised for their patient friendliness and overall effectiveness in delivering dry, inhalable therapeutics. As such, cDPIs are becoming the clear choice for delivering a growing number of these best-in-class respiratory therapeutics.[6]

Looking to the future, cDPIs have become an exciting area of development and look to be an ongoing area of interest for researchers pursuing new chemical entities (NCEs) to treat the unmet needs of a variety of patient groups.[7]

Lonza's Capsugel® Zephyr™ DPI portfolio represents a highly customisable offering that can be tailored for optimal capsule-formulation and capsule-device compatibility across the spectrum of industry requirements, supported with value-added R&D, QA and regulatory services.

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