Hovione Technology

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SCALING UP FOR HIGH DOSE DELIVERY TO THE LUNGS

The interest in high dose compound delivery to the lungs is growing and driving the development of dry powder inhalers with enhanced dose delivery capability, in the range of 100 mg or more of active ingredient. In this article, João Ventura Fernandes, PhD, Business Development Manager; Gonçalo Rebelo de Andrade, PhD, MBA, Director; and Peter Villax, Chief Executive Officer, all of Hovione Technology, describe the scaling up of the currently marketed TwinCaps© inhaler into the new TwinMax™ design for high-dose delivery of challenging drug-alone formulations in single to short-term treatments and emergency situations.

The use of dry powder inhalers (DPIs) is expanding beyond asthma and chronic obstructive disease (COPD) into new therapeutic targets that include pulmonary arterial hypertension, idiopathic pulmonary fibrosis, anti-emetics, anti-diabetic, anti-virals and orally inhaled vaccines and antibiotics. Recent product launches together with the noticeably strong DPI pipeline on the non-asthma, non-COPD market[1] provide evidence of this expansion.

The growing interest in delivering anti-virals, antibiotics, vaccines, peptides or other drugs systemically via the lung in a single or a short-term treatment, has fueled the development of inhalers which comprise:

- A prefilled unit dose of powder – for therapeutic benefit and convenience of use
- Are disposable – for reasons of safety and hygiene
- Result in an economically viable product.

In addition, single-use disposable DPIs provide an attractive replacement alternative to the present use of multi-dose inhaler devices in emergency and hospitalisation situations, by providing the dose that is needed, instead of multiple doses the majority of which will remain unused. The economic benefit is therefore significant.

THE TWINCAPS® DPI

In 2006, Hovione began to develop a new DPI to deliver a long-acting neuraminidase inhibitor for the treatment of influenza. The target was the administration of the anti-influenza drug under pandemic situations, without or with minimal medical supervision and to inhaler-naïve patients, which would not be re-used to prevent contamination through the inhaler. It was therefore highly advantageous to have a sufficiently economic DPI that would be used once and disposed of.

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Moreover, the majority of patients being inhaler naïve, it was fundamental to make the inhaler extremely simple and with the lowest possible number of user steps, as the fewer the parts, the fewer the number of patient errors and the greater the acceptance and compliance.[2,3]

The answer to this challenge was TwinCaps®, a single-use disposable inhaler comprising only two plastic parts: a body and a shuttle. The shuttle is a moveable component with two prefilled powder doses held in place by the body, which also

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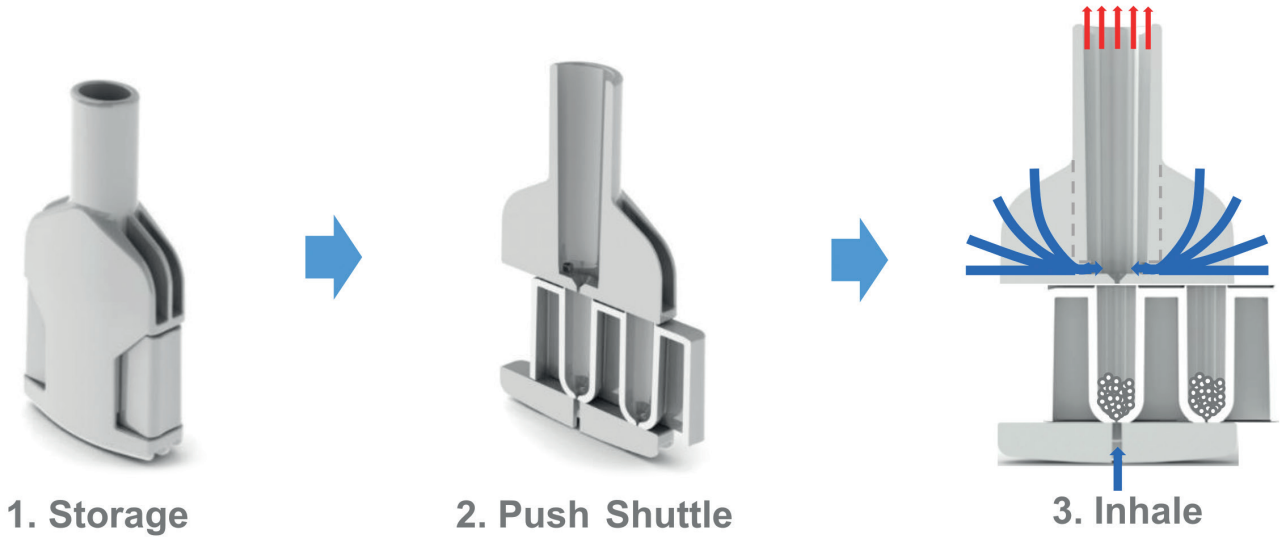

Figure 1: Using TwinCaps®. In storage, the shuttle is leak-proof. In use, the patient removes the inhaler from a foil protective pouch, pushes the shuttle to the inhalation position and inhales. The process is repeated for the second dose. The total dose is thus divided into two smaller doses.

provides the mouthpiece. In use, the patient simply slides the shuttle from the storage position to the inhalation position and inhales, as shown in Figure 1, repeating the operation for the second dose. The device is then discarded.

EFFECTIVE & GRADUAL DELIVERY

An important innovation in TwinCaps® was the successful leak-proof containment of the powder dose inside the shuttle compartments, without resorting to film strips or foils, which add to complexity in manufacturing. This is achieved through a close fit between the body and the shuttle while ensuring a smooth sliding movement, which even elderly patients or patients with dexterity difficulties can operate.

In addition to powder containment and storage function, the prefilled shuttle compartment is turned into a dispersion engine once the patient pushes it into the inhalation position. This is a second key innovation in TwinCaps®. Making use of the power of Computational Fluid Dynamics (CFD) in inhaler design,[4,5] Figure 2 shows that the compartment design creates a strong bottom jet featuring high turbulent kinetic energy that acts as a primary powder dispersion mechanism. An effective dispersion is further assisted by significant recirculation zones arising from the jet expansion through the restricted compartment design. Such flow recirculation additionally contributes to increasing the particle residence time, which is beneficial to a gradual dose delivery to the patient during inhalation.

TwinCaps® was launched in Japan in 2010, as part of Daiichi Sankyo's Inavir® drug product. Its simple use, effective delivery and ease of manufacture brought commercial success and Inavir became the best-selling drug in the Japanese influenza treatment market and TwinCaps® the world's third largest-selling unit-dose inhaler.

A NEW CHALLENGE

In its original design, TwinCaps® was capable of delivering up to 20 mg of active drug per dose compartment, for a total of 40 mg per inhaler. However, orally inhaled antibiotics as well as new drugs in development require substantially higher payload capabilities – up to a total dose of 100 mg of active ingredient, or even more.

The high dose of active pharmaceutical ingredient (API) adds to the challenge – little air space is left inside the dose compartment for adequate dispersion and entrainment, leading to the need to reduce or eliminate flight-enhancing excipients to make more space for the active, and thus negatively affecting the potential for high dose delivery. This challenge needs to be addressed at formulation and inhaler levels. New particle engineering technologies, such as spray-drying, have enabled API-alone formulations, with the added benefit that even APIs which are chemically incompatible with known inhalation excipients can now be formulated and delivered.

Spray-drying is capable of generating improved control over particle size distribution and reproducibility, reducing amorphous content in crystalline product formulations and enhancing overall drug stability.[6] Such particle engineered API-alone formulations are then normally characterised by high adhesion and cohesion properties resulting from the low median

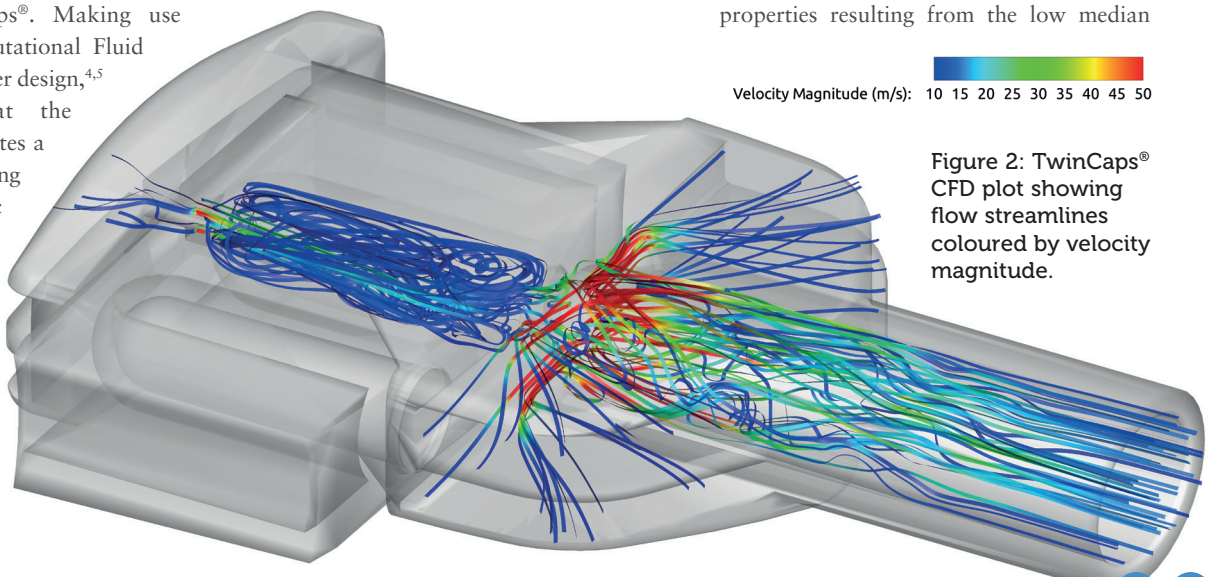

Figure 2: TwinCaps® CFD plot showing flow streamlines coloured by velocity magnitude.

particle size by volume, typically below 3 µm, required for producing drug particles within the inhalable range.

The reduced delivery potential of highly cohesive and adhesive, high-dose, API-only formulations needs to be overcome by the aerodynamic efficiency of the inhaler. To deliver such challenging products, whether antibiotics, vaccines, proteins or peptides, powder inhalers need to be significantly more efficient. Taking TwinCaps® as the starting point, we initiated a development programme to scale-up its delivered dose.

FAST DEVELOPMENT

The development objectives specified keeping the same body-and-shuttle design, the same filling principle and the same actuation manoeuvre. Thus there was only the opportunity to work on and adapt the dispersion mechanism of the TwinCaps® inhaler to increase the drug payload by a factor of two to three times.

An accelerated inhaler development methodology was followed based on three steps:

- First, the generation of amorphous composite particles spray-dried out of a trehalose/leucine solution with median particle size by volume below 3 µm (Figure 3), and high cohesiveness and adhesiveness. These challenging particles model closely the behaviour of certain drug-alone formulations.
- Second, the rapid iterative development and prototyping of scaled-up TwinCaps® inhalers using 3D printing technology. This resulted in seven different models over the course of eight weeks of work and concentrated primarily on enhancing dispersion features in the device.
- Third, the rapid screening of the aerodynamic performance of each new inhaler configuration with the model particles, using a total dose of 80-100 mg and the gravimetric Fast Screening Impactor (FSI) testing for determination of the emitted mass (EM) and fine particle fraction (FPF).

SCALING UP DELIVERY

The first scaling-up iteration consisted of a simple linear increase in every TwinCaps® dimension, so as to accommodate a total dose of 80 mg with a bulk density in the range of 0.2-0.5 g/cm^3. As shown in Table 1, at a pressure drop of 4 kPa and a flow rate of 40 L/min, in three replicate testing, the EM of powder from the device was very low, about 50% of the nominal dose, and the relative standard deviation was high, indicating a need for inventive re-engineering of the compartment design.

PROTOTYPE	EM (%)	EM RSD (%)	FPF (%)	FPF RSD (%)
1. Scaled up TwinCaps®	53.9	16.7	54.9	12.3
2. Improved iteration	80.5	5.2	37.8	33.5
3. Improved iteration	85.7	1.7	40.6	1.0
4. Improved iteration	75.6	5.2	38.9	0.8
5. Improved iteration	88.5	4.3	28.7	2.1
6. Improved iteration	92.8	1.1	39.8	9.5
8. Final improvement	91.2	1.4	40.7	1.7

Table 1: Progress of delivery and deposition performance through seven TwinCaps® scale-up iterations. Data in red indicate less than favourable results; data in green, favourable results.

For that purpose, new inhaler designs were provided with additional lateral air vents in the shuttle, forming pairs at various heights of the powder compartment, each pair providing a non-tangential admission of air. The new constructions were then tested with the same payload of model drug particles and ultimately the EM of powder reached 91%, FPF was 41% of the emitted dose and both with high reproducibility. Powder retention within the compartment itself was observed to be residual.

This indicates that the re-design of TwinCaps® to achieve large dose delivery of challenging powders was experimentally successful and the new enhanced device was named TwinMax™.

Following the development process which used the model trehalose/leucine formulation, TwinMax was then tested with a spray-dried, API-only formulation of a novel synthetic protein, AP301, intended for the treatment of pulmonary oedema arising from high altitude exposure, blood transfusions or lung infections.[7] Targeting treatment in emergency situations through a single-use disposable inhaler, initial proof of concept results showed that TwinMax enabled a reproducible delivery of a total dose of 100 mg of a spray-dried drug-alone formulation, achieving a fine particle dose of 30 mg in *in vitro* aerodynamic performance characterisation studies.[8]

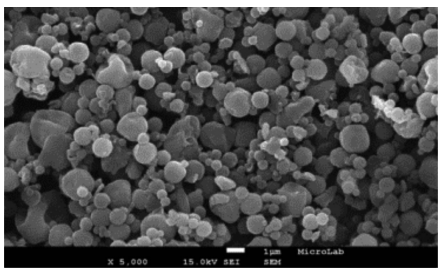

Figure 3: SEM image of spray-dried trehalose/leucine composite particles.

ENHANCED AERODYNAMICS

The result of the innovative re-engineering process of the powder compartment design presented in Table 1 is further detailed in Figure 4 through the use of computational fluid dynamics (CFD). The new compartment design is characterised by creating high flow velocity magnitudes at the bottom of the compartment and near the side walls, which induce non-uniform axial and tangential flow components varying across the powder compartment's length. These induce an air flow pattern with both high-flow turbulent kinetic energy and high flow vorticity within the compartment which effectively contribute to enhancing the primary powder dispersion mechanism for high dose drug delivery.

CONCLUSION

The interest in delivering high dose compounds to the lung, in the range of 100 mg or more of active ingredient, is driving the development of DPIs with enhanced dose delivery capability. Using

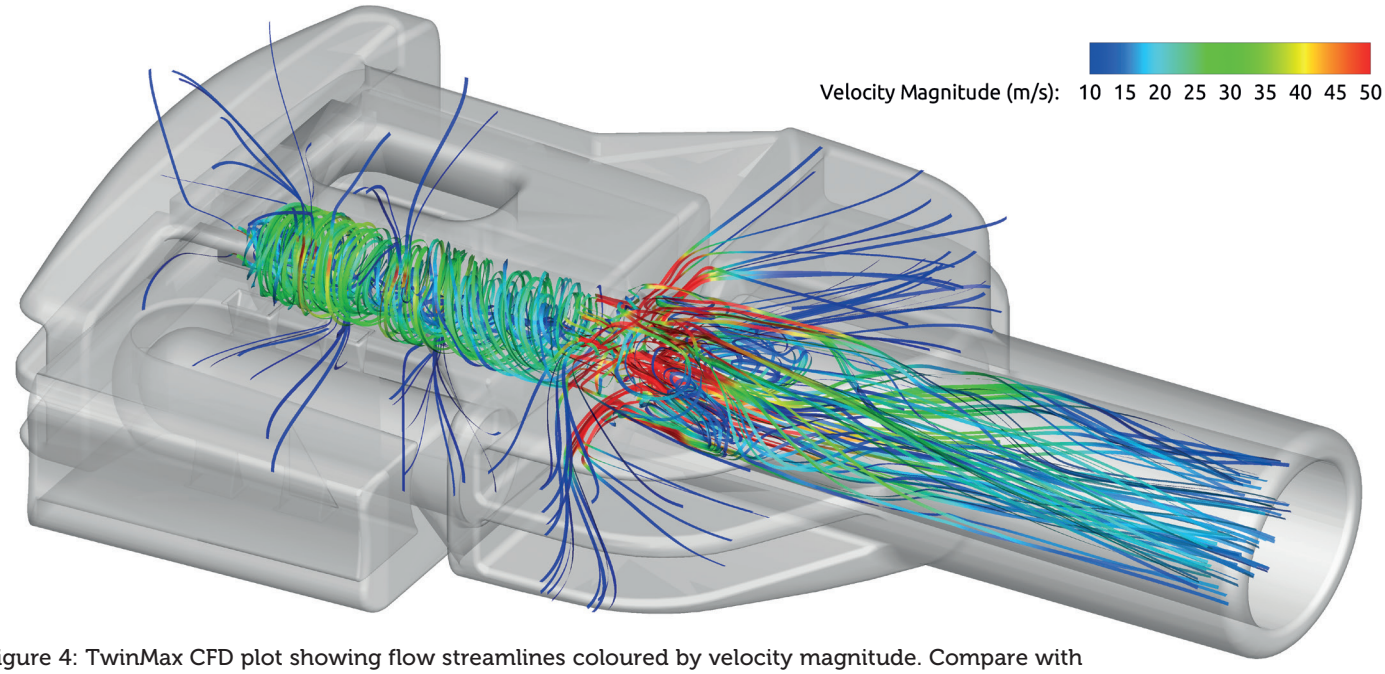

Figure 4: TwinMax CFD plot showing flow streamlines coloured by velocity magnitude. Compare with TwinCaps® in Figure 2. TwinMax displays faster velocities in the powder compartment due to additional side vents. Lower speeds in the mouthpiece are comparable in both devices.

fast development tools such as CFD and 3D printing, the currently marketed TwinCaps® DPI has been scaled-up to the new TwinMax design for high-dose delivery for single to short-term treatments and emergency situations. The TwinMax inhaler combined with spray-drying formulation technology has been shown to be capable of delivering a total dose of 100 mg of a drug and presents a simple, cost-effective solution to deliver drugs requiring large doses for effective therapy.

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ABOUT THE AUTHORS

João Ventura Fernandes is Business Development Manager at Hovione Technology. A mechanical engineer with a PhD in Engineering Design and over eight years' experience in product design in the aerospace and pharmaceutical industries. He worked previously in product design at Volvo Aero and Rolls-Royce jet engines and joined Hovione in 2014, quickly becoming a skilled device developer, scientist and inventor.

Gonçalo Rebelo de Andrade is Director at Hovione Technology. He holds a Ph.D. in Biochemistry from Ludwig Maximillian University in Munich and earned his Lisbon MBA course degree at Nova/Catolica Business School. He joined the Hovione group in 2013 as a business development manager for inhalation drug development services and for the dry powder inhalers within Hovione's portfolio, which he led until March 2016. Gonçalo Andrade brings 15 years' experience in the life sciences sector in the US, Germany and Portugal where he worked for both large MNC companies and startups and a clear vision on the hurdles connected to the drug development of inhaled drugs.

Peter Villax is Chief Executive Officer at Hovione Technology. He joined Hovione in 1982 as a computer programmer, then switched to pharmaceutical development in 1990, soon becoming interested in pulmonary delivery and in the development of DPIs. In 2007 Hovione licensed TwinCaps® to Daiichi Sankyo for the delivery of Inavir®, becoming market leader in the influenza space in Japan. He acquired significant experience as an inventor of devices, as a patent writer and as licensor of technology patents.