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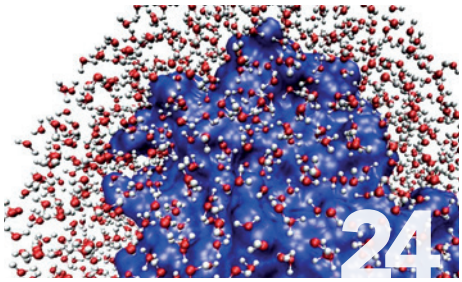

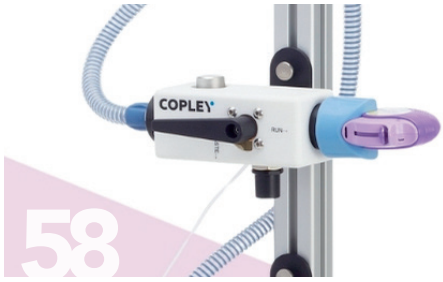

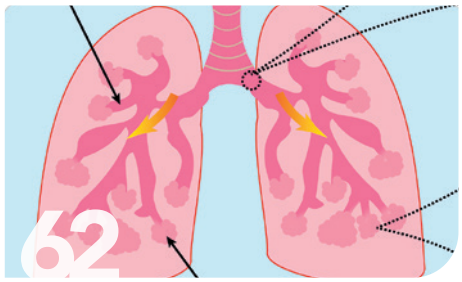

PULMONARY & NASAL DRUG DELIVERY

ONdrugDelivery Issue N° 170, April 16th, 2025

This edition is one in the ONdrugDelivery series of publications. Each issue focuses on a specific topic within the field of drug delivery, and is supported by industry leaders in that field.

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Expanding Horizons:
Advancing the Possibilities of Inhaled and Intranasal Drug Delivery

In this issue of ONdrugDelivery, we cover orally inhaled and nasal drug products. In particular, this issue focuses on advanced delivery systems that are pushing the boundaries of what inhalable therapies are capable of, from novel delivery devices to formulation techniques. While the inhalation space has its share of long-established mainstays, such as metered dose inhalers, the articles in this issue instead take a closer look at the challenges of broadening the scope of what can be achieved via inhalation, bringing the advantages of this tried and tested delivery route to new therapy areas and levels of efficacy.

The issue begins with an article from our Key Sponsor, **Aptar Pharma** (Page 08), providing an overview of the novel advanced devices that Aptar is bringing to market, including CHI's Quattrii dry powder inhaler (DPI), PULMOTREE's Kolibri nebuliser and Aptar's own Orbital high-dose DPI. Aptar's article is accompanied by a deeper dive into Kolibri from **PULMOTREE** (Page 16), discussing the advantages of using realistic breathing profiles for aerosol characterisation, and an Expert View from **CHI** (Page 24) on the challenges of developing and delivering dry powders for biologic formulations. Further to CHI's article, **Catalent** and **Roquette** (Page 52) also contribute to the subject of dry powders with a piece on the expertise required for processing and encapsulating dry powders, with a keen insight into challenges presented by relative humidity.

Soft mist inhalers (SMIs) also feature prominently in this issue, with an article from **Merxin Ltd** (Page 46) on the potential for SMIs to be a key factor in bringing the exciting field of psychedelic treatments for mental healthcare to the inhalation space. In addition to this, we feature a preview for Merxin Ltd's upcoming **SMI.London 2025** conference (Page 30), which is focused exclusively on the subject of SMIs, including an overview of the speakers who will be presenting at the event.

However, advanced inhalers are not this issue's sole focus – there is also a strong showing for intranasal delivery. **Nemera** (Page 36) has an insightful piece on the company's efforts to develop a nasal spray that can consistently deliver medications designed to cross the blood-brain barrier by precisely and reliably targeting the olfactory cleft. As well as this, **Renaissance Lakewood** (Page 42) presents an Expert View investigating the advantages of the nasal route for existing medications via drug repositioning, making use of regulatory approaches such as the US FDA's 505(b)(2) pathway.

Rounding out the issue, **Copley Scientific** (Page 58) presents an in-depth look at how to overcome the stubbornly persistent challenge of low adherence to inhalable therapies, with a particular emphasis on the regulatory perspective. Lastly, **Springboard** (Page 64) provides a rigorous discussion of the potential of polymeric nanoparticles, elucidating how this technology could push the boundaries of what inhalable formulations are capable of, and tackle key challenges at the forefront of inhalable drug delivery.

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THE POWER OF PULMONARY: ADVANCES IN INHALED DRUG DELIVERY EXPAND RESPIRATORY TREATMENT OPTIONS

Aptar pharma

Jonathan Mulpas of **Aptar Pharma** discusses how advanced inhaled drug delivery devices, such as dry powder inhalers and non-propellant liquid inhalers, can meet currently unmet needs in the inhalation space, focusing on devices that Aptar and its partners are developing to realise this potential and the expertise that Aptar can offer in this area.

Recent advances in inhaled drug delivery technology are making inhalation a viable option for a wide range of new drugs. Historically, most inhaled products required low but frequent doses of a drug, targeted respiratory indications such as asthma or chronic obstructive pulmonary disease (COPD) and were administered from a pressurised metered dose inhaler (pMDI). Since their introduction to the market, pMDIs have proven to be a reliable and well-established vehicle to treat these common conditions.

However, the advent of newer advanced inhaled drug delivery technologies, such as dry powder inhalers (DPIs) and non-propellant liquid inhalers (NPLIs), has brought new capabilities and distinct advantages that are proving to be game changers in the inhaled drug delivery space. These advanced inhalation technologies not

"FROM CYSTIC FIBROSIS TO TUBERCULOSIS AND A RANGE OF INFECTIOUS DISEASES, THE LATEST GENERATION OF ADVANCED INHALED DRUG DELIVERY TECHNOLOGIES CAN PROVIDE NUMEROUS BENEFITS TO DRUGMAKERS AND PATIENTS ALIKE."

only retain the reliability and convenience of traditional pMDIs but can also provide highly controlled, targeted delivery and high dose loading for molecules and target indications not previously possible. From cystic fibrosis to tuberculosis and a range of infectious diseases, the latest generation of advanced inhaled drug delivery technologies can provide numerous benefits to drugmakers and patients alike.

CATEGORIES OF INHALATION DRUG DELIVERY TECHNOLOGY

Portable inhalation drug delivery technologies can be grouped into three main categories:

- **pMDIs:** Low-dose drug delivery in a suspension or solution with a propellant
- **DPIs:** Low- or high-dose powder inhalation
- **NPLIs:** Inhaled fine mist liquid dispensers for targeted delivery.

This article focuses on the latest advances in DPI and NPLI technology – how they enable drugmakers to meet currently unmet needs and deliver a wide range of new molecules and indications via inhalation. Aptar Pharma has added advanced inhaled drug delivery technology to its well-established portfolio of pMDI metering valves and has incorporated advanced inhalation technologies as part of its strategy to provide a full range of inhaled drug delivery solutions.

DPI VERSUS pMDI TECHNOLOGY

Having the ability to deliver dry powder formulations directly to the lungs can be an attractive option for a drugmaker. Dry powder formulations do not include any aqueous media and can therefore provide enhanced stability in a lightweight format, which is ideal for portability and extended shelf life.

On the other hand, pMDIs represent a well-accepted and proven drug delivery technology that uses a propellant to deliver fine droplets of drug formulation through the mouth and throat to the targeted lung area. They have long been used to effectively deliver low doses of drug product to respiratory patients for chronic conditions such as asthma and COPD. However, as traditional pMDI propellants contribute to the product's CO_2 footprint, Aptar is in the process of redeveloping its industry-standard pMDI metering valves to work with the latest lower-global-warming-potential propellants for greater sustainability.

> "PMDIs DO NOT PROVIDE THE LEVEL OF FLEXIBILITY OFFERED BY ADVANCED DPIS, WHICH ARE CAPABLE OF DELIVERING HIGH DOSES OF A RANGE OF DIFFERENT MOLECULE TYPES, INCLUDING BIOLOGICS, DIRECTLY TO THE LUNGS."

Going forward, pMDIs are expected to remain a staple and proven performer for low-dose inhaled delivery. However, pMDIs do not provide the level of flexibility offered by advanced DPIs, which are capable of delivering high doses of a range of different molecule types, including biologics, directly to the lungs.

ADVANCED DPI ADVANTAGES

Advanced DPI technology now enables drugmakers to administer high doses of API directly to a patient's lungs while avoiding their cough reflex, significantly increasing the number of potential applications for this non-invasive drug delivery route. Inhaled drug delivery not only provides targeted lung delivery but can also enhance the drug's bioavailability and provide rapid onset of action for faster symptom relief.

By delivering the API directly to the lungs, inhaled delivery can result in a reduced side effect profile by avoiding the higher doses of drug typically required for systemic drug delivery approaches. The most advanced DPI technologies are able to provide enhanced dosing precision, even in the face of highly variable patient lung function. In light of this, Aptar Pharma has developed solutions or partnered with leading inhaled drug delivery technology developers to offer some of the most advanced DPI and NPLI options available on the market.

Figure 1: The Quattrii DPI is capable of delivering carrier-based or API-only low-potency formulations of 50–150 mg fill mass.

QUATTRII DPI

Aptar Pharma is exclusively commercialising the Quattrii DPI (Figure 1) through a collaboration with Cambridge Healthcare Innovations (Cambridge, UK). The Quattrii DPI system can precisely deliver up to 100 mg of powder formulation to the lungs via its unique tunable vortex effect, created within the inhalation system. Able to separate formulation carriers from the product blend through classification, Quattrii creates a vortex in the blister upon inhalation that sweeps respirable-sized particles into the inhalation airflow while leaving the carrier particles behind. This process efficiently transports the powder deep into the lungs where it can be directly absorbed into the lung tissues. Alternatively, for engineered particles, the system can be tuned to deliver all of the powder formulation, without separation, directly to the lungs of the patient.

The Quattrii DPI reduces dose-to-dose variability, which is caused by differences in patient inhalation capabilities. Even when the patient has poor lung function, Quattrii efficiently transfers available inhalation energy to the powder formulation, which in turn aerosolises it and creates a consistent fine particle fraction for reliable dosing. This precise dosing also minimises unwanted mouth and throat deposition, instead focusing the delivery on the lungs. With a high payload capability of 100 mg of powder formulation, the Quattrii DPI system can now be used for a wider array of targeted lung treatments including antivirals, antifungals, antibiotics, antihypertensives and even cystic fibrosis drugs.

APTAR ORBITAL® DPI

Aptar's Orbital® DPI (Figure 2) was designed to provide progressive delivery of very high payload powder drug formulations to the lungs. Orbital's unique powder delivery system centres around a deagglomeration chamber where a puck composed of powder drug formulation is progressively released as the patient inhales through the rate-controlling orifices that access the chamber. As air is drawn through the peripheral inlets, powered by patient inhalation, the jets of air propel the powder puck in an orbital motion around the chamber, deagglomerating and releasing the desired amount of drug product with each inhalation.

Figure 2: Orbital can reliably deliver high doses of dry powder formulations directly to the lungs.

The result is that the inhalation-driven air jets drive the spinning puck to release the correct amount of drug powder, which is then carried through the mouth and throat for delivery to the lungs. The patient simply inhales from the device repeatedly until the entire puck has been completely deagglomerated to ensure that the full dose has been delivered. Each inhalation can be progressive, releasing only a partial dose, which reduces the risk of activating the patient cough reflex, which can contribute to increased patient compliance and consistent dosing.

Some conventional DPI technologies require the manual loading of multiple individual powder-filled gelatine capsules into the inhaler system one at a time to deliver a high dose. These complex manual loading systems can contribute to higher rates of dosing errors and reduced patient compliance. Conversely, the Orbital DPI uses a unique progressive dispensing system from a single drug formulation puck that eliminates the need to reload the device when delivering a high load dose (Figure 3).

The flexibility of the Orbital DPI allows it to be used for single- or multi-use applications. The Orbital system can be reused by simply loading a new puck into the DPI system every time a dose is required. Orbital pucks come in sealed airtight blister packaging that protects the drug product from air or contaminants until it is required for use, further enhancing the shelf life of the product. Orbital is easy to use, requiring only a simple prime and breath step, resulting in short administration times.

"ORBITAL IS EASY TO USE, REQUIRING ONLY A SIMPLE PRIME AND BREATH STEP, RESULTING IN SHORT ADMINISTRATION TIMES."

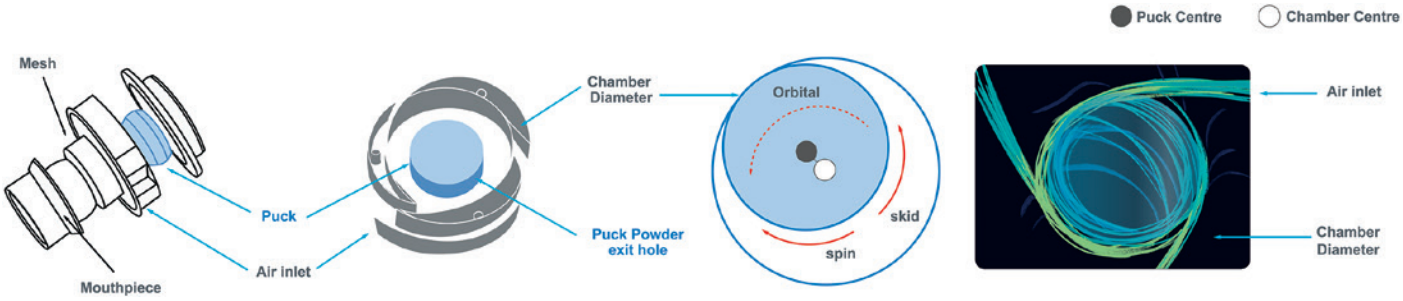

Figure 3: Description of the Orbital chamber, powder release and deagglomeration mechanism.

Orbital is also compatible with a wide range of formulations and molecule types and can reliably deliver 100 mg to over 400 mg of formulation from each powder puck. With scalable solutions from Phase I to commercial, the high payload capabilities of the Orbital DPI expand the number and types of APIs that can be administered via this safe and convenient drug delivery route.

KOLIBRI NPLI

The Kolibri digital NPLI is the result of an exclusive collaboration between PULMOTREE (Munich, Germany) and Aptar Pharma, designed to fulfil the unmet needs of inhaled drug delivery when using a fine mist – many of the currently available liquid inhaler technologies cannot achieve sufficient control of the aerosol deposition pattern to reliably target the deeper parts of the lungs.

Many older liquid inhalation technologies cannot compensate for the varied inhalation capabilities of different patients or variations in the inhalation manoeuvres they carry out. These factors can result in inconsistent and uncontrolled aerosol deposition. Other traditional nebulisers are non-portable and require that the patient remains stationary for extended periods of time to deliver a low-concentration liquid formulation to the lungs.

On the other hand, the Kolibri NPLI (Figure 4) is highly portable and provides new features combined with levels of performance that can enhance the patient experience. With the incorporation of the Intelligent Administration System (iNAS), Kolibri provides visual and haptic feedback to the patient regarding their inhalation manoeuvres, effectively training them on how to optimise their inhalation technique. This real-time guidance allows Kolibri to provide much more efficient targeted delivery to the desired areas of the lungs for optimal drug delivery, while enhancing efficacy and reducing drug loss (Figure 5).

Figure 4: Kolibri, a digital mesh nebuliser system for inhaled drug delivery.

The Kolibri NPLI is an advanced soft mist drug delivery system that incorporates integrated digital health connectivity, designed to resolve many of the limitations of existing nebuliser-like inhalation devices. Packed with innovative new features, the Kolibri vibrating-mesh nebuliser is triggered by the user's breath. Kolibri's performance can be optimised for the requirements of specific medications, patient groups or even market strategies.

Device data regarding inhalation technique, inspiratory flow, inhaled volume, time, date and aerosol generator life meter can be captured and automatically uploaded to the cloud for review and analysis almost anywhere. This makes Kolibri ideal for use in clinical studies or for self-administered home use. Physicians or researchers can conveniently monitor patient usage and determine the patient's compliance from a distance. When connected to the Kolibri Connect smartphone app, patients can stay up to date with their dosing schedule through automated reminders and also review their user data via a single convenient interface. The proprietary key-and-lock system ensures that the device operates to its designed level of performance by locking out the use of non-genuine or expired aerosol heads for patient safety and the elimination of commercial product piracy risks *(see this issue, page 16, for more detail on Kolibri)*.

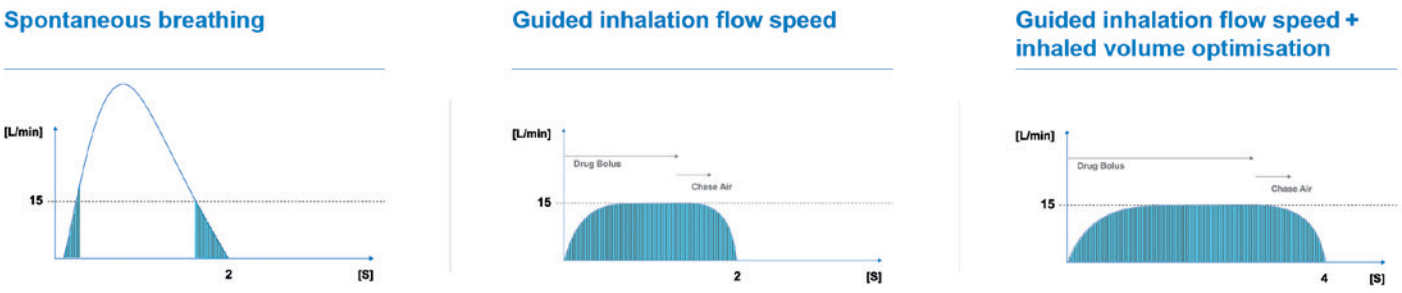

Figure 5: Kolibri's unique drug deposition optimisation through inspiratory flow control.

APTAR'S INHALATION DEVELOPMENT EXPERTISE

Successfully developing optimised drug delivery products for inhalation takes not only high-quality devices, but also specialised scientific and regulatory knowledge with supporting services. The path from device to lungs for liquid mists or powders is complex, with substantial differences between every patient and product. As a leader in the inhalation drug delivery space, Aptar Pharma offers its customers specialised development services that can reliably support the creation of compliant and effective inhaled drug products.

Aptar Pharma's Nanopharm offers comprehensive orally inhaled and nasal drug product development services that can optimise formulations for each customer molecule and support drug delivery system selection. The company's proprietary SmartTrack™ platform uses clinically relevant *in vitro* tests and *in silico* models, such as computational fluid dynamics, to support the acceleration of the development process, in some cases eliminating the need for Phase I clinical studies.

Aptar Pharma's regulatory experts also provide comprehensive regulatory process support to customers, particularly for complex drug-device combination products, including the provision of a host of fully supportable filing-ready data sets. Furthermore, Aptar Pharma's Noble group is available to provide medical device training solutions, human factors engineering, market insight services and patient onboarding strategies, simplifying the path to market for those developing innovative inhalation drug delivery products.

Aptar Pharma offers its customers a fully integrated service to bring advanced inhaled drug delivery products to market supported by its global product supply capabilities. Aptar Pharma has a proven track record of successfully supporting a wide variety of customer products, with over 150 US FDA approved NDAs, ANDAs and INDs using Aptar Pharma drug delivery technologies since 2020 alone. Aptar Pharma also protects its product innovations with over 750 patent families for enhanced intellectual property protection and market differentiation.

"AS A LEADER IN THE INHALATION DRUG DELIVERY SPACE, APTAR PHARMA OFFERS ITS CUSTOMERS SPECIALISED DEVELOPMENT SERVICES THAT CAN RELIABLY SUPPORT THE CREATION OF COMPLIANT AND EFFECTIVE INHALED DRUG PRODUCTS."

CONCLUSION

Aptar Pharma has invested in growing its portfolio of advanced inhaled drug delivery technologies because it sees an opportunity to safely and effectively treat more respiratory conditions via this non-invasive and reliable delivery route. With advances in new inhalation devices, the digitalisation of drug delivery and the creation of specialised drug development and support services, the future opportunities for inhaled drug delivery products will continue to grow. Aptar Pharma prides itself on delivering comprehensive services along the drug development pathway that help to take its customers through the journey from formulation to patient.

Jonathan Mulpas

Jonathan Mulpas is Business Development Director for the Pulmonary Category Team at Aptar Pharma. Mr Mulpas holds an engineering degree from École Centrale Paris (France) and a master's degree in Aeronautics from Beihang University in Beijing (China). Having previously worked at Airbus (Toulouse, France), Mr Mulpas joined Aptar Pharma in 2018 where he spent six years in the R&D team, holding various roles in the development of pulmonary products. In his current business development position in Aptar Pharma's Pulmonary Category Team, Mr Mulpas is responsible for Aptar's DPI and NPLI programmes.

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GWP, global warming potential; **HFA**, hydrofluoroalkane; **HFO**, hydrofluoroolefin; **pMDI**, pressurized metered dose inhaler.

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REALISTIC BREATHING PROFILES IN *IN SILICO* MODELS: A PARTNERSHIP APPROACH

PULMOTREE

X

Aptar pharma

Dr Carolina Dantas and **Ulf Krueger** of **PULMOTREE**, along with **Howard Burnett** of **Aptar Pharma**, discuss the critical need for precision when delivering biologics to the lungs, how PULMOTREE's Kolibri is able to achieve this using guided breathing, and how the use of realistic breathing profiles can improve outcomes and decrease risk with *in vitro* and *in silico* testing.

THE CHALLENGES OF INHALED BIOLOGICS

Respiratory delivery of biologics presents significant challenges, particularly when it comes to ensuring efficient and reproducible drug deposition in the targeted lung regions. A device that can provide precise drug delivery is crucial for maximising therapeutic effects while minimising drug losses, particularly given the high cost of biologics, their complex formulations and the need to maintain stability throughout the delivery process.

One of the primary factors that influences the efficacy of pulmonary drug delivery is the patient's breathing manoeuvre, which can vary significantly. Variability in breathing patterns can lead to inconsistent lung deposition, impacting both therapy efficacy and safety. Studies have shown that, if the breathing manoeuvre is controlled, this variability can be reduced.[1] As demand for more efficient drug-nebuliser combinations grows, innovative solutions that enhance aerosol delivery and improve targeted lung deposition are essential.

Figure 1: Kolibri™ Mesh Nebuliser platform.

"KOLIBRI USES A HAPTIC FEEDBACK MECHANISM TO SUPPORT AND GUIDE THE PATIENT'S INHALATION, ENSURING AN OPTIMAL BREATHING PATTERN THROUGHOUT THE NEBULISED TREATMENT."

THE KOLIBRI™ MESH NEBULISER: ADDRESSING THE CHALLENGES

The Kolibri Mesh Nebuliser platform addresses these challenges with its guided inhalation system, integrating an innovative feedback mechanism that optimises aerosol performance, minimises variability in patient breathing patterns and ensures precise drug deposition (Figure 1). Kolibri uses a haptic feedback mechanism to support and guide the patient's inhalation, ensuring an optimal breathing pattern throughout the nebulised treatment. This haptic feedback works by guiding users to maintain an ideal inhaled flow rate, providing a pleasant positive vibration when inhalation remains within a predefined optimal range. Conversely, if the inhalation flow rate exceeds this limit, the system provides a discouraging negative vibration to prompt adjustment.

To further reduce aerosol loss, in addition to its breath-triggered mechanism, Kolibri only activates nebulisation when the patient's inhaled flow rate stays within a predefined optimal range tailored to the target deposition area. The device's Intelligent Administration System (iNAS) technology promotes extended inhalations, guiding users to sustain each breath for up to the individual's maximum capacity to enhance the inhaled volume and therefore obtain more deep lung drug deposition.

Additionally, Kolibri automatically measures and records detailed parameters regarding the breathing manoeuvre, such as inhaled flow rate, duration and adherence, thereby enabling the creation of a comprehensive characterisation of the patient's breathing profile on an inhalation-by-inhalation basis. These real-time monitoring capabilities provide valuable insights into adherence and therapy effectiveness.

FEEDBACK TECHNOLOGY SUCCESSFULLY REDUCES PATIENT VARIABILITY

PULMOTREE has conducted detailed validation testing to assess the effectiveness of Kolibri's feedback technology. The study recorded and analysed volunteers' breathing profiles while inhaling saline solution with Kolibri. The results demonstrated that the feedback system can successfully guide users' breathing manoeuvres by encouraging deeper and slower inhalations, defined as an inhaled flow rate below 15 L/min for six seconds, with high consistency.[2] A relevant reduction

"THIS STUDY RESULTED IN THE ESTABLISHMENT OF A GUIDED BREATHING PROFILE FOR KOLIBRI, WHICH IS REPRESENTATIVE OF HOW PATIENTS USE THE DEVICE."

of both intra- and inter-patient variability associated with individual breathing manoeuvres was observed in most of the participants (Figure 2).

This study resulted in the establishment of a guided breathing profile for Kolibri, which is representative of how patients use the device. This realistic breathing profile is based on user data from the validation test, where the feedback technology was set to guide a "long and deep inhalation" (Figure 3), and the profile parameters include an inhaled volume of 1500 mL, an inhalation time of six seconds, an inhalation-to-exhalation ratio of 1.6:6 and a peak flow of 15 L/min.

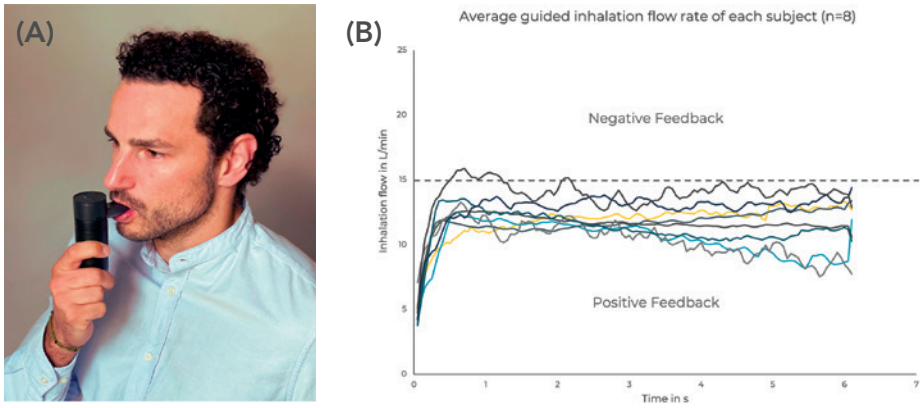

Figure 2: Participant (A) of the Kolibri™ device validation study and the reduced inter-individual variability of the average inhalation flow rate (B).

THE POTENTIAL OF REALISTIC BREATHING PROFILES IN AEROSOL CHARACTERISATION

Current *in vitro* testing standards, such as USP <1601> and Ph Eur 2.9.44, rely on standardised breathing profiles that fail to reflect real patient use, often leading to discrepancies with *in vivo* outcomes. Incorporating realistic breathing profiles into *in vitro* and *in silico* testing can enhance the predictive accuracy of aerosol drug delivery systems by addressing these limitations.

- ***In Vitro* Testing**: Using realistic breathing profiles in delivered dose testing can provide more representative and predictive results than standard sinusoidal patterns.
- ***In Silico* Modelling**: Integrating patient-specific breathing profiles and lung geometries can enable more precise simulations of regional lung deposition, optimising drug formulation and device matching.

By incorporating realistic inhalation data during early development phases, pharmaceutical companies can improve the predictive power of their studies, ensuring a better match with real-world performance. This approach helps to mitigate risks in drug-device development, reducing costly late-stage failures and streamlining regulatory approval processes.

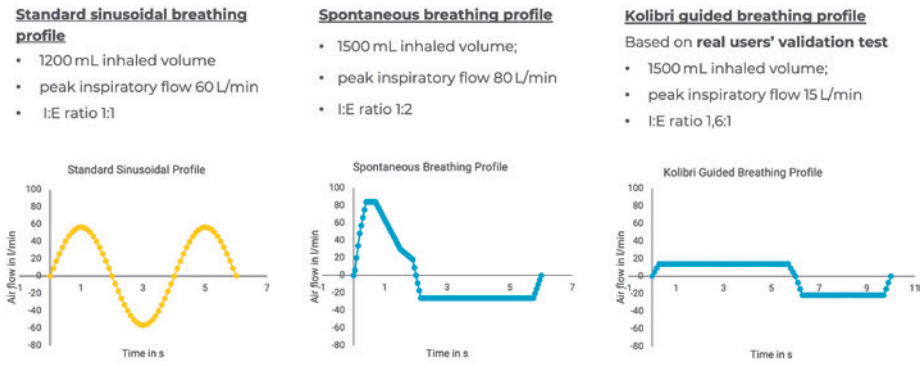

Figure 3: Comparison of standard sinusoidal (yellow) versus realistic breathing profiles (blue), spontaneous unguided and Kolibri guided, applied to investigate the differences in regional lung deposition.

A COLLABORATIVE CASE STUDY: OPTIMISING AEROSOL DEPOSITION

A collaboration between PULMOTREE and Aptar Pharma through Nanopharm (Cwmbran, UK), Fluidda (Kontich, Belgium) and Ockham Biotech (Fareham, UK) showcases how current joint capabilities can enhance drug-nebuliser performance.

OCK4 by Ockham Biotech is a heparin derivative, classified as a high molecular weight biologic, developed to be nebulised and target the small airways and alveolar lung regions. To ensure optimal drug delivery, the Kolibri Mesh Nebuliser platform was tailored specifically for OCK4 through an appropriate mesh selection and customisation of individual device features.

In the context of the Kolibri-OCK4 combination product development, PULMOTREE aimed to assess the impact of the Kolibri guided breathing profile on the deposition of OCK4 through advanced *in silico* simulations. Using two different *in silico* models, a comparison was made between the regional lung deposition of OCK4 using two different breathing profiles – a realistic Kolibri guided breathing profile versus a spontaneous unguided breathing profile (Figure 3).[3]

"IN THE CONTEXT OF THE KOLIBRI-OCK4 COMBINATION PRODUCT DEVELOPMENT, PULMOTREE AIMED TO ASSESS THE IMPACT OF THE KOLIBRI GUIDED BREATHING PROFILE ON THE DEPOSITION OF OCK4 THROUGH ADVANCED *IN SILICO* SIMULATIONS."

Regional Deposition Model

A model based on the National Council on the Radiation Protection and Measurements (NCRP) model implemented in the Mimetikos Preludium software (Emmace, Lund, Sweden) was developed by Nanopharm to predict aerosol distribution in an idealised healthy lung geometry (Weibel model of the lung). The Kolibri guided breathing profile demonstrated (Figure 4):

- 45% higher deposition in the target regions for OCK4 (bronchiolar and alveolar) compared with the spontaneous breathing profile
- A more favourable pattern for deep lung deposition due to higher alveolar deposition (41.3% versus 27.9%) and lower extra-thoracic deposition (12.4% versus 23.4%).

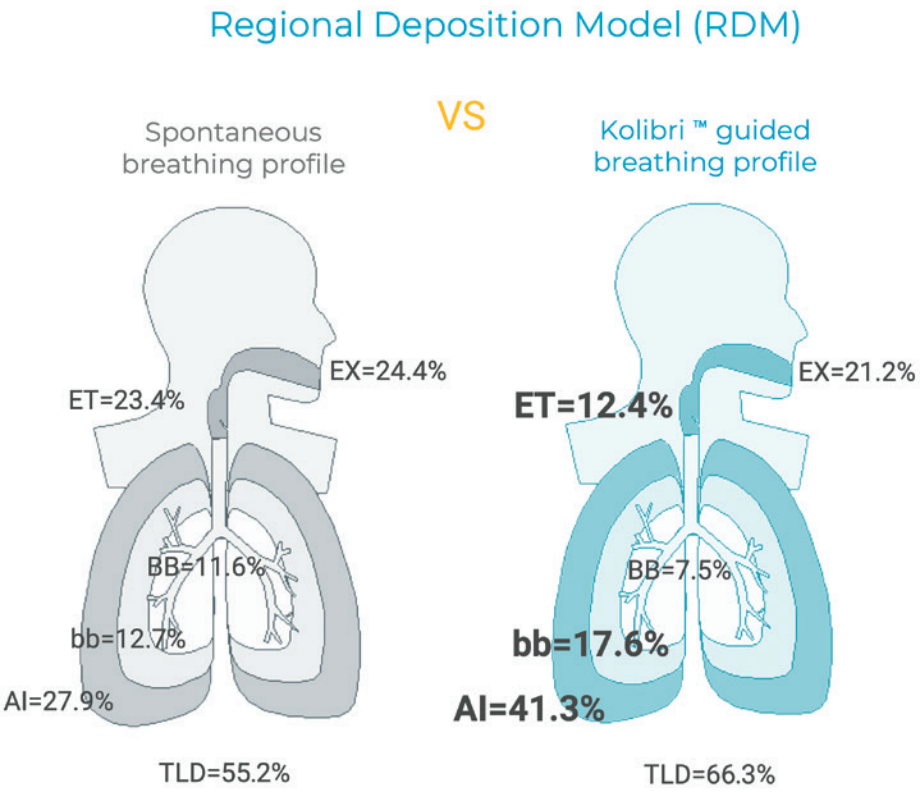

Figure 4: RDM predicted lung deposition (mean % of DD) in the extra thoracic (ET), tracheobronchial (BB; generations 1-8), bronchiolar (bb; generations 9-15), alveolar-interstitial (AI; generations 16-23) regions and the exhaled fraction (EX). Total Lung Deposition (TLD), equal to the sum of BB, bb and AI.

Functional Respiratory Imaging

The functional respiratory imaging conducted by Fluidda was based on 3D lung models taken from computed tomography (CT) scans. It simulated deposition by applying computational fluid dynamics to two disease models: cystic fibrosis (CF) and non-cystic fibrosis bronchiectasis (NCFB), as shown in Figure 5.

Compared with the spontaneous profile, the Kolibri guided breathing profile demonstrated:

- Lower extra-thoracic (16.5% and 19.0% versus 25.2% and 24.2%) and higher intra-thoracic (78.2% and 77.1% versus 58.0% and 62.4%) deposition in both CF and NCFB patients
- Higher peripheral deposition – 58.8% (CF) and 51.4% (NCFB).

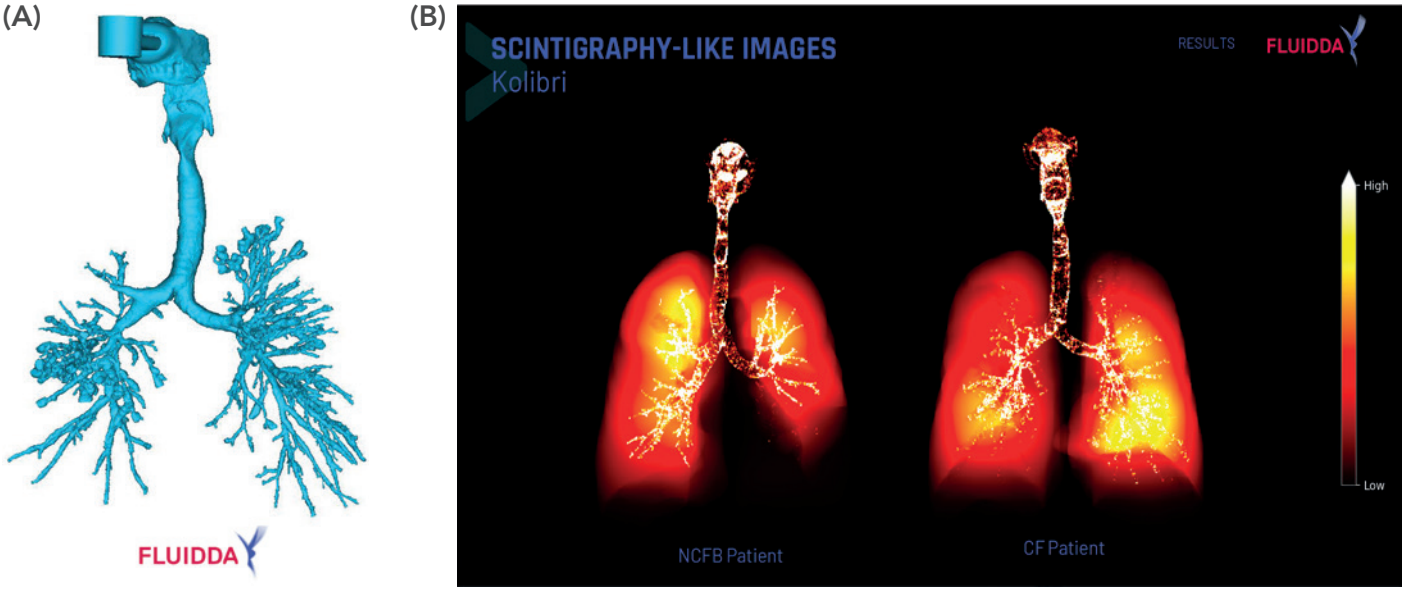

Figure 5: Reverse engineered CT scan of Kolibri™ virtually coupled to the mouth of a CF patient (A); FRI predicted lung deposition in scintigraphy-like images (B).

In these two *in silico* models, including both healthy and diseased lung models, the realistic Kolibri guided breathing profile demonstrated a more favourable pattern for deep lung deposition compared with a spontaneous unguided breathing profile.

THE POWER OF COLLABORATION: UNLOCKING NEW POSSIBILITIES

The current synergy between PULMOTREE and Aptar enables a seamless integration of cutting-edge nebuliser technology with realistic breathing profiles, providing a comprehensive approach to aerosol characterisation. By combining *in vitro* and *in silico* studies, this partnership creates a robust ecosystem for pharmaceutical partners seeking to optimise the combination of their inhalation formulations and the chosen device. The collaboration offers multiple advantages for partners, including:

- Risk reduction in clinical development by providing access to realistic and representative data from *in vitro* and *in silico* testing
- Optimised drug-nebuliser matching and tailoring, ensuring safer and better therapeutic outcomes
- Regulatory advantages, including realistic data that can improve *in vitro/in vivo* correlation, supporting regulatory submissions.

CONCLUSION: A STEP FORWARD FOR NEBULISED BIOLOGICS

By leveraging Kolibri's guided inhalation technology and its strong industry collaboration with Aptar, PULMOTREE is transforming the respiratory delivery of biologics. The fast and seamless integration of real patient data into drug development enables improved nebuliser performance, optimised aerosol deposition and, ultimately, enhanced clinical outcomes. As the industry moves toward more efficient and personalised drug-device combination products in respiratory drug delivery, PULMOTREE and Aptar stand at the forefront of this transformation.

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Dr Carolina Dantas

Carolina Dantas, MD, Head of Medical and Scientific Affairs at PULMOTREE, brings her expertise as a pulmonologist to PULMOTREE, providing the valuable insight of both physicians and patients. Specialising in respiratory infectious diseases and lung-related indications, such as cystic fibrosis and bronchiectasis, she has vast hands-on clinical experience with inhaled drug therapies. Dr Dantas' search for innovation in healthcare matches PULMOTREE's forward-thinking approach to the evolution of respiratory therapies. Besides her knowledge in clinical research, Dr Dantas is an accomplished communicator in science, with several published scientific papers, a book chapter and several original presentations at international conferences. Dr Dantas holds a master's degree in Medicine and is a member of the Sociedade Portuguesa de Pneumologia, the European Respiratory Society (ERS) and the International Society for Aerosols in Medicine.

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Ulf Krueger

Ulf Krueger is the Founder and Chief Executive Officer of PULMOTREE. His comprehensive experience involves key areas across the non-propellant liquid inhaler lifecycle, from research and development, through corporate strategy to successful commercialisation. In his former position as Director – Fox Nebuliser Programs at Vectura, he was responsible for the entire sector of the proprietary mesh nebulisers business, prior to which he held various positions in the research and development department at PARI. He has a background in biomedical engineering, is listed as an inventor on numerous patents and is a recognised speaker and conference chairman. Among other assignments, Mr Krueger is involved as a PhD student mentor for the TANDEM programme at RWTH Aachen University (Germany) and as chairman of the "New Devices, Emerging Therapies and e-Health" network group of the International Society for Aerosols in Medicine, where he is committed to promoting and supporting young and underrepresented scientists.

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Howard Burnett is Vice-President, Head of Global Pulmonary Category for Aptar Pharma. He has more than 35 years of experience in the field of inhalation devices for treatment of respiratory conditions. Mr Burnett has a background in mechanical engineering, having studied particle physics as part of his bachelor's degree from the University of Leeds (UK). His postgraduate qualifications include management studies and education. He has held management positions in R&D, engineering, operations, marketing and business development.

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BLISTERS, BONDS AND BIOLOGICS: HOW TO ACHIEVE STABILITY OF DRY POWDER BIOLOGICS

Dr Heather Jameson of Cambridge Healthcare Innovations and **Dave Farrow** of Aptar Pharma cover the challenging formulation science required to develop a viable dry powder aerosol and examine the inhaler device requirements necessary to protect the formulation throughout its shelf life while also ensuring consistent, high-performance delivery.

"AS TECHNOLOGY ADVANCES AND UNDERSTANDING OF DISEASE MECHANISMS DEEPENS, DRY POWDER BIOLOGICAL AEROSOLS ARE POISED TO PLAY AN INCREASINGLY KEY ROLE IN MEDICINE, OFFERING TARGETED THERAPIES WITH IMPROVED EFFICACY AND REDUCED SIDE EFFECTS."

Dry powder biological aerosols hold immense potential to transform the treatment of respiratory and systemic diseases.[1,2] This rapidly evolving field is driven by unmet medical needs, promising clinical results and significant investment in research and development. As technology advances and understanding of disease mechanisms deepens, dry powder biological aerosols are poised to play an increasingly key role in medicine, offering targeted therapies with improved efficacy and reduced side effects.

However, solid-state biological aerosols are fiendishly difficult to develop into drug products, requiring a strong synergistic programme involving formulation science and delivery device technologies. Additionally, biologic formulations are highly sensitive to environmental conditions, so choosing an inhaler device with the right primary packaging is essential.

Various biological modalities are being investigated and developed for aerosol delivery, each with unique properties and therapeutic applications (Table 1). These modalities are often selected for dry powder delivery due to their suitability for this format or for the advantages that a dry powder format might bring. Dry powder inhalers offer advantages such as portability, ease of use and improved stability compared with liquid formulations.

FORMULATING BIOLOGICAL DRY POWDERS FOR INHALATION

Solid Versus Liquid State

Most biological modalities exist in a native liquid state, so converting them to a powder requires a drying step. While this can be complex, the possible advantages of dry powder aerosol products can be significant compared with the liquid versions.

There are cases when a liquid aerosol product works perfectly well and is a superior format. However, there are many cases, principally for high doses or for stability reasons, where a dry powder is needed to form a viable product.

Modality	Properties	Applications
Peptides	Short chains of amino acids, target specific receptors, modulate cellular processes	Asthma, pulmonary hypertension, cystic fibrosis
Proteins	Larger and more complex than peptides, crucial roles in biological processes	Cystic fibrosis, respiratory infections, tissue regeneration
Antibodies	Highly specific molecules, target and neutralise pathogens, modulate immune responses	Respiratory infections, including covid-19
mRNA	Genetic material, encodes proteins, used in vaccines and protein replacement therapies	Cystic fibrosis, genetic disorders, vaccines

Table 1: Types of biological modalities.

Dry Powders for Inhalation

Producing dry powders for inhalation can significantly affect protein aggregation behaviour. The impact of the drying process alters the biologic molecule's energy state, resulting in increased aggregation, fibrillisation, degradation, oxidation and other processes that can compromise stability, quality and bioavailability.

To be viable for inhalation, particles with a mass median aerodynamic diameter (MMAD) of typically less than 5.0 µm must be produced. Currently, there are two main methods that offer effective drying, particle size control and proven cGMP scalability – lyophilisation and spray drying – although there are many innovative technologies under development.

Lyophilisation, or freeze drying, is a widely used technique for stabilising biological modalities, particularly proteins and peptides. This process involves removing water from the formulation under low temperature and pressure. The powder first forms as a solid cake, which must then be ground down (a process called comminution) to achieve a powder with the required size and distribution. This process can involve high energies that can destroy biological modalities.

Spray drying, on the other hand, involves spraying a liquid formulation into a hot chamber, where the water or other solvent media rapidly evaporates, leaving behind a dry powder. Spray drying can be a faster and more cost-effective alternative to lyophilisation for some applications but can also be more complex in some respects.

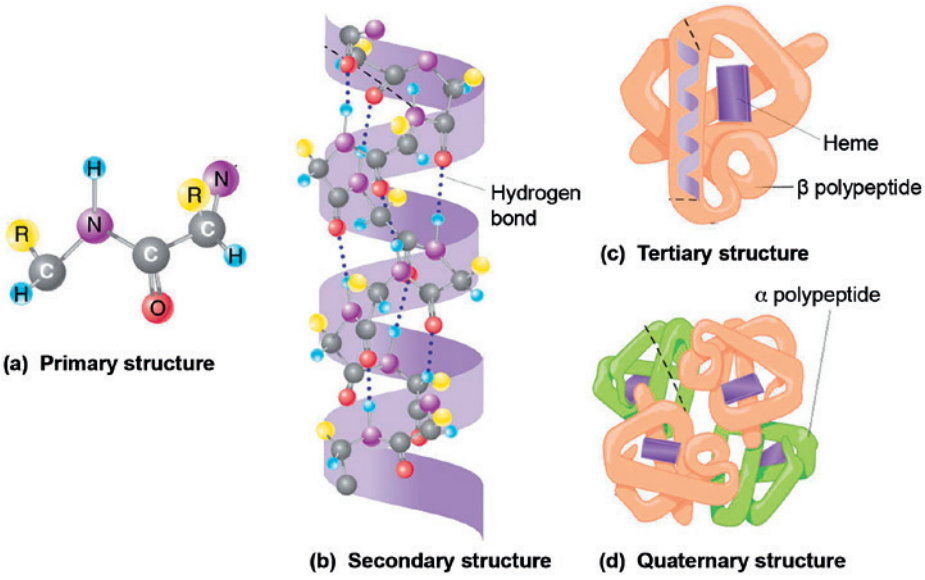

Figure 1: Biologics often have complex secondary, tertiary and quaternary structures that are intrinsic to their therapeutic activity.

For aerosols, spray drying has some distinct advantages. These include:

- Control over particle size
- Single-step process (no comminution step)
- Uniform spherical morphology
- Potential to engineer particles to have a force control agent surface coating to improve aerosolisation
- Readily form amorphous matrices (which is necessary for the complex biological structures).

Water Pinning

Unlike small-molecule drugs, biologics often have complex secondary, tertiary and quaternary structures that are intrinsic to their therapeutic activity (Figure 1). Biologic modalities usually exist in the liquid state and water plays a crucial role in keeping these complex structures intact.

Water binds to the surface of the biomolecule at certain specific points. Imagine a dressmaker pinning folded cloth to a dummy to make the dress – in this analogy the water acts as the pins (Figure 2). The cloth material is composed of the hydrogen bonding locking the fibres together, but it only takes a functional form when the water pins hold the shape. Therefore, any drying step that removes this water risks the loss of activity of the biomolecule. Luckily, there are mechanisms that allow the structures to be preserved in the drying process as the water is removed.

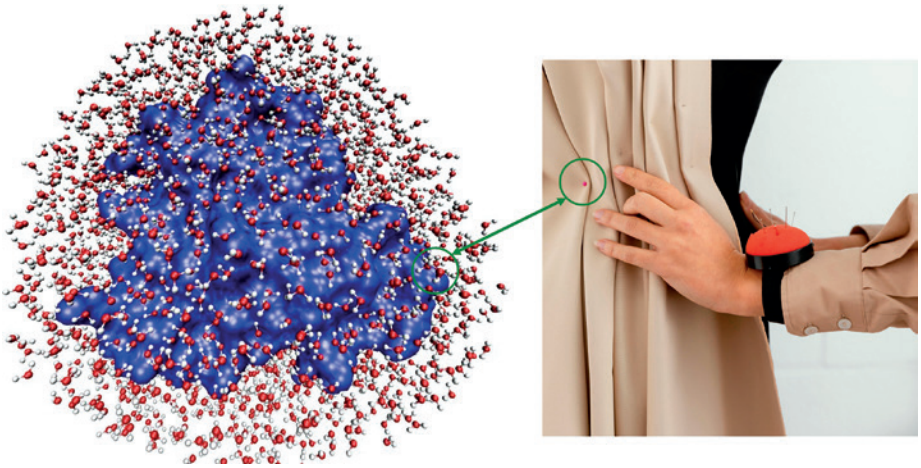

Figure 2: Water molecules play a crucial role in maintaining the complex biologic structures, like a dressmaker using pins to hold the fabric in place.[3]

"THESE EXCIPIENTS, OFTEN SUGARS SUCH AS TREHALOSE OR SUCROSE, HELP PROTECT THE PROTEIN'S STRUCTURE DURING DEHYDRATION AND ACT AS STABILISING AGENTS IN THE FINAL POWDER."

Solid-State Stabilisation

Before drying, biologic molecules are dissolved in an aqueous solution containing stabilising excipients. These excipients, often sugars such as trehalose or sucrose, help protect the protein's structure during dehydration and act as stabilising agents in the final powder.

As water is removed during the drying process, the biologic molecules must be stabilised within an amorphous matrix.[4] Two key stabilisation mechanisms occur (Figure 3):

1. **Mechanical Entrapment (Vitrification Theory)**: The solid, glass-like matrix is prepared, physically immobilising the biologic and preventing molecular motion. This protects the biomolecule from degradation by locking it in place in a rigid, amorphous structure.
2. **Water Entrapment (Hydrogen Bonding Theory)**: A small amount of bound water remains attached to the biomolecule, preserving its structure. Rather than forming hydrogen bonds directly with the excipient, the protein is coupled to the amorphous matrix through water molecules entrapped at the interface.

Although they are physically different mechanisms, both achieve the goal of supporting the biologic structure within an amorphous matrix via hydrogen bonding. Both mechanisms can occur simultaneously, with the balance between the mechanisms being influenced by the choice of excipients and the spray-drying conditions, such as temperature, feed rate and concentration.

Thermodynamic Stability

The amorphous matrix, categorised by a disordered molecular arrangement, forms around the surface of the modality. It needs to be amorphous to form a flexible format, ensuring conservation of the higher-order structure. It is critical that the matrices do not crystallise, as this would crush and distort the biomolecule, leading to structural degradation and significant loss of therapeutic activity.

However, an amorphous matrix is not thermodynamically stable. They desire to be crystalline. The Gibbs free energy of an amorphous state is higher than that of a crystalline state, due to the higher entropy and enthalpy of the amorphous state, making crystallisation a thermodynamically favoured process (Figure 4).

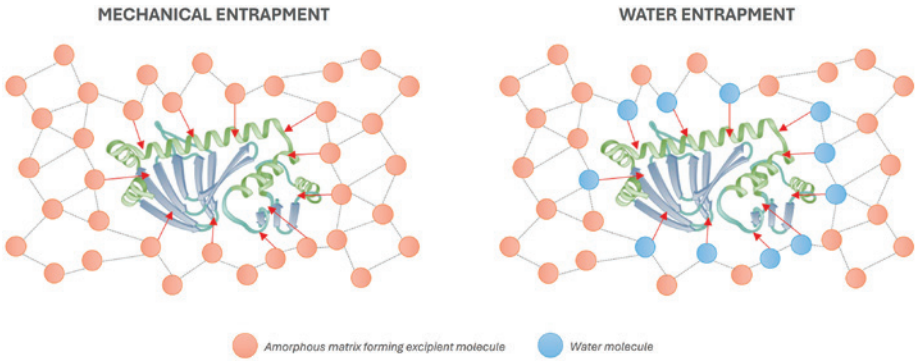

Figure 3: Two stabilisation mechanisms – mechanical entrapment and water entrapment.

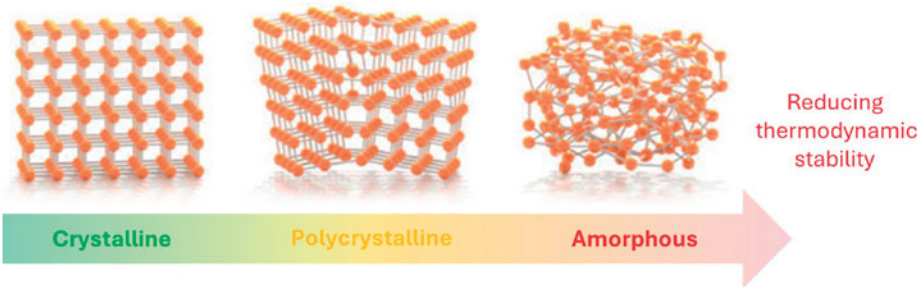

Figure 4: The amorphous state has higher Gibbs free energy than the crystalline state due to its greater entropy and enthalpy, making crystallisation thermodynamically favoured.

Keeping an amorphous matrix stable and preventing crystallisation is a key challenge for formulators. Amorphous matrices are highly hygroscopic, meaning that they readily absorb moisture. For crystallisation to occur, two factors are needed:

1. Heat, to break hydrogen bonds
2. A solvent, such as water, to help molecules rearrange into a crystalline structure.

Water, with its strong hydrogen bonding properties, can lower the energy needed for crystallisation and disrupt the amorphous structure on its own, which is a major concern for inhalable dry powders. The particles are carefully designed for optimal lung delivery, so they must be protected from moisture at all costs. Therefore, selecting the correct inhaler device and associated primary packaging closure system is crucial to achieving the promise of inhaled biologic therapies.

PRIMARY PACKAGING SYSTEMS AND THEIR SUITABILITY FOR BIOLOGIC AEROSOLS

Inhaler devices can be categorised into three groups based on the primary packaging of the formulation: reservoir, capsule and blister devices. Due to their inferior inherent moisture ingress protection, reservoir devices will not be discussed here.

Capsules Versus Blisters

Capsule devices are generally unit-dose devices, such as Berry Global's (Evansville, IN, US) RS01, where the user loads a capsule into the device for each dose. Gelatine was the industry-standard material for capsules, but it is now being phased out in favour of hydroxypropyl methylcellulose (HPMC). Capsules have minimal inherent moisture ingress protection, so the capsule is stored in a blister until needed. This has several disadvantages compared with storing the formulation directly in a blister:

- Additional cost of capsule plus blister
- Additional user steps of removing the capsule from the blister and inserting into the device

- Increased time between piercing the blister and inhalation of the formulation.

For biologic formulations, which are extremely sensitive to moisture ingress, several minutes of exposure to atmospheric humidity may be too long, particularly in humid climates. Furthermore, the conditions within the blister must be carefully controlled. If the environment inside the blister is too dry, the capsule shell becomes brittle and fragile, making it difficult to pierce as the capsule may shatter instead of opening cleanly.

Blister Sealing Considerations

A well-designed blister device is one of the best solutions for delivering biologic aerosols to the lung, due to the superior moisture ingress protection of blisters, which protect the formulation right up until the moment of actuation. Moreover, a breath-actuated mechanism can be incorporated, which ensures that the blister is only breached after the patient starts inhaling.

There are two primary mechanisms for "opening" the foil of the blister: peeling or piercing. Devices such as GSK's Diskus and Ellipta incorporate a mechanical system that peels open the foil to expose the dose at the right moment before inhalation. Peeling back the foil has the advantage that the foil is moved out of the way, meaning that it cannot impede the aerosolisation of the powder.

Figure 5: An example of a large-volume blister (1,414 µL).

"THE OPTIMUM BLISTER CAVITY SHAPE MAXIMISES VOLUME WHILE MINIMISING SURFACE AREA, THE AIM BEING TO MINIMISE THE AREA ONTO WHICH POWDER CAN BE DEPOSITED AND RETAINED – WHICH IS ESPECIALLY IMPORTANT FOR CARRIER-FREE FORMULATIONS."

However, to ensure that the foil does not rupture when pealed back, the strength of the seal must be intentionally limited, which limits the moisture protection. Therefore, to achieve the best moisture protection, the foil must be pierced. With considered piercer design, the pierced foil flaps can be folded out of the way of the airflow.

Blister Size and Shape

If blisters are to be pierced, then there must be space left inside the blister for the piercers to protrude into the blister volume. This means that the blisters cannot be brim-filled. Although this requires the volume of the blisters to be larger, allowing for head space in the blister makes the filling process easier and the sealing more robust, due to reduced risk of powder spilling onto the sealing surface.

Inhaled biologics require higher doses than traditional inhaled therapies for asthma and COPD, which will also necessitate larger blister cavities to accommodate more powder (Figure 5). Furthermore, engineered powders with small particle size distributions are cohesive (Geldart Class C) and pack inefficiently, leading to low densities.

The optimum blister cavity shape maximises volume while minimising surface area, the aim being to minimise the area onto which powder can be deposited and retained – which is especially important for carrier-free formulations. Maximising blister depth is also important to allow height for piercers to protrude into the blister volume. Sharp piercers are required to ensure reliable clean piercing without rupturing the foil, but generally require greater height than more blunt shapes.

On the other hand, over-stretching the coldform will lead to loss of moisture protection, due to the aluminium layer rupturing. Typically, for standard three-ply coldform, the stretch should be limited to less than 32%. A paraboloid is the most efficient blister shape, achieving the maximum volume and depth for a given diameter, while staying below the critical 32% stretch.

Blister shape also influences airflow patterns, affecting how powder is delivered to the patient. Efficient airflow is critical for aerosolisation and overcoming interparticle forces. Highly cohesive engineered particles require significant aerosolisation power to achieve effective deagglomeration. Both high-velocity airflows and high-momentum collisions of particles enhance deagglomeration.

Through considered, synergistic design of the piercers, airflow inlets and blister shape, an optimised cyclonic flow pattern can be established within the blister to achieve efficient aerosolisation and deagglomeration of solid-state biologic engineered powders.

CONCLUSION

The possibility and opportunity to develop engineered biological dry powders is significant, but so are the formulation challenges. The formulations themselves are thermodynamically unstable and prone to degradation or particle agglomeration over time. Making sure that the carefully and precisely engineered powder particles remain stable over the lifespan of the product is critical.

Engineered dry powder biologic formulations are particularly sensitive to moisture ingress. A well-designed large-volume blister-based inhaler device is the optimal solution for delivering biologic aerosols to the lung, due to the superior moisture ingress protection of blisters and the dose requirements. However, not all blister designs are created equal, and considered design is needed to achieve optimum stability and aerosolisation performance.

ABOUT THE COMPANY

Cambridge Healthcare Innovations (CHI) is a Cambridge-based medical device company dedicated to revolutionising respiratory medicine through novel DPI platforms. CHI provides three advanced DPI platforms – Quattrii, Aeolus and Occorix – that are designed to accommodate a wide range of payloads and applications, enhancing drug delivery efficiency and patient outcomes.

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Dr Heather Jameson

Heather Jameson, PhD, is a Senior Engineer at Cambridge Healthcare Innovations, working on the development of novel dry powder inhaler technology. She completed her PhD in Fluid Mechanics at the Whittle Laboratory (Cambridge UK), where her research focused on the downstream vorticity effects of leakage flows in the low-pressure turbines of large civil aircraft jet engines. Dr Jameson has published several thought-leadership articles, discussing trends in the fields of drug delivery and respiratory medicine. She is interested in applying fundamental fluid mechanics understanding to tackle the current challenges of inconsistent performance and poor usability of inhalation devices, to develop improved outcomes for patients.

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Dave Farrow

Dave Farrow is Director – Scientific Affairs at Aptar Pharma. He began his career as an Inhalation Scientist at Sanofi Aventis, working on exploratory development products through to commercial marketed products and the whole lifecycle in between. He then held a similar role at Novartis where he further developed his inhalation knowledge. Following this, Mr Farrow moved to Vectura as Particle Engineering Specialist, going on to become Principal Scientist, then manager of the Bioformulation and Particle Engineering group. At Charles River, he led and developed the team conducting safety assessment/toxicology studies with aerosols. Mr Farrow then moved to Albany Molecular Research Inc. (now Curia) leading the R&D groups and conducting business development activities before joining Nanopharm, starting as Director of Operations, then became Chief Operations Officer. Mr Farrow moved to Nanopharm's parent company, Aptar, and was appointed to Director of Science and Technology for Aptar Pharma prescription division in February 2024 and Director of Scientific Affairs for Aptar Pharma in 2025.

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CONFERENCE PREVIEW: SMI.LONDON

London, UK, June 25, 2025

Join colleagues from across the inhalation space at SMI.London 2025, the only conference dedicated to soft mist inhalers (SMIs) worldwide. The event will take place on Wednesday, June 25, 2025, at the Pullman London St Pancras, hosted by Merxin (King's Lynn, UK). This year's conference continues the important conversation on SMIs that began in 2023 and continued in 2024, exploring their growing role in the inhalation market and the benefits they offer to both patients and healthcare providers.

SMIs are quickly becoming the device of choice in inhalation drug delivery due to their low carbon footprint, superior deep lung deposition and versatility. Ideal for both local and systemic treatments, SMIs are user-friendly, easy to formulate for and able to integrate into inhaler portfolios seamlessly, making them a perfect fit for biologic therapies. SMI.London 2025 brings together suppliers and innovators in a dynamic environment designed to inspire new partnerships and growth opportunities in the inhalation drug delivery sector.

BRIEF OVERVIEW

This year's conference will delve into how SMIs are carving out their place in the inhalation market, highlighting the significant benefits they bring to both patients and the pharmaceutical industry. The event will provide an in-depth look at learning how to make, develop, use, file and launch SMIs, exploring the entire product journey from molecular development to finished dosage forms. Attendees will hear from key opinion leaders with extensive experience in inhaled

"ATTENDEES WILL HEAR FROM KEY OPINION LEADERS WITH EXTENSIVE EXPERIENCE IN INHALED DRUG DELIVERY, GAINING INSIGHTS INTO THE LATEST ADVANCEMENTS AND CHALLENGES IN THE FIELD."

drug delivery, gaining insights into the latest advancements and challenges in the field. Highlights of the 2024 conference include:

- An in-depth exploration of SMIs, including their position in the market, environmental impact, industry strategy in a competitive landscape, progress and innovation, and supply chain challenges
- Expert speakers with vast experience in inhaled drug delivery sharing valuable insights during varied presentations and panels
- Exciting sessions with topics ranging from the comparison of SMIs with nebulisers to innovations in customising lung delivery and transforming respiratory care with soft mist biologics.

The event was made possible by the support of founding partners, exhibitors and media partners, and provided a unique platform for professionals to learn, connect and shape the future of SMIs in respiratory care.

WHY SOFT MIST INHALERS?

Advantages Over Traditional Inhalers

Unlike traditional inhalers, SMIs release a slow-moving mist of medication, which is easier for patients to inhale and ensures better lung deposition. This makes SMIs more effective at delivering medication compared with metered dose inhalers (MDIs), which use propellants to create a fast-moving aerosol. The quick burst from MDIs can cause the medication to land in the mouth or throat rather than the lungs, reducing effectiveness.

Because SMIs do not require precise co-ordination between inhalation and device activation, they are significantly easier to use than MDIs, making them ideal for people with limited dexterity, such as children or the elderly. In contrast, MDIs require patients to activate the inhaler while inhaling, which can be difficult for some.

SMIs also offer benefits over dry powder inhalers (DPIs), another traditional inhaler type. DPIs deliver medication as powder and require a forceful inhale to activate, which may not be suitable for everyone, especially those with limited lung capacity due to chronic respiratory diseases. Another advantage SMIs have over DPIs when it comes to the delivery of biologics is that most biologics are naturally liquid formulations, so can be deployed in an SMI with minimal hassle, whereas, for a DPI, the formulation must be dried to make a powder, which can be a difficult and delicate process.

> "UNLIKE TRADITIONAL INHALERS, SMIs RELEASE A SLOW-MOVING MIST OF MEDICATION, WHICH IS EASIER FOR PATIENTS TO INHALE AND ENSURES BETTER LUNG DEPOSITION."

Sustainability Benefits

Another key factor in the rise of SMIs is that they make a significant contribution towards sustainability in the pharmaceutical industry. Unlike MDIs, which use hydrofluoroalkane (HFA) propellants that are harmful to the environment, SMIs do not rely on chemical propellants. Instead, they use mechanical energy to create a fine mist, greatly reducing their carbon footprint to near zero compared with equivalent MDIs. This makes SMIs a much more environmentally friendly option for inhalation therapies.

Moreover, SMIs provide precise dosing, ensuring that patients receive the exact medication they need, reducing waste compared with other inhalers where medication can be left in the device or incorrectly administered. The design of SMIs typically includes reusable components with replaceable cartridges, which cuts down on plastic waste and the need for disposable inhalers, further reducing the overall environmental impact associated with single-use devices. By promoting reusable inhalers and minimising material waste, SMIs can help address the growing concern of pharmaceutical waste and contribute to meeting the challenge of making sustainable inhalation devices.

SMI.London 2025, being the only conference worldwide devoted solely to SMIs, is dedicated to promoting eco-friendly technology in the inhalation space. The event encourages attendees to connect, fostering collaboration on future eco-friendly projects aimed at improving both care for patients and the impact of therapies on the environment.

WHY ATTEND SMI.LONDON 2025?

Over the past year, significant advancements have been made in the development and application of SMIs, enhancing drug delivery efficiency and the patient experience. SMIs have become a viable alternative for delivering biologic formulations and their design minimises the need for patient co-ordination and inspiratory effort, optimising lung deposition. As an excellent example of the progress made with SMIs, at SMI.London 2024, two research groups – one from Istanbul and another from Monash University (Melbourne, Australia) – were highlighted for their research on delivering vaccines and biologics via an SMI, including the successful delivery of a covid-19 vaccine.

"SMIs HAVE BECOME A VIABLE ALTERNATIVE FOR DELIVERING BIOLOGIC FORMULATIONS AND THEIR DESIGN MINIMISES THE NEED FOR PATIENT CO-ORDINATION AND INSPIRATORY EFFORT, OPTIMISING LUNG DEPOSITION."

SMI.London 2025 will provide a platform for companies within the inhalation technology industry to exchange ideas and best practices. Manufacturers, developers and tech innovators will be able to network, form partnerships and engage in frank discussion of the latest advancements and challenges in SMI design, functionality, manufacturing and commercialisation. This collaboration fosters innovation and helps to accelerate the development of more efficient, patient-friendly inhaler technologies.

Academics, researchers, engineers and scientists can all contribute valuable knowledge and findings on the latest scientific developments in drug delivery, nano-formulation and pharmacology. Through presentations and discussions, SMI.London 2025 will provide a forum for those at the forefront of academia to collaborate with industry leaders to explore new formulations and technologies, potentially leading to breakthrough advancements in SMI devices and treatments.

At SMI.London 2025, industry leaders, experts and innovators will present the latest research, trends and advancements in SMI technology. Sessions will cover key topics, including SMI design, regulatory updates, clinical applications and patient outcomes, which will help attendees to stay ahead of the curve, with sterile filling being introduced as a new topic for this year. Attendees will have access to whitepapers, case studies and expert insights that can support their research, development and implementation of SMI technologies.

SPEAKERS AT SMI.LONDON 2025

PROF DANIELA TRAINI: Exploring Nasal siRNA-Liquid Nanoparticle SMI Therapies

Professor Traini is an expert in respiratory drug delivery, aerosol science and nanoparticle formulation. She is the Chief Scientific Officer at Ab Initio Pharma (Sydney, Australia) and is based at Macquarie University and the Woolcock Institute of Medical Research. A former Australian Research Council (ARC) Future Fellow and National Health and Medical Research (NHMRC) investigator, she has published over 300 papers with around 8,000 citations (h-index 46). Her research spans particle engineering, biologic drug aerosols and nose-to-brain delivery. She collaborates with industry partners, including Aptar Pharma (IL, US), Kindeva (MN, US), Resyca (Enschede, The Netherlands) and MedSpray (Enschede, The Netherlands), as well as serving on the ARC and NHMRC committees.

DR DEBORAH JONES: Seeing Through the Mist – SMI Spray Characterisation

Dr Jones holds a wealth of experience in the orally inhaled and nasal drug product industry, forging client relationships and delivering tailored solutions. Her extensive business development experience and passion for precision instrumentation, regulatory compliance and improving patient outcomes drives her commitment to contributing to the advancement of healthcare globally. Dr Jones completed a PhD in Chemistry at King's College London (UK), specialising in biosensors for clinical applications, and held postdoctoral research positions at both King's College London and Oxford University (UK).

DR WILLIAM GANLEY: Links Between Solution Properties, Spray and Lung Deposition in SMIs

Dr Ganley started his career as a postdoctoral researcher in the Pharmaceutical Surface Science Laboratory at the University of Bath (UK), focusing on advancing physical characterisation and simulation techniques for DPIs. In 2019, he joined Nanopharm (Cwmbran, Wales) as Head of Computational Pharmaceutics, where he led the development of Nanopharm's modelling and simulation platforms. He is now a senior member of the Science & Technology department at Nanopharm, where he supports customers in development and regulatory strategy and manages a portfolio of R&D projects.

DR MARKO BLOM & DR CHRISTIAN WALK: Innovating Spray Nozzle Technology – How Microfluidic Manufacturing Drives Precision

Dr Blom serves as the Chief Technology Officer at Micronit (Enschede, Netherlands), where he has played a key role since 2005. With a PhD in Applied Physics, Dr Blom has been deeply involved in the development of microfluidic and microelectromechanical systems (MEMS) technologies. His leadership has driven significant advancements in lab-on-a-chip systems, particularly for biomedical applications.

Dr Walk holds BSc and MSc degrees in microsystems engineering from the University of Freiburg (Germany) and a PhD in complementary metal-oxide semiconductor and MEMS pressure sensor technology. With over a decade of experience at Fraunhofer Institutes (Germany), he now leads the drug delivery market segment as Business Development Manager at Micronit.

REMI ROSIERE: Liquid Nanoparticles and SMIs – Extending Formulation and Treatment Options

Dr Rosiere is a pharmacist by training and obtained a PhD at Université Libre de Bruxelles (Belgium), where he still holds a position as a lecturer. He has been the lead researcher in charge of the InhaTarget spin-off project since its beginning. This project led to the launch of the pharma start-up InhaTarget Therapeutics (Brussels, Belgium), which he co-founded in 2019. Dr Rosiere is the current Chief Scientific Officer of InhaTarget Therapeutics and is responsible for all R&D aspects of the company. He specialises in drug formulations for inhalation (e.g. advanced drug delivery systems, controlled-release formulations, carrier-based and carrier-free formulations, particle engineering, nanomedicine) and non-clinical development (analytical development, *in vitro* and *in vivo* studies, animal models).

DR PHILIPPE ROGUEDA: Aerosolisation of Wegovy With MRX004

Dr Rogueda co-founded Merxin Ltd in 2015. His expertise spans multiple facets of the inhalation field, particularly DPIs and SMIs. His passion lies in the development of SMI technology, particularly for biologics, which he believes hold immense potential to revolutionise the delivery of therapeutic treatments. With over a decade of experience in the inhalation sector, Dr Rogueda's career includes significant roles at organisations such as Actavis (now Allergan), Novartis and AstraZeneca, along with academic contributions as an adjunct senior lecturer at Monash University (Melbourne, Australia). His deep knowledge and innovative approach to inhalation technologies make him a key figure in advancing medical device development for improved drug delivery systems.

LAURY LIVEMONT: Sterile Filling of SMI Cartridges

Ms Livemont is an experienced project manager at Unither Pharmaceuticals (Paris, France), where she has contributed to various roles over the past several years. Currently, she serves as the Euroject Project Manager, a role she has held since September 2021. With over 13 years at Unither Pharmaceuticals, Ms Livemont has built a strong background in pharmaceutical development and project management. She holds a Diplôme

d'Université in Managing a Responsibility Center from the Institut Français de Gestion (Paris, France) and an engineering degree in Chemistry from École des Hautes Études d'Ingénieur (Lille, France), where she specialised in formulation.

DR NICHOLAS BUCHMANN: Expanding the SMI World – Options and Applications

Dr Buchmann holds a PhD in Biomedical Engineering from Canterbury University (New Zealand). After spending several years as a postdoctoral researcher in the field of Aerospace Aerodynamics at Melbourne University (Australia) and Munich University of Armed Forces (Germany), he has gained significant experience in the development of smart nebuliser and inhalation devices for inhaled combination products. He has extensive knowledge in medical device development and managing complex development programmes and portfolios for inhalation drug-device-combination products. Dr Buchmann held roles at Vectura (Chippenham, UK) as Programme Manager for the development of generic MDIs and at Pari GmbH (Starnberg, Germany) as Technology Manager for the nebuliser and eFlow platform. In his current role as Chief Technical Officer at Resyca, he is responsible for the development of next-generation soft mist inhalers, pharmaceutical development and programme management.

EXHIBITORS AND ONLINE ACCESS

SMI.London 2025 is excited to have 12 exhibitors already signed up, eager to showcase their latest innovations. There is still space available, so do not miss out – register now at **www.smi.london** or reach out to the conference organisers at **info@smi.london** for more information.

SMI.London 2025 is an in-person event only. However, following the event, the organisers will post the speakers' slides on the conference website for all those who were unable to attend.

> "SMI.LONDON 2025 IS MORE THAN JUST A CONFERENCE – IT IS A UNIQUE OPPORTUNITY TO SHAPE THE FUTURE OF SMI TECHNOLOGY."

FINAL THOUGHTS

SMI.London 2025 is more than just a conference – it is a unique opportunity to shape the future of SMI technology. As the future of inhalation therapy continues to evolve, strategic collaboration and knowledge sharing are crucial. Do not miss the opportunity to be part of the conversation and help shape the future of inhalation therapy.

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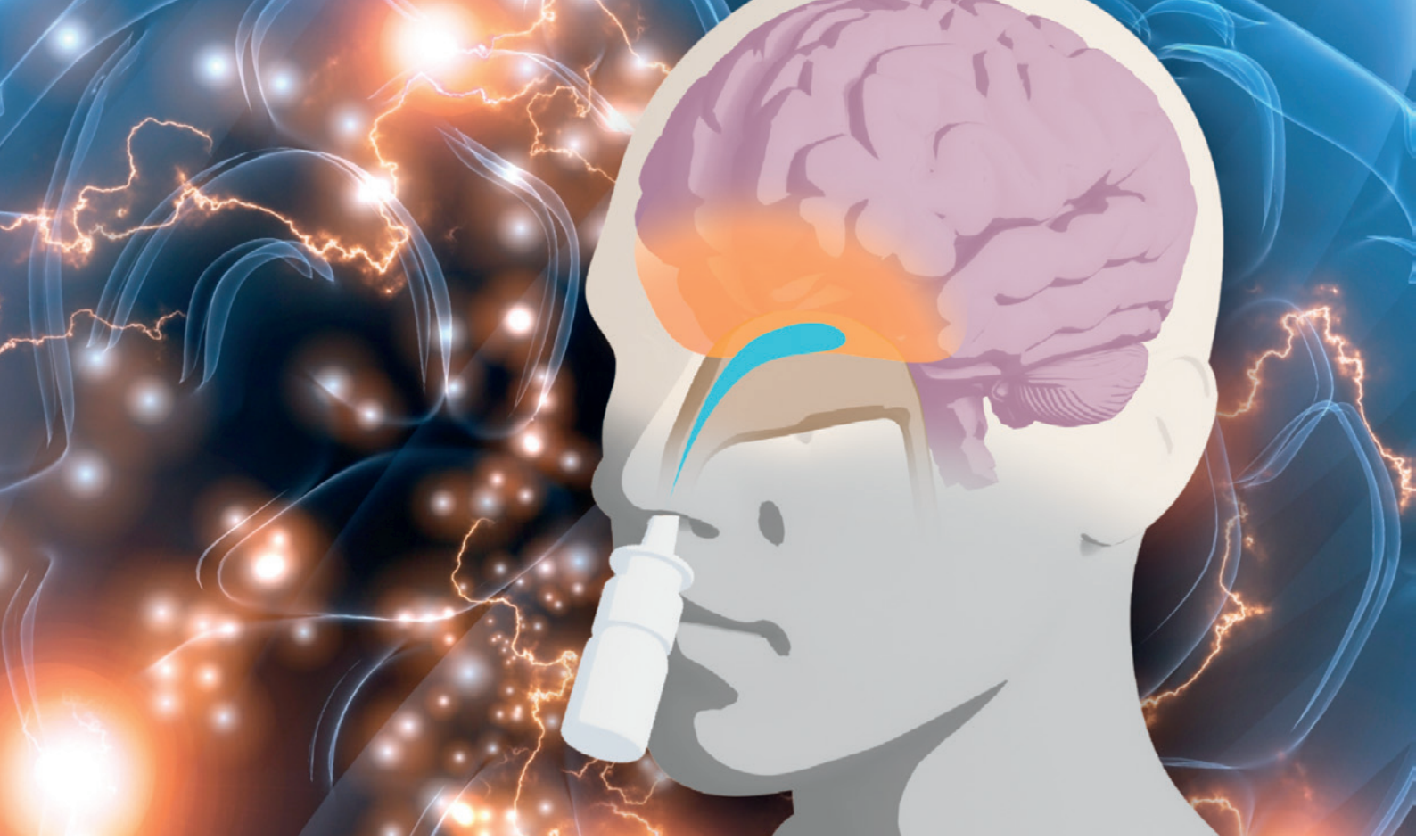

NOSE-TO-BRAIN DELIVERY: PATIENT-CENTRIC DEVICE DEVELOPMENT AND PERFORMANCE TESTING

Nemera
we put patients first

Sophie Conte and **Alain Regard**, both of **Nemera**, describe the company's journey in nose-to-brain device development, highlighting the evaluation tools, methods and usability testing developed in-house to steer innovative device design and engineering.

The nose has been used as a portal to deliver therapeutic substances for thousands of years. In Amazonian cultures, simple handmade tools are used to administer pharmacologically active "rapeh" powders to the nose for ceremonial and medicinal purposes. In contemporary medicine, the intranasal devices used to deliver synthetic therapeutic compounds are technologically intricate. Nonetheless, achieving consistent and effective nose-to-brain (N2B) drug delivery remains a complex challenge.

MULTI-DIMENSIONAL CHALLENGES IN N2B DRUG DELIVERY

Nasal drug delivery is a promising route for direct brain targeting, especially in central nervous system (CNS) disorders and neurodegenerative diseases, such as Parkinson's and Alzheimer's diseases, as well as some brain cancers.[1] Drug development pipelines include small molecules, proteins, peptides and nucleic acid-based candidates. Today, achieving clinically effective N2B drug delivery is close to becoming a reality thanks to the multidisciplinary approach integrating pharmaceutics, pharmacology and ergonomic device engineering to overcome numerous challenges.

Formulation Challenges

Formulation-based drug delivery technologies, such as functional excipients, complex formulation and processing technologies, feature in the multifaceted approach in systemic and direct-to-brain nasal delivery. Formulations are designed

to protect the API (e.g. encapsulation); increase residence time (e.g. muco-adhesive and thermogelling excipients); and enhance permeation, absorption and uptake into transport systems and tissues (e.g. solubilisers and permeability enhancers).

Formulation viscosity has a significant impact on deliverability to a precise target in the nasal cavity and on device performance. Ideally, an N2B delivery device must achieve consistent performance across a range of viscosities.

Anatomical and Physiological Challenges

CNS and direct-to-brain drug delivery via the nose has gained significant interest and traction due to the identification and greater understanding of three different transport pathways:

- **The Olfactory Mucosal Pathway:** The olfactory cleft epithelium is unciliated and associated with reduced drug clearance and increased residence time. Absorption occurs through paracellular junctions leading to uptake into cerebrospinal fluid and transport to the brain, bypassing the blood–brain barrier (BBB). This pathway is purported to result in faster onset of clinical effects.
- **The Trigeminal Nerve Pathway:** The epithelium in this area is a major drug deposition target site for systemic drug delivery. It is highly innervated with trigeminal nerves, and may also be a minor pathway for CNS and brain delivery for drug compounds unable to pass the BBB.
- **The Olfactory Nerve Pathway:** The olfactory nerves in the upper nasal cavity provide a localised target for drug delivery; as these nerves transmit sensory information related to smell from the nasal cavity to the brain, it is proposed that this may constitute another gateway to CNS uptake and brain delivery.

For direct N2B delivery, the olfactory mucosal pathway is considered the most promising. However, achieving precise drug deposition in this small, inaccessible area – high-up, towards the back of the nasal cavity and approximately 7 cm from the nostrils – requires the design of a device with specific performance features with respect to plume characteristics, velocity and trajectory.

"CREATING A DEVICE FOR N2B DELIVERY REQUIRES A MAJOR SHIFT IN DESIGN SPACE AND ENGINEERING."

Usability Challenges in Intranasal Device Design

Usability and human factors engineering (HFE) studies are crucial for developing user-friendly and safe devices that foster patient adherence and acceptability. Devices that are uncomfortable, difficult to use or intimidating are less likely to be used correctly and consistently. These studies engage patients, caregivers and healthcare professionals to identify key design factors, such as comfort (minimise discomfort during insertion and dose expulsion), ease of use (intuitive design that simplifies administration and addresses dexterity issues) and safety of use (clear, concise instructions and training materials to ensure proper use).

NEMERA'S DEVICE DEVELOPMENT APPROACH: FROM SPRAY TO GUIDED STREAM TECHNOLOGY

Creating a device for N2B delivery requires a major shift in design space and engineering. Nemera's approach aims to develop an easy-to-use device capable of targeted, precise and acceptable drug deposition in the olfactory cleft, where:

- **Targeted** means delivering a volume of drug formulation with stable jet characteristics in an accurate trajectory
- **Precise** means ensuring that the trajectory of the formulation is reproducible, within an optimum range, by limiting variability in the device's angle of insertion in the patient's nostril
- **Acceptable** means minimising discomfort during insertion and dose expulsion, limiting backflow and irritation
- **Easy-to-use** means intuitive use during administration, minimising human error.

Nemera's initial investigations have included a successful collaboration with Professor Ben Forbes of King's College London (UK) in a clinical study that explored the intranasal delivery of insulin to the brain. Different configurations of Nemera's standard nasal sprays were used to administer a liquid insulin formulation in healthy volunteers. The pharmacodynamic effects were detected by MRI scanning, and results indicated that a degree of insulin delivery to the brain was achieved with a standard nasal spray configuration. An *in vitro* nasal cast model with high-performance liquid chromatography analysis revealed quantitative and qualitative insights about intranasal insulin spray performance. While all spray configurations achieved high overall insulin deposition in the nasal cavity, the amount of drug reaching the olfactory cleft region was low.[2]

Results of this study and others led Nemera to design a specific device configuration with the aim of achieving >50% drug deposition in the olfactory cleft. Initial prototype devices have been refined, culminating in the "Guided Stream technology" for direct N2B delivery. Tests with the company's latest prototype indicate a reproducible delivery trajectory and significantly higher targeted placebo formulation deposition in the target olfactory area.

Innovative Evaluation Approaches in Device Development

Evaluating prototype delivery devices in an emerging field, such as N2B drug delivery, is technically and intellectually challenging. There are relatively few novel device evaluation studies published in the scientific literature and no standard testing set-ups and protocols. This confounds comparative and correlative observation but also drives pragmatic solution finding and invention in design of experiment (DoE) approaches.

3D Nasal Cast Models

Research indicates that the conditions of intranasal device administration have the biggest impact on targeted drug deposition in the olfactory cleft. Therefore, an anatomically relevant 3D nasal cast is essential to evaluate the sensitivity of the device with respect to the variables of administration, including insertion depth and orientation.

Nemera has extensive knowledge in developing, validating and using different nasal casts in its R&D programmes, which has led to the development of a nasal cast specially adapted for N2B delivery and deposition studies, based on the work of Dr Jan Brüning of the Charité – Universitätsmedizin Berlin (Germany) and partners. Their approach to address the problem of inter-patient anatomical variability in research was to propose a standardised geometry representative of a healthy nasal cavity, generated using CT scans and segmentation data from 25 symptom-free subjects, coupled with statistical shape model techniques.[3] These data were used to create a nasal cast model, 3D printed in a translucent, high-resolution polymer, to enable both qualitative (through visual observation and photography) and quantitative (through extraction and quantification of deposition) assessments.

In Vitro Investigation of Intranasal Device Performance and Drug Deposition

The nasal cast is the central tool for evaluating and quantifying drug deposition and for sensitivity studies that investigate the impact of device orientation, insertion depth and viscosity of the formulation, as well as "jet" characteristics on formulation deposition. This requires integrating the nasal cast with additional equipment in specialised experimental set-ups and protocols.

- **Jet characterisation** is associated with targeted drug delivery and is evaluated using Nemera's optic bench set-up, which uses high-speed imaging equipment to assess jet width, jet cone, front speed and deposition efficacy.[4] Custom software analyses video and image data of the actuation event and jet shot.
- **Jet impaction force** is an extremely important variable to measure, as it affects patient comfort and acceptability and must be optimised in device design. If too strong, the force of the jet hitting the nasal wall epithelium and olfactory area can cause discomfort. With limited research in this area, Nemera's experimental set-up to measure jet impaction force is based on research by Guo *et al* (2009),[5] which integrated an automated actuator in the nasal cast. Nemera has shown that the impaction force generated by Guided Stream technology is similar to that of a commercial pressurised nasal saline product, as well as to the data generated by Guo *et al* on nasal sprays.[6]
- **Deposition studies** are performed with the nasal cast integrated with equipment for automated actuation, and a system for simulating physiological breathing can be added. The platform enables precise control of device orientation during administration to investigate the sensitivity of device orientation, insertion depth and viscosity of the formulation.

"NEMERA HAS SHOWN THAT THE IMPACTION FORCE GENERATED BY GUIDED STREAM TECHNOLOGY IS SIMILAR TO THAT OF A COMMERCIAL PRESSURISED NASAL SALINE PRODUCT."

Figure 1. *In vitro* administration bench, double inclination base and automated actuation apparatus for intranasal device sensitivity studies.

Nemera's *in vitro* DoE for evaluating Guided Stream technology prototypes use the nasal cast set-up with a double inclination base and an automated actuator to investigate the range in which the combined administration parameters achieve the targeted drug deposition levels of >50% (Figures 1 and 2).

Intranasal Device Usability and Human Factors Programme

Usability studies are designed to simulate real life use, and Nemera's engineers have developed a wearable headset with orientation sensors on both the headset and the device itself. This equipment enables the monitoring of the device orientation relative to the patient's head during simulated administration to explore variables that impact device administration and, therefore, clinical efficacy.

Voice of the Patient and HFE studies undertaken by Nemera Insight, (IL, US) were integrated in the early phases of device design. These studies revealed key user preferences about device portability, acceptable activation steps and features that maximise user confidence and comfort while minimising irritation. Nemera's Guided Stream technology devices will be further evaluated in an HFE test programme later in 2025.

ON TARGET FOR N2B DELIVERY

To conclude, Nemera's innovative and robust experimental approach has resulted in the development of Guided Stream technology devices and strengthened the company's expertise in the field of device performance characterisation. Outcomes are extremely promising with prototype devices achieving consistently high levels of deposition in the target olfactory cleft area, with limited sensitivity to administration variables. Nemera's devices are available for early phase clinical evaluation, and the company is confident that Guided Stream technology will, ultimately, contribute to the development of safe and effective treatments for patients.

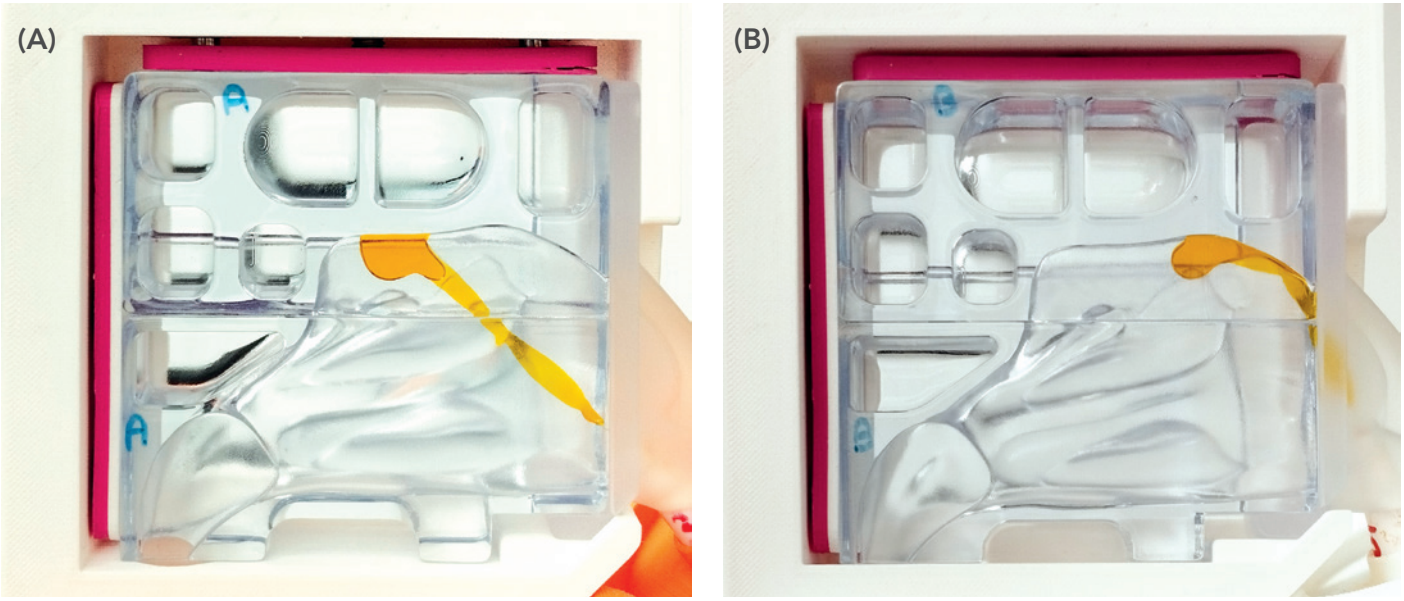

Figure 2. Performance of a prototype Guided Stream technology device delivering a placebo dyed formulation to the upper back (A) and upper front (B) of the target olfactory area in Nemera's nasal cast.

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Sophie Conte

Sophie Conte is Global Category Manager for the Ear, Nose, Throat and Dermal franchises at Nemera. Ms Conte's marketing experience spans diverse segments of the healthcare industry, including medical marketing, communications and education, excipient manufacturing, digital health solutions and combination device manufacturing. She drives the strategic marketing programmes for the portfolio of drug combination devices and develops go-to-market strategies for new own-IP product launches.

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Alain Regard

Alain Regard is Technology Product Manager at Insight by Nemera. Mr Regard graduated in Polymer Engineering and Processing from École Superieure de Plasturgie (ESP) in Oyonnax, France, and began his professional career as a design engineer in the automotive industry. Mr Regard joined Nemera in 2010 as a Product Development Leader working on multiple projects related to pumps, sprays and pMDIs. He currently leads Nemera's innovation and early-stage concepts research in nasal drug delivery. Mr Regard has a track record of 14 published patent families in drug delivery. His main fields of expertise are design of nasal drug dispensing devices, atomisation, and spray generation and characterisation, as well as ear, nose and throat anatomy and physiology.

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Expert View

MEETING THE DEMAND FOR PATIENT CENTRICITY WITH NASAL SPRAY REPOSITIONING

Eric Kaneps of Renaissance Lakewood discusses key emerging drug delivery trends poised to help the pharmaceutical industry meet the growing demand for patient-centric solutions, with a particular focus on nasal drug delivery, as the nasal spray repositioning of existing drugs offers a range of benefits, including rapid onset of action, improved bioavailability and ease of administration for patients.

"THERE IS NOW WIDESPREAD RECOGNITION THAT THE 'ONE-SIZE-FITS-ALL' APPROACH IS INADEQUATE, LEADING THE INDUSTRY TO MOVE TOWARD PERSONALISED MEDICINE, WITH TREATMENTS AND DELIVERY METHODS TAILORED TO INDIVIDUAL PATIENT NEEDS, PREFERENCES AND LIFESTYLES."

The pharmaceutical industry's growing focus on patient centricity has driven the development of drug delivery systems that prioritise not only therapeutic efficacy but also patient convenience and safety. In recent years, the emphasis on the patient experience has been at the forefront of many industry discussions, with regulatory agencies reinforcing the idea that patient-centric models should be at the centre of pharmaceutical companies' approaches.[1] Many organisations have adopted patient focus as a key strategic imperative at every stage of drug development, manufacturing and commercialisation.[2]

Patient-centric drug delivery systems are becoming increasingly vital for improving treatment outcomes and enhancing the overall patient experience. These systems prioritise convenience and safety, which, combined with therapeutic efficacy, result in improved outcomes. By offering user-friendly and convenient administration methods, these systems can significantly improve patients' adherence to treatment regimens, which is vital for chronic conditions requiring long-term treatment.

THE SHIFT FROM TREATING THE DISEASE TO TREATING THE PATIENT

The increasing emphasis on patient centricity is fundamentally reshaping the landscape of drug delivery systems. There is now widespread recognition that the "one-size-fits-all" approach is inadequate, leading the industry to move more towards personalised medicine, with treatments and delivery methods tailored to individual patient needs, preferences and lifestyles.

"FROM THE PATIENT-CENTRIC PERSPECTIVE, NASAL DELIVERY HAS PROVEN TO BE AN ATTRACTIVE OPTION FOR CONDITIONS REQUIRING SWIFT THERAPEUTIC ACTION AND DRUGS WHERE PATIENT CONVENIENCE AND ADHERENCE ARE CRITICAL."

Consequently, there is a push towards simplified administration and less frequent dosing with user-friendly devices that make it easier for patients to adhere to their prescribed medication regimens, resulting in more consistent drug levels and better therapeutic effects. This is especially important when treating chronic diseases, such as respiratory conditions, where long-term consistency is a necessity. Modern targeted drug delivery systems also ensure that medications reach the specific site of action, maximising their effectiveness while minimising systemic side effects.

From the patient-centric perspective, nasal delivery has proven to be an attractive option for conditions requiring swift therapeutic action and drugs where patient convenience and adherence are critical. Nasal products are often easy to use and can be readily self-administered. Importantly, nasal delivery enables rapid and efficient drug absorption into the bloodstream, preventing drugs from metabolising before reaching their target.

CURRENT AND FUTURE NASAL DRUG DELIVERY TRENDS

Several emerging trends in nasal drug delivery systems are helping the industry meet the demand for patient-centric solutions, significantly impacting the market and patient outcomes both now and in the near future. These trends are transforming how drugs are administered and addressing critical factors such as patient convenience, safety and therapeutic efficacy.

Nasal Spray Repositioning

This strategy involves reformulating existing drugs for intranasal delivery, unlocking a range of benefits for patients and potentially breathing new life into older therapies. One of the primary advantages of nasal sprays is improved patient comfort and compliance. These sprays offer a distinct advantage over other routes of administration, such as injections, due to their ease of use and convenience for self-administration. This enhanced convenience can promote better patient adherence to treatment regimens, ultimately improving overall therapeutic effectiveness and patient comfort.

Nasal drug delivery can also offer enhanced efficacy and safety. Drugs delivered orally typically pass through the digestive system and are extensively metabolised, limiting bioavailability. Intranasal delivery bypasses this first-pass metabolism, potentially enhancing therapeutic effects and lowering dosing requirements. The nasal mucosa allows for rapid drug absorption and, in some cases, direct drug delivery to the central nervous system, making it valuable for conditions requiring immediate relief, such as seizures, migraines or panic attacks.

Repositioning an existing drug as a nasal spray can open up expanded market opportunities. It can be particularly beneficial for patient populations who may have difficulty with other routes of administration, such as paediatric or geriatric patients, or those with conditions affecting the gastrointestinal tract.

Preservative-Free Formulations

There is a growing demand for preservative-free formulations in nasal sprays. Although crucial for preventing microbial growth in multidose pharmaceutical products, preservatives can sometimes cause allergic reactions, particularly in sensitive patients or with long-term use.[3] Common preservatives, such as benzalkonium chloride, can cause nasal mucosal irritation, dryness and even damage to the cilia, which are crucial for the nasal cavity's natural clearance mechanisms.[4] This irritation can exacerbate existing nasal conditions or lead to rhinitis medicamentosa, a rebound congestion effect that worsens symptoms.

Due to these side effects, patients are increasingly aware of the ingredients in their medications and actively seek preservative-free options for improved comfort and quality of life. Eliminating preservatives not only enhances patient comfort and safety but also addresses concerns about potential long-term effects and drug stability. This is because removing preservatives mitigates concerns about potential cumulative adverse effects of prolonged exposure, providing peace of mind and promoting better long-term health outcomes.

Advancements in aseptic manufacturing techniques and specialised container systems have enabled the production of safe and effective preservative-free nasal sprays. These innovations ensure that preservative-free products maintain sterility and stability throughout their shelf life. Strict aseptic manufacturing processes, including controlled environments and sterile filtration, minimise the risk of microbial contamination throughout production. Real-time monitoring and rigorous quality control standards have paved the way for producing safe and effective preservative-free nasal sprays.

Innovative Nasal Spray Devices

New nasal spray device technologies are constantly emerging, offering improved usability, dose accuracy and portability. These advancements can significantly impact patient adherence, particularly for complex drug regimens or chronic conditions, which often require multiple medications to be taken at varying times, creating a complex daily routine. This complexity can lead to confusion and errors. User-friendly devices that are easy to handle, provide clear dosing instructions and minimise discomfort can empower patients to take control of their treatment and achieve better outcomes.

Selecting an appropriate nasal spray device is a pivotal decision in the development process, with far-reaching implications for patient experience and regulatory approval. Device compatibility with the drug's formulation, precise dosing, targeted delivery and user-friendliness are paramount to ensure optimal therapeutic outcomes and minimise side effects. Modern devices are engineered to produce finer, more consistent sprays, ensuring that the medication reaches the targeted areas within the nasal cavity, which helps to optimise drug absorption and efficacy. Innovations in nozzle design and spray pump technology allow for precise control over spray patterns, minimising medication waste and reducing the risk of it running down the throat.

Nasal spray developers must rely on experts who fully understand the interplay between device design, formulation characteristics and intended use to guide them in this critical selection. By harmonising these elements, specialists can ensure optimal drug delivery and efficacy, with patient safety being a particular focus. Their expertise is also crucial for navigating complex regulatory requirements and ensuring prompt product approval.

> "SELECTING AN APPROPRIATE NASAL SPRAY DEVICE IS A PIVOTAL DECISION IN THE DEVELOPMENT PROCESS, WITH FAR-REACHING IMPLICATIONS FOR PATIENT EXPERIENCE AND REGULATORY APPROVAL."

NASAL SPRAY REPOSITIONING CHALLENGES AND SOLUTIONS

Although nasal spray repositioning offers significant promise, it is not without its challenges. One key challenge is

market competition. Unlike novel drugs with potential first-mover advantage, repositioned therapies typically compete with existing treatments for the same indication, including other nasal sprays. This competitive landscape intensifies the pressure to streamline development and manufacturing processes while ensuring that the product offers unique benefits.

Navigating the regulatory landscape for nasal spray repositioning requires a thorough understanding of the approval process and a keen awareness of potential pitfalls. A successful regulatory strategy requires efficiency and accuracy, while a well-prepared submission package helps expedite the review process and avoid delays that can hinder timely product approval.

Collaborating with a partner with a proven track record of successful submissions, particularly those with extensive experience with the 505(b)(2) pathway (Box 1), can be a significant advantage. Developing a stable and effective nasal spray formulation for a repositioned drug requires specialised knowledge and an understanding of the challenges involved to ensure that the final product meets the unique requirements of nasal drug delivery. Careful device selection is also a critical factor in the success of any nasal spray product, especially for repositioned therapies.

As the demand for patient-centric drug delivery options continues to expand, nasal spray repositioning is poised to become an increasingly vital tool for the pharmaceutical industry. Further development of nasal spray formulations is expected for a wide range of therapeutic areas. Advancements in formulation technologies, such as novel excipients and penetration enhancers, will continue to expand the possibilities for nasal spray repositioning, enabling the nasal delivery of a broader range of drugs.

BOX 1: THE 505(b)(2) PATHWAY

The growing demand for patient-centric drug delivery options and the unique advantages of intranasal administration have positioned nasal sprays as a key area of focus in pharmaceutical development. Using regulatory pathways such as the 505(b)(2) pathway in the US, pharmaceutical companies can efficiently reposition existing drugs as nasal sprays, capitalising on this market opportunity and bringing new therapies to patients.

By allowing companies to draw on existing safety data, the 505(b)(2) pathway can bring improved formulations to market more quickly, enhancing patient comfort and reducing potential irritation or allergic reactions. This regulatory pathway can encourage developing and adopting innovative nasal spray devices by providing a streamlined approval process. Used correctly, it can be a valuable tool for pharmaceutical companies seeking to bring patient-centric nasal spray solutions and novel nasal spray devices to the market more efficiently.

ACCELERATING NASAL PRODUCT DEVELOPMENT

Nasal spray product development and manufacturing require extensive experience and expertise to navigate effectively. The ability to anticipate and address challenges proactively helps companies to maintain momentum and avoid costly delays as the project progresses to clinical phases and towards commercialisation. Partnering with an experienced contract development and manufacturing organisation (CDMO) can offer several benefits in developing and manufacturing nasal spray products.

CDMOs with expertise in nasal spray development can help expedite products to clinical phases. They achieve this by employing various strategic approaches and specialised capabilities. Experienced CDMOs are also well-equipped to navigate the complexities and challenges of nasal spray development – their expertise allows them to proactively anticipate and address potential issues, reducing the risk of costly delays and setbacks.

Crucially, CDMOs with a deep understanding of regulatory guidelines and established relationships with regulatory bodies can help ensure compliance with stringent regulatory requirements. This is particularly important as products move toward commercial stages. In-house regulatory support can provide clients with direct access to experts who are well-versed in the intricacies of nasal drug development regulations. A range of strategic approaches, dedicated equipment and processes for clinical manufacturing and transparent communication across various disciplines help to accelerate timelines and get treatments to patients fast.

By prioritising patient needs and preferences, the pharmaceutical industry can continue to advance drug delivery systems that enhance therapeutic efficacy and improve patient convenience, safety and overall treatment experiences. Collaboration between pharmaceutical companies, specialised contract partners and regulatory bodies will be essential to navigate these complexities and bring novel, patient-centric solutions to market.

ABOUT THE COMPANY

Renaissance Lakewood is a US-based global contract development and manufacturing organisation (CDMO) for pharmaceutical and biotech companies. With more than

"CRUCIALLY, CDMOs WITH A DEEP UNDERSTANDING OF REGULATORY GUIDELINES AND ESTABLISHED RELATIONSHIPS WITH REGULATORY BODIES CAN HELP ENSURE COMPLIANCE WITH STRINGENT REGULATORY REQUIREMENTS."

20 years of experience in nasal sprays and sterile injectable dosage forms, Renaissance has an unparalleled track record of providing exceptional service and resources to clients from the development stage through commercial launch.

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Eric Kaneps

Eric Kaneps is the Vice-President of Sales & Marketing at Renaissance Lakewood. He has more than 25 years of experience in sales, business development, and account management in the pharmaceutical industry. Mr Kaneps worked at DPT Laboratories as the Director of Business Development from 2001–2016. In this role, he transitioned the over-the-counter (OTC)/consumer health business towards pharmaceutical-based nasal and injectable products, which became the foundation for the new, renamed entity Renaissance Lakewood. In between his roles at the Lakewood site, Mr Kaneps was Senior Vice-President of Business Development for Pharma-Tech Industries, a contract manufacturing organisation that specialises in prescription and OTC ingestible and topical products. Mr Kaneps holds a BS BA in International Business & Economics from The Ohio State University (OH, US).

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TRANSFORMING MENTAL HEALTHCARE: THE RISE OF INHALABLE PSYCHEDELICS?

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Dr Philippe Rogueda of **Merxin Ltd** discusses how inhaled psychedelic therapies are emerging as a potential game-changer in mental health due to their fast onset and precise dosing, and how their potential has resulted in a growing pipeline of therapies, paving the way for a new era in mental healthcare.

In 2022, the WHO published its largest review of world mental health since the turn of the century. It urged all countries to accelerate the implementation of the "Comprehensive Mental Health Action Plan 2013–2030", including strengthening care by changing where, how and by whom mental health care is delivered and received.

The issue of global mental health has driven research for faster-acting, more effective treatments, with growing recognition that traditional psychiatric medications often fail to meet the needs of patients. Many antidepressants take four to six weeks to reach full efficacy, and only approximately 30% of patients with major depressive disorder (MDD) achieve remission after first-line treatment. For those with treatment-resistant depression (TRD), post-traumatic stress disorder (PTSD) and severe anxiety disorders, the limitations of existing therapies can be life-threatening.

"WITH 18 INHALABLE PSYCHEDELIC DRUGS CURRENTLY IN DEVELOPMENT, THE SECTOR IS GAINING MOMENTUM AS PHARMACEUTICAL COMPANIES, BIOTECH FIRMS AND DRUG DELIVERY SPECIALISTS EXPLORE ITS POTENTIAL."

Could innovations in inhaled psychedelic therapies (iPTx) be the breakthrough solution? With 18 inhalable psychedelic drugs currently in development, the sector is gaining momentum as pharmaceutical companies, biotech firms and drug delivery specialists explore its potential. Inhalable therapies can deliver measurable effects within minutes, making them well-suited for treating acute psychiatric episodes, rapid intervention in suicidal ideation and emergency mental healthcare.

GAINING MOMENTUM IN PSYCHEDELIC DRUG DEVELOPMENT

Over the past decade, psychedelics have transitioned from countercultural obscurity to cutting-edge pharmaceutical research. Between 2018 and 2024, according to GlobalData's clinical trials database, the number of clinical trials investigating psychedelic therapies increased by 137% – from 48 to 114 – reflecting a surge of interest in their potential. The global psychedelic drugs market is predicted to surpass US$8 billion (£6.3 billion) by 2030, supported by a 15% compound annual growth rate.

While much of this growth has been driven by oral and intravenous psychedelic formulations, inhalable therapies are gaining traction as an effective alternative. Formulations for nasal sprays and soft mist inhalers (SMIs), for example, offer good bioavailability, fast onset and precise dosing, positioning them as potential game-changers in psychiatric medicine. Unlike traditional antidepressants, which require chronic daily use, many psychedelic treatments exert long-lasting effects after just a single session – an important distinction that could transform how depression and PTSD are managed.

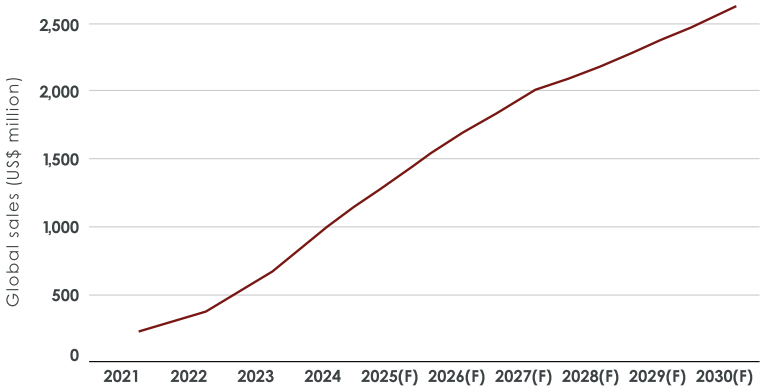

Figure 1: In 2030, total Spravato sales are forecast to reach $2.6 billion.

"UNLIKE TRADITIONAL ANTIDEPRESSANTS, WHICH REQUIRE CHRONIC DAILY USE, MANY PSYCHEDELIC TREATMENTS EXERT LONG-LASTING EFFECTS AFTER JUST A SINGLE SESSION – AN IMPORTANT DISTINCTION THAT COULD TRANSFORM HOW DEPRESSION AND PTSD ARE MANAGED."

THE FIRST MAJOR iPTx SUCCESS: SPRAVATO'S MARKET IMPACT

The first inhalable psychedelic to receive regulatory approval was Johnson & Johnson's Spravato (esketamine) nasal spray, which the US FDA approved in 2019 for TRD, indicated for patients who have taken two or more oral antidepressants and still experience symptoms.[1] For the first four weeks, Spravato is taken twice a week under the supervision of a healthcare provider. After that, it is typically taken once a week. In clinical trials, the most significant reduction in depressive symptoms was seen at 24 hours after first use.

By offering rapid symptom relief, Spravato has proven that iPTx can be a viable, scalable treatment option. Its commercial impact has been significant, with sales reaching $689 million in 2023 with forecasts signalling major growth over the decade (Figure 1). This has not only demonstrated strong market demand but has also encouraged greater investment in nasal spray and inhalation-based psychedelic treatments.

Spravato's success has also paved the way for regulatory progress. Historically, regulatory agencies have been hesitant to approve psychedelic-based medicines, but Spravato's performance has set an important precedent, providing a framework for future psychedelic inhalation therapies.

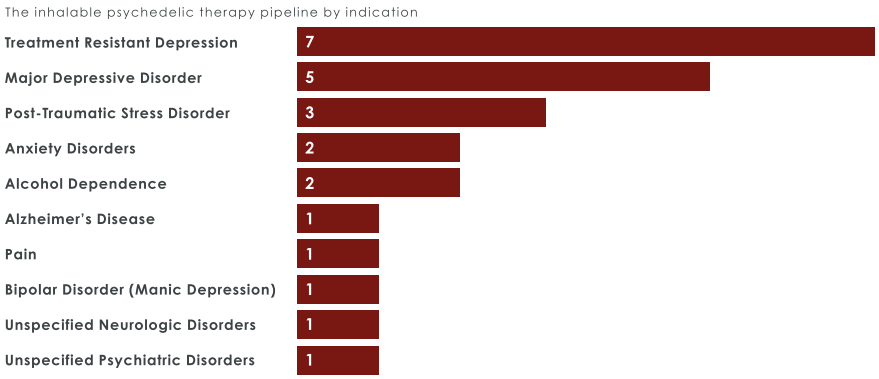

Figure 2: Most inhaled psychedelics in development are indicated for depression.

iPTx IN 2025: WHAT IS IN THE PIPELINE?

With 18 inhalable psychedelic therapies in development, drug makers are targeting various psychiatric and neurological conditions, with depression, PTSD, anxiety disorders, addiction treatment and neurodegenerative diseases among the key areas of focus (Figure 2). The expanding

pipeline indicates growing confidence in the potential of iPTx, with several therapies expected to enter late-stage trials within the next five years (Figure 3).

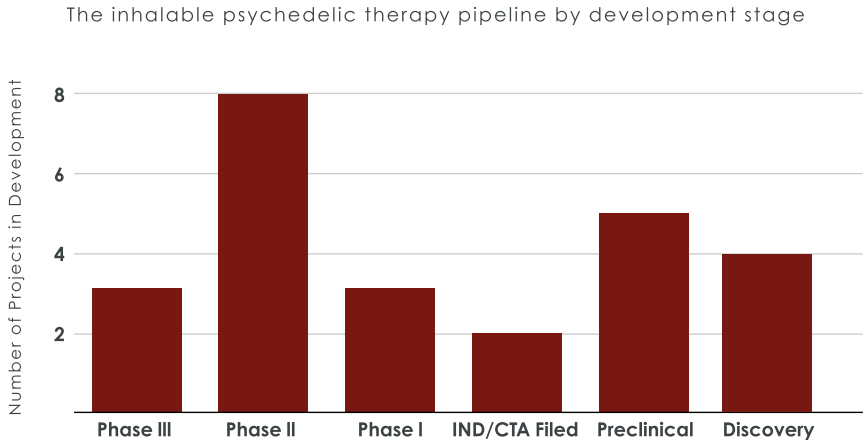

Figure 3: The largest portion of the pipeline is in Phase II development.

Ketamine-Based Compounds

Beyond esketamine, there are further ketamine-based compounds demonstrating therapeutic potential. Currently in clinical trials for MDD and PTSD, ketamine hydrochloride is a racemic mixture of ketamine that has been used for anaesthesia, pain management and psychiatric disorders. It acts as an N-methyl-D-aspartate (NMDA) receptor agonist and has been under development with intranasal formulations in the US and China.[2]

Meanwhile, as a combination therapy with intranasal administration, ketamine with sufentanil enhances ketamine's antidepressant and analgesic effects. Sufentanil is an opioid analgesic and this combination is being investigated by a Danish pharmaceutical company in a Phase III paediatric trial for pain management.[3]

A pharmaceutical company based in Florida (US) is also developing ketamine-based drugs for intranasal delivery. SPC-14 is a preclinical-stage combination therapy being investigated for Alzheimer's disease.[4] The ketamine acts by targeting NMDA receptors, while the other API targets 5-hydroxytryptamine receptor 4, potentially treating the cognitive and neuropsychiatric symptoms of the disease.

Tryptamine-Based Compounds

Fast-acting dimethyltryptamine (DMT) acts as a 5-hydroxytryptamine receptor 2 agonist, which can induce profound alterations in perception and cognition. Inhaled DMT formulations are currently being developed for MDD and PTSD, using its ability to promote neuroplasticity. There are two inhalable DMT formulations currently in development in Canada, one being a liquid inhaled formulation indicated for TRD that is supported by positive initial results in a Phase II trial.[5]

"THE STUDY REVEALED A SIMILAR ONSET OF EFFECT AND DOSE PROFILE TO INTRAVENOUS DMT, YET THE INHALED FORMULATION HAD AN APPROXIMATELY 300% LONGER DURATION OF ACTION AND MORE THAN A 40% IMPROVEMENT IN ITS BIOAVAILABILITY."

5-methoxy-DMT (or mebufotenin) is a potent short-acting psychedelic found in certain plant species and toad venoms. Synthetic formulations have shown its potential for treating depression, anxiety and substance-abuse disorders by rapidly modulating serotonin receptors and inducing therapeutic dissociative states. At least two companies are currently working on clinical-stage inhalable mebufotenin drugs. One lead candidate is currently being examined in a Phase II trial for MDD and TRD, having already completed open-label Phase II trials in patients with bipolar II disorder and postpartum depression. The candidate is formulated for inhalable administration.[6]

Meanwhile, a British biotech has opted for nasal administration of its mebufotenin candidate, which is now in Phase II trials. It has completed an open-label study in patients with alcohol dependence and is recruiting for studies in patients with MDD and TRD. Findings from an open-label Phase IIa study in TRD patients were positive – a single 10 mg dose had a rapid antidepressant effect, with 55% of patients demonstrating a 50% or greater improvement in depression symptoms the following day.[7]

In 2024, a Canadian biotech raised $150 million to progress two clinical-stage programmes with inhaled drug delivery.[8] This news came in the same month that the FDA granted breakthrough therapy designation to a deuterated psilocybin analogue with a similar structure to neurotransmitters such as serotonin. It has now initiated a Phase III programme in participants with moderate-to-severe MDD and plans to initiate a second pivotal study in the first half of 2025.

Its second candidate is an inhalable deuterated DMT designed for anxiety disorders that is currently being evaluated in a Phase II study. It has a shorter onset and duration than traditional psychedelics, making it well-suited for

controlled therapeutic settings. In 2022, it published pharmacokinetic data from preclinical studies demonstrating the benefits of delivering its deuterated DMT molecule via inhalation. Specifically, the study revealed a similar onset of effect and dose profile to intravenous DMT, yet the inhaled formulation had an approximately 300% longer duration of action and more than a 40% improvement in its bioavailability.[9]

THE ROLE OF DRUG DELIVERY INNOVATION

The effectiveness of inhalable psychedelics depends not only on the therapeutic compounds themselves but also on the precision of their delivery systems. Unlike traditional psychiatric medications, which can be swallowed, injected or infused intravenously, these novel therapies require specialised inhalation devices to ensure consistent dosing.

This is where Merxin Ltd plays a crucial role. As a leader in inhalation technology, the company designs high-performance drug delivery devices that optimise patient experience and therapeutic efficacy. By ensuring that pharmaceutical innovators have access to next-generation inhalation platforms, Merxin Ltd is shaping the future of inhalable psychedelic treatments. The company's product portfolio includes devices such as MRX004 SMI, designed to deliver fine mist sprays for efficient drug absorption, and MRX006 multidose dry powder inhaler, which operates on an open-inhale-close mechanism, making it suitable for various therapeutic applications.

"BY ENSURING THAT PHARMACEUTICAL INNOVATORS HAVE ACCESS TO NEXT-GENERATION INHALATION PLATFORMS, MERXIN LTD IS SHAPING THE FUTURE OF INHALABLE PSYCHEDELIC TREATMENTS."

FUTURE OUTLOOK FOR iPTx

The potential behind inhalable psychedelics is undeniable. The success of Spravato, combined with a growing pipeline of new therapies, suggests that psychiatric treatment could be on the verge of a major transformation. By offering rapid symptom relief, precise dosing and improved bioavailability, these therapies have the potential to redefine mental health treatment.

As investment, research and regulatory acceptance continue to grow, inhalable psychedelics are poised to reshape the future of mental health treatment. For pharmaceutical companies, biotech firms and drug delivery specialists, the shift towards iPTx presents significant commercial opportunities. By harnessing advanced inhalation technologies and partnering with inhalation device industry leaders, such as Merxin Ltd, pharmaceutical companies can position themselves at the forefront of this nascent market.

Dr Philippe Rogueda

Philippe Rogueda, PhD, co-founded Merxin Ltd in 2015 and currently serves as Chief Business Officer. His expertise spans across multiple facets of the inhalation field, particularly with dry powder and SMIs. Dr Rogueda's passion lies in the development of SMI technology, particularly for biologics, which he believes holds immense potential to revolutionise the delivery of inhaled therapies. With over a decade of experience in the inhalation sector, Dr Rogueda's deep knowledge and innovative approach to inhalation technologies make him a key figure in advancing medical device development for improved drug delivery systems.

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SEP/OCT **NEW ISSUE TOPIC** Dual Chamber Delivery Systems DEADLINE: **Aug 14, 2025**	**OCT** Prefilled Syringes & Injection Devices DEADLINE: **Sep 4 , 2025**	**OCT/NOV** Sustainability in Drug Delivery DEADLINE: **Sep 18, 2025**
NOV Pulmonary & Nasal Drug Delivery DEADLINE: **Oct 2, 2025**	**DEC** **NEW ISSUE TOPIC** Delivering Gene & Cell Therapeutics DEADLINE: **Nov 6, 2025**	**JAN 2026** Prefilled Syringes & Injection Devices DEADLINE: **Dec 4, 2025**
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20 YEARS ON drugDELIVERY

MANUFACTURE OF MOISTURE-SENSITIVE POWDERS FOR INHALATION

Alan Watts and **Yusuf Ahmed** of **Catalent**, along with **Gabriela Dujovny** of **Roquette**, discuss manufacturing methods for inhalation powders and explain how moisture protection is an essential consideration throughout the manufacturing process.

Inhalation powders have been used for decades to treat lung diseases, as well as conditions requiring rapid systemic therapy. Patients benefit from dry powder formulations because they can often be dosed in a single breath, use devices that are pocket-sized and do not require refrigeration. Manufacture by spray drying has improved on traditional blended formulations by enabling higher-loaded doses and reducing oropharyngeal deposition. However, these powders present new challenges for manufacture, specifically for handling the intermediate powder, which is poorly flowing and often sensitive to moisture. Additionally, these powders require encapsulation in specialised capsules, such as Qualicaps' (Roquette) Quali-V®-I Extra Dry Hypromellose capsules to ensure product dryness and stability. With proven experience in commercial production of spray-dried products for inhalation, Catalent has the infrastructure in place to manufacture, control and release these speciality products effectively.[1]

SPRAY DRYING INHALATION POWDERS

Spray drying is a widely used technique in pharmaceutical and food industries to produce dry powders from liquid feedstock. It is the preferred method for engineering inhalable powders, offering the benefits of high potency and a high respirable fraction for both small- and large-molecule formulations in a continuous and scalable process. During spray drying, water (and

any other solvent present) is rapidly driven off causing solute precipitation and particle formation. Excipients commonly used in spray drying of inhalation powders are often sugars (e.g. trehalose, sucrose) and polyols (e.g. mannitol), which can stabilise the API in a glassy matrix and impart stability to large molecules by replacing the hydrogen bonds that were occupied by water.

It is extremely important that control over process and facility moisture is maintained to stabilise these powders. Often, total water content within these powders will be below 5% w/w to maintain their physical and chemical stability, allow for sufficient powder flow during filling operations and, most importantly, aerosolise effectively when inspiratory flow is encountered.

Formulating and Collecting

Formulation approaches to inhalation powder can enable protection from ambient moisture, at least for short durations. When spray drying, functional excipients, such as leucine, can be used to create a hydrophobic shell that preferentially accumulates on the outer surface of the forming particle, improving moisture protection of the dried powder while also reducing particle surface energy and cohesion. While shell formers provide some moisture protection, it remains necessary to further protect spray-dried powder from high relative humidity (RH) environments during powder collection from the spray drier, as well as in subsequent manufacturing unit operations.

During the spray drying operation, dried powders are collected into intermediate containers where they will begin to cool. It is important, however, to protect these powders when drying conditions result in moisture-saturated air within the process, as these cooling powders can serve as a surface for water condensation. This can be achieved by jacketing collection vessels to maintain higher collection temperatures or by sweeping collection vessels with dry nitrogen gas.

POWDER ENCAPSULATION

Intermediate bulk containers (IBCs) are often used to collect and store bulk spray-dried powder before moving to the encapsulation unit operation. All IBC sampling for intermediate release should be conducted under low, controlled RH conditions.

Low RH Control Within Encapsulation Suite

Encapsulation requires that the powder be fed into equipment, where it will come into contact with multiple surfaces and be exposed to the environmental air for extended periods, often several hours for the filling operation. Encapsulators, such as the Harro Höfliger (Allmersbach im Tal, Germany) Modu-C series (Figure 1), are designed to handle poorly flowing powders and enable accurate filling at low masses using drum-filling technology.[2] Operation of this equipment in a low and controlled RH can be accomplished by using containment around the equipment or by controlling the environment of the entire suite. By controlling the suite environment, the Catalent Boston (MA, US) site can provide ultra-low RH filling while allowing operators to interact with the equipment without the restriction of containment.

"BY CONTROLLING THE SUITE ENVIRONMENT, THE CATALENT BOSTON SITE CAN PROVIDE ULTRA-LOW RH FILLING WHILE ALLOWING OPERATORS TO INTERACT WITH THE EQUIPMENT WITHOUT THE RESTRICTION OF CONTAINMENT."

Figure 1: Commercial-scale encapsulation (Harro Höfliger Modu-C MS, left) and blistering (Pharmaworks TF2, right) within Catalent Boston.

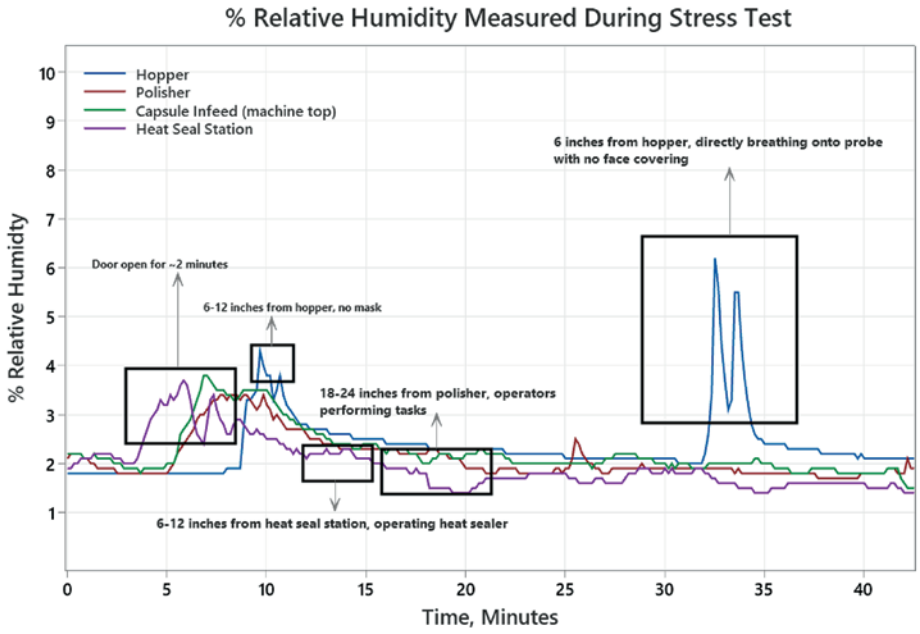

Figure 2: Relative humidity changes due to operator presence at various points in an ultra-low RH encapsulation suite.

To fully evaluate the environmental conditions that a powder might be exposed to during filling, a study was performed where a series of humidity probes were installed at key points throughout the encapsulation suite. Probes were placed at locations in the suite where operators might interact with the equipment or material: at the feed hopper inside the Modu-C unit; at the capsule polisher; on top of the unit at the capsule infeed; and at the bagged-capsule heat-seal station. While maintaining a 2% RH in the filling suite, these probes were monitored and challenged by various exposures that could potentially occur during normal operation. Operators were gowned as usual for normal GMP operation to test impact on local RH throughout the suite. As seen in Figure 2, the largest impact was a positive control where the operator removed their facemask, breathing 6" away from one of the probes to cause a spike to 6% RH. When testing anticipated normal operations, opening the suite door for two minutes had the greatest impact, causing an increase in RH of all probes to between 3% and 4%. This testing demonstrated that operator presence in the suite might have some impact on RH; however, it is likely to be insignificant.

For an actual filling operation, probes remained in place for this three-hour process. With all operators present, baseline RH was maintained between 2% and 3% with minor spikes to ~4% RH, likely due to the door opening when operators entered and exited the suite. During the entire filling operation, RH was successfully maintained below 5%.

Low-Moisture Capsules

While controlled RH within the manufacturing environment is extremely important, capsule selection and handling can also greatly impact the protection of moisture-sensitive powders. Relatively high levels of moisture in traditional hydroxypropyl methylcellulose (HPMC) capsules (4–6%) or gelatin capsules (>10%), will transfer into a dry powder product during storage and should be avoided with moisture-sensitive formulations. Quali-V®-I Extra Dry Hypromellose capsules are specifically designed for inhalation applications, offering a low moisture content that is ideal for moisture-sensitive dry powder inhaler (DPI) formulations. These capsules, derived from standard HPMC Quali-V®-I inhalation-grade capsules, undergo an enhanced manufacturing process that reduces moisture to 2–3.5% w/w, while preserving their mechanical integrity for reliable drug delivery.

When Quali-V®-I Extra Dry capsules were tested under various mechanical stresses, the results showed that the reduced moisture content did not affect their structural integrity, performing similarly to normal HPMC capsules.[3] Maintaining normal mechanical properties helps to ensure capsule integrity during encapsulation and blistering operations, as well as reliable aerosol performance during product release testing and patient use.

Like the powder intermediate, Extra Dry capsules can also adsorb moisture from the production environment. Thus, care should be taken to only expose these capsules to low RH conditions so that moisture is not adsorbed. Dynamic vapour sorption (DVS) run on 0% RH dried HPMC capsules shows a gradual uptake in moisture as the

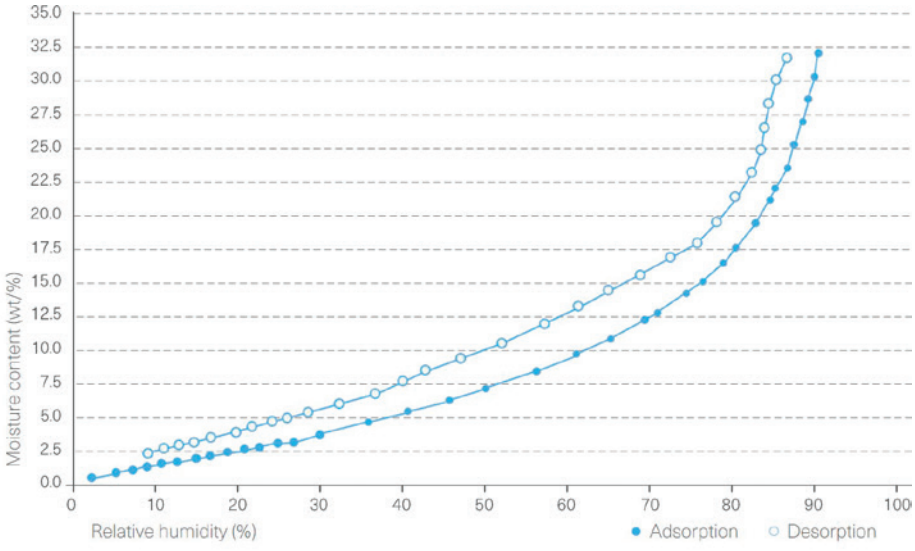

Figure 3: A DVS isotherm of an HPMC capsule.

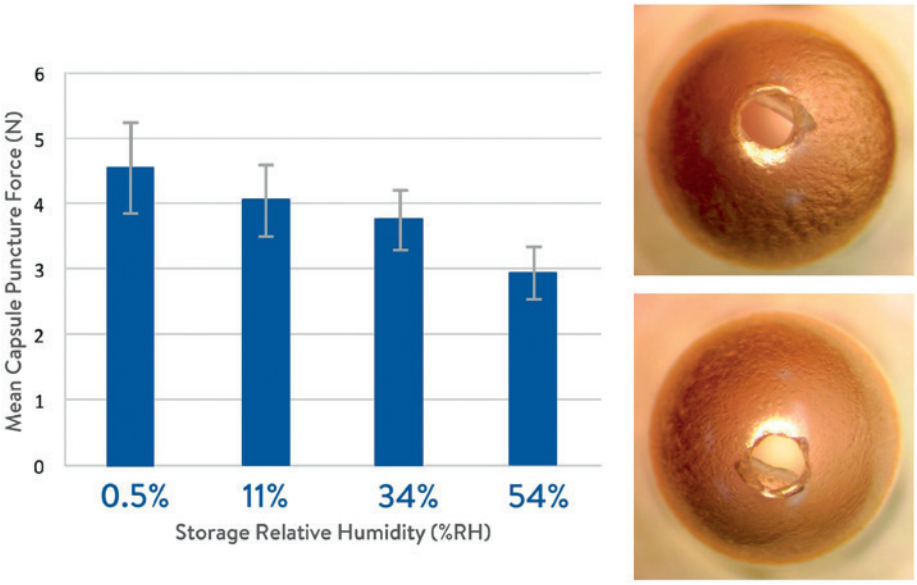

Figure 4: Puncture force change with various HPMC capsule storage conditions (left) and images of capsule punctures after 0.5% RH storage (right).

"CAREFUL CONSIDERATION OF THE INTEGRITY OF THE BLISTER SEAL IS NECESSARY, AS IT IS THE MOST LIKELY POTENTIAL PATHWAY FOR MOISTURE TO INGRESS."

environmental RH is increased (Figure 3). Of note, at 40% RH (ambient RH), capsules equilibrate to a moisture content of >5% – outside of the specification limit for Extra Dry capsules – which has the potential to result in instability of a moisture-sensitive powder. It is critical, therefore, that Extra Dry capsules are handled, filled and packaged in a controlled environment that does not increase their moisture content.

A study was conducted to assess the effect of capsule moisture content on the mechanical properties of HPMC capsules used in DPIs. Capsules were conditioned at 11%, 34%, 54% and 0.5% RH, resulting in moisture contents ranging from 1.3% to 6.5% w/w. Puncture-resistance tests revealed that lower moisture content increased the puncture force slightly, with minimal impact on capsule puncture geometry (Figure 4).[4] Even at very low RH (0.5%), capsules maintained their mechanical integrity, supporting their suitability for use in DPI products without fragmentation.

CAPSULE BLISTERING

Upon completion of powder encapsulation, moisture-sensitive products must then be blistered to allow for commercial packing and long-term stability. Like encapsulation, it is essential that this operation be performed under low RH so that filled capsules do not adsorb moisture from the manufacturing environment.

Blistering Materials

Materials and blister card design are critical to ensure protection from moisture. Cold-form aluminium cavities and aluminium lidding allow for superior moisture protection compared with polymeric cavities. Careful consideration of the integrity of the blister seal is necessary, as it is the most likely potential pathway for moisture ingress. Blister design elements, such as length from seal edge to cavity and seal integrity, can vary with heat and dwell time, and have been shown to have meaningful impact on the long-term stability of blistered moisture-sensitive material.[5]

In some instances, extra moisture protection is required and can be enabled by incorporation of desiccating materials within the blister card. Foils are available where a water-adsorbing polymer layer is embedded in the composite foil itself, while other solutions have used blister cavities intended to contain desiccant packs, which are connected via channels to drug product-containing cavities.

CONCLUSION

Moisture control is essential for nearly all tableted or powdered pharmaceutical products. For spray-dried inhalation products, protection from environmental moisture is essential throughout the manufacturing process and should be prioritised when selecting container closure materials, such as HPMC capsules or blistering materials. With several years of commercial manufacturing experience and proven facility controls in place, Catalent Boston has established a fit-for-purpose environment to spray, fill and blister moisture-sensitive powders.

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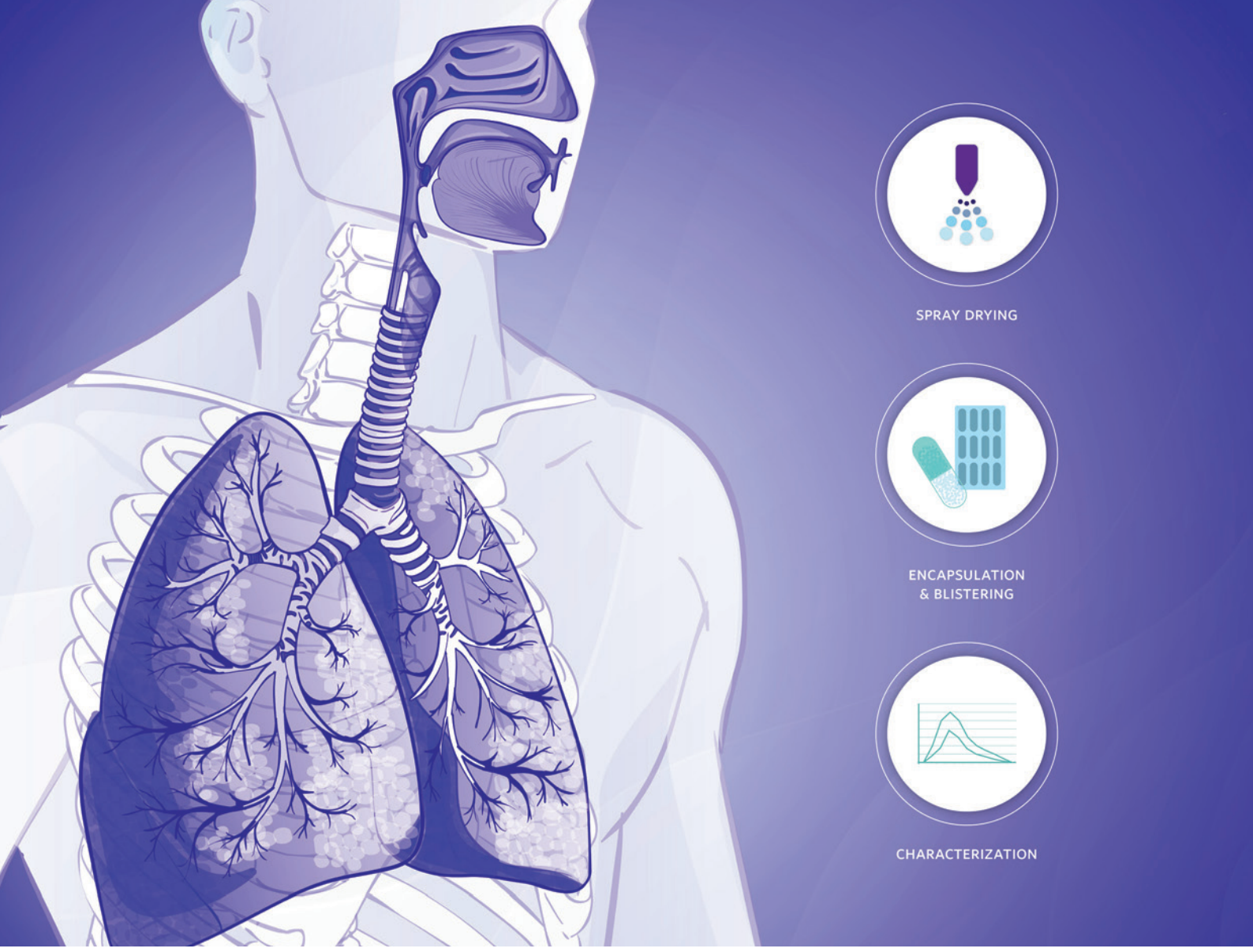

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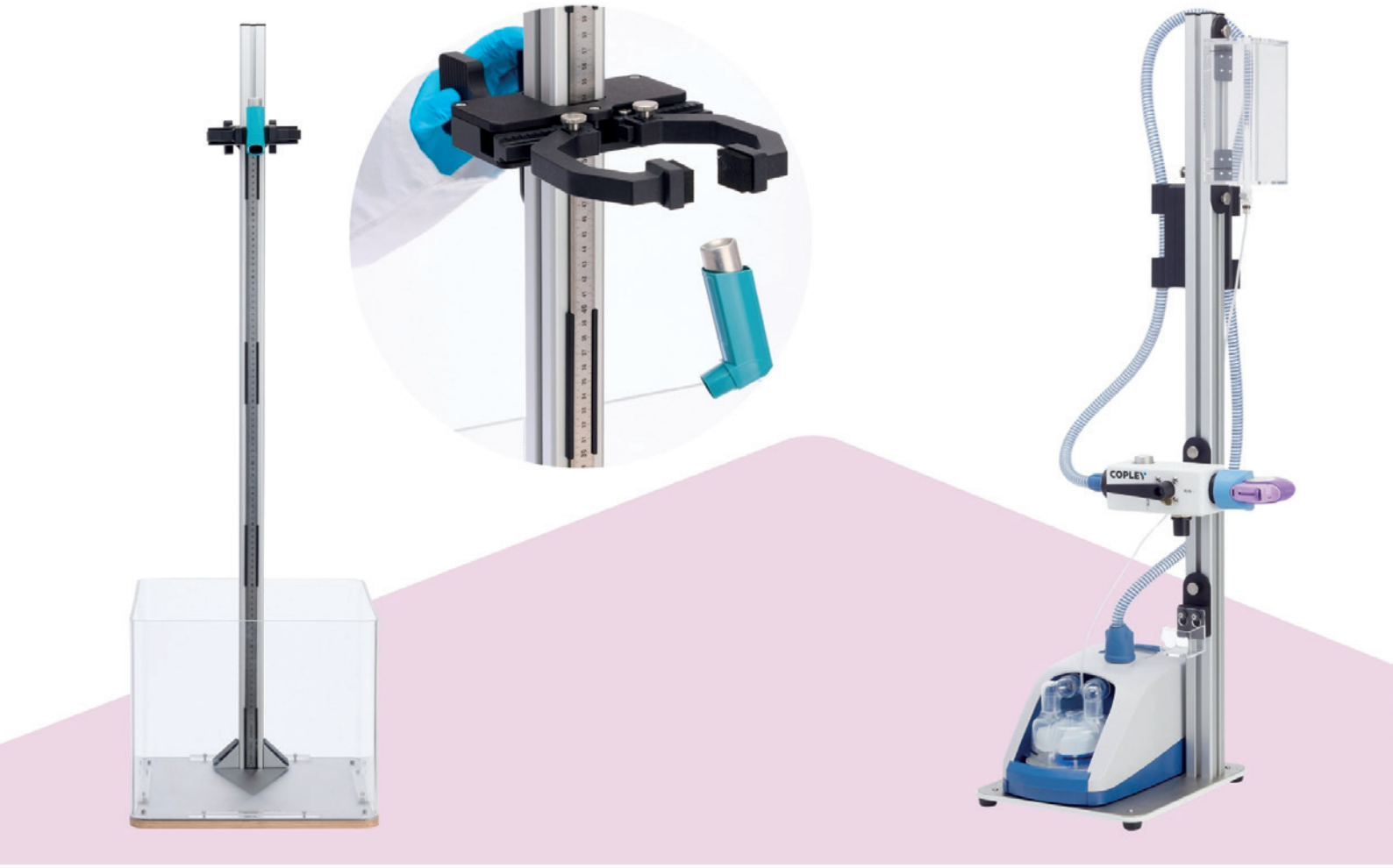

DEVELOPING ROBUST ORALLY INHALED PRODUCTS TO ACHIEVE BETTER PATIENT OUTCOMES

COPLEY

Dr Clair Brooks of **Copley Scientific** looks at some of the in-use issues and patient effects that good design of devices for orally inhaled drug products can address within the context of regulatory requirements for the demonstration of robustness.

It is sobering to imagine the transformation in patient outcomes that could be achieved through the better use of existing therapies for respiratory diseases. Reported non-adherence in asthma sufferers runs at 30–70%,[1] with complementary studies of inhaler technique indicating that as many as 50–80% of those suffering from chronic obstructive pulmonary disease and asthma are unable to use their prescribed orally inhaled products (OIPs) properly.[2]

The potential impacts of this problem are far reaching. In the UK, for example, asthma accounts for 1,200 deaths, 50,000 hospital admissions and £6 billion in lost productivity per year;[1] the overuse of reliever medication alone has been associated with an environmental footprint of 250,000 tonnes of CO_2 equivalent per year.[3] And this problem is a persistent one, with little improvement observed over the last four decades.

Patient non-adherence and product misuse is a complex, multifactorial issue, but device design and performance have a defining role to play in addressing it. Compared with alternative solutions, such as enhanced healthcare practice and digitisation, inherently robust OIPs can be both highly effective and cost-efficient.

THE PERSISTENT PROBLEM OF INHALER MISUSE

The combination product classification applied to OIPs highlights the interplay between device and formulation that defines performance. However, in practice, there

"IT IS TEMPTING TO BELIEVE THAT PATIENTS CAN BE 'TRAINED OUT' OF BEHAVIOURAL IMPACTS, BUT EXPERIENCE AND STATISTICS SUGGEST OTHERWISE."

is a third factor in play – the patient. When it comes to clinical efficacy, it is the interplay between device, formulation and patient that defines the dose received and its therapeutic effect. This sets inhaled drug delivery apart from other administration routes and is an important area of focus for OIP developers.

Patient-related effects may be linked to patient physiology and disease state, or to patient behaviour – intentional or otherwise. For example, the breathing profile applied during product use is a function of the patient's inherent breathing capabilities (physiology and disease state) and how adept they are at performing a specified inhalation manoeuvre (behaviour).

It is tempting to believe that patients can be "trained out" of behavioural impacts, but experience and statistics suggest otherwise. Studies show that many healthcare professionals are unable to demonstrate correct inhaler technique[2] and time constraints add to the difficulty of delivering sufficient, effective training and refresher training. Despite efforts to improve and the high degree of detail required in information for use instructions, device misuse remains stubbornly high.

One explanation for this is that some misuse is purposeful. A patient that fails to recognise the importance of preventer medication may be poorly motivated to adhere rigorously to a regime that shows little outward sign of effect. Cost may also be a factor in some geographies, leading to the intentional "preserving" of medication. On the other hand, there are undoubtedly patients that are trying hard to use their OIPs as directed and failing.

Better device design has a role to play in reducing this problem. Connected and digital devices are one approach that has a growing track record of success. For example, trials of Hailie® (Adherium, Melbourne, Australia) with child patients show that it can reduce both the use of rescue medication and hospital admissions by 45% and 80%, respectively, and a UK NHS study to improve outcomes for high-risk children and young adults is currently underway.[4–6] Simply by recording usage patterns and prompting adherence, such solutions can make a major difference to patient outcomes, with the ability to monitor applied inhalation profiles an additional important benefit for dry powder inhalers (DPIs). That said, cost is a major limitation with respect to uptake, depending on healthcare structure and funding.

Designing more robust performance into conventional inhalers is arguably the more broadly beneficial alternative. In the first instance, doing so relies on identifying common issues associated with patient behaviour and inhaler use, and developing testing strategies to investigate them.

THE REGULATORY PERSPECTIVE

US FDA and EMA guidance includes a range of drug characterisation studies that reflect the potential for variability associated with patient physiology, behaviour and day-to-day use.[7–9] Depending on the specific OIP and guidance being followed, examples include:

- Shaking requirements for suspension-based formulations, notably metered dose inhalers (MDIs)
- Initial priming and re-priming requirements, following storage in various orientations
- Low-temperature performance, following storage at sub-zero temperatures
- Performance after temperature cycling, between sub-zero and above room temperature
- Effect of environmental moisture.

The need to assess robustness is also specifically listed with associated studies designed to confirm "that the MDI or DPI product is of sufficiently robust design to withstand shipping conditions and typical patient usage".[7] The additional information supplied to support study design references the need to assess the impact of actions such as dropping, agitation and shipping, with the latest draft of the EMA guidance providing the most detail in this area.[9] It highlights the value of:

- Assessing the performance of the device when activated at the frequency indicated in the product information
- Demonstrating the robust performance of any lock-out device or digital sensor
- Determining the vibrational stability of powder mixtures
- Carrying out dropping simulation studies with products that are towards their end of life (e.g. at dose 180 for a 200-dose product), due to the potential impact of releasing the accumulated drug (Figure 1).

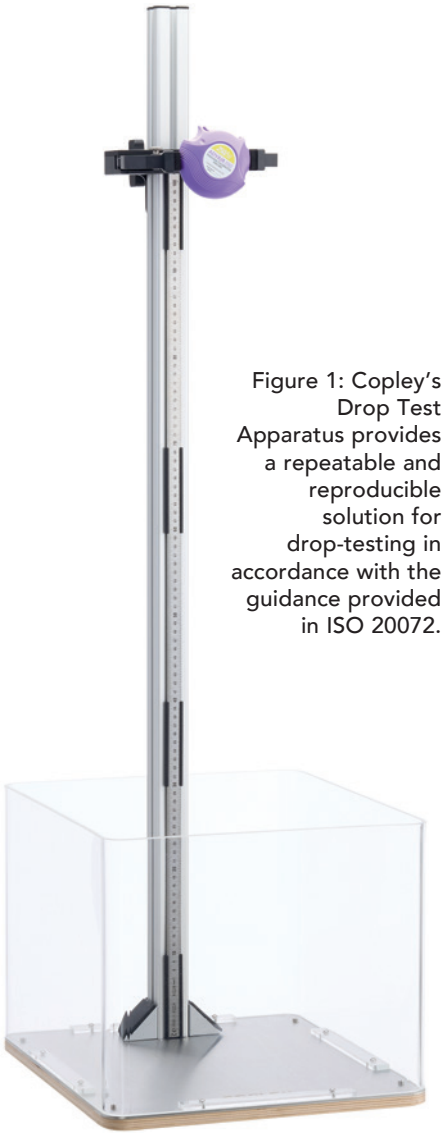

Figure 1: Copley's Drop Test Apparatus provides a repeatable and reproducible solution for drop-testing in accordance with the guidance provided in ISO 20072.

"FOCUSING ON SPECIFIC BEHAVIOURAL ISSUES WIDELY KNOWN TO CAUSE VARIABILITY IN DRUG DELIVERY CAN DELIVER ADDITIONAL INSIGHTS TO SUPPORT INNOVATION TOWARDS MORE ROBUST PERFORMANCE IN THE BROADEST SENSE OF THE WORD."

The extent to which these tests accurately capture the impact of "typical patient usage" defines their value for those working to make devices as robust as possible, who may also choose to investigate beyond the indicated studies. Focusing on specific behavioural issues widely known to cause variability in drug delivery can deliver additional insights to support innovation towards more robust performance in the broadest sense of the word.

STUDY SPOTLIGHT: INVESTIGATING THE EFFECT OF EXHALATION THROUGH A DPI

The passive nature of DPI devices makes them uniquely sensitive to the inhalation manoeuvre applied during use. This is reflected in:

- Compendial methods for DPIs, for which flow rate is determined from the resistance of the device, rather than being fixed
- The requirement for product characterisation studies across a range of flow rates that are relevant to the target patient population[7] or in the 30–90 L/min range[9]
- Studies of the impact of the applied flow rate profile, notably the rise time to peak inspiratory flow rate, by product developers adopting more clinically relevant test methods.[10]

However, it is not just inhalation during product use that can be a source of variability; the exhalation manoeuvre that precedes it can be too. With DPIs, exhaling to functional residual capacity, or just below, empties the lungs, readying them for the deep inhalation required for successful drug delivery. Unfortunately, studies show that many patients prepare incorrectly, with failures at the exhalation stage highlighted as the most common error associated with DPI technique.[11–13]

Failure to exhale away from the inhaler was observed in approximately 80% of patients in one study,[14] while the specific issue of exhalation through the inhaler is reported in 14–22% of unsupervised patients.[15] Furthermore, there is evidence of a lack of understanding of the importance of exhalation by healthcare professionals and considerable resistance to improvement by training.[15]

This is problematic given the potential for exhalation into the device to blow out the dose and, more critically, the susceptibility of DPI formulations to moisture, notably with respect to their tendency to agglomerate. DPI formulations and devices are matched to ensure that a correctly applied inhalation manoeuvre supplies sufficient energy to disperse the formulation to a respirable particle size. If the energy needed to achieve such dispersion increases, due to stronger inter-particulate bonds, then more of the drug will be delivered in the form of larger and/or agglomerated particles and therefore not reach the lung.

"FAILURE TO EXHALE AWAY FROM THE INHALER WAS OBSERVED IN APPROXIMATELY 80% OF PATIENTS IN ONE STUDY, WHILE THE SPECIFIC ISSUE OF EXHALATION THROUGH THE INHALER IS REPORTED IN 14–22% OF UNSUPERVISED PATIENTS."

Experimental studies support this hypothesis. For example, Holmes *et al* found that delivered dose fell to less than 50% of the label claim when air with a relative humidity of 80% was introduced into a Diskus™ DPI (salmeterol/fluticasone, GSK) prior to inhalation.[15] Measurements of the relative humidity of exhaled air have shown it to vary widely across a range from approximately 40% to 90%, so this figure is clinically representative with respect to studying the impact of an incorrect exhalation manoeuvre.[16]

In this study, the exhalation profile applied to the device was varied with respect to:

1. Flow rate (30, 60, 90 and 120 L/min)
2. Distance between mouthpiece and air source (0, 5 and 10 cm)
3. Duration (2, 4 and 6 s)
4. Relative humidity (RH) of the air used (28% and 80%).

Delivered dose testing was carried out using standard compendial methods to assess the impact of all four variables on drug delivery, relative to the label claim.

The results showed that blowing air into the device ahead of use has a negative impact in all scenarios but is especially problematic when the air has a high RH. The introduction of humid (RH 80%) as opposed to dry (RH 28%) air was found to make drug delivery more variable and unpredictable, and to reduce the average amount of drug delivered. Distance from the inhaler was the single most influential factor, with less than 50% of label claim delivered on average following the introduction of humid air at a distance of 0 cm, at all flow rates. At a distance of 5 cm, a similar deterioration in drug delivery was observed at flow rates above 30 L/min.

To investigate this effect in more detail, back-to-back aerodynamic particle size distribution (APSD) measurements were recorded. Here, introducing humid air at a flow rate of 60 L/min for a duration of 4 s at a distance of 5 cm was shown to decrease fine particle fraction (FPF), the >5 µm fraction of the dose, by approximately 40% relative to results obtained in the absence

of an exhalation step. This is attributable to clumping or agglomeration of the powder formulation and an associated increase in particle size.

FPF is a primary focus for OIP developers because of the tendency for particles in this size fraction to deposit in the lung. A low FPF is associated with reduced deposition in the lung and a corresponding decrease in clinical efficacy or a higher likelihood of over-prescribing and an increased risk of side effects. The magnitude of the potential impact of this common error in DPI use therefore highlights the extent to which effects beyond those routinely studied under the heading "typical patient usage" can compromise drug delivery. Analytical tools, such as Copley's Patient Exhalation Simulator (Figure 2), are correspondingly valuable for those working to eliminate potential consequences of misuse.

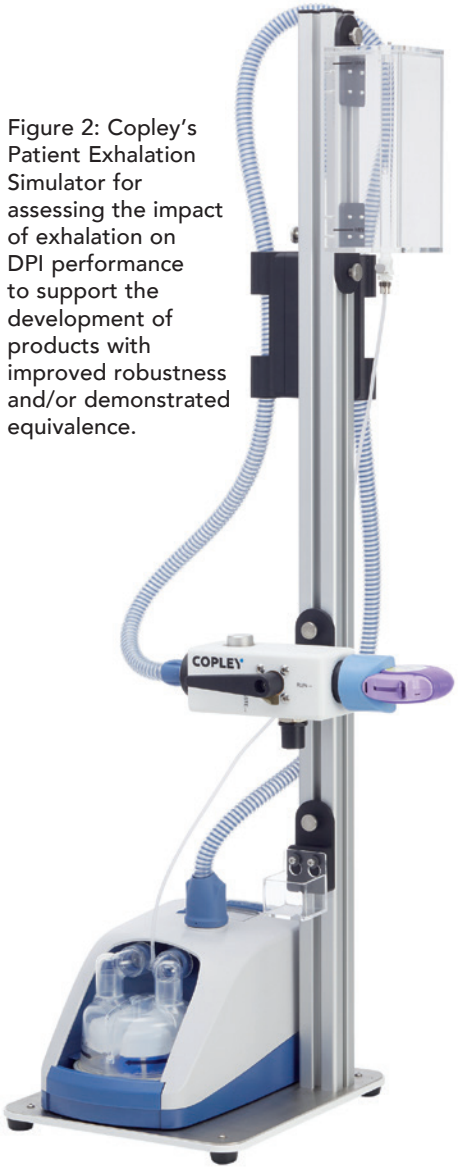

Figure 2: Copley's Patient Exhalation Simulator for assessing the impact of exhalation on DPI performance to support the development of products with improved robustness and/or demonstrated equivalence.

"THE MAGNITUDE OF THE POTENTIAL IMPACT OF THIS COMMON ERROR IN DPI USE THEREFORE HIGHLIGHTS THE EXTENT TO WHICH EFFECTS BEYOND THOSE ROUTINELY STUDIED UNDER THE HEADING 'TYPICAL PATIENT USAGE' CAN COMPROMISE DRUG DELIVERY."

TOWARDS PATIENT INDEPENDENT PERFORMANCE

Developing a better understanding of how OIPs and, similarly, nasal drug products work for different individuals applying different techniques is becoming a common theme across the inhalation community. FDA product-specific guidelines now routinely invite the use of small and large throats and representative breathing profiles to measure realistic APSDs and confirm bioequivalence in OIPs across a range of patient groups. Additionally, scoping the impact of device orientation is proving critical for those targeting regional deposition in the nasal cavities.

The focus of such studies is often the detection of variability and difference, but the same methods support efforts to develop products that are less sensitive to patient misuse – to go beyond existing definitions of robustness to ensure that products are designed from the ground up to work consistently for all patients types, even if technique is less than optimal. There is merit in making OIPs and nasal products of all types as robust as possible, and a growing number of testing solutions are being developed to support those looking to do so.

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Expert View

SHIELDED THERAPEUTICS: COULD POLYMERIC NANOPARTICLES SAFEGUARD A NEW GENERATION OF INHALED DRUGS?

Kamaal de Silva and **Dr Ethan Miller** of Springboard provide an overview of the benefits of polymeric nanoparticles in pulmonary drug delivery and their potential to overcome key challenges in respiratory medicine, while summarising the range of pulmonary delivery devices that could benefit from their use.

Polymeric nanoparticles (PNPs) represent a groundbreaking advancement at the cutting edge of pulmonary drug delivery, holding great promise for overcoming key challenges in respiratory medicine. Vital therapeutics, such as small molecules, proteins and nucleic acids, could be encapsulated in engineered nanoscale vehicles to evade the natural defences that protect critical areas of the respiratory system.

PNPs offer significant advantages for drug delivery over the more commonly used lipid nanoparticles (LNPs), which are at a more advanced stage across the industry. For example, Translate Bio's (Sanofi) MRT5005, an inhaled LNP carrying mRNA administered by nebulisation, is currently in the "Study to Evaluate the Safety & Tolerability of MRT5005 Administered by Nebulization in Adults With Cystic Fibrosis (RESTORE-CF)" Phase I/II trial. Compared with LNPs, PNPs provide greater stability, thus resisting enzymatic degradation and fusion in biological environments.[1] They also provide a wider variety of methods for controlled drug release and can be functionalised for targeted delivery. With good biocompatibility, reduced immunogenicity and improved mucus penetration, PNPs could present a more effective alternative to LNPs for pulmonary drug delivery.

"TO ACHIEVE THE RIGHT PARTICLE SIZE FOR THE APPLICATION, THE INHALATION DEVICE USED FOR DELIVERY OF PNPS MUST BE CAREFULLY CHOSEN OR DESIGNED TO ENSURE THAT THE DELIVERY OF THE THERAPEUTIC DOES NOT FAIL AT THE FINAL HURDLE."

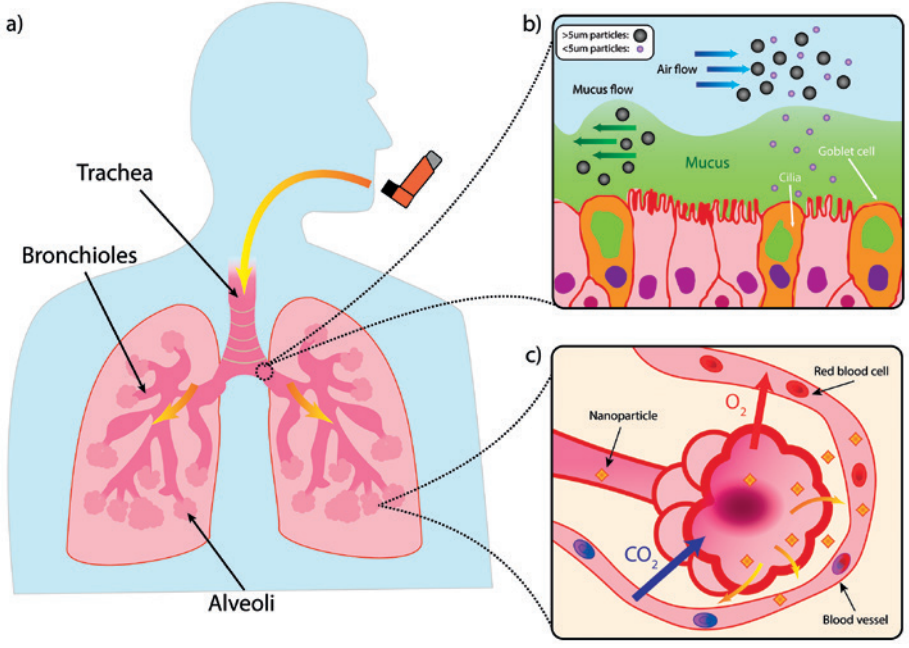

Figure 1: Structure of lung and mucociliary escalator. a) Simplified illustration of a lung. b) Illustration of mucociliary escalator clearing larger particles from the airways. c) Diagram of alveoli with large surface area to facilitate gaseous exchange but also provide route for systemic delivery of nanoparticles via the blood stream.

BREACHING THE FORTRESS

Drugs intended to have systemic effects must reach the alveoli – the deep lung region with a huge surface area totalling an estimated 140 m^2 and a rich blood supply, both of which facilitate gas exchange. To protect this vital function, the lungs have a unique and multilayered defence system that filters out any foreign invaders. Particles larger than 5 µm are subject to the mucociliary escalator; the self-clearing mechanism consisting of the mucous layer and cilia underneath, as shown in Figure 1.

While technically they may be able to "reach" the alveolar region due to their size, submicron particles (i.e. <1,000 nm-sized particles) have such low inertia that they would simply be exhaled.[2] PNPs therefore require a supporting medium to achieve particle sizes between 1 µm and 5 µm, which is the correct range for deposition in the deep lung via sedimentation.[3] The closer the particles can get to the smaller end of this scale, the better for alveolar access.[4]

To achieve this, inhalation devices are therefore designed to give a high fine particle fraction (FPF), which is the percentage of aerosolised particles <5 µm, and a low mass median aerodynamic diameter (MMAD); the representative diameter below which 50% of the particle population of an aerosol lies. PNPs could also have classical respiratory applications where the target may be the bronchi and bronchioles themselves, for example, facilitating the delivery of bronchodilators or corticosteroids.

To achieve the right particle size for the application, the inhalation device used for delivery of PNPs must be carefully chosen or designed to ensure that the delivery of the therapeutic does not fail at the final hurdle. Table 1 shows some potential options for PNP-based delivery devices.

Once the device has delivered it to its intended location in the lung, the PNP can then carry out its key functions, which could be a mixture of:

- Protecting sensitive therapeutics, such as nucleic acids and proteins, from degradation in the harsh respiratory environment to enhance their delivery efficiency. Respiratory mucus contains nucleases and proteases that would quickly degrade them via enzymatic attack.[15]
- Targeting specific cell types within the lung (e.g. tumour cells) using ligands placed on the shell, for example, antibodies or peptides.[3]
- Providing transport mechanisms for biologics that, if unprotected, would be immobilised by mucin fibres – PNPs with muco-inert coatings, such as polyethylene glycol (PEG), can reduce adhesion for better diffusion through the mucous mesh.[16]

Technology	MMAD (µm)	Suitability for Systemic Delivery	Suitability for PNP Delivery
Pressurised metered dose inhalers (pMDIs)	1.2–8	The technology is suboptimal due to generally larger-sized particles, inconsistent lung deposition rates (8–53%) and high oropharyngeal loss[5]	The high-pressure storage environment (~5.6 barg)[6] and high shear forces during actuation could disrupt PNPs
Dry powder inhalers (DPIs)	1.8–4.8	Particle sizes can be engineered to an optimal size, as is the case for MannKind's (CT, US) Afrezza (insulin) with an MMAD of 2.5 µm,[7] but lung deposition rates (7–69%) are highly dependent on the patient's inspiratory flow rate[5]	High suitability, inherent capability to avoid nanoparticle aggregation and enhance stability[3]
Soft mist inhalers (SMIs)	3.7	Produces a slow-moving mist with a FPF of 60% and lung deposition rate of 39–67%, excellent for deep lung penetration[6]	Excellent suitability, and Miao H *et al* (2023) showed that lipid nanoparticles, which are weaker against shear, can survive atomisation[8]
Thermal vaporisation (Ferrer's Staccato)	2	Generates an ultrafine aerosol with an FPF of 90%, enabling rapid alveolar absorption, without using any excipients[9] – currently US FDA approved for the delivery of loxapine, an antipsychotic medication	The heat generated during vaporisation is likely to degrade temperature-sensitive PNPs
Jet and ultrasonic nebulisers	2.1–6.8	Capable of providing small droplets,[10–12] but low lung deposition rates (5–13%)[13] mean that a lot of the drug will be wasted, and there may be a wide range in performance between device manufacturers	High shear forces can disrupt liposomes[4] but PNPs might be more resistant
Vibrating mesh nebulisers	3–5	Generates a uniform, slow-moving aerosol with high FPFs of 50–70%[14] for deep lung penetration	Demonstrated excellent suitability for delivering vesicles such as liposomes, and can even function to break up aggregates[4]

Table 1: Pulmonary delivery devices and their suitability for systemic and PNP delivery.

- Evading phagocytosis by macrophages by engineering the shell or surrounding matrix of the PNP, thus sidestepping one of the primary clearing functions of the innate immune system. For most microspheres, engulfment via macrophage is something to be avoided; however, there are some cases, such as vaccines, where triggering a macrophage response is the aim of the therapy.[17]
- Improving drug uptake into the cells via endocytosis-based pathways.[3]
- Translocating from the alveoli to the systemic circulation, which, for certain drugs, could remove the need for intravenous administration.[3]

NANOSCALE BLUEPRINTS

Figure 2 provides some examples of the wide variety of different PNPs that can be used in pulmonary delivery. Much of the literature categorises PNPs into two types:[19, 20]

- **Nanocapsules:** The drug is usually dissolved in an aqueous or oily reservoir, the release of which is controlled by a polymeric membrane wrapped around it.
- **Nanospheres:** A continuous matrix system where the drug is retained inside or adsorbed onto its surface.

Within the above categories, PNPs can be divided further into specific shapes, such as:[20]

- **Polymersomes:** Artificial hollow spheres (vesicles) with membranes built from amphiphilic block copolymers (e.g. PEG), which are comparable to liposomes – vesicles formed from naturally occurring lipids.
- **Polymer Micelle:** Also built from amphiphilic block copolymers that instead form nanospheres with a hydrophilic core and hydrophobic coating.
- **Dendrimers:** Hyperbranched polymers, such as polyethyleneimine (PEI), with complex 3D architectures. Active functional groups on the outer surface can be used to conjugate biomolecules and contrast agents for imaging. They are mostly used for the delivery of nucleic acids or small molecules, which can be enclosed within.

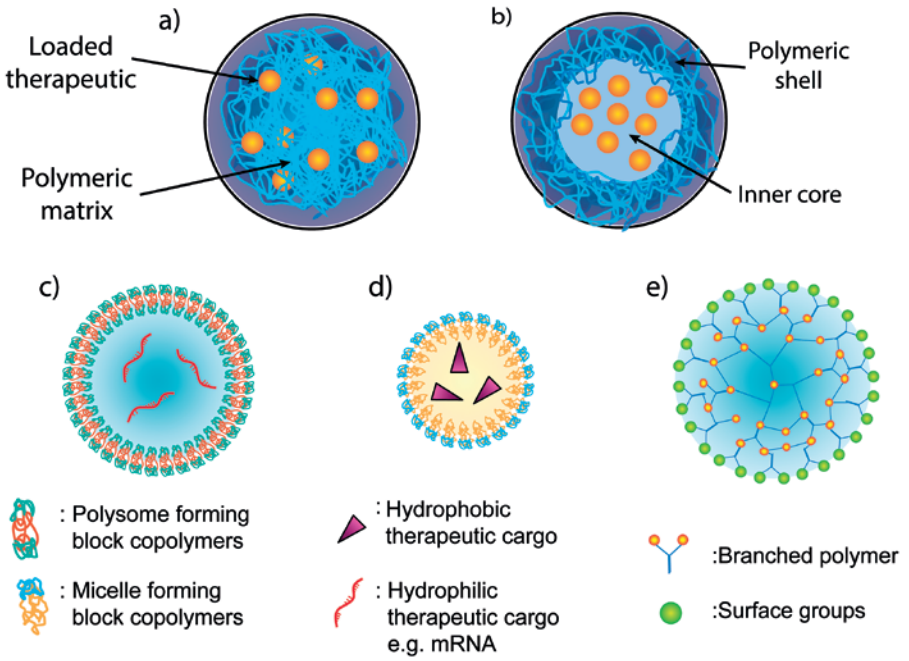

Figure 2: Different structures of PNPs. The main categories of PNP for pulmonary delivery are (a) nanospheres and (b) nanocapsules. Nanoparticles can also exist in various shapes, including (c) polymersomes, (d) polymer micelles and (e) dendrimers.

PNPs can be constructed from a wide range of polymer materials, examples of which are shown in Table 2, along with potential pulmonary applications that are currently under research.

SEMI-AUTOMATED ASSEMBLY

A multitude of different processes exist to create the PNPs in Table 2, which either involve monomer polymerisation as part of the process or the dispersion of pre-formed polymers. Polymerisation techniques, used for polymers such as poly(lactic-co-glycolic acid) (PLGA), polylactic acid (PLA) and polycaprolactone (PCL), usually involve the formation of an emulsion, which can go on to self-assemble into nanoparticles.

When using pre-formed polymers to form PNPs, such as polystyrene, polyvinylcarbazole (PVK) and poly(methyl methacrylate) (PMMA), a solvent is normally used, and precipitation of nanoparticles can be induced by removal of the solvent by evaporation/diffusion, adding salt or desolvation. In both categories of PNP formation, surfactants, such as polyvinyl alcohol (PVA) or crosslinkers, can also be used to control size and prevent aggregation, but need to be eliminated from the final product.[18]

Compared with the LNP processes used for covid-19 vaccines, which used microfluidics at small scale and were scaled up by using confined impinging jet mixers,[22] more steps are required to synthesise PNPs and, therefore, much more research is required to optimise them for mass production. PLGA and PLA are promising candidates for scalability, as these materials are widely used across the industry. Operti *et al* (2022) demonstrated an encapsulation efficiency of 80% for PLGA nanoparticles encapsulating celecoxib using sonication[23] and, in 2024, Maurizii

"INTERACTIONS BETWEEN PNPS AND BIOLOGICAL BARRIERS DEPEND STRONGLY ON THE PHYSICOCHEMICAL CHARACTERISTICS OF THE NANOPARTICLE SURFACE, SIZE, SHAPE AND HYDROPHOBICITY."

Type	Polymer	Mechanisms of Action	Potential Applications
Natural	Chitosan	• Mucoadhesion • Cellular uptake • Endosomal escape (proton sponge) • Intracytoplasmic release of payload	• Asthma • Lung cancer
	Gelatin	• Cellular uptake • Endosomal escape (proton sponge)	• Tuberculosis • Protein and mRNA delivery • Anti-tumoural
Synthetic	PLGA	• Mucoadhesion (with surface modification) • Cellular uptake • Endosomal escape (proton sponge)	• Cystic fibrosis • Asthma • Tuberculosis • COPD • Anti-tumoural • Drug delivery
	PLA	• Hydrolysis • Endocytosis • Endosomal escape (proton sponge)	• Drug delivery
	PEtOx	• Endocytosis	• Anti-inflammatory • Respiratory infections
	PCL	• Cellular uptake • Micropinocytosis • Late endosome	• Pulmonary inflammatory diseases • Pulmonary hypertension
	PEI	• Cellular uptake • Endosomal escape (proton sponge) • Nuclear uptake • Organelle disturbance	• Gene therapy • Lung tumour inhibition
	Polystyrene	• Cellular uptake	• Drug delivery
	PVA	• Cellular uptake • Macropinocytosis	• Respiratory infections • Smoke filtration • Nasal drug delivery

Table 2: PNPs with pulmonary applications.[21]

et al demonstrated 90% encapsulation efficiency for chitosan nanoparticles using microfluidic-assisted ionotropic gelation.[24]

FINE-TUNED FUNCTION

Interactions between PNPs and biological barriers depend strongly on the physicochemical characteristics of the nanoparticle surface, size, shape and hydrophobicity. One associated challenge is the electrostatic and hydrophobic interactions between PNPs and the mucus barrier, as well as exopolysaccharide biofilms present in the pulmonary tracts.[25] PEGylation of the PNP surface gives it a sufficiently hydrophilic surface and improves its ability to penetrate mucus and biofilm layers, enhancing drug delivery.[25] This technique was successfully applied to polyethylenimine-graft-poly(ethylene glycol) (PEI-g-PEG) nanoparticles acting as a nanocarrier of mRNA for gene transfection specifically targeting lung tissue in mice models.[26] Notably, these functionalised PNPs could be stored in lyophilised form at -20°C for over four months, without a measurable change in particle size or transfection activity, demonstrating exceptional stability.[26] Additionally, recent studies have even indicated that replacing PEG functionalisation of nanoparticles with zwitterionic polymers may also improve nebuliser stability and delivery efficacy, as well as reduce aggregation.[27]

PNPs can also be functionalised to exist more stably in the micro-environment of the lung. PNPs responsive to reactive oxygen species (ROS) have emerged as a promising platform for pulmonary drug delivery, offering targeted and efficient therapeutic modulation of lung injury microenvironments. When lung tissue is damaged, cells release large amounts of ROS into the lung microenvironment, which can lead to oxidative damage and increase inflammation and tissue injury.

In a 2022 study by Muhammad *et al*, this ROS response was used to hallmark lung injury and trigger therapeutic release from PNPs.[28] By incorporating ROS-sensitive linkages within the polymer matrix, PNPs loaded with anti-inflammatory dexamethasone can achieve more targeted drug release, improving local anti-inflammatory responses, minimising systemic exposure and maximising therapeutic efficacy. Compared with free dexamethasone, PNPs exhibit superior pharmacokinetics and biodistribution, maximising drug retention in pulmonary tissues while minimising off-target effects. This study highlights the promise of ROS-responsive PNPs as a game changer for treating lung diseases driven by oxidative stress, such as acute lung injury (ALI) and chronic obstructive pulmonary disease (COPD), opening the door for future breakthroughs in pulmonary nanomedicine.

"NANOPARTICLES CAN BE ENGINEERED FOR INHALATION DELIVERY, ENSURING DEEP LUNG PENETRATION AND PROLONGED THERAPEUTIC ACTION."

In pulmonary diseases such as COPD, pneumonia and ALI, thermally triggered PNPs can enhance drug retention in the lungs while reducing off-target toxicity. Additionally, these nanoparticles can be engineered for inhalation, ensuring deep lung penetration and prolonged therapeutic action.

A MINIATURE FUTURE

PNPs represent a paradigm shift in pulmonary drug delivery, overcoming physiological barriers through rational design. Their stability, modularity and compatibility with inhalation devices position them as versatile platforms for treating a huge range of conditions. Future studies must address scalability and toxicity challenges and continue to explore combinatorial therapies that harness the unique physiochemical properties of PNPs. In the future, it is likely that PNPs will play a central role in the evolution of inhalation technology.

ABOUT THE COMPANY

Springboard is a technology and design consultancy, which creates and develops new products and technology, including products in the field of medtech and drug delivery devices, assisting companies in resolving technical challenges and decreasing time to market. Springboard is part of the Sanner Group, which provides high quality, agile and cost-effective manufacturing for medical devices, including drug delivery devices.

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Kamaal de Silva, Principal Mechanical Engineer, is an experienced engineer who has led design and development projects at Springboard on a range of drug delivery devices, including infusion pumps, on-body delivery systems, autoinjectors, pen injectors and soft mist inhalers. He is committed to developing innovative solutions that enhance the user experience and improve healthcare outcomes. Mr de Silva studied Mechanical Engineering at Imperial College London, UK. His extensive experience has led to a comprehensive understanding of design, manufacturing and scientific principles that he can use to create robust, risk averse designs.

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