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THE SCIENCE BEHIND CAPSULE-BASED DRY POWDER INHALATION TECHNOLOGY

Here, Fernando Díez, Scientific Business Development Manager, Justin Kalafat, Business Development Manager (North America), and Jnanadeva Bhat, PhD, General Manager, Product Development & New Product Offerings, all of ACG, explain the mechanics behind cDPIs, from the scientific perspective, before looking to the future of cDPIs in the market.

INTRODUCTION

Inhalation delivery to the respiratory system has gained wide acceptance as an effective, non-invasive method for local and systemic delivery of active pharmaceutical ingredients (APIs). The unique features of the lung (i.e. large surface area, thin alveolar capillary membrane, low enzymatic activity and avoidance of first-pass metabolism¹) all contribute to the preference for this dosage form.

Legacy products in this dosage form targeted chronic obstructive pulmonary disease (COPD) and asthma, however, many new medical conditions are being explored. Parkinson's disease, pulmonary hypertension, biologics and other treatment

areas are seeing increasing development activity in the area of inhalation delivery as an alternative to more traditional dosage forms.

There are various technologies available within the inhalation category. One popular, proven and convenient system is the capsule-based dry powder inhaler (cDPI). Some examples of commercial cDPI products are shown in Table 1. cDPIs, such as that shown in Figure 1, use a hard capsule that contains a mixture of powders composing the drug which is loaded inside an inhalation device. Patients operate the device to puncture, open or cut the capsule, and then take a deep breath to inhale the powder, using air as the vector of drug displacement. Lactose, known for good

Product	Generic Name of API	Capsule Type	Company
Onbrez	indacaterol maleate	gelatin	Novartis
Foradil	formoterol fumarate	gelatin	Novartis
Seebri	glycopyrronium bromide	HPMC	Novartis
Spiriva	tiotropium bromide	gelatin/PEG	Boehringer
Tobi Podhaler	tobramycin	HPMC	Novartis
Ultibro	glycopyrronium/ indacaterol	HPMC	Novartis

Table 1: Commercial cDPI products.



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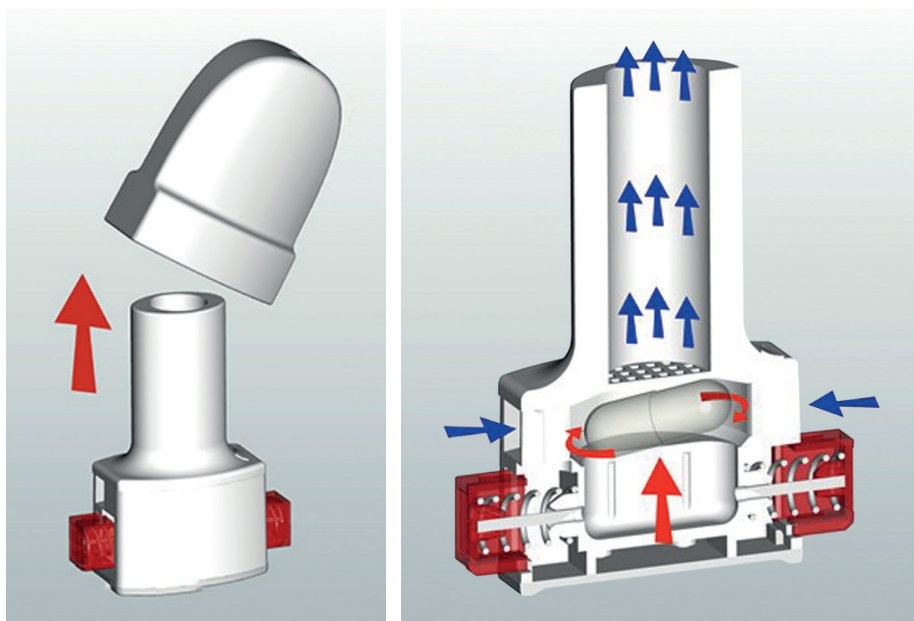


Figure 1: A cDPI (images from Plastiaple).

“The maximum force to open hard capsules is in the range of 3-5 N. To understand this order of magnitude, consider that the values for the force exerted during a keystroke whilst typing are in the range of 3.5-6.8 N. Opening a capsule is as easy as pressing a button.”

lung tolerance, is typically used as a carrier in the powder mixture along with the active ingredient to deliver drugs to the target. The system is simple, economical and eco-friendly, cDPIs have a carbon footprint 18 times lower than pressurised metered dose inhalers (MDIs).

THE FUNDAMENTAL LAWS OF INHALATION TECHNOLOGY

The inhalation dosage delivery and cDPIs in particular follow two laws:

- 1st law: The higher the quantity of powder that leaves the capsule, the higher the efficiency of the process. The parameter is measured by the emitted dose (ED).
- 2nd law: Particle size does matter, as the geometric diameter of the active ingredients within the formulation need to be in the range 1-5 μm . The parameter that measures this effect is called fine particle fraction (FPF).

To understand the need for such minute particle sizes better, it is necessary to consider how drug particles

pass through the respiratory system. The pathway through the lungs is not a straight line, in fact it's full of twists and turns (Figure 2). To reach the alveoli the particle must change direction continuously. If not, it will contact the wall of the airways

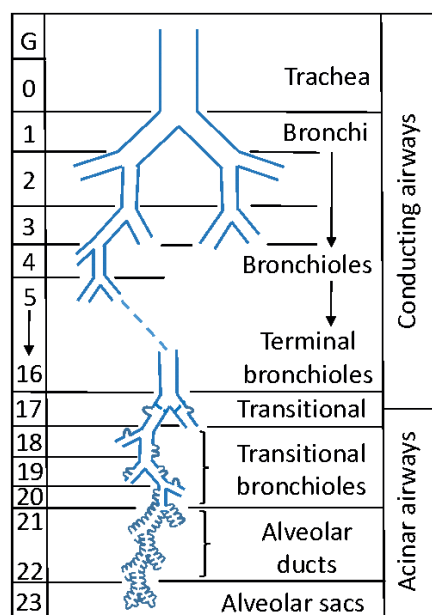


Figure 2: The way to the lung (Weibel model).³

and not reach the alveoli effectively. In fluid physics, there is a dimensionless number called the Stokes number (STK) which gives an idea of the ability of a particle to change direction with flow.² It is defined as:

$$\text{STK} = K d_p^2$$

Where K is a constant and d_p the particle diameter.

The key factor is whether the STK is greater or less than one:

- If $\text{STK} > 1$, the particle will detach from a flow, especially where the flow decelerates abruptly.
- If $\text{STK} < 1$, the particle follows fluid streamlines closely as it is able to change directions.

It then clearly follows that large particles with high velocity will not flow along the trajectory of the airways. This is due to inertia causing them to impact the wall of the bronchi and deposit there. Correlation *in vitro/in vivo* studies have shown that the limit size for a particle is 5 μm .¹ Additionally, particles whose diameter is lower than 1 μm will be exhaled.

CAPSULE-BASED DRY POWDER INHALERS

Puncturing

For hard shell capsules to function effectively as drug reservoirs in cDPIs, the capsule must be capable of being punctured efficiently. Sharpened pins or thin blades cut the capsules to release the powder medication upon inspiration, with low forces being necessary for the puncturing process. It is critical that capsule fragments do not hinder the outflow of the powder. For example, if a pin punctures the capsule, then the flap produced must stay attached and remain open, not closing or obstructing the opening.

Hard capsules fulfil these conditions. One can observe the initial linear slope of the curve (following the Young's modulus) which resists the force due to the elasticity of capsule. It reaches the threshold immediately prior to puncturing. Afterwards, there is a subsequent reduction in the force that is determined by the frictional forces between the pin and the perimeter of the punctured hole created in the capsule, including any "flap" that may be present. The force then becomes relatively constant. This is attributable to a more constant friction

Force/ Deformation for Hard Capsules

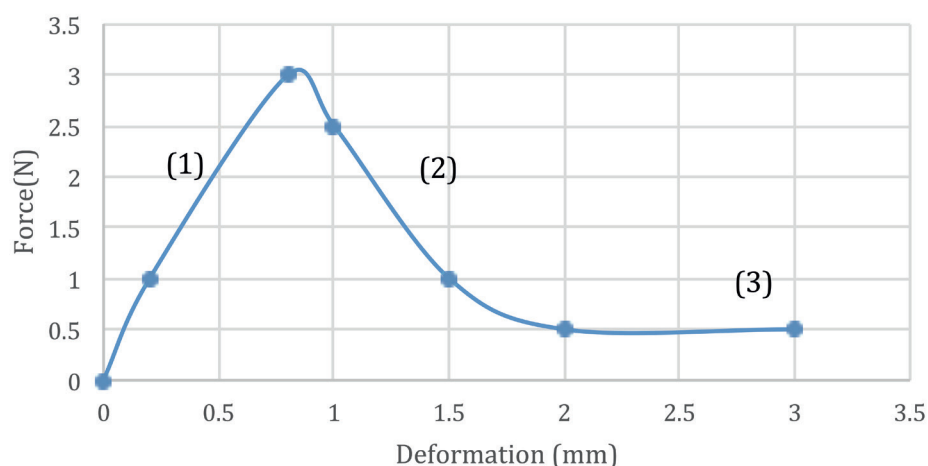


Figure 3: Standard graph of the displacement of a conical pin on a hard capsule versus the recorded force. The numerals indicate the various steps involved in the puncturing process (Redrawn from Ref 4).

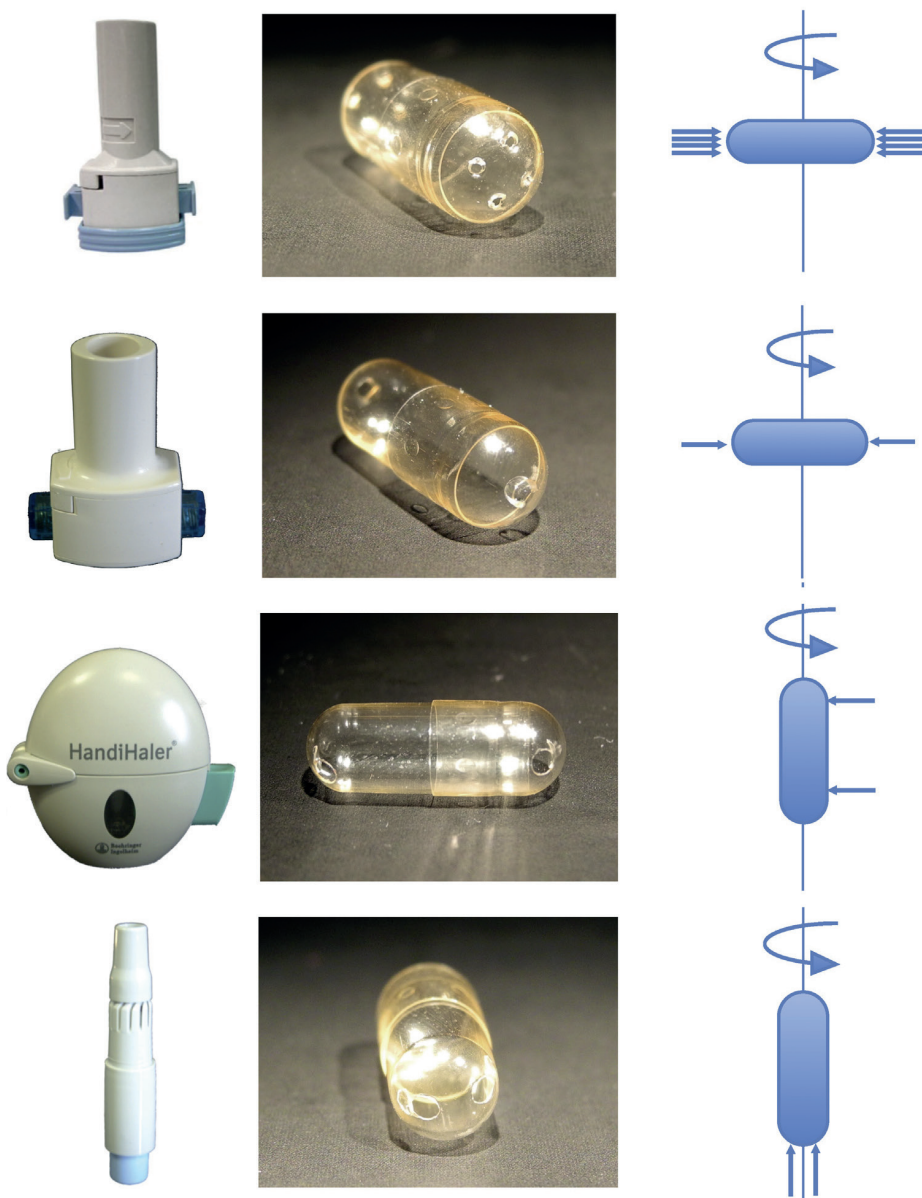


Figure 4: Capsule rotation modes for different inhalation devices.¹⁰ (Reproduced with kind permission from the International Journal of Pharmaceutics.)

force between the perimeter of the capsule puncture and the pins.⁴

The maximum force to open hard capsules is in the range of 3-5 N. To understand this order of magnitude, consider that the values for the force exerted during a keystroke whilst typing are in the range of 3.5-6.8 N.⁵ Opening a capsule is as easy as pressing a button.

The capsule profile shown in Figure 3 assures us that there are no pieces being shed and that the flap stays attached during the process. If this happens, the constant force value would drop until it reaches zero.

Aerosolisation

Powders in the range 1-5 μm are characterised by highly cohesive and adhesive properties that make processing them rather difficult. To overcome this, the micronised API is mixed with coarser excipient particles. The larger size of these carrier particles, usually in the range of 50-200 μm , improves powder flow and thereby improves powder dosing and dispensing. Additionally, the excipient acts as a diluent and increases the amount of powder that must be dosed from the microgram range, to the milligram range, a scale that makes dosing more feasible.⁶

Upon aerosolisation and inhalation of a powder, carrier particles deposit in the mouth and throat regions. It is therefore essential for drug particles that are attached to the carrier particle surface to detach from it, so that they do not deposit together with the carrier particles, instead depositing in the targeted lower respiratory airways.

This powder de-agglomeration is key to the success of the process. It depends on the fluid dynamic shear which may be enhanced by turbulence. Capsules contribute to creating this turbulence by rotating inside the inhaler device. The physical law behind this is the conservation of angular momentum.⁷ They can reach angular velocities of 2800 rpm inside the device,⁸ creating a high turbulence. For comparison, the spin speed of a washing machine is about 1600 rpm.

“Capsules contribute to creating this turbulence by rotating inside the inhaler device. They can reach angular velocities of 2800 rpm inside the device.”

Upon inhalation, the flow field generated within a cDPI acts to rotate the capsule at high speed. This ejects powder contained in the capsule through the created holes into the surrounding flow field.⁹ The break up can occur through a number of capsule-induced de-agglomeration mechanisms:

- Impact of the powder agglomerates with internal walls of the capsule.
- Forcing powder agglomerates through the small holes in the capsule, breaking up large agglomerates, preventing slugs from exiting the capsule.
- High speed impactions with the surrounding walls of the device when the particles are ejected from the capsule.
- The spinning capsule could act as a rotor to de-agglomerate ejected capsules through mechanical impaction with the external walls of the capsule.

Figure 4 shows different capsule rotation modes for four example inhalers.

Capsule Internal Surface

The capsule manufacturing process requires the use of a surface lubricant on the mould pins on which the capsules are formed. It enables the dried capsule parts (caps and bodies) to be removed from the moulds without damage. The nature and quantity of lubricant that remains in the capsule will modify the capsule surface properties. This plays a role in capsule aerosolisation performance.

The capsule internal surface is not flat (see Figure 5) and it seems that low quantities of internal lubricant do not fill all the surface pores, meaning the powder occupies these points. This makes it more complicated for the drug to exit the capsule. On the other hand, if the lubricant

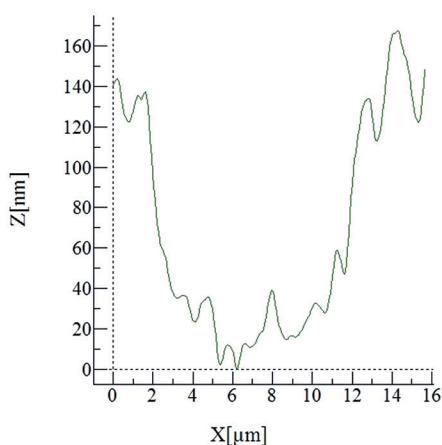


Figure 5: Capsule internal surface profile.¹¹

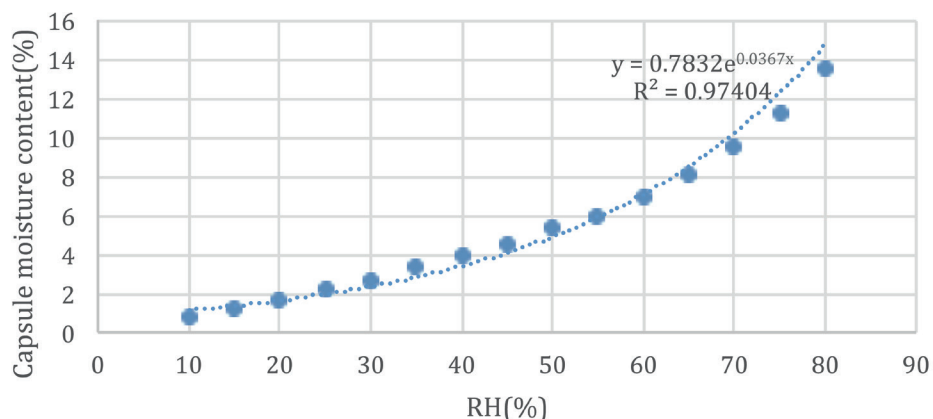


Figure 6: Correlation between HPMC capsule moisture content and RH. Exponential fitting.

content is high, adhesion between the capsule and powder may occur, reducing the process efficiency.

Stability/Moisture Content

Water is one of the enemies of inhalation drugs for the following reasons:

- Most inhalation drugs are moisture sensitive and are degraded by water.
- In presence of high relative humidity (RH), the capillary forces are significant, increasing the drug particle size. This reduces FPF and the efficiency of the process.
- Many inhalation drugs are only active in amorphous form. Amorphous solids are thermodynamically unstable, thus potentially can undergo crystallisation upon storage. The tendency to crystallise is increased with humidity, as water plasticises the solid, lowering its glass transition temperature.

Stored at RH not exceeding 65% HPMC capsules have a low moisture content of 3-8%, and these levels can be further reduced without any influence of their mechanical properties (Figure 6). These capsules do not become brittle in arid conditions, unlike gelatin capsules. A normal procedure for desiccation would be filling the capsules and storing them at low relative humidity (i.e. 11%, which corresponds to a capsule moisture content of 1%), followed by blistering and packaging.

cDPI MARKET OPPORTUNITIES AND FUTURE

cDPIs belong to the broader category of dry powder inhalers (DPIs). According to a BCC Research report¹² the CAGR for this technology is likely to be 12.5% in the period 2013-2018, while other alternatives

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like MDIs may grow at a more modest 4.2% CAGR. Interest in cDPI technology has increased thanks to an overall trend in favour of respiratory delivery methods and the rise of inhalable biotherapeutics.

Apart from their conventional applications in asthma and COPD, cDPIs can also be used for systematic disorders as diabetes, cancer and neurological diseases.¹³ Two good examples where inhalation capsules are used are oxytocin (peptide hormone) and levodopa (Parkinson’s disease).

There are exciting innovation projects in the development pipeline such as the use of new inhalation devices applying a magnetic field to increase the capsule rotational speed (Maxwell law) or the use of magnetic particles to increase the FPF of the delivery.¹⁴

CONCLUSION

Simplicity of use, flexibility of application, ease and economy of availability, proven performance and exciting innovations in the pipeline are some of the reasons why cDPI technology has gained wide acceptance and has a promising future.

Developing a cDPI drug involves subject specific knowledge, expertise and capable partners. One of the critical elements in the value chain is choosing the right type of hard gelatin or HPMC capsules. Several considerations are involved in this which are unlike the conventional dissolution and disintegration parameters typically associated with the capsule. Other critical elements are the choice of an appropriate device, formulation expertise, technology for precision encapsulation and optimum packaging.

An experienced partner like ACG with capabilities in integrated pharma manufacturing technologies can bring in valuable expertise and partner with customers to develop a complete solution.

The present outlook for cDPI technology is excellent, with continued advancement and a more promising future.

ABOUT THE COMPANY

ACG has been serving the pharmaceutical industry for five decades and is the second largest manufacturer of empty hard capsules in the world. The group comprises 13 companies, including subsidiaries in China, the US, Indonesia, Brazil and Europe.

ACG has a presence in over 100 countries with its products and services, employing more than 3,000 members of staff that strive to provide world-class technologies across multiple domains. It offers a complete range of solutions beginning with empty capsules, granulation and coating, capsule filling, tableting, packaging films, blister packing and carton packing, to end-of-line solutions. With over 20,000 machine installations

worldwide, it speaks volumes of the high quality standards followed at ACG, as well as compliance with major international quality certifications and legislations.

ACG is committed to a core corporate competence. Its research teams strive to develop innovative technologies in order to continually give customers the benefit of a cost competitive edge plus world-class technology. SciTech Centre, the group's R&D centre located in the heart of Mumbai, is a government recognised research institution. Especially in the last 25 years, the company has witnessed breakthroughs in development-including, controlled-release pharmaceutical engineering, dosage forms and veterinary and agricultural research, all with an emphasis on delivery systems.

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ABOUT THE AUTHORS

Fernando Díez is Scientific Business Development Manager for ACG and holds an MBA and degree in chemistry. He creates new business opportunities outside of the formal review/tender process and fosters relations with external research institutes and R&D centres. He has a wealth of experience in the pharmaceutical industry, having worked with renowned multi-national companies.

Justin Kalafat is a Business Development Manager at ACG North America, LLC, collaborating with the pharmaceutical and dietary supplement industries across North America on expanding ACG's capsule market share. Prior to joining ACG in 2014, his background includes degrees in chemistry and roles within the generic pharmaceutical industry in quality control and procurement. His experience enables strategies to be developed with customers, R&D focused institutions and universities on the technical aspects of capsules as a dosage form solution.

Jnanadeva Bhat, PhD, is General Manager, Product Development & New Product Offerings at ACG Associated Capsules and has been supporting new development, evaluating of new products and in charge of the application lab and customer interface for the last ten years. He has more than 20 years of experience in formulation R&D and has handled almost all types of dosage form development, including hard capsules, tablets, soft-gelatin capsules, injectables and lyophilised products across multiple regulated markets.

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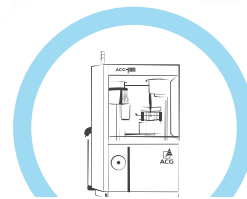
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