

# ADVANCED CAPSULE TECHNOLOGIES: DRY POWDER INHALERS TO TARGET DISEASE

In this article, Frédérique Bordes-Picard Business Development Manager for Innovative Products, and Julien Lamps, Product Manager, both of Lonza Capsules and Health Ingredients, discuss the value of capsule-based dry powder inhalers in the modern respiratory market, the factors driving development in this area and considerations for matching a capsule to a device and formulation.

The current prevalence of respiratory diseases is driving a renewed interest in capsule-based dry powder inhalers (cDPIs). Asthma and chronic obstructive pulmonary disease (COPD) are currently the two leading respiratory conditions globally; according to estimates from the World Health Organization (WHO), COPD will become the third leading cause of death worldwide by 2030.<sup>1</sup>

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.<sup>2</sup> cDPIs are recognised for their cost efficiency, 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.<sup>3</sup>

## CAPSULES: DELIVERING INHALABLE ORAL SOLID DOSES SIMPLY & COST EFFECTIVELY

There are a variety of attributes that 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 (CoG) 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

"cDPIs are recognised for their cost efficiency, patient friendliness and overall effectiveness in delivering dry, inhalable therapeutics."

most manufactured and best understood dosage forms consumed – and DPIs that use them only expand upon their intrinsic value.

## RESPIRATORY MARKET SEGMENTATION

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
- 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.<sup>4</sup>

When considering dry powder inhaler technology, there are three further subdivisions based on how the powder is stored and dosed: capsule, reservoir and blister. cDPIs meter each dose by containing it in an individual hard capsule



**Frédérique Bordes-Picard**  
Business Development Manager  
for Innovative Products  
T: +33 3 89 20 57 09  
E: frederique.bordes-picard@lonza.com



**Julien Lamps**  
Product Manager  
T: +33 3 89 20 57 09  
E: julien.lamps@lonza.com

**Lonza – Capsules and Health Ingredients**  
10, Rue Timken  
F-68027 Colmar  
Cedex  
France

[www.lonza.com](http://www.lonza.com)

“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.”

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 mechanism to meter the dose. Finally, blister-type devices employ a “magazine” fed approach with each dose presented in its individual blister for aerosolisation.

#### 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.<sup>5</sup> Asthma and COPD have been underserved 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 capex, capsules offer a simpler, more cost-effective route into new markets.

#### DEVICE COMPATIBILITY

There are many “off-the-shelf” capsule-based DPI 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. 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.

#### MANAGING FORMULATION-CAPSULE INTERACTIONS

As the formulation needs to be quickly and thoroughly evacuated from both capsule and device, it is important that its 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 cDPI 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. Depending on material and design, capsules can manage a wide range of dry powder formulations, from standard to 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 application. Capsules frequently come as a portfolio, allowing developers and manufacturers to customise polymer formulations in many ways – controlling water content is a key consideration for many, due to the trend towards hygroscopic formulations.

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.

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 1 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 hydroscopic 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

“Structural integrity is therefore is a key consideration for developers looking to ensure downstream patient-centricity and support patient compliance efforts with their products.”

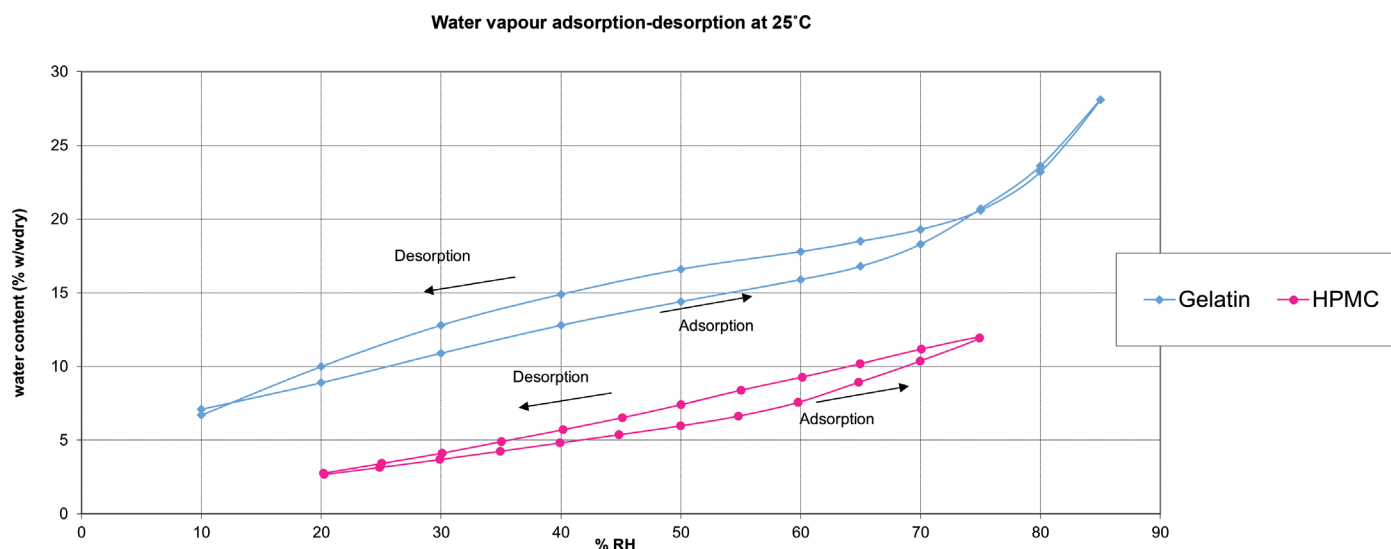


Figure 1: Water vapour adsorption-desorption at 25°C.

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 2).

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 loss on drying (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

Capsules are a highly adaptable form, offering a range of customisation options to ensure formulation suitability and

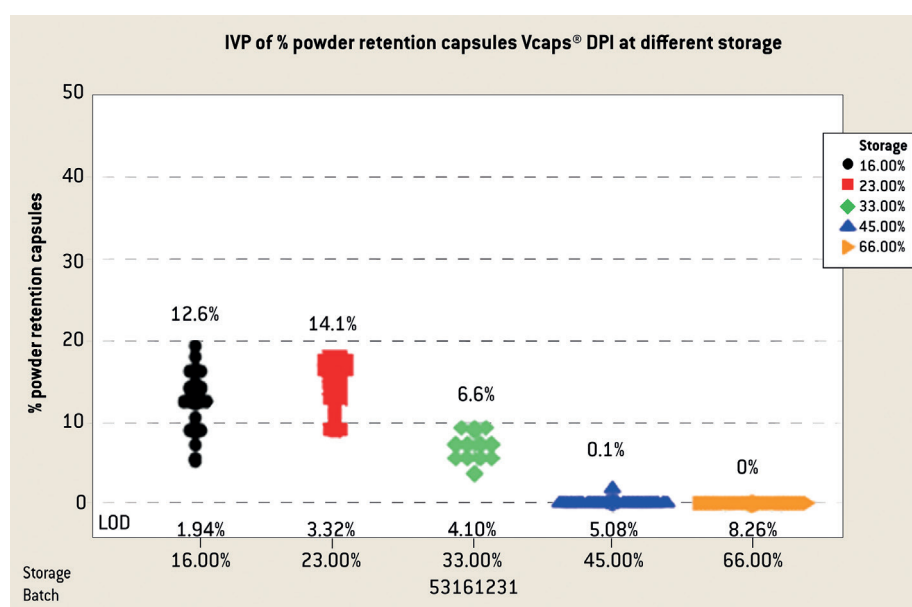


Figure 2: Individual value plot of percentage powder retention in DPI capsules under different storage conditions.

flexibility in size, catering for higher dosing requirements. As a result, there is increasing interest in expanding cDPI delivery beyond respiratory indications and to use it for treating 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).<sup>6</sup>

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.<sup>7</sup>

## ABOUT THE COMPANY

Lonza Capsules and Health Ingredients is a global capsule and equipment developer and manufacturer which designs and produces innovative products for a wide range of oral dosage forms across the pharmaceutical and consumer health and nutrition market. By combining science, engineering and expertise with innovation and flexibility, the company provides quality products to more than 4,000 customers in over 100 countries and can offer advice on how to achieve customised solutions that optimise formulations and align with project and consumer requirements.

"There is increasing interest in expanding cDPI delivery beyond respiratory indications and to use it for treating diseases such as Parkinson's and Alzheimer's through systemic delivery."



## REFERENCES

1. World Health Organization, "Burden of COPD". WHO website.
2. Atkins PJ, "Dry Powder Inhalers: An Overview". *Respiratory Care*, 2005, Vol 50(10), pp 1304–1312.
3. Ventura Fernandes J, Villax P, "Dry Powder Inhalers: Towards Effective, Affordable, Sustainable Respiratory Healthcare". *ONdrugDelivery Magazine*, Issue 102 (Nov 2019), pp 5–8.
4. US FDA, "FDA Approves First Generic of a Commonly Used Albuterol Inhaler to Treat and Prevent Bronchospasm". FDA News Release, April 2020.
5. Ebert A, Ventura Fernandes J, Sule A, Sule S, "A Simple Affordable DPI: Meeting the Needs of Emerging Markets". *ONdrugDelivery Magazine*, Issue 80 (Nov 2017), pp 10–14.
6. Erdo F et al, "Evaluation of Intranasal Delivery Route of Drug Administration for Brain Targeting". *Brain Res Bull*, 2018, Vol 143, pp 155–170.
7. Williams G, "The Future of DPIs: Aligning Design With Market Demands". *Drug Development & Delivery*, Nov/Dec 2012, pp 26–29.

## ABOUT THE AUTHORS

**Frederique Bordes-Picard** is Business Development Manager for Innovative Products at Lonza Capsules and Health Ingredients. Ms Bordes-Picard is a biochemical engineer by training (Bordeaux Polytechnic Institute), she also holds a Master of Business Administration from KEDGE Business School. Ms Bordes-Picard has been working in the pharmaceutical industry for more than 20 years, first at AstraZeneca UK working on analytical development of therapeutic proteins and antibodies within Bertin Pharma (now Eurofins), mainly on generic product development and licensing out. Ms Bordes-Picard joined Lonza Capsules and Health Ingredients in 2010 as Pharmaceutical Business Development Manager providing technical and regulatory support for new capsule-based product developments. She has developed specific expertise around cDPI product development and filing, supporting multiple companies working on innovative or generic DPI projects.

**Julien Lamps** is Product Manager for Lonza's Capsule and Health Ingredients business unit, focusing primarily on inhalation and HPMC portfolios. Mr Lamps graduated from Ecole Nationale Supérieure de Chimie de Lille with an engineering degree in chemistry in 2004. He later joined Capsugel as a Quality Assurance Engineer in the Colmar plant in 2011. In this role he worked at the interphase of operations and customers, specialising in co-ordinating new product introductions to develop innovative offers around modified release profiles.

# Extractables & Leachables USA 2020

**100% Virtual**  
**26-28 October**



Continuing the energy from past years, Smithers' 9th annual Extractables and Leachables USA conference will bring together companies from the entire supply chain, making it easy to network with peers, and leading to new, beneficial connections. The event is a must for the E&L industry, wherein players need to stay on top of market changes, fluctuating regulations, medical device strategies, and safety standards for consumer safety and product success. Smithers' E&L 2020 gathers industry experts to discuss these topics, and more. The program consists of two days of industry-leading presentations by over 20 expert speakers, supplemented by valuable networking breaks, an included networking lunch, and networking reception.

**For more information:**

[eandl-conference.com/usa](http://eandl-conference.com/usa)  
@SmithersELevent  
#EL2020USA

