PULMONARY & NASAL DELIVERY

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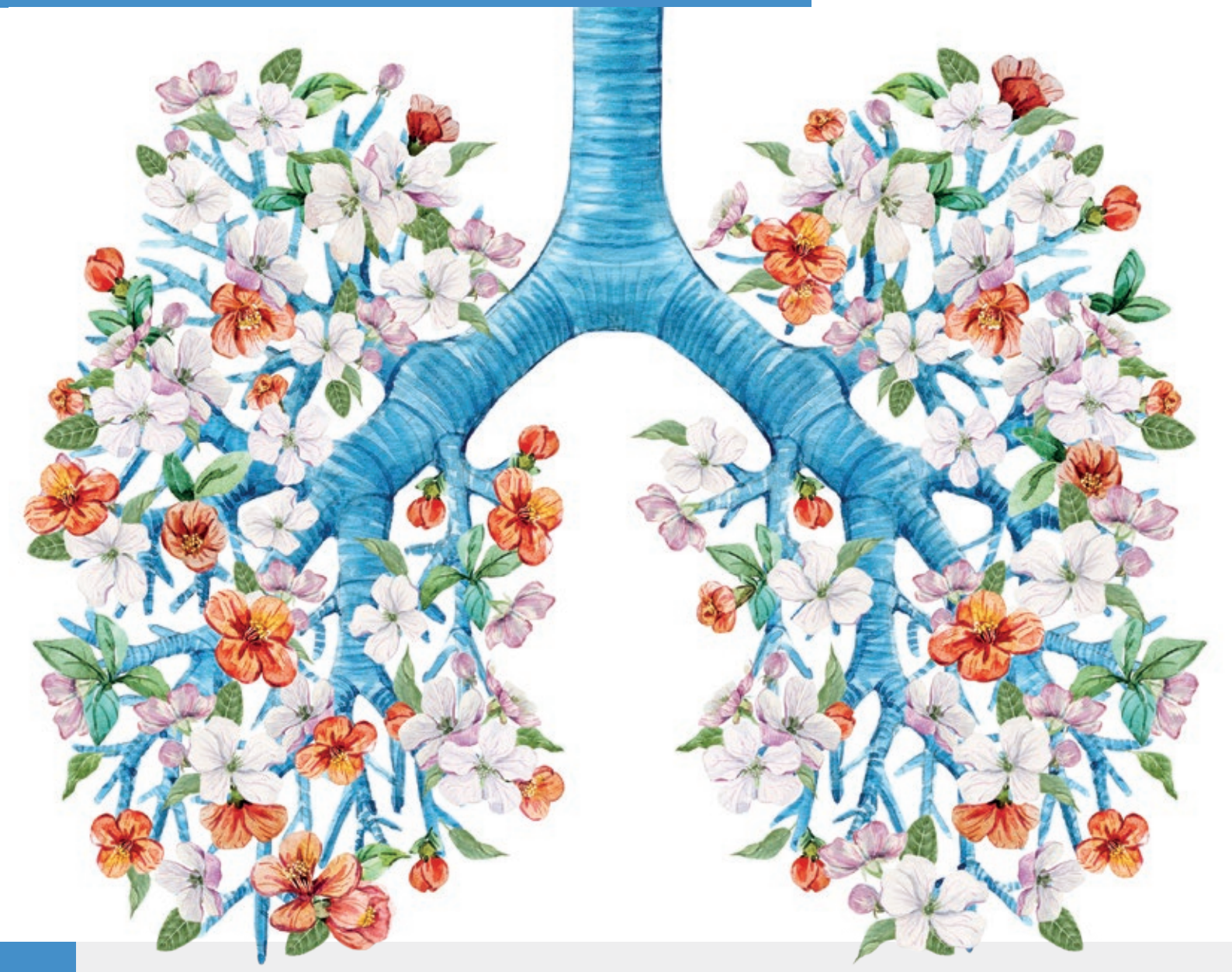

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ONdrugDelivery Issue N° 131, April 11th, 2022

PULMONARY & NASAL DELIVERY

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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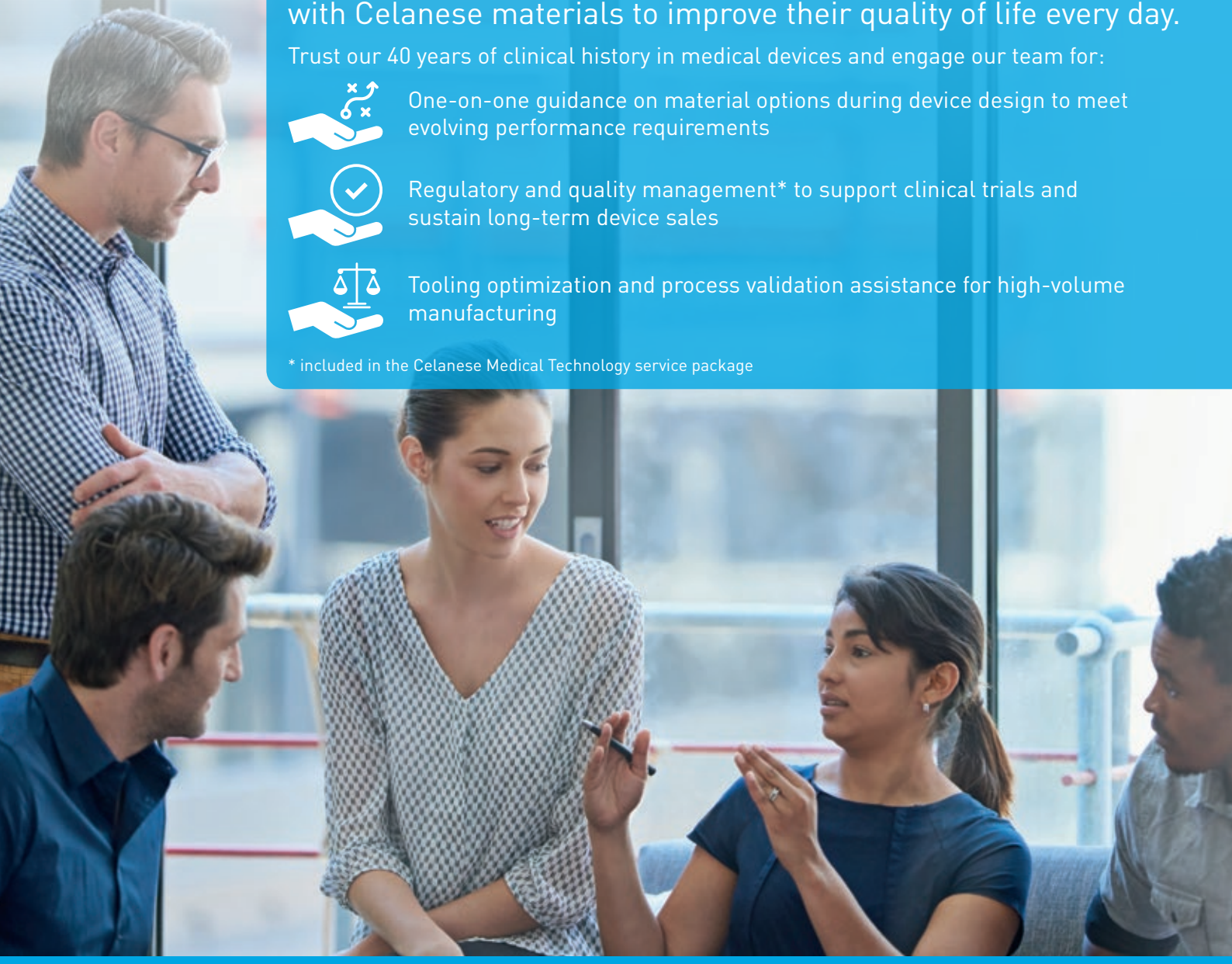

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WAITING WITH BATED BREATH – WHAT'S IN STORE FOR 2022?

Here, Rob Udale, Principal Engineer, Inhalation Lead, and Heather Jameson, Senior Engineer, both of Springboard, discuss the exciting developments taking place in the design of inhalation devices and share their predictions for the top five inhalation trends to watch as 2022 unfolds, and beyond.

SUSTAINABILITY AND GREENER LIFECYCLE MANAGEMENT

November 2021 saw the largest climate change conference of its type to date, COP26, bringing a new wave of eco-awareness that has permeated almost every industry. Medical engineering is no exception, and we are seeing early signs of a revolution in the sustainability and reusability of inhalation devices.

Over the last half-century, many drug delivery devices have been designed with disposability in mind. Disposability has its advantages:

- High-volume manufacture brings efficiencies of scale
- Single-use, disposable devices can have fewer use steps and can be easier to use
- It can be easier to guarantee user safety with a disposable device.

But if we look back to some of the first inhalation devices from the late 20th century, such as Boehringer Ingelheim's Aerohaler or GlaxoSmithKline's Diskhaler, we find a very different story. Those early devices were reusable with a loadable primary pack.

Now, in 2022, we are beginning to see a move "back to the future" and a return to those reusable devices (Figure 1). The driving forces for this move include:

- Patients and other stakeholders becoming more sensitive to the environmental impact of fully disposable devices, in particular that from plastic waste.
- The current generation of devices tending to be more complicated and costly than the previous generation. For example, pressurised metered dose inhalers (pMDIs) are now more likely to have a dose counter or a breath actuation mechanism. The economics of fully disposable devices sets an upper limit on their cost.

> "In addition to reducing the carbon footprint of individual inhalation devices, medical device companies are also increasingly committed to finding carbon-neutral manufacturing solutions and assessing the impact of their devices' full lifecycles."

Figure 1: The new reusable version of Boehringer Ingelheim's Respimat® has a 71% smaller carbon footprint after six months of use compared with its disposable counterpart.

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- The "connectivity" aspect of many new devices. The electronics and batteries that are typically involved lend themselves to reusable modules.
- Potential future changes in reimbursement structures to incentivise reuse.

In addition to reducing the carbon footprint of individual inhalation devices, medical device companies are also increasingly committed to finding carbon-neutral manufacturing solutions and assessing the impact of their devices' full lifecycles. It was fantastic to hear announcements at COP26 that FTSE100 companies, including AstraZeneca and GSK, are now committed to eliminating their contribution to climate change by 2050.[1]

This reinforces messaging earlier in 2021 when both AstraZeneca and Chiesi announced a commitment to develop pMDIs with near-zero global warming potential.[2,3] One way that manufacturers are planning to achieve this is by recapturing some of the embodied energy within the waste materials; Chiesi launched an inhaler recycling scheme in February 2021 that covers any inhaler from any manufacturer, which could reduce the waste caused by the 73 million inhalers prescribed each year in the UK[4] – change is afoot!

Highlighting this industry trend, Springboard has been working on several projects that aim to reduce the environmental impact of inhalation devices, frequently following methods defined in the ISO 14000 standard on environmental management. In line with this, lifecycle assessments should be undertaken and updated throughout the device development process to ensure that devices meet the requirements of both the end-user and wider stakeholders. We should expect to see more devices that:

- Are either reusable or have reusable subassemblies.
- Have reduced embodied energy due to the smart use of biopolymers and recycled plastics or the selection of materials and manufacturing methods that have reduced environmental impacts.
- Are designed with device end-of-life in mind, including active management of their waste streams – recover, reclaim and reuse are core imperatives here.

This is a trend that we very much hope to see continued in 2022.

SOFT MIST INHALERS

With Spiriva, a successful drug for the treatment of chronic obstructive pulmonary disease (COPD), beginning to come off-patent across the globe, several companies have designs for generic alternatives in the pipeline, from Merxin (King's Lynn, UK) to Softhale (Diepenbeek, Belgium), and we should expect other novel soft mist device platforms to follow (Figure 2). These companies will be looking to capitalise on the established properties that make soft mist designs so attractive, such as:

- Their aerosolised and propellant-free drug solutions are expelled in a slow jet, which reduces undesired oropharyngeal deposition.
- This slower jet velocity makes it much easier to perform the sequence successfully between actuation and inhalation.
- The aerosol fine droplet fraction from Respimat, a very successful soft mist inhaler, is reported to be approximately double that of a pMDI, meaning half the dose with a Respimat can achieve the same therapeutic outcome as the full dose administered by a pMDI.[5]

We could expect to see soft mist inhaler designs with new developments to the drug storage container that allow them to contain more doses and potentially to deliver ethanol-based formulations, such as corticosteroids. It is likely that new designs will also seek to minimise the need for overfilling, thereby reducing costs, especially for higher value drugs such as biologics – the third trend.

BIOLOGICS AND LARGER DOSES

Biologics for inhalation is another area to watch for in 2022 – continued growth and recent advancements in biologics and biosimilars[6] across industries (including parenteral drug delivery) are likely to filter through to the design and development of

> "Over the last decade, there has been a socio-medical trend towards reduced dosing frequency to minimise intrusion of therapies into patients' lives."

Figure 2: Soft mist inhalers are likely to become a staple of the inhalation market alongside DPIs and pMDIs.

> "Smart devices have been heralded as a major trend for the future for at least the last decade, and many will be wondering whether 2022 will be the year that finally brings their widespread adoption."

inhaled drugs and their delivery devices. An example of this is seen in the continued interest in technologies that offer non-parenteral insulin delivery solutions.

Additionally, over the last decade, there has been a socio-medical trend towards reduced dosing frequency to minimise intrusion of therapies into patients' lives. In recent years, a focus on delivering larger dose volumes has gone some way towards addressing this unmet need. Of course, solutions with reduced dosing frequency require a correspondingly greater focus on patient adherence, including technology that assists users through reminders and data tracking. Therefore, alongside the drive towards these larger doses, we will continue to see the trend towards smart inhalation devices.

Inhalation may become the delivery method of choice to address these advancements in 2022 and beyond. Of the inhalation platforms, dry powder inhalers (DPIs) and nasal delivery systems are well suited to large-molecule delivery, so expect exciting growth in this area.

CONNECTED HEALTH

Smart devices have been heralded as a major trend for the future for at least the last decade, and many will be wondering whether 2022 will be the year that finally brings their widespread adoption. Generally, the old adage holds true: "In the field of medical technology, evolution rather than revolution often wins out."

The drive towards reusable devices and the increased interest in delivering larger molecules with reduced dosing frequency may be the impetus needed finally to help establish smart inhalation devices. This progress will be incremental, as there are still significant challenges within device design:

- How to demonstrate value to the payer.
- How to tackle the issue of data collection and patient trust when very few consumers believe companies handle their data responsibly.[7]
- How to manage the device strategy – as a connected add-on or upgrade, or as a fully integrated device from the ground up.
- How to mitigate cybersecurity risks and navigate a regulatory landscape that is currently struggling to keep up with the rapid pace of development.

However, there are encouraging signs that these hurdles are being overcome. An example of this is Teva's CareTRx inhaler sensor, which is already being tested in the UK NHS.[8] Medical device manufacturers are realising the need for high-quality input data, gathered in a way that does not burden the end-user. Devices and their apps need to fit into patients' lifestyles, match their needs and have a prosumer experience in line with the world of consumer electronics.

Additionally, we may see a greater focus on device training incorporated within the user experience to tackle the issues of incorrect technique on the user's part, either external to device usage, such as through a connected app, or as an integrated feature.

NASAL INHALATION

The final trend to watch for in 2022 is nasal inhalation, a delivery method with huge growth potential (Figure 3). The market was valued at US$7.8 billion (£5.7 billion) in 2018 and is predicted to reach close to $12 billion by the end of 2025.[9] Nasal inhalation systems offer several attractive benefits:

- A less-invasive drug delivery method that is preferable to injections. Factors include ease of learning and use, device portability, safety and comfort.[10]
- Ability to deliver drugs across the blood-brain barrier.
- Faster absorption than is possible with enteral solutions.
- Better molecule survival rates than oral delivery forms.
- Best inhalation delivery method for larger molecule solutions, including biologics.

There is active research towards developing drugs that can bypass the blood-brain barrier to aid in treating conditions such as schizophrenia and epilepsy. Nasal inhalation offers a powerful solution; consequently, there has been recent interest in harnessing this delivery system to provide enhanced delivery of established molecules, such as ketamine and cannabinoids, which will likely have a faster route to market than novel chemicals.

Figure 3: Nasal drug delivery is set to be an area with huge potential for growth.

"Nasal drug delivery is a highly versatile method of administration for both local and systemic drugs, for emergency doses and managing long-term conditions, and in preventative vaccines."

One particularly pertinent use of nasal inhalation systems is that of vaccine delivery. Covid-19 has led to significant investment in the global vaccines market, and this can be expected to continue as co-operative international efforts to vaccinate developing countries get underway. Nasal inhalation of vaccines has several key advantages – needle-phobia affects 3.5%–10% of the UK population[11] and may drive vaccine hesitancy, and nasal vaccines are able to instigate mucosal immunity directly at the site of infection.[12]

Another important benefit lies within the "rescue treatment" setting. Numerous medical conditions call for swift drug administration and rapid onset. Using a nasal spray that provides a rapid onset is an ideal solution that can be used by anyone; examples can already be seen in emergency-use medications, such as naloxone for opioid overdose.

Finally, advancements in nasal inhalation have exciting implications for biologics research. Successful nasal delivery of peptides has already been demonstrated for the treatment of conditions such as osteoporosis, haemophilia and vitamin B12 deficiency. However, larger molecules continue to present a challenge to nasal inhalation methods due to the limited permeability of the nasal mucosa, and further research will be required to develop a solution.

Nasal drug delivery is a highly versatile method of administration for both local and systemic drugs, for emergency doses and managing long-term conditions, and in preventative vaccines. Key to this is the flexibility of the device to the drug's formulation (its suitability for water-based or hydroalcoholic formulations, suspensions, emulsions and powders) and the fact that the nasal devices tend to be convenient, discreet, easy to use and easy to carry.

To some degree, nasal inhalation does lag behind other inhalation devices in the incorporation of dose counters, locks and connected elements. We may therefore see more nasal delivery devices with these features incorporated in the future.

FINAL REMARKS

This article has outlined five key inhalation trends to watch in 2022. Some perennial themes emerge – connectivity, efficacy, safety, cost-efficiency and ease of use. There are also, however, themes that are products of the rapid changes the world has undergone over the last few years; primarily a renewed interest in alternative vaccine delivery methods and a commitment to sustainability and greener products that are hopefully here to stay.

ABOUT THE COMPANY

Springboard specialises in developing devices from concept to manufacture for regulated markets. The company is expert at creating innovative yet robust designs and solving difficult technical problems quickly. Springboard does not have internal projects so it is as fast and cost effective as possible, and the intellectual property belongs to its clients.

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Rob Udale is a Principal Engineer at Springboard, where he leads engineering and scientific teams developing new medical devices, including surgical tools, injectors and inhalers. He has been the named inventor on multiple patents and is a Chartered Engineer. He read Engineering at Cambridge University (UK), where he developed his background in both fluids and mechanics at the prestigious Whittle Laboratory. In developing devices, Mr Udale seeks to balance technical, user and commercial requirements to produce simple and robust solutions.

Heather Jameson is a Senior Engineer at Springboard, taking a leading role in planning and executing both design and test projects and has worked on the design and development of several drug delivery devices. She read Engineering at Cambridge University (UK), before completing a PhD in Fluid Mechanics at the distinguished Whittle Laboratory. She continues to play an active part in university relations in addition to her public speaking engagements on STEM and outreach.

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INVITATION TO PARTICIPATE IN STANDARDISATION OF PARTICLE MEASUREMENTS FOR PHARMACEUTICALS

In this article, Caterina Minelli, PhD, Science Area Leader at the National Physical Laboratory, discusses the importance of co-operation between metrology institutes and the pharmaceutical industry in the pursuit of improving analytical techniques and standards for the characterisation of particle attributes in drug development.

Innovation in the field of analytical technology and the standards for measuring particle attributes is a continual process, driven in large part by the importance of particles in the development and manufacture of pharmaceutical formulations. Characterisation of particles is central to ensuring the efficacy of many medicinal products, including dry powder inhalers, APIs, excipients within solid oral dosages, micro-particulates and both oil and solid phases in topical formulations. Advanced therapies that use liposomal and lipid nanoparticles, along with other nano preparations, are vital to treatments including anticancer therapeutics, vaccines and vectors for gene delivery applications. Particle characterisation is integral to understanding the performance and implementation of quality control for medicines.

The pace of innovation and the increasing complexity of particle-based products pose a substantial regulatory challenge and ensuring that the measurement infrastructure remains relevant and comprehensive is essential to enable new medicine development. It is not surprising, then, that the measurement technology serving the pharmaceutical industry is continuously evolving, and that standard bodies, regulators and national metrology institutes are proactive in developing the underpinning measurement infrastructure. The collaboration of such institutions with the pharmaceutical industry is essential for defining and prioritising measurement needs.

"The pace of innovation and the increasing complexity of particle-based products pose a substantial regulatory challenge and ensuring that the measurement infrastructure remains relevant and comprehensive is essential to enable new medicine development."

MEASURING CRITICAL ATTRIBUTES

There are many different characteristics, or attributes, of particles that can be measured. However, it is not always clear which of these attributes are critical to pharmaceutical product performance. Furthermore, the selection of which attributes should be measured may change during the lifecycle of a product, with many more attributes typically being measured in the development phase than in manufacturing control.

The type and specifications of analytical instruments employed also changes across the different stages of a product's lifecycle. During development, a detailed mechanistic understanding of a drug's mode of action or the performance of a formulation requires state-of-the-art measurement capabilities and expertise, which may be available in-house but is often accessed through specialist outsourcing partnerships. As a product progresses towards larger volume manufacturing, the number of measured attributes is reduced, while the quality infrastructure typically relies on analytical instrumentation that is available at the production site. Sensitivity, precision and accuracy requirements for the analytical instrumentation change in accordance with the product phase.

There is a wide variety of particle types used in therapeutic formulations and their constituent materials and no single analytical technique addresses all types of particles. Particle measurements during the product lifecycle may include physical

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and chemical characteristics, drug loading, release profile and particle fate in animal models, to mention just a few. Measurement methods are best used in concert to provide complementary pieces of information that, like the pieces of a jigsaw, may be combined to enable measurement experts to build a complete picture of a product. To reap the benefits of this synergistic approach, effort should be invested into ensuring that both sample preparation and measurement approaches are consistent across techniques to enable comparability.

"Knowledge of the changes that particles undergo with time and when exposed to different environments can enable a better mechanistic understanding of their mode of action."

It is important to consider that particles are dynamic systems and that their attributes may change with time or with the environment that they are exposed to. For this reason, particle formulation measurements must be taken with the particles in both their pristine state and in either simulated or real biological environments over time. Knowledge of the changes that particles undergo with time and when exposed to different environments can enable a better mechanistic understanding of their mode of action. In a similar way, it is useful to measure particles while exposing them to varying temperature and humidity levels in order to inform understanding of potential changes to the product during storage and ageing. Both of these examples involve significant complexity from a measurement technology point of view.

One aspect of this complexity is the challenge of measuring particles in matrices, including those of a biological nature. The ability to measure particle products in complex matrices requires that either:

- The particles are separated from the matrix prior to measurement
- The analytical method can distinguish between the particle and the matrix.

To address the first, significant effort is invested in developing preparative protocols and technologies that minimise changes to particle attributes during separation. These protocols tend to be designed on a bespoke basis for each product and matrix combination and the time needed for their development and validation should not be underestimated.

Methods that can distinguish the particles from the matrix include both imaging and spectroscopy. Among the available imaging methods, optical and electron microscopies are widespread but are best coupled with chemical strategies to identify the products within the matrices. For example, fluorescence dyes conjugated with the molecules of interest afford multiplexed fluorescence imaging, including super-resolution methods. Among label-free methods, some types of Raman spectroscopy and mass spectrometry enable the location and quantification of the product ingredients within biological cells and tissues or a medical device. Raman-based and fluorescence-based microscopies are also suited to *in vitro* imaging where, for example, the migration of active ingredients following their release may be observed and measured.

"A robust measurement infrastructure for pharmaceutical product development and manufacturing ensures that particle attributes can be compared over time and at different production sites with confidence."

BUILDING CONFIDENCE IN MEASUREMENTS

A robust measurement infrastructure for pharmaceutical product development and manufacturing ensures that particle attributes can be compared over time and at different production sites with confidence. This is essential for evaluating product consistency across different batches and changes due to ageing, as well as informing the decisions that will direct product improvements and diversification.

Documentary standards and reference materials underpin the confident use of analytical technology. Such standards are typically either expert reports or prescriptive protocols describing terminology, practice for sample preparation and measurement, and relevant aspects of data analysis. Importantly, documentary standards contain knowledge about the potential sources of errors in a measurement and enable the description of particle attributes in terms of values with associated uncertainties. Published standards are periodically updated to enable them to keep pace with innovations in measurement technology.

Standards result from significant expertise developed by measurement laboratories and instrument manufacturers, generally over a number of years, and are cowritten and internationally reviewed by measurement experts. Technical committees (TCs) relevant to particle metrology include the International Organisation for Standardisation (ISO) TC 229 – Nanotechnologies and TC 24 – Particle Characterisation; ASTM International E55 – Manufacture of Pharmaceutical and Biopharmaceutical Products and E56 – Nanotechnology; the European Committee for Standardisation (CEN) TC 352 – Nanotechnologies; and the British Standards Institution (BSI) LBI/37 – Particle Characterisation Including Sieving. Pharmacopoeias also contain practice and reference databases useful to particle analysis. The interactions across these technical committees are vital and it is not unusual for one expert to sit on many related committees, but harmonisation of standards could be improved through more effective co-operation between bodies.

Lists of published documentary standards are typically available on the websites of the standards bodies where they are available for purchase or through open access models. The standards body websites also often list the documentary standards currently under development; relevant examples include a document to define liposome-related terminology (ISO/AWI TS 4958), a guide to measuring nanoparticle agglomeration and aggregation (CEN/TC 352) and a guide to characterising the encapsulation, extraction and analysis of mRNA in lipid nanoparticles (ASTM WK75607).

To prepare for the development of a documentary standard, it is usual to complete one or more inter-laboratory studies or round-robin comparisons. Depending on the type of study and the nature of the organisations involved, the primary focus of the study may alter. For example, participation in the highest level of inter-laboratory comparisons organised by the International Bureau of Weights and Measures (BIPM) is restricted to designated national measurement institutes (NMIs) and the focus is on the accuracy and reproducibility of the measurement.

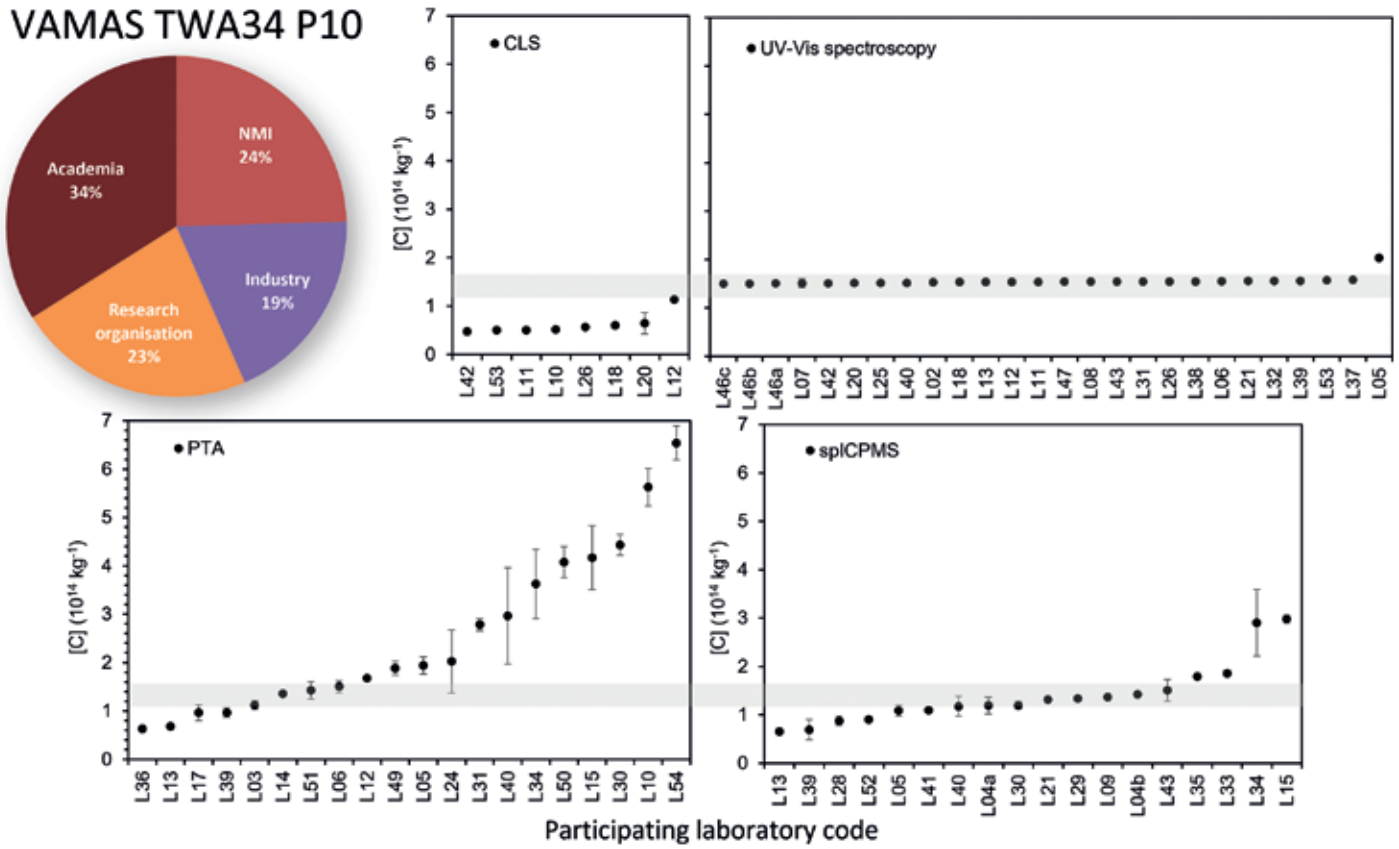

Figure 1: Outcome of the VAMAS TWA 34 Project 10 inter-laboratory comparison on the measurement of the number concentration of colloidal gold by centrifugal liquid sedimentation (CLS), UV-visible spectroscopy, particle tracking analysis (PTA) and single particle inductively coupled plasma mass spectrometry (spICPMS). The pie chart shows the background of the laboratories enrolled to the study. The pie chart shows the background of the laboratories participating in the study.

Organisations such as the Versailles Project on Advanced Materials and Standards (VAMAS) encourage wider participation from industry, academia and research laboratories with a primary focus on comparability in measurement results and on testing of sample preparation and measurement protocols prior to standardisation. The outcomes of BIPM studies are used to enable the participating institutes to generate approved calibration and measurement capabilities (CMCs) and to state the attributes of certified reference materials (CRMs) with a clear uncertainty statement in both cases. Both CMCs and CRMs are the highest point of reference for evaluating measurement outcome.

Inter-laboratory comparisons open to a broader community of participants, such as those run under VAMAS, are required to establish and disseminate best practice, underpin and test documentary standards, and benchmark participating laboratories' measurement capability. For example, Figure 1 shows the outcome of a large VAMAS interlaboratory study organised by the National Physical Laboratory (NPL) on measuring the number concentration of colloidal gold.[1] The study provided objective data to compare practice and performance associated with five independent methods and to cross-validate independent measurement approaches, which is important for regulatory purposes.

The study clearly highlighted that some methods have very small between-lab variability, suggesting them as methods of choice for quality control purposes. However, where accuracy is required and for other types of particles, the choice may be different. Not all methods are suitable for all materials and particle size ranges; some materials may become unstable upon dilution or samples may be expensive and limited in volume, which imposes different methodological requirements. The outcomes from this study are currently being incorporated into a draft ISO technical report (ISO/DTR 24672) scheduled for publication in late 2022. Through this ISO document, best practice for particle number concentration measurement will be available to the entire community.

An important aspect of a VAMAS study is that the publication of its datasets, combined with the commercial availability of the test materials, offers a straightforward route for laboratories to benchmark and demonstrate the performance of their measurement capability. Confidence in measurement capability enables faster development and more robust quality frameworks and product regulatory submissions. For this reason, there is a need to extend inter-laboratory comparisons to a broader selection of particles that mimic the attributes of real particle-based products more closely, and which are dispersed or distributed in relevant matrices.

INVITATION TO COLLABORATE

ISO/DTR 24672 is just one of the many efforts that the particle metrology community is engaged in with the intention of continuing to develop a robust measurement framework to underpin product development, manufacturing and regulatory approval. There is a need to maintain such frameworks' relevance and fitness for purpose. This is a significant challenge considering the fast pace of innovation in pharmaceutical products and the fact that documentary standards are usually developed over several years.

There is a need to grow the channels of communications between the pharmaceutical industry, the metrology community and regulators to inform the discussion on product innovation and

> "There is a need to grow the channels of communications between the pharmaceutical industry, the metrology community and regulators to inform the discussion on product innovation and standardisation needs."

standardisation needs. For example, particle-based products are increasing in complexity, becoming more structured and sophisticated in the way they deliver their therapeutic cargo while improving their safety profile. Efforts to develop a robust metrology framework in biology are underway but are relatively new, with more work needed to fully standardise measurement methods supporting *in vitro* and *in vivo* testing.[2] Finally, the step change promised by the digitisation of the industry requires robust documentary standards that establish a common vocabulary and enable the implementation of findable, accessible, interoperable and reusable (FAIR) data principles.

ABOUT THE AUTHOR

Caterina Minelli, PhD, leads the UK National Physical Laboratory's research into the development of the metrology underpinning the industrial exploitation of particle systems, with a focus on development and manufacturing of pharmaceuticals and nanomedicines. She acts as a UK expert in a number of standard technical committees, including the ISO TC229 (Nanotechnologies), ISO TC24/SC4 (Particle Characterisation) and ASTM E56.08 (Nano-enabled Materials). Dr Minelli developed her professional career working for private and national laboratories across the globe. She complements her research experience through insightful secondments, including within the former UK Department of Business, Innovation and Skills to work on the development of the Government Science and Innovation Strategy.

Stronger collaboration between NMIs, industry, governments and regulators will accelerate the pace of innovation and the commercialisation of particle-based products, from paediatric medicines to new vaccines. Initiatives such as inter-laboratory studies are an excellent vehicle for collaboration. There is a need for the industry and measurement development scientists to engage at early stages of product development to identify challenges, understand the complexities involved and start developing the next generation of analytics capable of tackling such obstacles to innovation. There are some excellent examples of funding schemes made available by governments around the world to foster this co-operation, but more strategic routes to embed the work of NMIs within industrial innovation must be opened. Finally, the pharmaceutical industry and regulators play a critical role in determining measurement priorities, directing the metrology community to develop methods, standards and reference materials that can accelerate the delivery of improved therapeutics and ultimately bring improved outcomes to patients.

ABOUT THE COMPANY

The National Physical Laboratory (NPL) is the UK's national metrology institute, developing and maintaining the national primary measurement standards. It is a public corporation owned by the UK Department of Business, Energy and Industrial Strategy and is part of the National Measurement System, which provides the UK with a national measurement infrastructure. NPL undertakes excellent science and engineering to deliver extraordinary impact for the UK and provide the measurement capability that underpins the UK's prosperity and quality of life. From accelerating new antibiotics and more effective cancer treatments to developing unhackable quantum communications and superfast 5G, NPL expertise is crucial in researching, developing and testing new products and processes.

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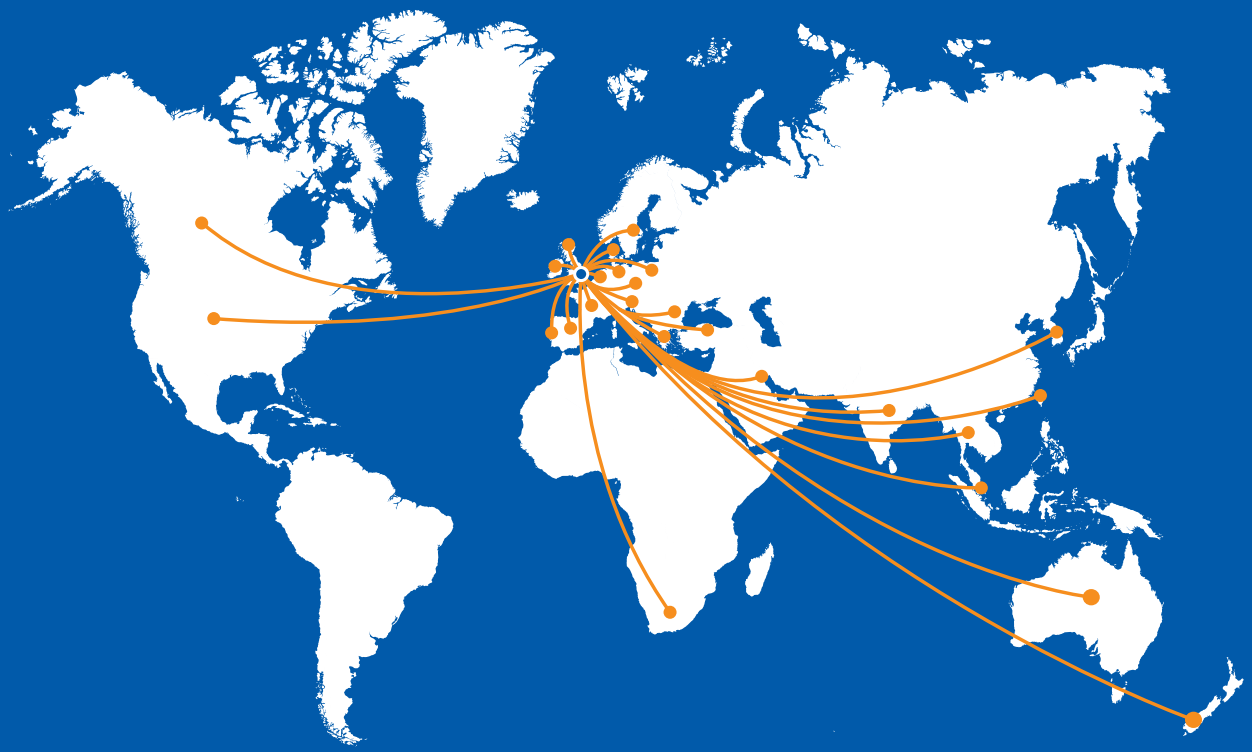

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INTERVIEW

In this exclusive interview, Jon Lenn and Jon Volmer, both of MedPharm, talked with Guy Furness, Publisher of ONdrugDelivery, about the importance of nasal modelling, focusing on MedPharm's own nasal cavity modelling technology, MedCast, its unique characteristics and benefits and the value it brings to the company's offering for nasally delivered products.

JON LENN, PHD CHIEF SCIENTIFIC OFFICER

Jon Lenn, Chief Scientific Officer, MedPharm, has direct responsibility for the company's global scientific operations. Since joining in 2015, he has led MedPharm's development of cutting-edge performance models for assessing the penetration and activity of clients' products targeted towards key biochemical pathways. He has played a critical role in MedPharm's growth, as well as the development and success of the US facility.

Dr Lenn has more than 15 years' experience in developing dermatological projects with Connetics, which was acquired by Stiefel, itself subsequently acquired by GSK, and has been directly involved with the development and approval of eight products. He received his PhD on the topical delivery of macromolecules from the University of Reading, UK.

JON VOLMER, PHD SENIOR DIRECTOR OF RESEARCH BIOLOGY & INNOVATION OFFICER

Jon Volmer joined MedPharm in 2016 to generate new technologies, systems and biological models and expand MedPharm's capabilities for serving the needs of current clients, as well as to expand the company into new areas of expertise. He has more than 15 years' experience developing a variety of biological models and technological lab support equipment in fields including immunology, microbiology, pulmonary disease and mechanical modelling.

Dr Volmer received his PhD on the biochemical basis of inflammatory remodelling in the lung from the University of Texas Graduate School of Biomedical Sciences (TX, US).

"If you design a nasal delivery system properly, you can hit the olfactory bulb, which can result in rapid delivery of the drug directly to the CNS."

Q To start with, can you give us a broad overview of what advantages the nasal route offers for drug delivery?

JV Nasal delivery is rapid, relatively painless and easy for the patient to administer, especially compared with injections. From a delivery perspective, the nose is highly vascularised, especially around the turbinate regions, so the nasal route is very attractive for systemic delivery. There's also a moist surface for the formulation to cling to, so the drug can easily diffuse across the barrier and then get into the systemic circulation.

That's only the beginning, however. One of the more exciting aspects of nasal delivery is that it can access the central nervous system (CNS). If you design a nasal delivery system properly, you can hit the olfactory bulb, which can result in rapid delivery of the drug directly to the CNS. So nasal delivery gives you a way to get drugs into the CNS that you simply can't get any other way.

Thinking about practical applications, nasal delivery is well-suited for emergency medications, such as delivering naloxone to counteract opioid overdoses. You can use a nasal spray on someone who's unconscious; you just spray the device in their nose while they're breathing and the medication will take effect. Of course, the rapidity of nasal delivery is also a huge advantage in emergency situations; when a crisis occurs, you want the medication to kick in as quickly as possible – nasal delivery is perfect for that.

It's also one of the few alternatives to injection for getting a large molecule into systemic circulation. Nasal delivery won't work for all large molecules but it's certainly viable for much larger molecules than, for example, topical administration via the skin. You can even get some proteins across the nasal epithelium.

Of course, there's also interest in the nasal route from a vaccine perspective. With vaccines, you've got all the advantages

I've outlined already – speed, little pain, systemic delivery and so on – coupled with the fact that the nose is often a primary route of infection for the diseases you're vaccinating against, which is a major plus. Nasal vaccination is definitely a trend I think we're going to see a lot more of.

JL To expand on that from the formulation side, nasal delivery has the advantage of not having to deal with a cornified barrier, instead you have active and passive transport that, in practice, simplifies the formulation approach. Compared with the skin, the obstacles you need to overcome to deliver a drug successfully via the nasal cavity are significantly less challenging. You do have to deal with mucociliary clearance, but that's much easier to deal with than the protective barrier, or stratum corneum, of the skin.

Q Let's discuss modelling. Briefly, why is it useful to model the nasal cavity when developing drugs for nasal administration?

JL When you're looking at a drug-device combination product, you can examine and test the geometry and characteristics of the spray and the formulation as it comes out of the device. However, if that's all the information you have, then you have to make some assumptions on where it is going to go when you spray it inside the nasal cavity. As such, you're somewhat limited if you're trying to deliver the formulation to a very specific location or if you want good data on how much drug is really being deposited at the target site.

That's where physical modelling comes in. Conceptually, what we have done is create a physical 3D model where you can insert a device, spray the formulation and then break apart the main components of the cavity, extract the drug and quantify how much drug has been deposited in the different compartments, as well as potentially what may have gone into the lung. Therefore, modelling the nasal cavity allows formulators and device designers to access additional information that enhances their ability to optimise their product.

JV Modelling is particularly helpful for formulations that are trying to hit the olfactory bulb. If you're targeting systemic delivery, it's relatively easy to hit the turbinates, which iswhere you typically target delivery to get a drug into the systemic circulation. However, getting a drug through the nasal cavity to reach the olfactory bulb takes a specialised device. There's also the inverse, where you're targeting systemic delivery but need to make sure that the drug doesn't hit the olfactory bulb at all – drugs where you do not want it going to the CNS. These two scenarios are where physical modelling is especially important because it offers that knowledge and increased awareness of exactly where the drug is being deposited in the nose.

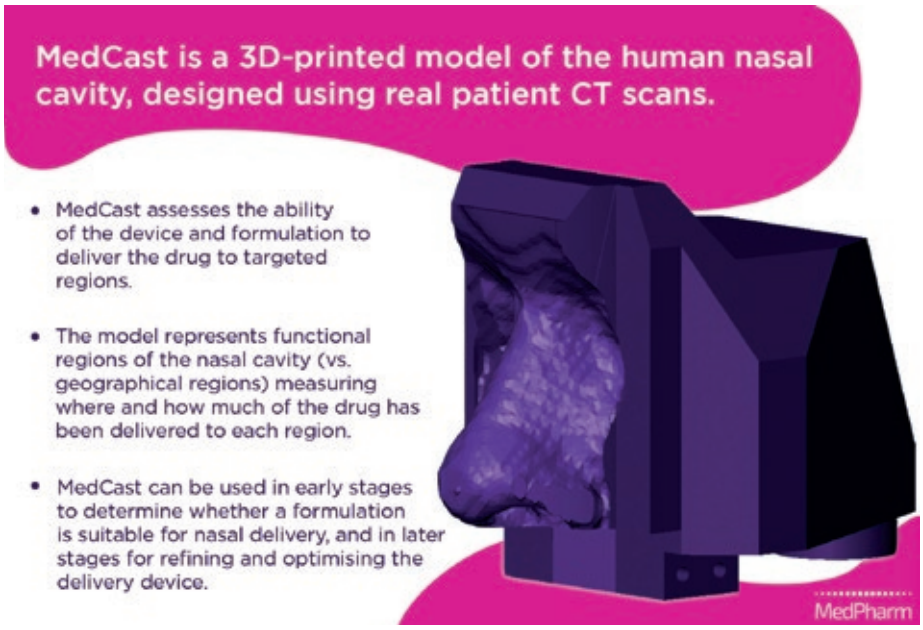

Figure 1: Digital render and summary of the MedCast model.

Q Getting into the specifics, can you give our readers some detail on MedCast, MedPharm's own nasal cavity model?

JV We started with CT scans of people's heads and applied specialised modelling software to build digital 3D models, which we use as the basis of MedCast (Figure 1). We can then use 3D printing to make models out of various materials, which allows us to look at which materials are best suited for the chemistry of a specific drug-formulation combination. This variety of available materials gives us the ability to make sure that whatever material we're using to make the MedCast in a specific instance will be able to bind the drug, hold onto it and then release it for analysis without modifying the device geometry.

In terms of function, we can use a controlled airflow system in conjunction with the MedCast so that it models inhalation, exhalation or held breath, depending on how the nasal delivery device is intended to work. Then we administer the drug into the model and the drug distributes through it as it would in a patient's nasal cavity. We can then disassemble the MedCast and quantify the drug deposition in the regions of interest.

There are other nasal models similar to MedCast but, generally, they divide the nose by geographic region – for example, upper, middle and lower. In contrast, MedCast divides into functional regions, which we identify based on anatomical cues from the specific CT scans that we use. This matters because it is the functional region that determines whether you're going to get local, systemic or CNS delivery,

"With MedCast, we can take the model apart into the specific functional regions for a specific modelled nose and then extract the deposited drug from each to see a relative ratio of drug in each functional region, which is what you really want to know from a drug delivery standpoint."

"Then you have further variation within each patient group and, with MedCast, we're aiming to get a representative sample across those differences."

or if the formulation is going to go down into the lung. With MedCast, we can take the model apart into the specific functional regions for a specific modelled nose and then extract the deposited drug from each to see a relative ratio of drug in each functional region, which is what you really want to know from a drug delivery standpoint. The ability to design MedCasts based on a cross-section of the population further reduces the risk once the device hits a real human population.

This plays a large part in why we're using individual CT scans – MedCast is not just one model, it's multiple models, all from different patient categories. For example, men and women are going to be different, children and adults are going to be different. Then you have further variation within each patient group and, with MedCast, we're aiming to get a representative sample across those differences. So, depending on how detailed you want to be, we can use multiple different models based on the target patient demographic for a given drug.

JL An interesting note from the design process is that we've found that the model works best when we make the front part of the nose out of a pliable material. With the early prototypes, we quickly realised that, if you made the nostrils too hard, the model wouldn't accept a device properly. Once we started making the front out of more pliable material, we were able to play around a little bit with the orientation of a device if needed. The end result being that you have the added advantage where, while not perfectly realistic, MedCast is close to what the front part of your nose would feel like.

Q How does MedCast sit within MedPharm's operations as a CDMO?

JL As a CDMO, we're able to put an additional level of rigour into development, analysis and increasing throughput that wouldn't necessarily be possible if innovation and modelling weren't built into our processes. With MedPharm, a partner can come to us and we can help them get their API into a device and start testing it, and MedCast is a key part of that – it's all in-house, which allows us to optimise our development programmes and really get the most out of them.

JV MedCast is useful in multiple ways for drug development. First off, you can use it right at the start of development to determine whether or not a formulation is suitable for nasal delivery in the first place – you don't want to get to the stage where your formulation is in a nasal delivery device only to realise that it's the wrong delivery route. Then, when you get a formulation that is suitable, MedCast is ideal for refining and optimising the device so that it delivers the formulation where you want in the quantity you want.

Q To round things out, let's discuss MedPharm's operations more broadly. Can you give us an overview of where MedPharm sits within the drug delivery sphere and what your core competencies are?

JL At a very high level, MedPharm's core expertise is topical and transdermal. We've put all our effort into that specific niche so that we're able to focus on really developing expertise that wouldn't be possible if we diluted our attention across more delivery routes. To clarify, we define topical administration as delivering a compound locally to a tissue, and then transdermal delivery is interfacing with epithelium, aiming to deliver the drug into the systemic absorption. With these definitions, we're somewhat agnostic when it comes to the epithelia in question – it can be the skin, the nose, the eyes or any other easily accessible mucosal epithelium.

This focus strongly influences how we approach everything, from formulation design to the biology itself. It also means that we're able to develop very specific models for the routes of administration we excel in. Going back to MedCast as an example, we also have a reconstructed model of the nasal epithelium built from primary human nasal epithelial cells that helps to get a clearer picture of the biology. Coupled with practical data on deposition during delivery in the MedCast, we can help optimise that formulation and really de-risk a development project before it gets into the clinic. So, these are all preclinical and non-clinical assays that we highly recommend to make sure that you have the best formulation and device prior to undertaking expensive clinical trials.

"MedPharm has the advantage that we are able to do all of this in-house. By performing a broad sweep of development tasks co-ordinated under one umbrella, you reduce the risk of losing information while it's being transferred from one group to another."

> "Developing that robust and rigorous package in order to enter the clinic is what we do best."

JV MedPharm has the advantage that we are able to do all of this in-house. By performing a broad sweep of development tasks co-ordinated under one umbrella, you reduce the risk of losing information while it's being transferred from one group to another. That can be a significant problem if, for example, you have one group working on the formulation, another on the device and yet another running tests with a nasal cavity model. So, while we're working on a nasal formulation, in addition to doing performance testing with MedCast, we can also be looking at irritations, potential adverse effects in the epithelium, delivery through the nasal epithelium and, in some cases, drug effect assays.

JL In summary, developing that robust and rigorous package in order to enter the clinic is what we do best.

Jon Lenn and Jon Volmer will be running a workshop entitled "De-risking Pharmaceutical Nasal Development Programs" at RDD 2022, Orlando, FL, US, on May 3rd. They would be pleased to see you there.

ABOUT THE COMPANY

MedPharm is a global contract provider of topical and transdermal product design, formulation development and manufacturing services. MedPharm's experts excel at reducing risk and accelerating development times for proprietary and generic pharmaceutical customers through its unique, cost-effective and industry-leading performance-testing models. Well-established as the global leader in dermatology, mucosal membrane and transdermal product development, MedPharm can also offer innovative, proprietary solutions for ophthalmic and airway preparations. MedPharm has facilities in both the UK and US.

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NOSE-TO-BRAIN DRUG ADMINISTRATION AND A NOVEL APPROACH WITH AN OLD FAMILIAR

Here, Marie-Christine Klein, PhD, Head of Development & Regulatory Affairs, and Andreas Bilstein, PhD, General Manager, both at URSATEC, and Rouven Kraus, Head of Sales at Aero Pump, look at the advantages of the nose-to-brain route and soft mist nasal sprays for drug administration.

Bestselling intranasal drugs mostly cover the locally acting symptoms of colds and allergies. However, nasal drug delivery opens up a sophisticated plethora of possibilities, based on the anatomical advantages of the nasal cavity and its close proximity to the blood-brain barrier (BBB) – the brain protector and stressor of drug administration.

In contrast to other organs where a vivid exchange of molecules between blood and organs exists, the brain tissue is separated from the blood by the BBB, which consists of different cell types that fuse to an extremely tight barrier. The BBB's physiology is such that only very small, lipophilic molecules, or molecules with their own specialised transport systems in the brain epithelium, can overcome it. This means that, on one hand, the BBB can be viewed as an evolutionary marvel, effective at safeguarding the brain against pathogens and toxins and creating a highly specialised environment. But on the other hand, from the point of view of pharmaceutical therapeutics, the BBB can be seen as a barrier in the negative sense, hindering effective drug targeting of brain-associated disorders of the central nervous system (CNS). To open the BBB pharmacologically to facilitate drug uptake is both difficult and dangerous because it is always accompanied by the danger of an ingress of toxic plasma proteins and, as a consequence, neurotherapeutics. Sometimes, drug design is able to adapt or exploit these special circumstances, but most of the potential neurotherapeutics (roughly 98%) will not be able to reach their intended target.[1]

ANATOMY OF THE OLFACTORY REGION

One possibility to bypass the BBB and enter the brain is drug administration via nerval structures that invade the brain, the so-called trigeminal and olfactory pathways. Zooming into the anatomy of the upper respiratory tract, the close connection of the brain and the nasal cavity becomes obvious.

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The nasal cavity and its mucosa are essential for passaging and purifying inhaled air. The very anterior region of the nose, the so-called vestibular region, has a surface of ~0.6 cm^2, and its main mission is to filter inhaled particles with the nasal hairs.[2] The prefiltered air flows further along the cavity in the respiratory region. This region, covering the majority of the nasal cavity with a volume of ~130 cm^2, is highly vascularised tissue.[2] That means many small blood vessels innervate the epithelium underneath and enable an extensive exchange of molecules, which is also important for systemic administration of drugs.[3] The respiratory region has interfaces with branches of the trigeminal nerves that originate in the brain and provide a direct connection to the CNS.[4]

In the respiratory region, intruding particles such as dust or bacteria are trapped by the mucus and transported towards the throat. This is facilitated by various cells producing and transporting mucus, resulting in mucociliary clearance. Further, molecules that enter the nasal cavity are dissolved in the mucus and transported to a specialised region in the nasal cavity, the olfactory region. It lies in the very roof of the cavity (Figure 1) where the olfactory mucosa has a unique structure. It is interspersed with olfactory neurons that access the molecules that are transported to the olfactory region in fluid film – a perfect environment for odorous molecules. The nervous anchors of the neurons congregate to form the olfactory nerve and provide a direct connection from the nose to the brain. Simplified, molecules that enter the nose are translated in the brain into the sense of olfaction.

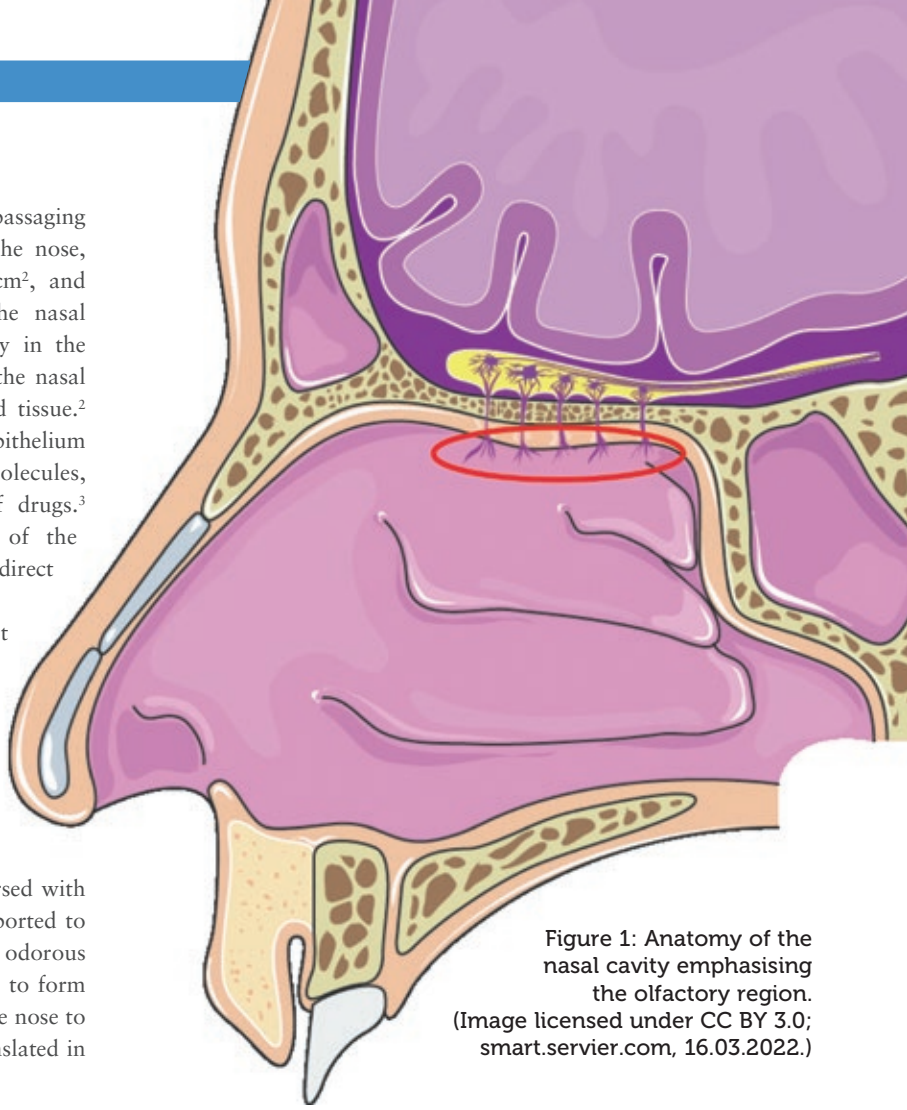

Figure 1: Anatomy of the nasal cavity emphasising the olfactory region. (Image licensed under CC BY 3.0; smart.servier.com, 16.03.2022.)

NOSE-TO-BRAIN ROUTE OF DRUG ADMINISTRATION: CHANCES AND LIMITATIONS

The nose-to-brain route of drug administration combines a lot of advantages. The possibility of bypassing the BBB opens up a noteworthy research area for the treatment of neurodegenerative diseases for which promising data already exist, e.g. on Parkinson's disease[5] or intranasally administered insulin for memory loss.[6] The very common and established use of nasal sprays or drops supports self-administration and, at the same time, good treatment adherence. Moreover, the risk of infection is diminished and a vast number of side effects from invasive methods, such as intracerebroventricular administration, which is used to apply chemotherapeutics to circumvent the BBB, are eliminated.

Another advantage of the intranasal route consists of overcoming the hepatic first-pass effect that results in higher bioavailability of the drug, in a lower dosing and, consequently, in fewer side effects. The limitations of the nose-to-brain target route are mainly the anatomically given small volumes (25–200 µL) that can be applied to the nasal cavity, which may limit the use for potent drugs. Moreover, the driving force of the ciliated cells of the respiratory cavity towards the pharynx, the so-called mucociliary clearance, limits the drug interaction time with the epithelium and is also influenced by the chemical nature of the drug molecule and its formulation. Chemical properties, such as the polarity, the pH value and the viscosity, play a crucial role in drug formulation for intranasal applications.

> "Another advantage of the intranasal route consists of overcoming the hepatic first-pass effect that results in higher bioavailability of the drug, in a lower dosing and, consequently, in fewer side effects."

A major task for future research in this area is to formulate drugs that can overcome the limitations of intranasal administration in general and the nose-to-brain target route specifically. Key to this will be an adequate and formulation-compatible delivery system that allows a targeting of the olfactory region within the nasal cavity.

DELIVERY OF DRUGS TO THE OLFACTORY REGION

For effective drug uptake by the nose-to-brain pathway, the formulation is dependent on both the chemical and biological ability to permeate the epithelium and drug deposition in the olfactory region. To derive characteristics that allow an approximated prediction of effective targeting, some technical performance factors influencing the deposition need to be taken into consideration. These characteristics would be the droplet size distribution, aerodynamics, the plume geometry and the spray pattern of the administered nasal drugs.

Data from laser diffraction allow the evaluation of the spray distribution generated by the applicator system of choice. If small droplets <5 µm are generated, they will not usually stay in the nasal cavity but will find their way to the lower respiratory tract. The higher the droplet size, the more anterior parts of the nasal cavity will be targeted. It is not clear what is the best droplet size to reach the olfactory region but there are suggestions that a diameter of ~10 µm may be favourable.[7]

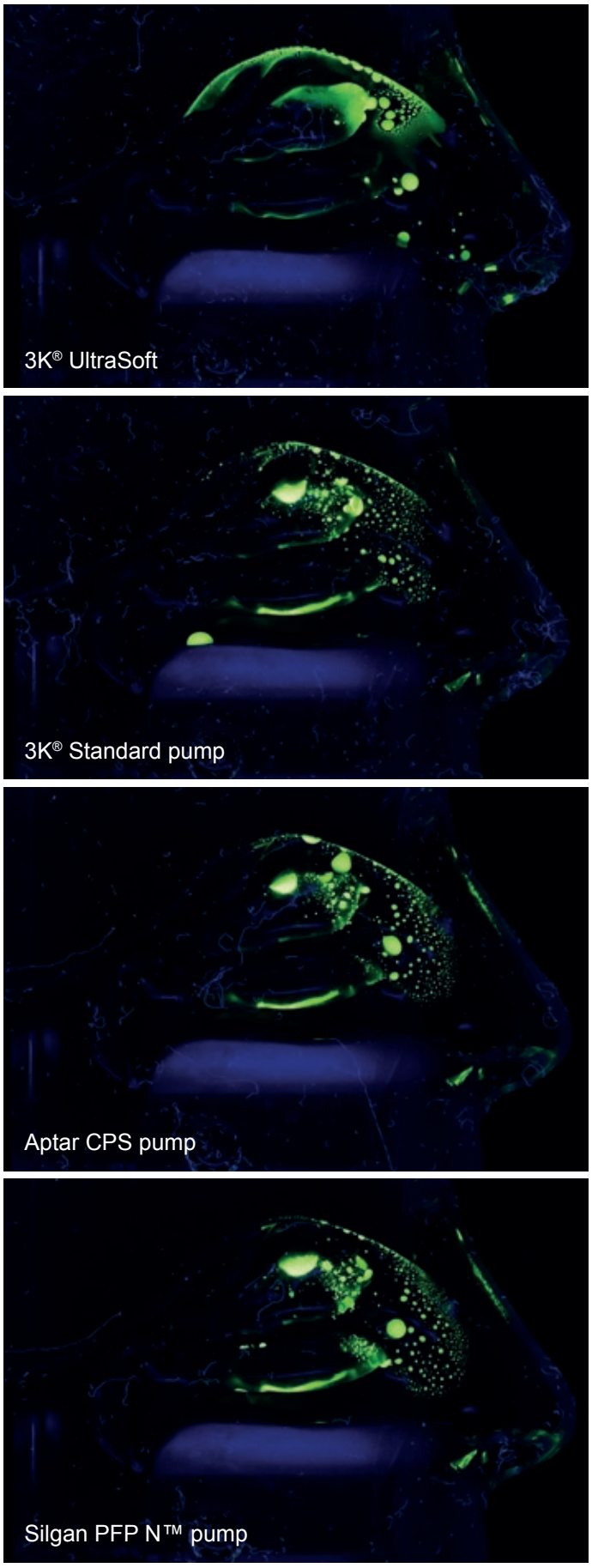

Figure 2: Comparison of different pumps concerning their distribution pattern of an aqueous solution in a Koken® nasal cast under continuous air flow of 15 L/min.

Standard nasal sprays, which are commonly used for treating local pathologies such as nasal constriction and allergy symptoms, mainly have a spraying profile that generates droplets >50 µm that are deposited with a high velocity. To target the olfactory region with its small surface fraction of the total cavity (5.2 %),[8] a well-balanced droplet size must be created that ensures the deposition mainly at the entry of the nose and, at the same time, excludes deposition at the very anterior part to prevent a quick removal.[9]

"Using a pump that unites the short actuation time and easy handling of a standard spray pump, and a distribution pattern that resembles a nebulising system applied over several minutes,[10] is a winning alternative."

An easily accessible model to gain the global information on spray deposition in the whole respiratory tract is the Koken® nasal cast (Koken Co, Toyko, Japan) model. Although limited by being based on the anatomy of one individuum, it allows the deduction of the deposition profile of a formulation applied to the model. Allocating the cast in different fractions representing, for example, the olfactory region, the vestibule and the turbinates may be an advantage in fine tuning the formulation in the respective application system and provide a winning tool in the formulation development.

The strong correlation of the deposition profile in the upper respiratory tract and aerodynamics suggests that liquid nebulising could be an optimised means of targeting the olfactory region by combining low velocity and smaller droplet sizes.[10]

SOFT MIST NASAL SPRAY AS A NEW TOOL FOR DRUG ADMINISTRATION

Established nasal spray pumps are limited in their ability to fulfil the described drug delivery needs. Therefore, using a pump that unites the short actuation time and easy handling of a standard spray pump, and a distribution pattern that resembles a nebulising system applied over several minutes,[10] is a winning alternative. Together with Medspray (Enschede, the Netherlands), a soft mist nasal spray pump has been developed that combines the nebulisation technology with an easy, effective and well-known application system, a 3K® metered dose nasal spray pump. A set of pilot data is depicted in Figure 2 and compares different pumps in their distribution pattern of an aqueous solution with a fluorescence dye. The evenly spread spray mist of the 3K® UltraSoft pump reaches every compartment of the nasal cavity, including the olfactory region. This is an outstanding result, which may result from the long actuation time (~1 sec) in combination with small droplet size distribution of the spray pump compared with the other pumps under examination.

Since the intranasal application is highly dependent on both anatomical differences of the nasal cavity between individuals and their actuation behaviour, two different spray angles were tested regarding their ability to target the olfactory region. The results are shown in Figure 3.

Compared with the other spray pumps tested, the standard 3K® pump achieved the best coverage of the olfactory region (14%).

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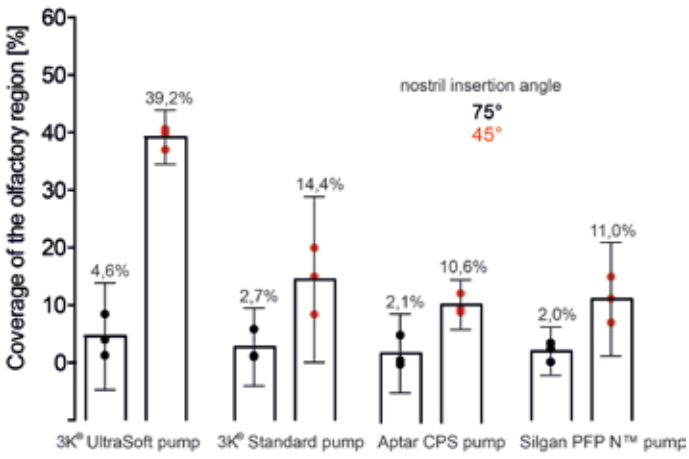

Figure 3: Influence of different spray angles and different pump systems in the coverage of the olfactory system by quantification of an aqueous solution distributed in a Koken® nasal cast.

A further remarkable increase and optimised coverage of ~40% of the olfactory region was achieved by the soft mist pump when the spray head was inserted into the nostril with an insertion angle of 45°. This is an astonishing result considering that the olfactory region represents only ~5% surface fraction of the total nasal cavity.

For future research, it is reasonable to assume that by using the soft mist spray pump and generating an evenly spread distribution pattern over the whole respiratory region, a positive effect on the intranasal systemic target can also be achieved, as the velocity and droplet size are ideal to overcome the anatomical and application constraints due to the slow application and reduced spray force with less impaction.

CONCLUSION

The nose-to-brain route of drug administration via nasal spray combines some powerful advantages of drug availability, being a fast-onset treatment solution with high bioavailability, the potential to reduce side effects and self-administration with a perfectly easy and safe usability profile.

In contrast to explanation-intensive and costly systems dedicated to a nose-to-brain application, the soft mist generating spray pump could be a solution for nose-to-brain applications and exert an advantageous impact on the therapeutic possibility of brain-associated diseases. Moreover, it could also be an uncomplicated added value for a plethora of indications and may also generate better systemic uptake of existing drugs. Further, the ability to combine the soft mist pump with either a preservative-free or a preserved pump set-up results in a versatile application spectrum.

ABOUT THE COMPANIES

URSATEC GmbH was founded in 1993 to accomplish one mission: the establishment of preservative-free applications based on its proprietary packaging systems in different application areas, primarily nasal, dermal, buccal and otological fields. Having sold almost two billion units within the last 25 years, URSATEC systems are widely established. URSATEC is consistently expanding its business and offers full development service, dosage systems, primary packaging materials and filling services for OTC and Rx applications to the healthcare industry.

Aero Pump GmbH was founded in 1976 and is headquartered close to Frankfurt (Germany) airport. Aero Pump is a leading manufacturer of high-precision application systems for the pharmaceutical and healthcare industry, focused on innovation, multifunctionality and contemporary design. Its spray pumps and dropper systems are widely established in the market and are primarily used in nasal, ophthalmic, pulmonary and dermal fields, suitable for preserved and preservative-free OTC and prescription drugs.

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Andreas Bilstein, PhD, has been Managing Director of URSATEC since August 2020. He is a biologist and has more than 15 years of experience in developing preservative-free products for various applications.

Rouven Kraus has more than 10 years of experience in the drug delivery market. He started his career in sales for a domestic iron foundry in Mainz, Germany, and joined Aero Pump in 2012 to augment the sales of the company's drug delivery device portfolio. In his role, Mr Kraus manages global sales as well as the strategic approach to new developments and delivery technologies.

BREACHING THE BLOOD-BRAIN-BARRIER WITH PARTICLE-BASED NASAL DELIVERY SYSTEMS

Here, Tom French, Delivery Device Project Manager at 3P innovation, talks about the advantages of the nasal drug delivery route and crossing the blood-brain-barrier to treat central nervous system diseases.

New developments in particle science and powder filling technology have enabled pharmaceutical researchers to explore a new range of nasally delivered drugs. Administration via the nasal route means that these drugs can successfully cross the blood-brain-barrier (BBB) to address the as-yet unmet medical needs of patients suffering from a variety of central nervous system (CNS)-based diseases.

> "Recent developments in particle engineering have resulted in the ability to produce a dosage form that overcomes all the previously mentioned obstacles. It is now possible to produce powders of significantly reduced particle size."

Within the pharmaceutical and medical sector, there are a number of well-known and long-established drug delivery routes. These include intravenous, subcutaneous, pulmonary and the use of oral solid dosage forms. In addition, nasal administration is currently witnessing significant growth. Delivering drugs via the nose has shown remarkable advantages, including a rapid and high systemic availability, the avoidance of first pass metabolism by the liver and the possibility of targeting drugs directly from the nasal cavity to the brain.

Furthermore, by avoiding the gastrointestinal (GI) tract, patients generally experience fewer side-effects. However, getting the dose right is critical. Compared with the lungs and the intestines, for example, the nasal cavity has limited ability to accommodate dose absorption through the mucosal membrane. As such, any formulation must be relatively small in size and highly concentrated to be successful.

Despite these technical challenges, nasal administration presents opportunities to address large patient populations that traditionally have had very few treatment options. Key therapy areas with unmet needs include Parkinson's, multiple sclerosis, Alzheimer's, dementia and a number of other CNS-based diseases. Most treatments are only able to address the symptoms and provide palliative care because they are unable to cross the BBB.

However, recent developments in particle engineering have resulted in the ability to produce a dosage form that overcomes all the previously mentioned obstacles. It is now possible to produce powders of significantly reduced particle size.

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In addition, these can be formed with hollow centres, such that the overall weight and density are also reduced – often by an order of magnitude. Compatible with traditional spray drying technologies, these particles can be produced using spray-freeze drying and even 3D printing. Of key importance, however, is their ability to cross the BBB, avoid the GI tract (reducing side-effects) and remain in the limited area of the nasal cavity long enough to be absorbed.

There are challenges to overcome; the drug needs to be present in the right area of the nose long enough to be efficacious; compared with the huge surface area of the GI tract or the large volume of the lungs that's normally available for respiratory drugs, the surface area of the nose is very small. As such, the dose needs to be small, concentrated and accurate. Beyond the benefits already mentioned, the novel particles also exhibit higher levels of stability compared with, for instance, classic large molecule drugs, parenterals and biologics.

The significant differences between human and animal physiologies often makes it hard to correlate data between them, particularly in terms of stability testing, but the new powder particles have successfully demonstrated their ability to be stored safely in nasal delivery devices. 3P innovation is currently working on several novel vaccine delivery systems, including a nasal one. This means that, in powder form, the company can eliminate all the previously necessary cold chain requirements, making distribution easier and more cost-effective.

Being developed as a single-use self-applied vaccine, it can be sent out all over the world and enable people to inoculate themselves. In light of the recent and ongoing covid-19 pandemic, this is a significant breakthrough that could positively affect thousands if not millions of lives. The delivery system (a plastic nasal inhaler) is also more sustainable than complex injection systems (vials, stoppers, crimps, syringes, needles, etc).

Yet, because these particles are both small and hollow, they are also very delicate. Of paramount importance for their effective use is the ability to process them without affecting their characteristics. Because the dose size, concentration and weight are all critical, it is necessary to weigh every single dose and minimise any work induced by the processing equipment. Unfortunately, the physical properties of the powders that make them efficacious also make them unsuitable for processing by conventional powder-dispensing technologies. Most dosing technologies influence powder properties due to the fact that they rely on compaction or insertion – involving the application of energy or force – which could potentially damage a friable or fragile formulation.

> "For the device to deliver the concentrated microdose both accurately and repeatedly to the small surface area of the nasal cavity, it's imperative to protect the very delicate particles and ensure that their physical characteristics are unaffected."

Furthermore, as well as being susceptible to water, these particles have a high surface-energy-to-mass ratio, meaning that they are highly cohesive, flow poorly and are prone to compaction. Their hydroscopic nature causes surface adhesion, which, along with a very low bulk density, adversely impacts device performance. As mentioned prior, typical dosing technologies can compact the powder and damage the particle structure. So, given that avoiding compaction would result in less complex device requirements, a low-shear, non-compacting dosing technique was needed, otherwise nasal delivery of such powders could be rendered infeasible without a suitable powder-dispensing technology.

What is required is a powder dispensing technology that is gentle (low shear and compaction) and ideally gravimetric in nature, such that every dose is weighed precisely. These powders cannot be compacted or crushed. For the device to deliver the concentrated microdose both accurately and repeatedly to the small surface area of the nasal cavity, it is imperative to protect the very delicate particles and ensure that their physical characteristics are unaffected. (Figure 1).

There are not many technologies that can dose these powders into devices at such small dose sizes without impacting the particles and even fewer that can dose them accurately and repeatably enough to produce a manufacturing process that is economically viable. 3P innovation's patented Fill2Weight technology, which was originally developed for similar inhaled particles, enables nasal delivery of these engineered particles. It is no accident that the company has seen significant interest in its equipment for nasal drug delivery applications.

WHAT IS FILL2WEIGHT?

3P innovation's proprietary gravimetric platform dosing technology employs a multiparameter control system to ensure

Figure 1: Close-up of 3P's Fill2Weight gravimetric filler in their R500 Robotic Capsule Filler.

consistent and controlled flow, which is essential to achieve accurate dosing (Figure 2). By design, very little powder is contained within the dispensing head, such that the energy required to control the flow of the powder is minimised. Conventional volumetric systems (dosator/vacuum, dosator/tamping, pin/auger) compress the powder to achieve accurate dosing. Unfortunately, this leads to a level of consolidation. This is less than ideal for an inhaled or nasally delivered powder and, worse than that, fragile particles can be badly damaged.

At a basic level, Fill2Weight is a pin in a hole – a simple valve. The pin is lifted to open the valve. Unfortunately, most powders would simply bridge above the opening in the valve. However, the pin spins and has miniature stirrers just above the valve that prevent bridging and, even though most powders would still bridge here, the tip of the hopper is connected to a piezoceramic actuator that generates controlled vibration to prevent bridging. This is very similar to tapping a salt cellar to promote flow.

The pin opening, stirrer speed and vibration (frequency and amplitude) are all accurately controlled in response to feedback from a high-speed precision weighing device. Fill2Weight is controlled such that the system can initially open the valve to a high value to dispense inaccurately and quickly, then, as the target weight is approached, the valve can close to a slower and more predictable flow. This "two-slope" control strategy enables both speed and accuracy. The very localised application of vibration ensures that powder blends are not segregated or damaged. Unlike conventional powder dispensing technologies, Fill2Weight does not damage spray-dried particles and microspheres, which are ideal for efficacious nasal drug delivery.

> "Unlike conventional systems, Fill2Weight adjusts for changes in a powder's physical properties, including drying, taking on moisture (caking), aerating or densifying."

Figure 2: Fill2Weight – 3P's award-winning gravimetric platform dosing technology.

Real-time measurements during the dosing process ensure accuracy and, of course, every dose is check-weighed. Increasingly, clinical batches require 100% weight verification, which comes as standard with Fill2Weight. A custom-designed algorithm controls in-process dose parameter adjustments to improve dose consistency throughout the batch to overcome any inconsistencies, such as powder density variations in the feed hopper. Unlike conventional systems, Fill2Weight adjusts for changes in a powder's physical properties, including drying, taking on moisture (caking), aerating or densifying. Fill2Weight takes these changes in its stride by adjusting process parameters automatically.

Fill2Weight is also scalable – the number of heads can be increased to match production outputs with a need for tech transfer or traditional scale-up. This is why, at the design stage, Fill2Weight was designed to be as narrow as was practical; multiple Fill2Weight heads can be aligned next to each other above a production line in a compact arrangement. Being able to ramp up production from the bench to the clinic is critical for a new drug. Not only that, it can significantly reduce the regulatory approval timescale and expedite the drug-device matching process. These nasal products rely on a suitable drug delivery system that often has to be designed from scratch – they're frequently brand new and have never been used before (Figure 3).

DE-RISKING NOVEL NASAL DRUG DELIVERY PROJECTS

The commercial viability of nasal drug delivery has been enabled by novel manufacturing techniques (such as 3D printing), breakthroughs in material science and the development of engineered particles. The last piece of the puzzle is the ability to manufacture cost-effectively at clinical and commercial scale. The right equipment is absolutely necessary to assemble devices and fill this completely new drug delivery system. Companies may be looking for something that doesn't actually exist yet and need to produce it at small-, mid- and large-scale, which is something that 3P innovation can assist with.

Custom device assembly plays a large part in drug delivery, but successfully transferring a novel product through clinical trials and on to commercial manufacture and assembly at the various scales required can be challenging when there is no prior example to learn from.

De-risking production processes from a very early stage is essential. A balance needs to be reached between planning to scale without committing huge amounts of capital and quickly moving through the various approval phases without purchasing dedicated equipment. Projects are generally broken down into stages to protect the device owner from large capital outlay when significant unknowns exist due to the clinical landscape. However, very few companies can afford to wait 12 months between Phase I approval and implementing Phase II for a machine to be built!

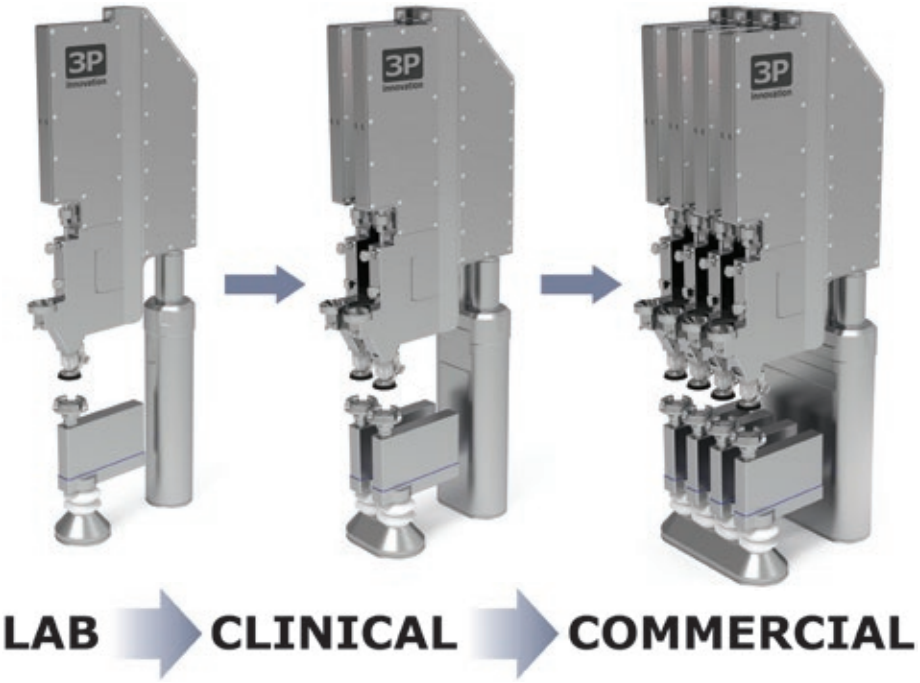

Figure 3: Fill2Weight is flexible and scalable.

"With the use of robots to replace human operators to expand production capacities rapidly, a small-scale investment can easily be subsequently augmented to cope with increasing demand during the clinical trial process."

The appropriate use of automation provides the answer. 3P innovation has developed a methodology of scaling automation from manually actuated benchtop equipment for early phase and clinical supply. By thinking about scaling at the outset, these processes can be later scaled-up or scaled-out as necessary for commercial supply. With the use of robots to replace human operators to expand production capacities rapidly, a small-scale investment can easily be subsequently augmented to cope with increasing demand during the clinical trial process. Additional tracks can be added over time to multiply outputs and extra machines can be installed to enhance output even further while spreading any perceived risk across multiple manufacturing lines.

CONCLUSION

This article has discussed how unmet clinical needs can be met by nasal delivery. Nasal delivery devices not only provide a convenient method of self-administration but their simplicity leads to improved compliance and adherence. This is particularly important as ever more clinical trials become decentralised. The initial driver of this growth in nasal delivery was developments in particle engineering that enabled superior efficacy. More recently, innovative powder dispensing technology has overcome the challenges associated with manufacture.

These technical advances have paved the way for the use of cold-chain-free vaccines and the treatment of a variety of CNS diseases. These simple devices also require fewer physical resources in their manufacture, leading to more sustainable vaccine delivery. In turn, they also reduce the burden on hospitals and healthcare systems around the world, as a highly trained healthcare professional is no longer required to deliver an injection. Furthermore, not needing patients in a specific location to run clinical trials and having tighter control of dose delivery offers many benefits, including reduced risk of over- or under-dosing, less waste and improved compliance. Advantages of the nasal route include avoiding needle phobia and improved adherence with single-use devices, which helps overcome some of the problems associated with geriatric participants.

Yet, to manufacture any kind of drug-device combination at scale requires a great deal of time and investment to navigate development, production and commercialisation steps. 3P innovation offers a powerful combination of standard technologies and machine platforms with custom automation skills and methodologies that provide the optimum mix of tailored solution with proven technology for the its customers. 3P innovation is very excited about the future of nasal drug delivery and its benefits for the planet.

ABOUT THE COMPANY

3P innovation is a life sciences engineering and custom automation company. The company works collaboratively with pharmaceutical and medical device customers to develop and industrialise new products through the design, manufacture and support of production equipment. Based in a purpose-built facility in Warwick, UK, this award-winning business employs over 70 people and services a multinational customer base with machines installed worldwide. Its specialisms include aseptic processing machines, powder and liquid filling technologies, and custom device manufacture, assembly and testing.

ABOUT THE AUTHOR

Tom French is Powder Devices Project Manager at 3P innovation Ltd and is responsible for leading a team of engineers focused on medical device design and industrialisation projects for powder-based therapeutics. Mr French has experience working on a large number of device-based projects with a range of multinational clients, from concept ideation through to commercialisation, leading core design work on drug delivery devices and underlying process development. He is team lead on DfM/DfA consultancy for medical devices in the parenteral and inhaled space with a focus on injection-moulded components, and is responsible for the process development, experimental design, testing and results analysis for a wide range of novel manufacturing processes. Mr French has extensive powder filling experience with a large range of technologies across both the inhaled and injectables landscape.

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ADDRESSING SYSTEMIC DELIVERY WITH A UNIT-DOSE NASAL SPRAY

In this article, Audrey Chandra, Category Project Manager, and Raphaële Audibert, Global Category Manager, Ear, Nose and Throat, both at Nemera, discuss the benefits of a unit-dose nasal spray for rapid treatment in an emergency.

Systemic-acting drugs are commonly administered through the injectable route. Rapid onset tends to make injection the most efficient route, especially in crises and life-threatening situations. It allows the medication to enter the bloodstream directly with accurate dosing and higher bioavailability than oral administration as it bypasses the hepatic metabolism.

Injections are invasive so normally require healthcare professionals' intervention. For instance, intravenous self-administration could be trickier to handle for novice users in a home setting. Moreover, needles may complicate drug administration, especially for patients with needle phobia.

Other delivery alternatives for systemic treatments, and especially nasal administration, are further explored to offer less-invasive treatment, providing the same efficacy. The complex nose anatomy offers various advantages. It avoids the first-pass metabolism, which therefore improves bioavailability. In addition, nasal devices are needle free, enabling easier self-administration, which increases the patient acceptance level. This leads to positive therapy outcomes as adherence and compliance of patients can be improved.

Conventionally, the nasal route (Figure 1) is used to treat chronic conditions, such as allergic rhinitis or sinusitis, by targeting the ostiomeatal complex (OMC) region using multidose nasal spray pumps. Nowadays, the nasal route is also used for the administration of medications systemically by targeting the nasal turbinates that occupy a highly vascularised large surface area of the nasal thin mucosa.

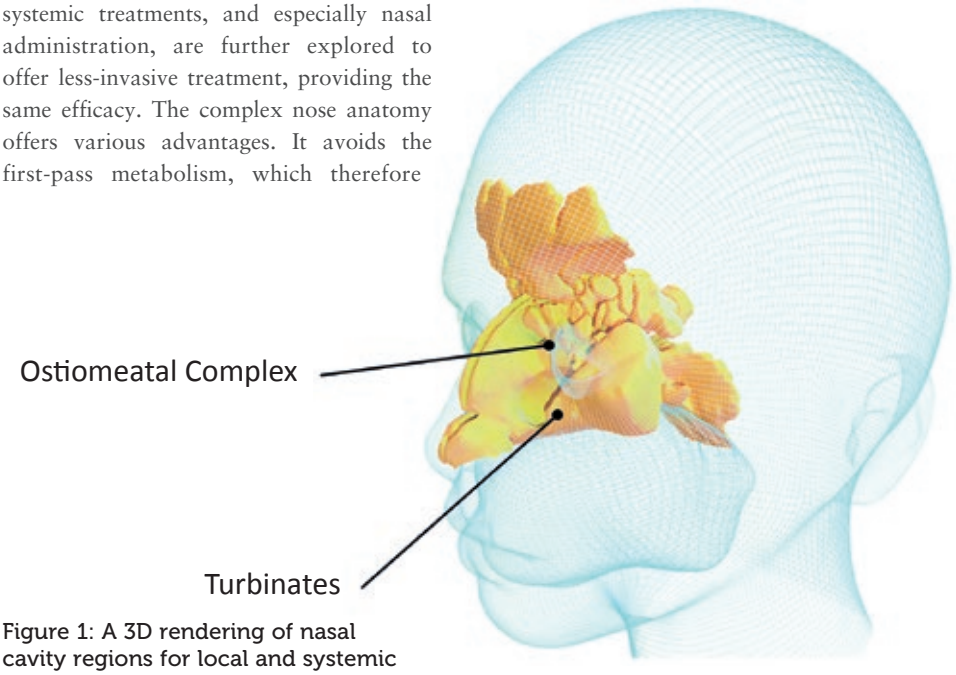

Figure 1: A 3D rendering of nasal cavity regions for local and systemic nasal-spray administration.

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Figure 2: Answering combination product needs with Nemera's holistic services.

> "An increasing number of prescribed systemic-acting drugs for acute conditions originally administered in injectable forms have been made available as unit-dose nasal sprays."

Multidose nasal spray pumps, however, are not well adapted for acute applications. If the device use is sporadic, repriming might be needed before use. Also, a large volume of drug content could be wasted if the device is used only once. Consequently, novel therapies are starting to emerge with precise, ready-to-use unit-dose nasal spray delivery to treat emergencies.

Thanks to the accessibility and simplicity of using nasal sprays, in recent years there has been a clear growing interest in exploiting the nasal route for systemic and acute indications, with many approved market references of unit-dose nasal sprays for various therapeutic areas, according to data from PharmaCircle. For example, a patient with a chronic condition suffering from breakthrough pain is normally prescribed potent drugs, such as opioids, which can lead to addiction and, potentially, overuse. In the case of an overdose, every second counts – an antidote needs to be administered straight away to save the patient's life.

However, often, actions cannot be executed immediately as healthcare professionals are not directly available to inject patients with the medications intravenously. This could lead to a worsening condition or even death. To prevent this, an increasing number of prescribed systemic-acting drugs for acute conditions originally administered in injectable forms have been made available as unit-dose nasal sprays. Patients and/or their caregivers can then administer a one-shot spray easily and rapidly, if necessary.

Unit-dose nasal sprays can also be used by patients suffering from migraines or seizures to obtain rapid relief without the intervention of a healthcare professional. To ensure patients' safety, the regulatory bodies impose stringent regulations on alternatives such as nasal spray delivery to ensure it is at least as effective as injection, especially for life-saving drugs. The reliability of the device acts as one of the key elements to save patients' lives.

ENSURING DEVICE ROBUSTNESS FOR PATIENT SAFETY

Involving patients and end users as early as possible during the device-design process is essential to ensure the device being developed is appropriate. A series of formative studies should take place to optimise device design to meet users' needs. Device manufacturers must ensure that the design of the unit-dose nasal spray device is intuitive for correct and easy drug administration, making it accessible for patients or caregivers to use without any training. The device must be able to administer the required dose of medication targeting the proper zone of the nasal cavity to enter the bloodstream. Also, the reliability and robustness of the device act as key elements in successful administration, where regulatory bodies require the device to work almost 100% of the time.

TAILORING THE DEVICE FOR A SPECIFIC COMBINATION PRODUCT

It is incumbent on pharma companies to ensure their selected device, in combination with their drug, is appropriate, safe and effective for the targeted population. Nemera works with customers to provide technical support, laboratory testing, human factors and patient experience activities necessary for a successful drug-device combination product development process (Figure 2). This also extends to, wherever possible, optimising the patient experience to create competitive differentiation and to ensure adherence and engagement with patients and clinical stakeholders.

Customers in generic markets might be interested in differentiation wherever possible, as many competitors are targeting the same reference drug or devices. In the case of generics, the regulatory authorities ask systematically if the device used corresponds to the criteria of human factors studies evaluations by comparing its user interface – inclusive of all materials that a user would interact with – with the originator.

One of the regulatory requirements is to perform user threshold analysis to understand the risks and therefore mitigate them. User-interface evaluations include labelling comparisons, comparative task analysis and physical comparison of the delivery device constituent parts. Usually, device manufacturers should conduct preliminary user threshold analysis to mitigate the risks found in the steps of use and in the physical comparison analysis, ensuring equivalent use

> "The spray characteristics obtained must provide correct shot weight, droplet size distribution, spray pattern and plume geometry, among other things."

of the device from the user perspective without compromising its safety; while the labelling comparison analysis should be completed by the pharma company. The results of preliminary user threshold analysis documentation by the device manufacturer can be used and leveraged by pharma laboratories to complete labelling analysis, thus filing full user threshold analysis to the US FDA. Going the extra mile, Nemera's front-end capabilities will be able to support specific combination product formative studies to be filed in specific dossiers to the regulatory authorities.

STATE-OF-THE-ART LABORATORY CAPABILITIES FOR COMBINATION PRODUCT TESTING

For successful administration, the drug formulation must have a high rate of mucosal and blood absorption while the device must deliver the formulation with consistent performance in addition to an optimised user interface. Combination product performances can be analysed by testing the nasal pumps together with the targeted formulations. The spray characteristics obtained must provide correct shot weight, droplet size distribution, spray pattern and plume geometry, among other things. The formulation's properties influence spray characteristics that need to be tested to obtain consistent performance. Thanks to Nemera's state-of-the-art laboratory capabilities, it offers formulation testing services to help pharma companies' formulation development.

Figure 3: UniSpray offers safe and intuitive handling for efficient drug delivery.

In the case of generics, the drug-device combination product needs to prove its bioequivalence in comparison with the originator. As first trials, Nemera offers preliminary *in vitro* bioequivalence (IVBE) studies to check the status of the generic drug and device combination compared with the originator. These tests can be redone during formulation development. Once the formulation is finalised, Nemera can also perform full IVBE studies for registration, which can then be included in the final dossier submitted to the authorities to prove IVBE of a specific nasal spray formulation with Nemera's device. The company's capability in method development assures reproducible device performance testing and its expertise allows it to perform statistical analysis for registration in different geographical areas.

FACING EMERGENCIES WITH A ROBUST UNIT-DOSE NASAL SPRAY

Nemera's UniSpray (Figure 3) delivers a single-metered 100 µL dose spray and can be used for new, repurposed or generic drugs. UniSpray has gone through different human factors studies, design verification and processes to ensure reliability and robustness of the device, assuring patients' safety and ease of use, and complying with the regulatory exigence with no risk of accidental activation.

This one-shot nasal spray is a ready-to-use primeless device with 360° functionality, enabling one-handed activation in an emergency. To ensure the correct use of the device, it offers an ergonomic design and intuitive usage.

To accelerate time to market for pharma companies, UniSpray is compatible with existing marketed primary drug containers and is adapted to fit conventional filling lines as well. In line with this objective, for generic drugs, the preliminary bioequivalence of selected molecules is performed by Nemera, which generates preliminary documentation to ensure device robustness, assuring spray characteristics equivalence and consistent performances. Customers then complete the process, based on their formulation. For new or repurposed drugs, spray performance adjustment can be done to ensure drug administration efficacy.

CONCLUSION

To bring drug-device combination products to market successfully, Nemera's expertise in human factors studies can help and support customers from the user's perspective to meet regulatory requirements. This is done by assessing the combination product with specific targeted populations according to the applications and therapeutic areas.

The right combination of device robustness and ease of use, as well as drug efficacy, plays a crucial role in nasal spray administration to deal with emergencies. Nemera's long-standing experience in developing and manufacturing complex multidose nasal devices has successfully brought more than 70 combination product references to the market across the globe, ultimately to serve patients. The company leverages its legacy and proven track record in multidose pump development and manufacturing for UniSpray's development targeting systemic and acute delivery intranasally.

Through capabilities in design research, human factors engineering, user experience design, engineering, lab services and regulatory support, Nemera is uniquely positioned to offer all the support that customers require through an integrated device platform and service programme.

Thanks to increased early-stage development capabilities, now Nemera teams can be a single partner for device platforms and integrated services – from front-end innovation, design research, human factors and design engineering to strong late-stage development, as well as clinical and commercial manufacturing capabilities.

ABOUT THE COMPANY

As a world-leading drug delivery device solutions provider, Nemera's purpose of putting patients first enables it to design and manufacture devices that maximise treatment efficacy. The company is a holistic partner and helps its customers succeed in the sprint to market with their combination products. From early device strategy to state-of-the-art manufacturing, Nemera is committed to the highest quality standards. Agile and open-minded, the company works with its customers as colleagues, going the extra mile together to fulfil its mission.

ABOUT THE AUTHORS

Audrey Chandra is the Category Project Manager at Nemera. She graduated from the Faculty of Medicine Universitas Atma Jaya, Indonesia and pursued her master's degree in Strategy and Business Development at Toulouse School of Management, France. Ms Chandra is in charge of the Dermal Category at Nemera, as well as providing strategic support for various other targeted marketing projects. She also works on diverse content management, along with communication activities co-ordination.

Raphaële Audibert is the Global Category Manager for Ear, Nose and Throat at Nemera, working on the identification of future needs and supporting existing products. Since graduating with a biomedical engineering degree from ISIFC (Besançon, France), she has worked in the medical device industry field (surgical instruments) before joining Nemera in 2016.

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CounterAct

NASAL DELIVERY SYSTEM EXPANDS PUBLIC AND PATIENT ACCESS TO NALOXONE TO MITIGATE THE OPIOID OVERDOSE EPIDEMIC

In this article, Todd D Pizitz, PhD, and Donald R Mealing, Co-Founders of CounterAct, discuss the ongoing US opioid epidemic, the CounterAct cap containing a single dose of naloxone to be attached to prescribed opioids, and a recent pilot market study done to gauge public enthusiasm for this life-saving technology.

The US opioid epidemic continues to persist without much relief in sight. So far, efforts to curb or reduce the death rate from opioid overdoses in the US have not impacted the daily death rate of 255 people.[1] Recent research has concluded that almost all US states have poorly developed paradigms for distributing naloxone and estimates that as many as 80% of opioid overdoses occurred in the presence of someone who could have counteracted the overdose with the administration of naloxone.[2] This growing death toll demonstrates an urgent unmet need for timely administration of naloxone to reverse opioid overdose.

Statistics show that, in 2020, 142 million opioid prescriptions were filled in the US.[3] Tragically, 10 million people in the US misused prescription opioids in 2020–21, resulting in 70,000 deaths from overdose and 500,000 non-lethal overdoses.[4] As such, opioid overdose is the leading cause of death for 25-to-64-year-olds in the US,[5] with a financial impact of more than US$1 trillion (£760 billion) in 2017.[6] So the question remains, what will it take to reverse this disturbing trend?

There is one overdose intervention strategy that has proven more effective in reversing the effects of opioid-induced respiratory failure than any other – the administration of naloxone during the critical minutes of an overdose emergency. In this regard, naloxone administered via a single dose nasal spray has saved countless lives in the hands of emergency first responders. The key question then becomes, "Would greater public access to naloxone prevent more opioid overdose fatalities?"

> "There is one overdose intervention strategy that has proven more effective in reversing the effects of opioid-induced respiratory failure than any other – the administration of naloxone during the critical minutes of an overdose emergency."

Efforts to expand access to naloxone in the US have resulted in co-prescription laws instructing prescribers who write opioid medications to also consider prescribing

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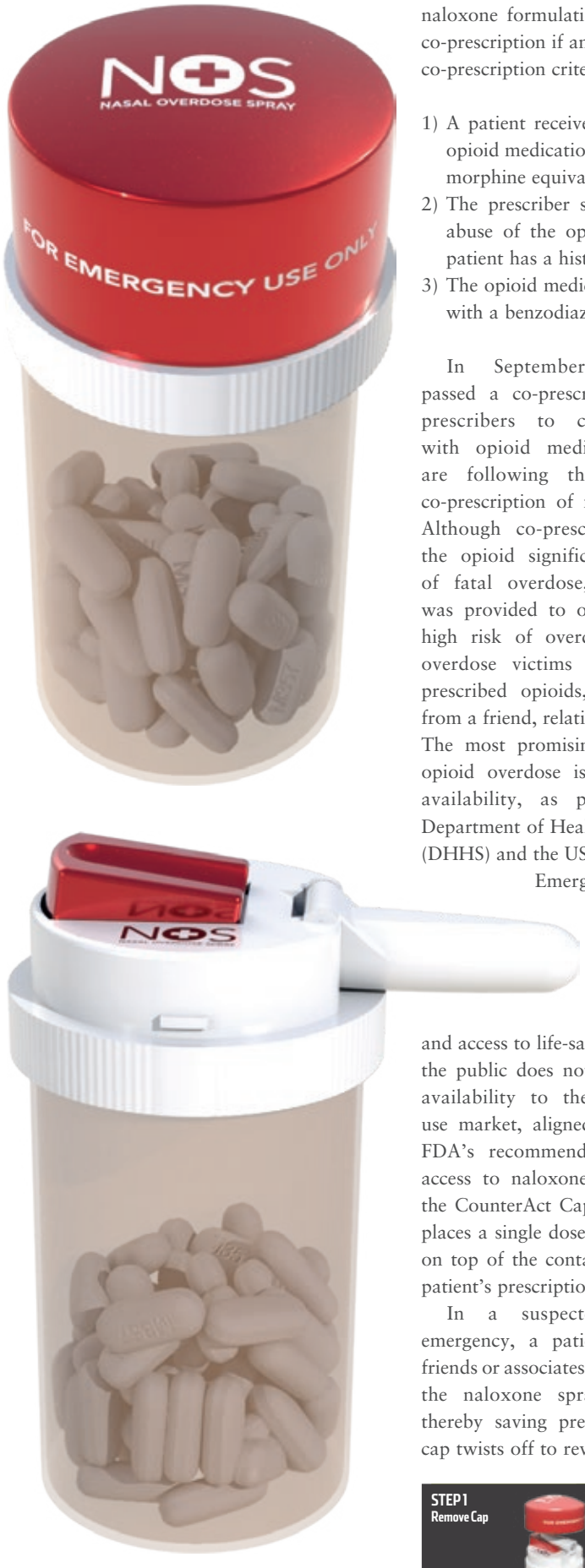

Figure 1: The CounterAct Cap contains a single dose of life-saving naloxone.

naloxone formulations and mandating the co-prescription if any of the following three co-prescription criteria are present:

1) A patient receives a prescription for an opioid medication that contains a 90 mL morphine equivalent
2) The prescriber suspects a potential for abuse of the opioid medication or the patient has a history of substance abuse
3) The opioid medication is also prescribed with a benzodiazepine medication.

In September 2018, California passed a co-prescription law mandating prescribers to co-prescribe naloxone with opioid medications. Other states are following the same pathway to co-prescription of naloxone with opioids. Although co-prescribing naloxone with the opioid significantly lowers the rate of fatal overdose, life-saving naloxone was provided to only 2% of patients at high risk of overdose.[7] Nearly 40% of overdose victims were using medically prescribed opioids, most often obtained from a friend, relative or medical provider.[8] The most promising approach to reduce opioid overdose is to increase naloxone availability, as promoted by the US Department of Health and Human Services (DHHS) and the US FDA.

Emergency medical services and most law enforcement agencies that serve as first responders have a sufficient supply of and access to life-saving naloxone, however the public does not. To expand naloxone availability to the home- and patient-use market, aligned with the DHHS and FDA's recommendation to increase the access to naloxone, CounterAct designed the CounterAct Cap. The CounterAct Cap places a single dose of life-saving naloxone on top of the container holding an opioid patient's prescription pills (Figure 1).

In a suspected opioid overdose emergency, a patient's family members, friends or associates can instantly administer the naloxone spray after calling 911, thereby saving precious time. The safety cap twists off to reveal a folded nozzle that is easily extended. Once the nozzle is fully extended, it can be placed into the overdose victim's nose, and the spring-loaded trigger can be pressed to instantly release a 4 mg dose of naloxone to the victim (Figure 2). The idea behind the CounterAct Cap was to have opioid medications and naloxone paired together, serving as a reminder of the necessity of prescriber compliance and that mismanagement and abuse of opioid medication can lead to death.

"The idea behind the CounterAct Cap was to have opioid medications and naloxone paired together, serving as a reminder of the necessity of prescriber compliance and that mismanagement and abuse of opioid medication can lead to death."

In 2021, CounterAct completed a pilot study of residents of several counties in Southern California to determine the market interest in the CounterAct Cap. All participants were shown pictures and videos of the CounterAct Cap to inform them of the device's utility and purpose. After a brief introduction to the device and personal review of collateral information, participants answered a series of questions.

A total of 43 participants were contacted, of which 29 met at least one of the inclusion criteria and were therefore included in the study. The demographics of the participants are listed in Table 1. The inclusion criteria consisted of experiencing at least one of the following:

- The participant had any experience with a naloxone-based product
- The participant had been involved in an opioid overdose either as a victim, observer or first responder
- The participant had a friend or family member who had overdosed on opioids.

Figure 2: Use instructions for the CounterAct Cap.

Age	Gender	Ethnicity	Employment Status	Marital Status
49.8 Years (Mean)	11 Males (38%) 18 Females (62%)	22 Caucasian (75%)	19 Employed (65%)	19 Married (65%)
		2 Latino (7%)		
		2 African-American (7%)		
		2 Asian (7%)		
		1 Native American (4%)		

Table 1: Demographics of market survey participants.

The participants meeting the inclusion criteria were asked the following questions:

- Do you think the CounterAct Cap would save lives in an opioid overdose emergency?
  - Yes: 29 (100%); No: 0; Uncertain: 0
- Would you want to have access to the CounterAct Cap if you have friends or family who use opioid medication?
  - Yes: 27 (93%); No: 0; Uncertain: 2 (7%)
- Would you request your pharmacist or doctor to prescribe the CounterAct Cap for friends or family members that are prescribed opioid medication?
  - Yes: 27 (93%); No: 0; Uncertain: 2 (7%)

The 29 participants were asked for general impressions of the Counteract Cap. The following is a sampling of statements from the participants:

- "I wish I had this when my son overdosed, rather than waiting for 911."
- "This could really save lives."
- "The cap on top of the pills makes it easy to get to in an emergency."
- "The combination of the two drugs together is great."
- "Is this available now from my doctor?"
- "Should be a must for every household."
- "Brilliant."
- "Great technology."
- "Where can we get one?"
- "This is awesome."

The participants in this pilot market interest survey demonstrated an overwhelmingly positive reaction to the CounterAct Cap. Since patient acceptance of the device is paramount for its use, the enthusiastic response from potential victims and family members provides critical support for CounterAct's goal of providing increased access to naloxone via the CounterAct Cap.

CounterAct has also surveyed those afflicted by the opioid overdose epidemic for their reactions to the Counteract Cap. Cammie Rice Wolf, Founder and Board Chair at Christopher Wolf Crusade (GA, US), who lost her son to an opioid overdose, was surprised that the CounterAct Cap was not in production and being developed due to its life-saving potential. She commented, "I believe the cap is also an answer for rural communities that are sometimes 50 to 100 miles from an emergency medical technician or hospital. In addition, when overdoses take place many times no one wants to call for help because of the ramifications, so they don't call for help."

CounterAct was issued a US patent for this life-saving device in March 2021. The company continues to collaborate with major drug and device manufacturers and investors to bring the CounterAct Cap to market.

ABOUT THE COMPANY

CounterAct is comprised of Co-Founders Todd Pizitz and Donald Mealing. The company has completed its pre-IND meeting with the FDA and has a developmental regulatory pathway mapped out – a 505(B)(2) regulatory path as a drug-device combination product. CounterAct has filed both national and international non-provisional patents.

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ABOUT THE AUTHORS

Todd Pizitz, PhD, is a licensed clinical and forensic psychologist in private practice. As a forensic psychologist, Dr Pizitz works with those afflicted with various types of addiction. For the past 20 years, he has worked closely with private and public defence attorneys, family court services, the US District Attorney's Office, County Adult and Juvenile Probation and Federal Probation.

Don Mealing is an entrepreneur with more than 25 years' experience as a Chief Executive Officer in a variety of successful businesses. He was Founder and Chief Executive Officer of American Corrective Counseling Services, one of the largest private counselling diversion companies servicing courts and prosecutors across the US criminal justice system. Mr Mealing has served on numerous boards, including 14 years on the board of Regents, Harris Manchester College, Oxford University (UK). Mr Mealing has lost three close relatives to opioid overdose.

NANOTECHNOLOGY: A NEXT-GENERATION TOOL FOR PULMONARY AND NASAL DELIVERY

Here, Frédérique Bordes-Picard, Vice-President of Business Development, Europe, at Nanoform, looks at the role of nanotechnology in the nasal and pulmonary routes of drug delivery and explains how nanoparticle solutions could transform patient comfort and compliance.

The nasal and pulmonary routes present exciting opportunities for localised treatment of respiratory disorders, such as asthma and chronic obstructive pulmonary disease (COPD). Drugs delivered directly to the site of action through local delivery can generate fewer side effects and more rapid onset – a significant patient benefit.

> "Drugs delivered through the nasal route with the correct size and aerodynamic properties may be able to cross the blood-brain barrier, creating exciting possibilities for the treatment of central nervous system disorders."

However, the full potential of inhaled therapies does not end there. Drug delivery to the periphery of the lung and into the bloodstream could facilitate rapid systemic delivery of drugs, including those unsuitable for oral administration due to poor absorption in the gastrointestinal (GI) tract. Meanwhile, drugs delivered through the nasal route with the correct size and aerodynamic properties may be able to cross the blood-brain barrier (BBB), creating exciting possibilities for the treatment of central nervous system (CNS) disorders.

While drug delivery devices can help to target drugs for either local or systemic action, few inhaled drugs for systemic delivery have reached the market to date.[1] This is, in part, due to the challenges associated with respiratory delivery. Powerful new technologies, such as nanoparticle engineering, could provide the means to increase the accessibility of pulmonary and nasal delivery, paving the way for a new wave of revolutionary treatments to reach the market.

THE IMPORTANCE OF PARTICLE SIZE

A significant driver for the development of inhalation therapies is increased patient-centricity. For example, the industry is working to move away from the intravenous (IV) route for biologics – drugs derived from biological sources, such as proteins and lipids – to enhance patients' quality of life and adherence to medication. By repurposing biological drugs as inhalation therapies, it may be possible to avoid the inconvenience associated with injections. Equally, bypassing systemic delivery through local administration can help avoid first-pass metabolism and reduce side effects, for both small molecules and biologics.

To tailor a dry powder drug formulation for local or systemic delivery through the pulmonary or nasal route, a number of factors must be considered. In particular, the aerodynamic diameter of drug particles – the diameter of a sphere of unit density that behaves the same aerodynamically as the particle of the test substance – is of paramount importance. Particle size, morphology and density are key contributors to the aerodynamic diameter. Particles less than 1 µm in size tend to be exhaled from the lung due to low inertia, while particles greater than 5 µm in size are too large to reach the deep lung and thus be absorbed into the bloodstream.[2] The size of particles, among other properties, can also impact residence time in the lung, with larger particles remaining in the lung for longer, which can be beneficial for local delivery.

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"The small size of the nanoparticles could make faster absorption possible, while the cluster remains the ideal size for optimum delivery, retention time and release to the lungs or nose upon deposition."

Meanwhile, drugs designed for local nasal delivery typically need to be larger than those designed for pulmonary delivery. This prevents them being inhaled into the lung, if this is not desirable. Particles in the 10–15 µm range typically are better suited to nasal delivery. As such, by carefully controlling particle size, it is possible to tailor drug particles for the target delivery route – whether nasal or pulmonary.

PRODUCING DRUG PARTICLES FOR NASAL AND PULMONARY DELIVERY

Historically, dry powder inhalation approaches for nasal and pulmonary delivery involved milling, mixing with a carrier/excipient and then filling into the drug delivery device. More specifically, adhesive mixtures composed of micron-sized API are adsorbed onto 50–200 µm carrier particles, such as lactose, often with the addition of fine milled or micronised lactose. The blend is then filled into a drug delivery device, typically reservoir, blister or capsule-based. However, such approaches involving milling to reduce particle size can result in an undesirable change in surface properties, such as cohesion and the generation of amorphous domains, which can lead to instability over time.

More modern approaches include spray drying to generate APIs with relatively large geometric diameters (a parameter used to quantify the size and shape of irregularly sized particles), with a low density and small aerodynamic diameter. Alternatively, spray drying can be used to produce light, porous particles of API co-processed with an excipient. An example of the former is Inbrija (levodopa inhalation powder) (Accorda Therapeutics, NY, US), while the antibiotic Tobi (tobramycin) (Novartis, Basel, Switzerland) is an approved version of the latter.

Inbrija is administered via a breath-actuated inhaler. It enables levodopa to bypass the GI tract and enter the bloodstream rapidly through the lungs instead. It has been shown to be effective in improving Parkinson's disease symptoms in patients experiencing "off" periods, where routine medication is not sufficient.[3] As a non-intrusive, convenient treatment option, Inbrija highlights the possibilities for creating patient-centric therapeutics by repurposing drugs for inhalation. However, spray-drying formulations, as in the case of Inbrija, while effective, often results in amorphous material and may require more complex formulations to ensure stability.

CREATING NEW POSSIBILITIES WITH NANOPARTICLE ENGINEERING

Advanced nanoparticle engineering techniques offer a means to reduce the size of drug particles to as small as 10 nm as part of a controlled process. While this is too small for direct delivery to the lung, nanoparticles can potentially be prepared as clusters. In this case, the small size of the nanoparticles could make faster absorption possible, while the cluster is prepared/generated at the ideal size for optimal delivery, retention time and release to the lungs or nose upon deposition.

This opens up a number of intriguing prospects. For example, fibrotic scarring observed in fibrotic respiratory diseases typically blocks particles in the 200 nm – 1 µm range. Particles smaller than that could potentially pass through, which could facilitate different treatment approaches.

Meanwhile, for nanoparticle engineering approaches to work successfully on biologics, care must be taken not to expose them to high temperatures or shear stress, which could impact biological activity negatively. Gentle nanoparticle engineering technologies that can produce stable biological nanoparticles as small as 50 nm, potentially alongside co-processing with the excipients to help maintain a uniform particle size and stability, hold enormous potential to facilitate delivery of biologics through the nasal and pulmonary routes.

DELIVERY TO THE BRAIN: FOLLOW YOUR NOSE

In addition to facilitating localised treatment of respiratory or nasal disorders, the nasal route may also represent a gateway for nanoparticles to reach the brain. Direct delivery to the brain is a major issue for drugs targeted at CNS disorders, such as Parkinson's or Alzheimer's disease. Designed to effectively block outside agents from entry, the BBB is impassable to approximately 98% of small molecules and almost all biologics.[4] Transport across the olfactory nerves and respiratory epithelium or trigeminal nerve in the nose could allow drugs administered nasally to bypass the BBB, solving a long-standing challenge in the industry.[5]

In combination with a purpose-built delivery device, nanoparticle clusters could provide a means to leverage this pathway. In this case, particles of carefully controlled size would be potentially rapidly absorbed intranasally and, subsequently, reach target areas in the brain, which could facilitate life-changing new treatments for currently incurable brain disorders.

A NEW FRONTIER IN PULMONARY AND NASAL DELIVERY

While further research is needed to confirm the many ways that nanoparticles could transform nasal and pulmonary delivery, the possibilities are multifold. From empowering a shift to a more patient-centric, localised route of administration for respiratory disorders to potentially overcoming the obstacle created by the impassable BBB, the opportunities to improve patients' lives through technological innovation make it an exciting time to be working in the field. In the future, there may be many more patient-centric therapeutics delivered through the nasal or pulmonary routes, aided and enhanced by nanoparticle engineering.

"Transport across the olfactory nerves and respiratory epithelium or trigeminal nerve in the nose could allow drugs administered nasally to bypass the BBB, solving a long-standing challenge in the industry."

ABOUT THE COMPANY

Nanoform is an innovative nanoparticle medicine enabling company that works together with pharma and biotech partners globally to provide hope for patients in developing new and improved medicines using Nanoform's platform technologies. The company focuses on reducing clinical attrition and on enhancing drug molecules' performance through its nanoforming technologies and formulation services. Nanoform's capabilities include GMP manufacturing, and its services span the small-to-large molecule development space with a focus on solving key issues in drug solubility and bioavailability and on enabling novel drug delivery applications.

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ABOUT THE AUTHOR

Frédérique Bordes-Picard is a biochemist engineer by training (Bordeaux Polytechnic Institute, France) and also holds an MBA from KEDGE Business School (Bordeaux, France). Ms Bordes-Picard has nearly 25 years' experience in the pharmaceutical industry, gained first at AstraZeneca, UK, working on the analytical development of therapeutic proteins and antibodies. She subsequently worked within the CDMO Bertin Pharma (now Eurofins), focusing mainly on generic product development and licensing. Ms Bordes-Picard then spent over 10 years at Capsugel, now Lonza, as Pharmaceutical Business Development Manager, providing technical and regulatory guidance in encapsulation solutions for new drug products for oral or pulmonary administration. She recently joined Nanoform as Vice-President of Business Development, Europe.

PERSONALISED AEROSOL LOADING AND MANAGEMENT (PALM): A HAND-HELD DEVICE FOR AEROSOL DRUG DELIVERY

In this article, Jason Brenker, PhD, Research Fellow, and Tuncay Alan, PhD, Senior Lecturer, both of Monash University, and Daniela Traini, PhD, Professor, Macquarie Medical School and the Woolcock Institute of Medical Research, introduce the PALM – Personalised Aerosol Loading and Management – device, a unique, advanced drug delivery device enabling personalised delivery of aerosols to improve the efficacy of inhaled medications and patient compliance.

INTRODUCTION

Respiratory drug delivery is primarily used for the treatment of chronic diseases, such as asthma and chronic obstructive pulmonary disease (COPD), both of which are inflammatory diseases of the lower airways. Over 13% of Australians and 16% of Americans are affected by these diseases and, despite new treatments, they continue to be among the leading causes of deaths in Australia (Australia, 11,202 people in 2019) and internationally (US, 224,987 people in 2019).[1]

There is also growing interest in using the extensive surface area of the lungs as a route for the systemic delivery of other therapeutic agents. This needle-free alternative to traditional oral formulation is especially advantageous for improving the absorption of poorly bioavailable drugs and reducing side effects. The region of the airway that needs to be targeted depends on the disease to be treated; generally, drugs used to treat inflammatory diseases, such as asthma, should be targeted to the bronchi, the walls of which consist of smooth muscles, whereas drugs for systemic delivery via the lungs should target regions deeper into the alveoli, which are rich in systemic capillaries (Figure 1).

Requirements of Respiratory Drug Delivery and Unmet Needs

The complex, convoluted geometric properties of both the lower and upper respiratory tracts provide numerous distinct challenges for the effective delivery of aerosolised drug compounds. Drug deposition in the respiratory tract primarily depends on three key parameters:

- The size and distribution of the aerosol particles/droplets.
- The rate of delivery of the aerosol to the patient.
- The patient's breathing pattern.

Particles with aerodynamic diameters in the range of 0.5–5 µm have the highest likelihood to reach the terminal bronchioles and alveolar regions, with larger particles (>5 µm in aerodynamic diameter) likely to become entrapped in the upper airways. However, optimum particle size varies from patient to patient due to differing lung

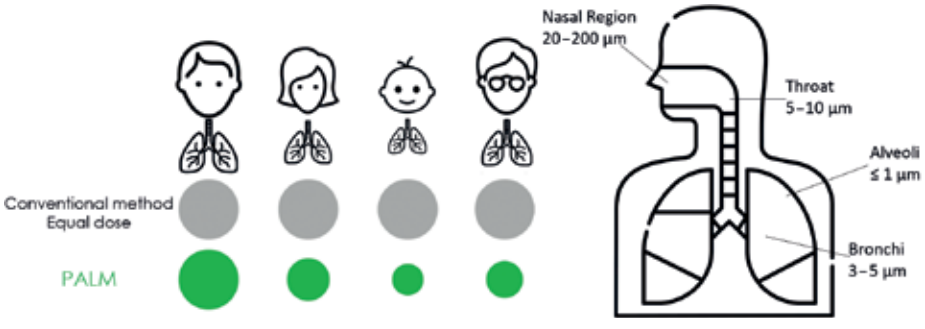

Figure 1: A comparison of the proposed design with existing approaches (left) and an indication of the typical deposition location of different particle sizes in the airways (right).

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Figure 2: Rendering of the PALM device (left) and image of the PALM device held in the hand (centre) and on the face (right).

capacities, disease states, age and gender (Figure 1).[2] Hence, a personalised approach capable of tuning the particle size is required for increased effectiveness. This is not currently possible with any commercially available device.

An Innovative Particle Delivery Method

To meet this need, researchers from Monash University, Macquarie Medical School and the Woolcock Institute of Medical Research have recently invented the Personalised Aerosol Loading and Management (PALM) device, a portable integrated aerosol system that can address the specific needs of patients for a specific delivery route (Figure 2). The device gives physicians precise control over their patient's treatment by tuning the particle size and provides users with an easier, more effective treatment.

The PALM device, with its microfluidic droplet generation and unique patented design, employs a small form-factor breathing device that sits comfortably in the palm and fits a variety of face shapes thanks to its universal design, created specifically to improve user experience and patient monitoring. Using built-in sensors, the PALM device can measure a patient's breathing cycle and deliver medication at exactly the right moment, eliminating co-ordination issues. Moreover, the particle size can be controlled on-demand to address the specific needs of patients. These capabilities ensure that the PALM device offers the greatest potential for successful lung deposition.

"The PALM device, with its microfluidic droplet generation and unique patented design, employs a small form-factor breathing device that sits comfortably in the palm and fits a variety of face shapes thanks to its universal design, created specifically to improve user experience and patient monitoring."

"Current device design has resulted in poor patient compliance and, consequently, poor treatment outcomes."

BACKGROUND

Issues with Current Inhaler Designs

Despite significant advances in new drug therapies and devices, current treatments cannot tune particle size to selectively target the route of administration. Current device design has resulted in poor patient compliance and, consequently, poor treatment outcomes.[3] Existing aerosol delivery devices are based on one of the three groups:

- Pressurised metered dose inhalers (pMDIs)
- Dry powder inhalers (DPIs)
- Nebulisers.

pMDIs, or "puffers", offer a cheap, convenient and portable solution and are widely used. They deliver aerosols in distinct, manually actuated pulses. While they appear to be easy to operate, research has shown that up to 60% of patients do not adhere to prescribed regimens and up to 90% of patients do not perform all essential steps required to use a pMDI correctly.[4] For the device to be useful, patients need to be trained in, and capable of, controlling their inhalation strength and holding their breath post inhalation for 5–10 seconds. For instance, Noble (FL, US) markets "respiratory trainer" devices to teach patients how to use pMDIs effectively,[5] and Adherium (Auckland, New Zealand) produces patient adherence and data management solutions, such as the Hailie platform.[6] Another major challenge for patients with compromised lung functions is effectively controlling breathing patterns; there is an even more significant disease burden (as measured through disability-adjusted life years) felt by the elderly (over 65 years) and the young (below 15 years).[1] These patients experience more difficulty administering medication through conventional devices due to a lack of dexterity. Incorrect inhaler techniques have not improved over the past few decades, which points to an urgent need for new approaches to delivering drugs to the lungs.[7]

A commonly identified problem among users is that they do not adhere to their treatment regimens when prescribed multiple devices, such as a preventer and reliever.[8] Patients prefer the use of a single device (often a reliever) and would not use an "add-on" component (spacer) even when prescribed to do so.

DPIs are portable devices that overcome patient training and coordination issues, as they are breath activated and can deliver a higher mg/dose. However, they require a very high inspiratory pressure (approximately 4 kPa) and, consequently, are not suitable for patients with compromised lung functions.[9]

Unlike pMDIs and DPIs, a conventional jet nebuliser delivers a set volume of fluid at a constant rate for as long as 15 minutes without any pause. Typically, they require a source of compressed air, which makes them bulky. Ultrasonically actuated mesh nebulisers employ a vibrating perforated plate in contact with the fluid to generate a mist of droplets, which offer advantages in portability and hence have become increasingly popular alternatives. However, they have several important limitations for personalised therapies:

- The aerosol particle diameter for each drug/device pair is fixed and cannot be tuned; often specific drug formulations are associated with specific mesh designs. However, since nebulisers are manufactured independently from the formulation, patients use them with different drugs, which can lead to variations in the performance.
- Due to high fabrication costs, it is not possible to employ single-use meshes. Hence, the components need to be cleaned in between uses. Poor cleaning often hampers the performance and may result in infections.
- The existing designs involving mouthpieces avoid bulky masks but are not practical for frequent use over extended periods.

PALM – A PATENTED MICROFLUIDIC TECHNOLOGY

At the heart of PALM is a patented microfluidic aerosol generation technique. The combination of microfluidic channels, a piezoelectric driving element, associated driving electronics and various sensors are all housed within a handheld device.

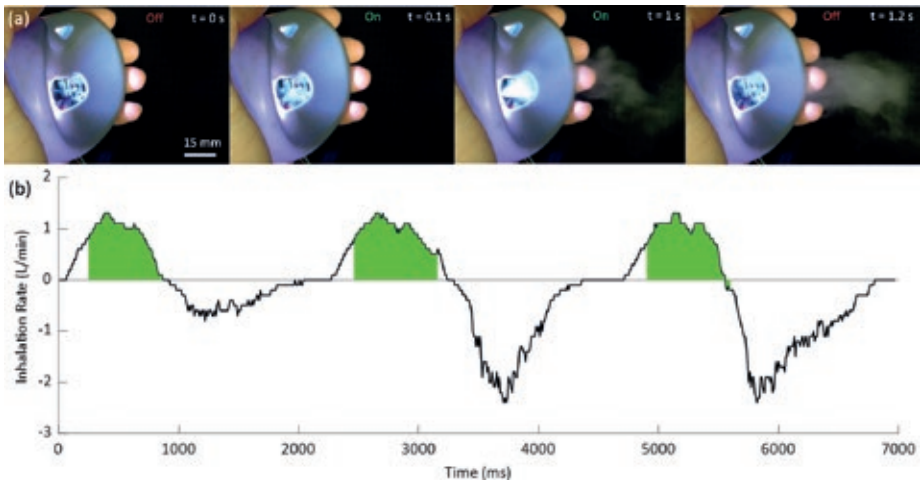

Figure 3: Example of an ejection of a mist of droplets during a 1.1 s pulse of the PALM device and a measured breathing cycle with device actuation indicated in green.

> "With PALM, drugs can be delivered in synchronised pulsed doses, uniquely combining the operational principles of pMDIs and nebulisers, and enabling a personalised aerosol delivery rate."

The microfluidic channels are photolithographically patterned hydrophilic channels etched into a hydrophobic substrate. The piezoelectric element and driving electronics are activated by a small form factor microcontroller that triggers actuation based on measurements from an airspeed sensor. Upon actuation, a controlled volume of fluid can be drawn into the channel through a rapid capillary driven flow. The subsequent high-frequency vibration of the fluid/air interface results in a highly uniform mist of micrometre-diameter droplets, as shown in Figure 3.

PALM has three key advantages. Firstly, the hydrophilic channels can deliver the fluid from an arbitrary reservoir to the active region of the nebulising chip through capillary action, as shown in Figure 3. Secondly, it constrains the fluid interface to the top of the channels ensuring a very well-defined and stable interface for nebulisation. Thirdly, the new microfluidic approach can initiate and stop particle ejection in under 0.1 s. As such, with PALM, drugs can be delivered in synchronised pulsed doses, uniquely combining the operational principles of pMDIs and nebulisers, and enabling a personalised aerosol delivery rate. A comparison of the performance of PALM with a mesh nebuliser and pMDI are shown in Table 1, highlighting the high fine particle fraction (FPF) and tight size distribution.

	PALM	Mesh Nebuliser	pMDI
Fine Particle Fraction (FPF) <5 µm	70.86 % ± 9.11	64.4 % 12.2	52.0 % ± 2.9
Mass Mean Aerodynamic Diameter (MMAD) µm	3.05 µm ± 9.11	3.99 µm ± 0.73	4.3 µm ± 0.19
Geometric Standard Deviation (GSD)	1.75 ± 0.04	1.82 ± 0.02	1.75 ± 0.04

Table 1: Comparison of key aerosol metrics for PALM device with the commercially available Philips Innospire Go, both aerosolising salbutamol sulphate with a flow rate of 15 L/min and an Intal 1 mg pMDI containing sodium cromoglycate with a flow rate of 30 L/min.[10]

> "The breathing cycles of a user are continuously monitored with airflow meters and the device is triggered when a target airflow rate is detected."

Synchronising Breathing Cycles with Drug Delivery

Currently, 45% of pMDI users are not able to co-ordinate their button-press and inhalation during pMDI activation correctly, and 44% do not inhale deeply or quickly enough to comply with the current correct technique.[7] The PALM method of delivery is designed to remove button-press activation, instead being reactive and activated automatically by inspiration. PALM synchronises the output of medication to the inhalation of the patient, thereby acting as a "breathing device". The breathing cycles of a user are continuously monitored with airflow meters, and the device is triggered when a target airflow rate is detected, as demonstrated in Figure 4. The device measures three breaths before calculating the target delivery window, shown here from 20% of inhalation time, until just before exhalation begins. PALM can then continue to administer medication until the total required dose is delivered.

SUMMARY

PALM combines a patented, highly responsive aerosol production approach with an airflow sensor and microcontroller to define the timing of aerosol delivery precisely. The developers have demonstrated that using the PALM device results in an improved FPF compared with typical devices currently available on the market. The developers envisage this combination of features and flexibility of dosing

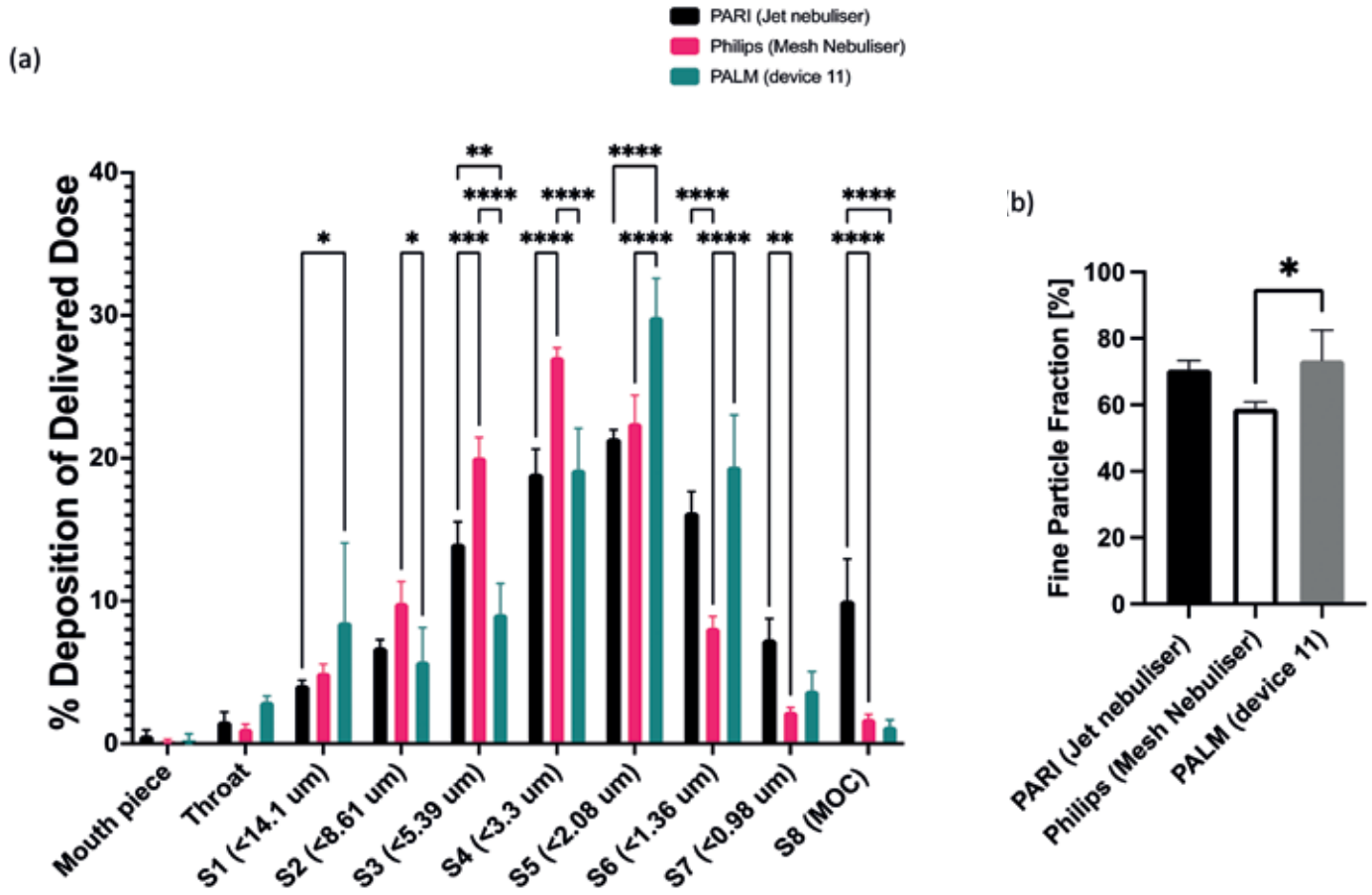

Figure 4: (A) Next-generation identification (NGI) comparison of salbutamol sulphate deposition using PALM (n=3), PARI (n=3) and Philips (n=3) nebulisers, flow rate 15 L/min. (B) Comparison of delivery device FPFs (values are means ± standard deviation, n=3). Statistical significance was determined using a two-way analysis of variance with Tukey's multiple comparison analysis, where *p<0.033, **p<0.0021, ***p<0.0002 and ****p<0.0001.

will improve adherence and the patient experience, while enabling the delivery of many different treatment regimes.

The authors will present a poster about this work, "Microfluidic Aerosol Generation: Development of a Next-Generation Hand-Held Device For Aerosol Drug Delivery", at RDD 2022 (Orlando, FL, US, May 1–5, 2022).

ABOUT THE DEVELOPMENT TEAM

Personalised Airway and Lung Management (PALM) is a world-first drug delivery technology designed by Monash University researchers. The team includes Dr Tuncay Alan and Dr Jason Brenker, microfluidic technology experts; Prof Bruce Thompson, a champion in respiratory medicine; pharmaceutical experts based at the Woolcock Institute in Sydney lead by Prof Daniela Traini and Dr Hui Xin Ong; and experts in healthcare device design lead by Prof Daphne Flynn from the Design Health Collab, also based at Monash University. The work is funded by a development grant from the National Health and Medical Research Council (NHMRC) of Australia (Grant 2000120).

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INVESTIGATING THE PROPELLANT PATHWAYS LEADING TO A SUSTAINABLE FUTURE FOR MDIS

In this article, Chris Baron, Director of Business Development, Pulmonary Category at Aptar Pharma, and Jag Shur, PhD, Vice-President, Science & Technology at Nanopharm, discuss the various dynamics involved in realising the full potential of MDIs to deliver both improved environmental performance and even better patient outcomes.

From the phones we use to the food we eat, every aspect of our daily lives carries with it an environmental cost. Through complex chains of production, distribution and consumption, modern living contributes to the generation of harmful emissions into the Earth's atmosphere, which, in turn, are responsible for trapping heat and causing the greenhouse effect that is responsible for global warming.

Carbon dioxide (CO_2) remains the leading greenhouse gas emitted through human activities. This is primarily a result of the burning of fossil fuels for transportation and energy but other activities, such as industrial processes and agricultural practices, are also contributing factors. As a result, global CO_2 emissions have increased around tenfold over the past century. In a bid to slow global warming and reduce the impact of climate change, governments and policymakers around the world have set out targets to reduce emissions of CO_2 and other greenhouse gases with global-warming potential (GWP), such as methane (CH_4) and nitrous oxide (N_2O).[1]

This list of gases with high GWP also includes synthetic fluorinated gases, or F-gases, which have a variety of applications, both industrial and medical. For example, F-gases are currently used as propellants in metered dose inhalers (MDIs), playing a vital role for millions of patients worldwide in the management of respiratory conditions such as asthma and chronic obstructive pulmonary disease (COPD).

While they are now the standard, F-gases were only introduced to MDIs in the 1990s as a replacement for the chlorofluorocarbons (CFCs) used previously. This change was driven by the fact that CFCs were found to have a depleting effect on the Earth's protective ozone layer, weakening its ability to absorb ultraviolet radiation from the sun and protect against warming. As a result, on September 16, 1987, global powers set down an agreed timeline for the phasing out of CFCs by January 1996 within the United Nations Environment Programme (UNEP) treaty known as the Montreal Protocol.

Because of their role as an essential healthcare product, CFC-based MDIs were exempt from this deadline until suitable alternatives were made available. This challenge prompted a surge of innovation in the sector that resulted in the introduction of the hydrofluorocarbons HFA 134a and HFA 227a as CFC replacements. The first products to employ these F-gases were Airomir (Teva, Jerusalem, Israel), which launched in the UK in 1995, and Proventil (Merck & Co, NJ, US), which was introduced to patients in the US in 1996. Eventually, CFCs were confirmed as being fully phased out of MDIs in Europe in 2010 and in the US in 2011.

With respect to repairing the ozone layer, the Montreal Protocol has been an unquestionable success. Experts suggest the Antarctic ozone hole will close by the 2060s, while ozone at other affected regions

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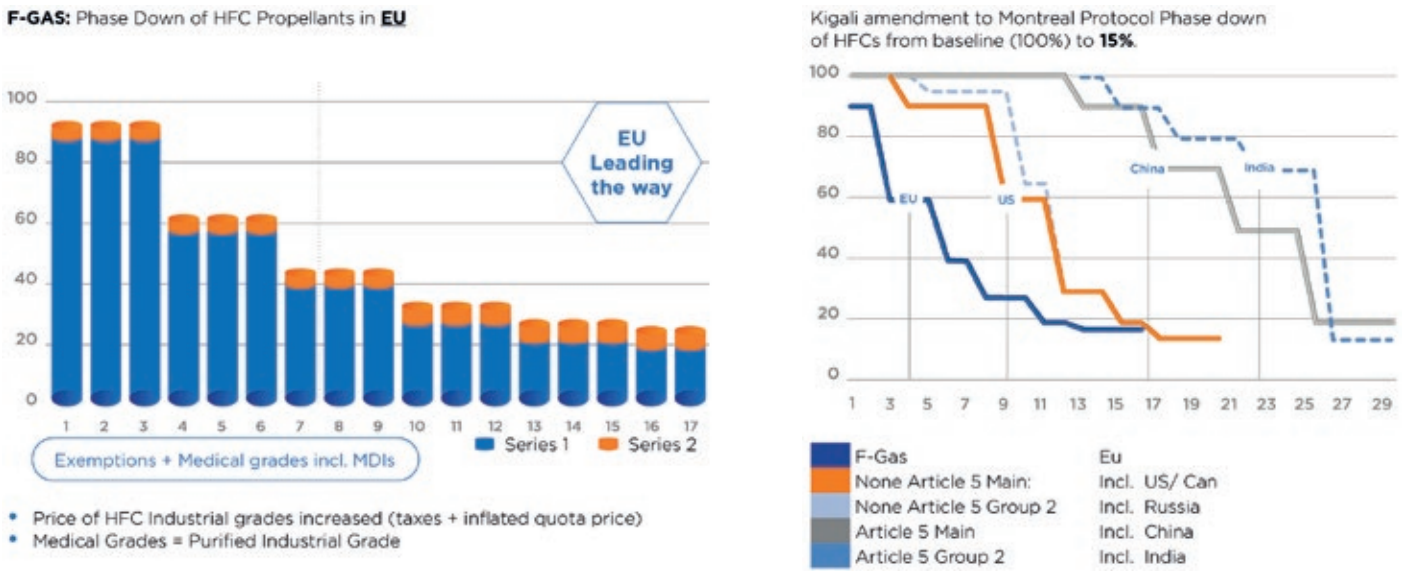

Figure 1: Regulation based on controlling emission of CO_2 – tonnes equivalent.

is expected to return to pre-1980s levels even sooner.[2] In addition, by moving away from CFC propellants, MDIs registered a reduction in CO_2 emissions, with values for HFA-based inhalers between three and nine times lower than those registered by their CFC predecessors when compared on a like-for-like basis.

In the intervening years, however, the emergence of further information about the properties of F-gases has prompted the need for further change. While they might not deplete the ozone layer like CFCs and are emitted in much lower volumes than CO_2, methane and nitrous oxide, F-gases have a comparatively higher GWP and, therefore, a proportionately higher impact on climate change.

Of course, efforts to limit the environmental impact of MDIs using F-gases must be understood within context. Healthcare, as a sector, is estimated to be responsible for 4–5% of worldwide greenhouse gas emissions, and that figure is driven by myriad factors.[3] Focusing on the NHS in the UK, medicines – including inhalers – are responsible for 25% of its overall carbon emissions. However, the overwhelming majority of that figure (80%) relates to manufacturing and freight emissions in the supply chain.[4] With inhalers responsible for 3% of the carbon footprint of the NHS, and 0.1% of the UK's total national carbon footprint,[5] a transition to lower GWP propellants will, therefore, ensure inhalation devices play their part in healthcare's broader push towards net-zero goals.

In Europe, this issue has been tackled through the F-Gas Regulation, which came into force in January 2015, incorporating bans and quotas on the use of F-gases with an objective to phase down their use to one-fifth of 2014 sales levels by 2030.[5] In the US, the Environmental Protection Agency is also driving the transition to F-gas alternatives through its Significant New Alternatives Policy and, more recently, via new regulation within the American Innovation and Manufacturing Act, which was enacted in December 2020. At an international level, the issue has been addressed through the 2016 Kigali Amendment to the Montreal Protocol, which commenced the phasing down of F-gases from January 2019 (Figure 1).

Given that the majority of inhalers currently in use are MDIs using either HFA 134a or HFA 227a, and as volumes of MDI F-gas in the US are projected to increase from 1,491 metric tons in 2020 to 1,595 in 2025,[6] there is a clear need for pharmaceutical companies and their drug delivery solutions partners to facilitate a safe, speedy and smooth transition to alternative MDI propellants.

This situation is further complicated by the likelihood of cost increases as sources of industrial-grade F-gas volumes decline. Indeed, significant rises have been registered in the price of HFA medical-grade propellant, in particular HFA 227a, throughout 2020 and 2021, which will impact the respective manufacturing costs for MDIs based on this propellant.

The transition to low-GWP propellants has been given further urgency by the environmental ambitions and sustainability targets being set out by major healthcare providers. For example, NHS Primary Care Networks in the UK has announced its intention to reward, where appropriate, the prescribing of lower carbon-footprint alternatives to MDIs, such as dry powder inhalers (DPIs) and soft mist inhalers (SMIs). This is in line with NHS England's stated goal for just 25% of prescribed non-salbutamol inhalers to be MDIs by 2023/24.[7,8] Future targets will also reward the prescribing of MDIs with a lower carbon footprint while also encouraging patients to return used inhalers to pharmacies for safe and environmentally friendly disposal.[4]

While framing the use of alternative device types as a straightforward switch might make the process sound simple, the reality is more complicated. Despite their specific advantages, DPIs and SMIs do not necessarily make for a true like-for-like choice, with MDIs offering significantly lower cost per dose in a device form that has been proven over many years as the dominant mechanism for the delivery of drugs targeting the respiratory system.

Beyond technical performance, it is also important to consider how MDIs are valued by patients. For millions of people, these devices are deeply embedded into their daily lives for maintenance medication, and they also know that they can rely on them to deliver rescue medication in times of emergency.

> "There is a clear need for pharmaceutical companies and their drug delivery solutions partners to facilitate a safe, speedy and smooth transition to alternative MDI propellants."

It is for these reasons that, in the respiratory drug delivery sector, sights are keenly trained on the successful transition to low-GWP propellants as current high-GWP variants are phased out. As with the transition away from CFCs, these new options must be assessed thoroughly using strict criteria, with robust evidence that they deliver continuity of both functional and pharmaceutical performance while answering concerns in the areas of toxicity, flammability and environmental impact.

> "Beyond technical performance, it is also important to consider how MDIs are valued by patients."

Based on these criteria, the leading propellant options for the next generation of low-GWP MDIs are HFA 152a and HFO 1234ze from the hydrofluoroolefin family. Much work has already been carried out by industry stakeholders to evaluate these gases. But further work is still required to build a complete picture of their chemical and physical properties as propellants, as well as their suitability and safety within drug delivery systems.

Thinking specifically of performance within an MDI, key areas to consider for these propellants are the solubility of an API in the propellant system; the profile of the emitted spray, looking at droplet size and evaporation of the propellant; and the electrostatic charge properties, which will define how they are handled and their relationship to regional deposition in the airways.

Aptar Pharma takes a holistic approach to drug delivery to enable pharma partners to answer such questions by drawing on the specialist expertise within its broad operational portfolio. Analytical studies carried out within its Nanopharm business, for example, have provided rich data and insights to compare the characteristics and performance of existing propellants against low-GWP alternatives.

The solubility of a drug substance in low-GWP propellants is a critical consideration on this journey. This measurement illuminates the potential for the formulation to be developed as either a solution or suspension. In the case of suspension systems, solubility level will also determine the stability of the particle size. In the case of solutions, it will directly influence the amount of co-solvent required, which, in turn, impacts the velocity of the aerosol and the droplet-evaporation kinetics.

To explore the issue of API-propellant solubility, Nanopharm has used high-pressure nuclear magnetic resonance spectroscopy. In one such study looking at beclomethasone in low-GWP and existing propellants, the solubility of HFA 152a was found to be 400 µg/mL, which was more than twice the level observed with HFA 227a and three times the level observed with HFA 134a and HFO 1234ze. Such findings have important implications for formulation design, including the potential to lower the co-solvent load in ethanol-based formulations where the propellant solubility is observed to be higher.

Nanopharm's work has also encompassed analysis of the aerosol process to measure variances in droplet size among the various propellants. This test environment uses phase doppler anemometry to measure the evolution of the droplet size issued from placebo canisters under no-flow conditions and also under flow rates of 30 L/min to approximate patient use.

Under no-flow conditions, the droplet size of HFO 1234ze aerosols decreased to a less significant degree before reaching stability. Under flow conditions, however, the droplet-size evolution of HFO 1234ze is more closely aligned with HFA 227a, demonstrating an initial decline in droplet size prior to a subsequent rise as distance increases. In the case of HFA 152a, meanwhile, the droplet-size evolution was observed as being similar to HFA 134a, with both propellants maintaining a small droplet size as they evolve.

Uncovering this level of understanding of droplet dynamics and the differences in aerosol velocity provides important insight into deposition behaviour and can be valuable in controlling aerosolisation through optimisation of actuator and valve design.

Along with electrostatic charge behaviour, the properties of these propellant aerosol systems are also likely to impact regional deposition in the airways. Nanopharm has collaborated with Dr Philip Kwok, Lecturer in Pharmaceutical Sciences in the School of Pharmacy at the University of Sydney (Australia), to investigate the aerosol charge of propellant systems using the Bipolar Charge Analyzer (BOLAR) system from Dekati (Kangasala, Finland). This collaborative research has been able to establish not just the net charge of propellants but charge polarity. Overall, the propellants demonstrated more electropositive charge. But it was notable that HFA 152a showed greatest charge propensity and HFO 1234ze showed the least, with near-neutral charges of both polarities – results that may be correlated to the previous findings on solubility.

Equipped with observed data on the behaviour of the propellants, Nanopharm has also investigated the fate of inhaled doses using its SmartTrack™ platform. This platform provides an assessment of aerosol properties under realistic conditions, facilitating an

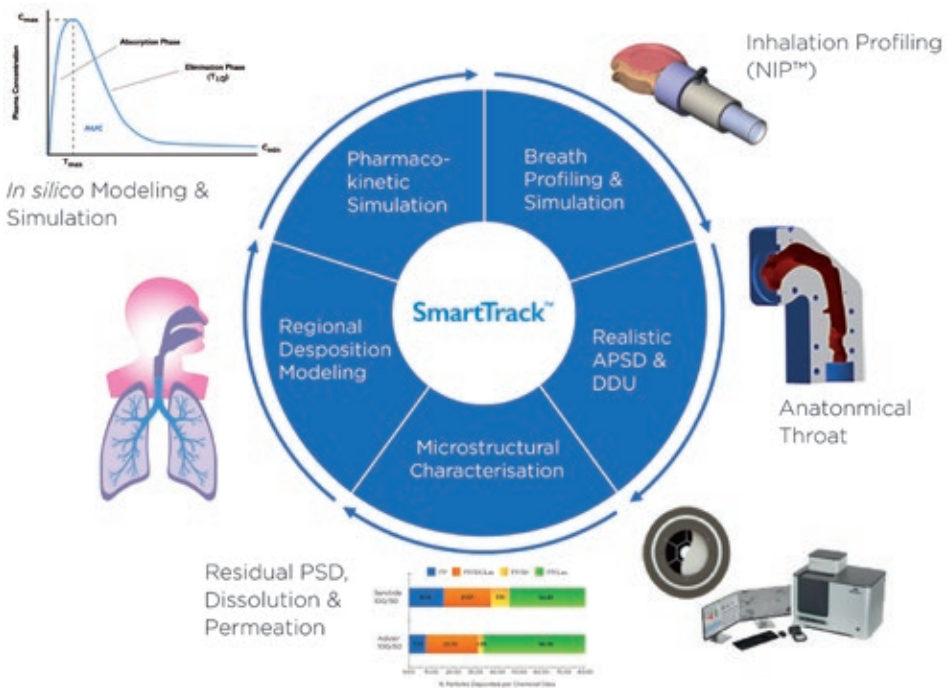

Figure 2: A combination of realistic *in vitro* testing and *in silico* modelling was used to compare the systemic exposure of salbutamol formulated into HFA 152a with Ventolin.

understanding of formulation microstructure using dissolution and spectroscopic methods, and employing physiologically based pharmacokinetic (PBPK) modelling to simulate regional deposition and systemic exposure.

In-house studies were carried out using SmartTrack™ to assess the differences in performance between a current Ventolin (salbutamol – GSK) inhaler and an approximated MDI containing salbutamol in combination with HFA 152a. Deposition analysis showed that the aerodynamic particle-size distribution was comparable in both cases, as was the predicted regional lung distribution.

A key difference, however, was the higher deposition levels in the throat and upper airways for the salbutamol/HFA 152a formulation, which led to a slightly lower total dose being emitted and lower deposition in the alveoli of the deep lung. This indicates the potential for variance in systemic effect while underlining the importance of the valve/actuator interaction in managing these variables (Figure 2).

Taken together, the results from these tests provide a range of illuminating datasets on variances between propellants in areas including API solubility, particle aerosolisation, electrostatic charge, deposition and distribution, all of which are highly valuable when making key decisions around formulation and device development. To ensure pharma partners are fully supported in this area, Aptar Pharma has also invested in a pilot mixing-and-filling suite to handle all MDI propellants, including HFO 1234ze and HFA 152a, with the first customer filling having taken place in September 2021.

From analysis of formulation and propellant to device development, regulatory support and commercialisation, Aptar Pharma's expanded suite of devices and harmonised service offerings are positioned to answer the increasingly complex questions regarding the low-GWP future of MDIs. Equipped with new metering valve technology featuring materials and geometry that are designed for optimal compatibility with formulations based on HFO 1234ze and HFA 152a, there is evidence of a clear development pathway between existing HFA-based MDIs and a new generation of MDIs using lower GWP alternatives.

ABOUT THE AUTHORS

Chris Baron is Director of Business Development, Pulmonary Category at Aptar Pharma. In this role, he is responsible for the global business development activities for Aptar Pharma's inhalation drug delivery devices, as well as their respective services pertaining to the application fields of asthma and COPD. With a degree in Mechanical Engineering, Mr Baron has over 28 years' industry experience in the field of inhalation drug delivery, specifically metering valve technologies for pressurised metered dose inhalers and their accessory peripheral device technologies, including dose indicators and breath-activated inhalers.

Jag Shur, Vice-President, Science & Technology and Co-Founder at Nanopharm, an Aptar Pharma company, is an internationally recognised expert in the investigation of the bioequivalence of OINDPs. Holding a BSc (Hons) in Chemistry, he completed his PhD entitled "Formulated Muco-Regulatory Agents in the Airways of Patients with Cystic Fibrosis" at Portsmouth School of Pharmacy in the UK. Dr Shur is also a post-doctoral fellow at the UCL School of Pharmacy (London, UK), having investigated the fabrication of micro particles for vaccine delivery using supercritical fluid technology.

Drawing on the learnings from the CFC-to-HFA transition, consistency will be an important factor in this journey, providing patients with the continuity of familiar, proven healthcare solutions that are, at the very least, comparable to existing solutions.

With the industry at an inflexion point, stakeholders in the sector have an opportunity to influence wider beneficial change beyond the transition to low-GWP propellants. Addressing levels of compliance and adherence among patients, for example, can help to tackle the estimated 250,000 tonnes of CO_2 equivalent generated annually from overuse of short-acting β2-agonist (SABA) inhalers in the UK,[9] while also avoiding medicine and device waste. Further possible measures include the use of primeless valves to minimise dose wastage, the inclusion of dose counters to encourage regimen adherence, the use of breath-activated inhalers to address co-ordination issues and improve patient compliance, and the integration of digital health platforms to further enhance patient engagement.

So, while we must focus on building our understanding of the properties of low-GWP alternative propellants and exploring all the new avenues they offer, it is also an opportune moment to zoom out and reflect on all the various dynamics surrounding formulation, device and delivery. It is only by taking this holistic approach that MDIs can truly realise their future potential in delivering both improved environmental performance and even better patient outcomes.

ABOUT THE COMPANY

For pharma customers worldwide, Aptar Pharma is the go-to drug delivery expert, from formulation to patient, providing innovative drug delivery systems, components and active material solutions across the widest range of delivery routes, including nasal, pulmonary, ophthalmic, dermal and injectables. Aptar Pharma Services provides early-stage to commercialisation support to accelerate and derisk the development journey. With a strong focus on innovation, the company is leading the way in developing digital healthcare devices to help improve patient adherence and compliance. With a global manufacturing footprint of 14 manufacturing sites, Aptar Pharma provides security of supply and local support to customers. Aptar Pharma is part of AptarGroup, Inc.

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Working daily to improve the health of our patients and our planet

As the market leader in pMDI valve technology for asthma and COPD, Aptar Pharma is committed to improving the environmental impact of our products and ensuring our devices are safe and effective.

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Testing Solutions for pMDI Drug Development

Pressurised metered dose inhalers (pMDIs) are a class of combination drug products dependent on the optimisation of a formulation, device design and human usage to deliver an accurate, reproducible dose. In the case of pMDI suspension products, the shaking profile is crucial for accurate dose delivery. Lack of appropriate shaking can deliver a high amount of the drug in the early doses followed by very little or no drug towards the end of the product's life. Other important influencing factors on pMDI performance include force-to-actuate and hold time to ensure that the metering valve is open long enough to deliver a complete dose. A minimal shake-to-fire delay is another crucial factor for maintaining the uniformity of the delivered dose (Figure 1).

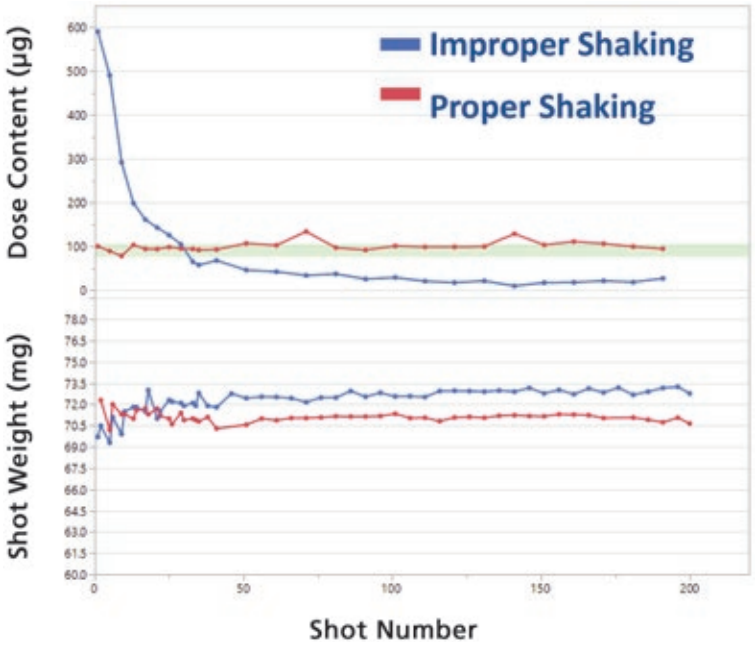

Figure 1: Example of dose content and shot weight for a suspension pMDI product with improper and proper shaking.

COMPLETE SUITE OF pMDI TESTING SOLUTIONS

Proveris by Design

Based on the quality by design (QbD) approach endorsed by the US FDA, Proveris by Design first provides the basis of experiments to identify the range of human usage parameters of a pMDI according to current regulatory guidelines for *in vitro* testing. Next, it offers strategies to test the range of design spaces and gain an understanding of the control space: which of these factors have the most impact on product performance? Lastly, it identifies the target operating space and control for key influencing factors in a tight range during the *in vitro* testing. One of the deliverables of the approach is a sensitivity map based on the design of experiments which shows how much influence certain factors identified

> "The insight gained into product performance can be used long after product approval to investigate and resolve any out-of-specification or out-of-trend disruptions to manufacturing."

Typical Influencing Factors for pMDI Products		Screening Experiments Category
Formulation	Morphology of API (size and shape) Formulation form (suspension/solution) Propellent Excipients	Performance testing
Device	Metering valve Actuator (sump geometry) Assembly process	Component characterisation
Human Usage	Shaking and shake-to-fire delay Hold time Product actuation force Actuation velocity	Functional testing

Table 1: Typical influencing factors for pMDI products and Proveris by Design screening experiments.

in the design space have on the overall performance of the product. In the R&D phase, clients engage Proveris Laboratories to perform tests using this method to produce consistent, high-quality data efficiently during product development and for preparation of regulatory submissions. The results show an overall reduction in approval timeline and minimised queries from regulatory agencies. Moreover, the insight gained into product performance can be used long after product approval to investigate and resolve any out-of-specification or out-of-trend disruptions to manufacturing (Table 1).

Ergo Studies

As a contract test service, Proveris Laboratories offers human-realistic actuation studies performed using proprietary Ergo technology to quantify accurately how trained testers in the targeted population actuate the product. Client device candidates, and/or reference products in the case of generic drug development projects, are evaluated to obtain key actuation parameters, such as stroke length, velocity, acceleration and hold time. This data is fully transferrable to Proveris Vereo automated actuators to enable reproducible actuations in a human-realistic way.

Vereo SFMDx Actuators

As with any pharmaceutical product, it is important to perform *in vitro* tests with repeatable, reproducible and robust methods for a smoother product development process. Vereo actuators provide fully controllable and repeatable shaking and actuation for commonly required regulatory tests, controlling up to six critical actuation parameters and four additional parameters related to shaking for pMDI devices. The flexible SFMDx actuator fits seamlessly into multiple testing workflows with identical actuation parameters implemented across all tests, ensuring data integrity and accuracy (Figure 2).

In vitro tests performed using Vereo SFMDx actuators (Figure 3) include:

- Delivered dose uniformity (DDU)
- Single actuation content uniformity (SAC)
- Valve/pump delivery (shot weight)
- Aerodynamic particle size distribution (APSD)
- Droplet size distribution (DSD)
- Spray pattern and plume geometry

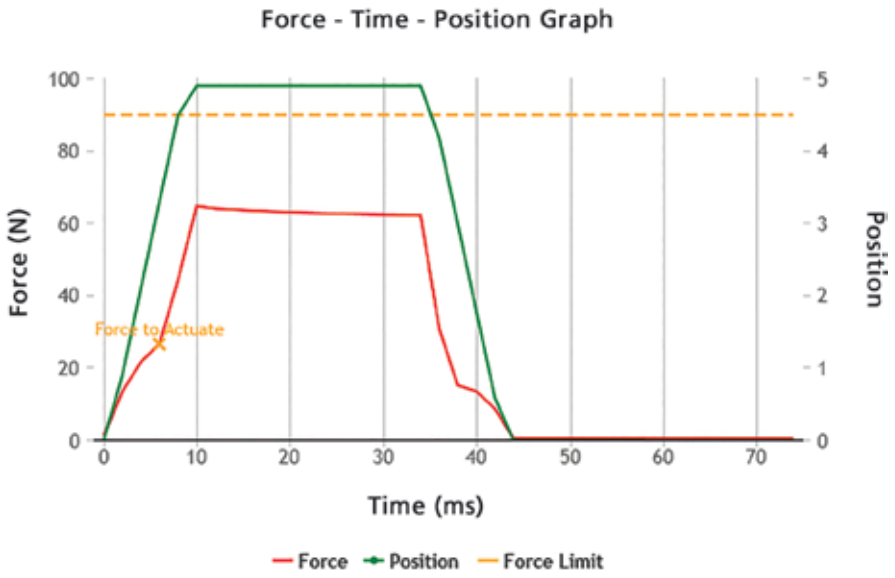

Figure 2: Proveris instrument users can create and evaluate products using force/position versus time plots generated by the system software.

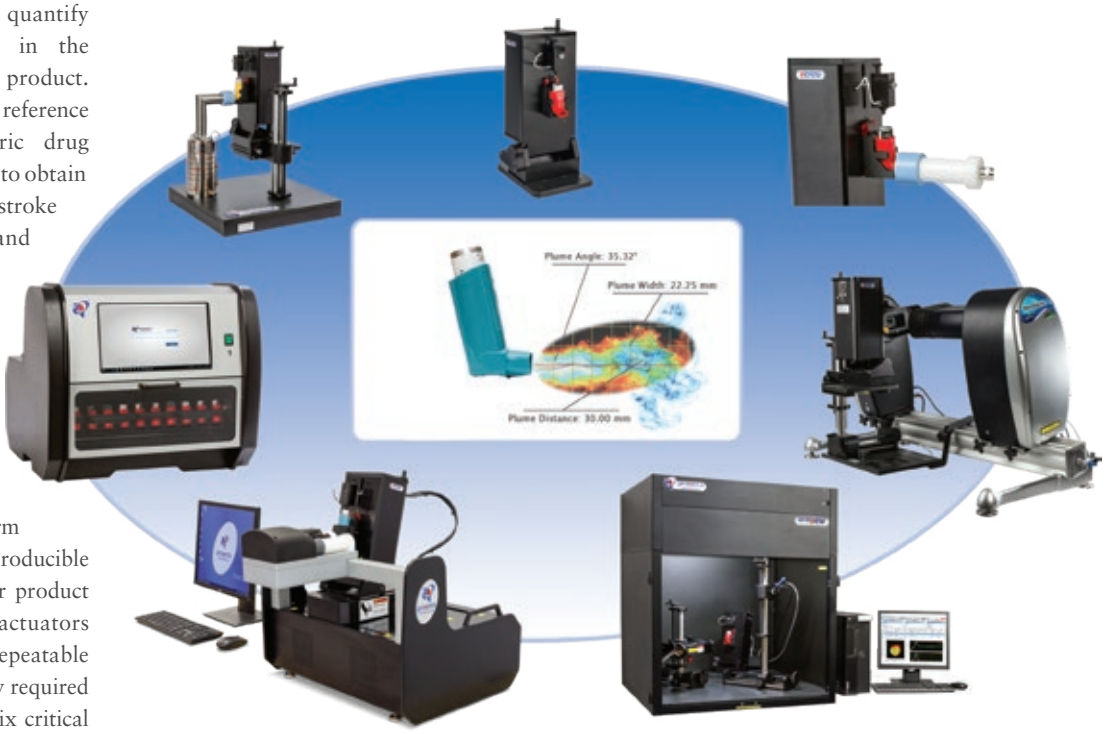

Figure 3: Proveris precision instruments and test workflows incorporate Vereo actuator technology for testing of pMDI products.

- Priming and repriming
- Product wasting for through-life testing

New Kinaero Cx pMDI Collection System

The newly introduced Kinaero Cx system easily integrates into DDU and APSD test workflows to automate parameters including shaking, actuation and dose/sample collection in a reliable, repeatable manner using proven Vereo actuator technology. To automate the whole workflow, users can run the Kinaero Cx alongside the Kinaero High-Throughput pMDI Fire-Down System for through-life testing, using a powerful common software platform consistent with full regulatory compliance (21 CFR Part 11).

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- System works with most pMDI devices

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EVOLUTION OF NEBULISATION FOR DRUG DELIVERY TO THE LUNGS

In this article, Daniel Lock, Specialist, Pharmaceutical Development, at Ventura, discusses the latest innovations in nebuliser technology for drug delivery to the lungs.

The term "nebuliser" represents a diverse and differentiated group of devices that deliver inhaled therapeutics to the lungs, encompassing jet nebulisers, ultrasonic nebulisers and, more recently, innovative vibrating-mesh nebuliser devices. The array of nebuliser devices now available is as diverse as the full range of delivery options available to innovators in the inhaled pharmaceutical sector, including pressurised metered dose inhalers (pMDIs), dry powder inhalers (DPIs) and soft mist inhalers (SMIs). To assume that all the nebuliser devices currently available offer the same benefits could be restrictive in terms of getting an inhaled pharmaceutical product to market.

Traditionally, nebulisers may have been viewed as the lesser-used, older-generation devices when compared with smaller, more scalable pMDIs and DPIs. However, there are some circumstances in which nebulisers are particularly suitable, such as helping the very young, infirm or physically or cognitively impaired to manage their respiratory conditions. For patients who are barely conscious or mechanically ventilated, a low-velocity aerosol with a particle-size distribution suitable for inhalation is ideal for administration without the need for active patient participation.

Nebulisers also provide emergency care for severe asthma attacks, exacerbations due to lung disease and serious inspiratory effects of viral infections, such as those witnessed during the covid-19 pandemic, as well as being able to deliver high doses of medication over extended treatment times. Additionally, where a drug cannot be delivered by DPI or pMDI due to it not being available in those dosage forms – including off-label use or because of a high total drug delivery requirement, such as might be the case with antibiotics and biologics – a nebuliser may be a highly effective alternative administration device (Figure 1). Furthermore, formulating a drug in a liquid

> "The long treatment times associated with nebulisers have been dramatically reduced by advances in device technology, paving the way for their use in a wider variety of product concepts."

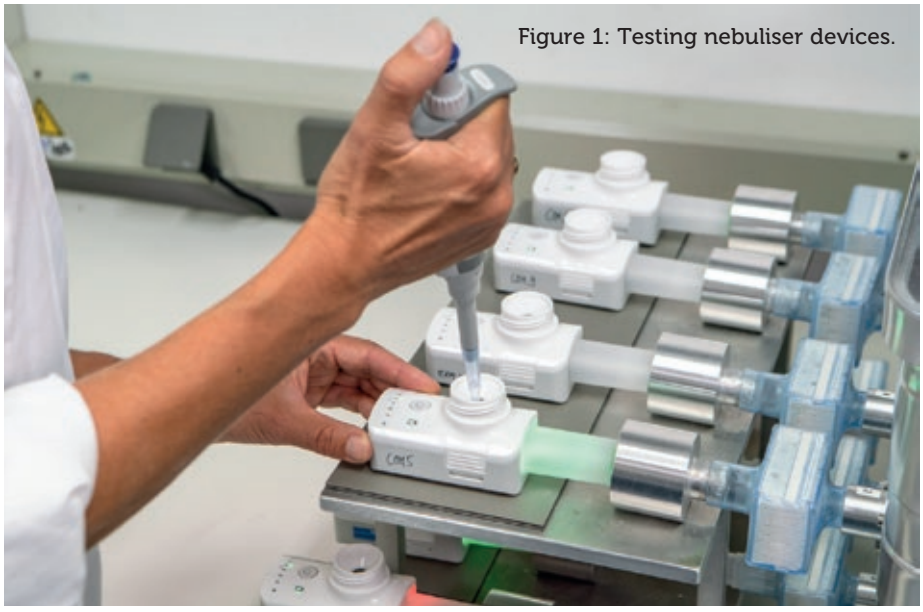

Figure 1: Testing nebuliser devices.

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preparation is often more straightforward in terms of costs and managing the stability of the API, while different fill volumes and/or concentrations make dose escalation and dose range finding simpler at an early stage.

Driven by advances in technology, innovations in inhaled therapeutics and covid-19, the profile of nebuliser users is changing and expanding. Nebulisers are now increasingly being considered for delivery of high-value, narrow therapeutic index medicaments; the management of lung disease for patients on the move; and delivery of specialised respiratory products not historically delivered using nebulisers, such as systemic or "off-target" delivery, cytokine and hormone therapies.

Nebulisation is not usually associated with precision. However, advances in technology have driven increased reproducibility for drug-nebuliser combination products. Similarly, the long treatment times associated with nebulisers have been dramatically reduced by advances in device technology, paving the way for their use in a wider variety of product concepts. They are evolving from simpler, air-driven devices to ultrasonic atomisers and, most recently, vibrating mesh nebulisers (Figure 2), becoming smarter, quieter, more portable and more efficient.

Air-driven jet nebulisers have traditionally dominated the market but innovators are increasingly focusing on vibrating mesh devices, which offer a low-velocity, actively produced aerosol. Unlike most DPIs, which are passive and high velocity – or pDMIs, which are active and high velocity – a mesh nebuliser has the ability to achieve precise control over when the formulation is aerosolised and for how long, and can also be tailored to the properties of the formulation being nebulised.

There are several successful vibrating mesh nebulisers on the market. These include devices that produce a continuous aerosol for tidally breathing patients – normal breathing at rest – and ones that incorporate sophisticated features, such as monitoring the breathing behaviour of the patient to time the bolus, thereby optimising drug delivery to the lungs and reducing waste to the environment. These types of devices can also include other advanced features, such as visual displays and automatic empty detection.

"The selection and design of the most appropriate nebuliser device depends on a number of factors, including the intended location of treatment, the severity of disease and the target patient population."

Figure 2: A handheld vibrating mesh device, which delivers nebulised drug products deep into the lungs.

The selection and design of the most appropriate nebuliser device depends on a number of factors, including the intended location of treatment, the severity of disease (relief of acute, life-threatening symptoms or management of a chronic condition) and the target patient population. Their use and nature can be diverse – compare an inline, continuously producing nebuliser device used for a patient attached to a ventilator with, at the other end of the spectrum, a small handheld device that provides audible and visual feedback and directs the patient to breathe in a particular manner. Both of these devices are considered nebulisers but fulfil very different roles. In the case of the inline, continuously producing nebuliser, its size and design is secondary compared with the specific patient need.

Likewise, if a patient is admitted to hospital gasping for breath and in a state of confusion, a device that requires precise co-ordination to operate could be dangerously inadequate – even if, in other circumstances, it would provide very high and effective doses to the lungs. On the other hand, such a precise and accurate device could be very well suited for the delivery of higher-cost, narrow therapeutic index medicaments in the domiciliary setting.

The use of functional respiratory imaging using high-resolution computed tomography (CT) scans and computational fluid dynamics has demonstrated that, by using a device that carefully controlled flow and volume, the lung deposition of idiopathic pulmonary fibrosis patients was approximately two-and-a-half times greater than with a continuously operating system used with tidal breathing.[1] Furthermore, the increase in the deep lung deposition achieved was of even greater magnitude.

The advent of "smart" nebuliser technology was instigated, in part, by the fact that nebulisers already had requirements for a power source and, later, battery power sources and circuit boards suitable for more advanced controls. In addition, device developers responded to market trends calling for greater patient compliance in clinical trials and for commercialised home-use products with an array of features and companion apps for connected devices. This created conditions for the development of more sophisticated drug delivery devices.

Vibrating-mesh nebulisers, for example, have been designed to "coach" the patient to inhale in a manner that can maximise lung deposition, especially in the deep lung. Particle size of the inhaled formulation is an important parameter for successful pulmonary delivery. However, it is not the only factor and can be less important if, for example, the patient's inhalation is

> "The development of smart nebuliser devices offers the opportunity to expand their use to wider patient groups, rather than simply for those who cannot use a pMDI or DPI effectively."

too shallow or too rapid. A well-controlled particle size distribution, a low-velocity aerosol and carefully guiding and training the patient have been shown to achieve extremely high lung doses, such that even particles larger than the typically accepted cut-off of 5 µm may reach the deeper regions of the lung.

The manner in which patients can be influenced to use a device varies but is governed by what is reasonable and, ultimately, what can be proven in well-designed human factors studies. For example, using a combination of soft control features, such as coloured lights and barometric or haptic feedback, can result in a high level of accuracy and reproducibility, allowing optimal deposition to become simple and intuitive. Devices can be designed to be breath actuated – they will not nebulise unless a pressure drop is detected and, if the patient stops inhaling midway through the breath pattern or exceeds the intended inhalation volume, they can be alerted by a sharp increase in device resistance, as well as audible and visible cues.

The development of smart nebuliser devices offers the opportunity to expand their use to wider patient groups, rather than simply for those who cannot use a pMDI or DPI effectively. Additionally, nebulisers will no longer be restricted to emergency respiratory care but will become real options for the delivery of cutting-edge, high-cost, high-tech or systemically acting treatments thanks to their increasingly efficient and precise delivery to the lung.

Device technology advancements are outpacing the clinical and commercial elements that determine their use but the increasing array of device features and associated connectivity presents some very interesting possibilities for the future. With increased control over the flow rate and inhalation volume, interpatient variance – at least in terms of regional deposition and topical exposure to drug product – could be significantly reduced.

The benefits of controlled breathing patterns already demonstrate a predicted reduction in total lung dose variability, which potentially could be taken a step further by using spirometry data to normalise for individual lung function – in essence, normalising for inspiratory capacity. The extent to which this is sensible is multivariate but there is no doubt that these features provide significant potential benefits for clinical development, whether or not the final device is a nebuliser product. Furthermore, as nebulisers are more frequently used in the domiciliary setting, this creates new and interesting areas for innovation to make their use, cleaning and maintenance more straightforward, with the ultimate goal of improving patient compliance.

Nebulisers are already attractive devices to obtain early-phase clinical data for new chemical entities. Couple this with connected health to collect important metadata and the potential to de-risk clinical trials by removing some of the inherent variability, and smart nebulisers offer the opportunity to significantly accelerate development and the understanding of products under development.

Traditional nebulisers will still be used and will continue to meet an important need. However, if the goal is to deliver high-cost speciality drug products precisely and efficiently, a smart nebuliser may offer the technology that can achieve this.

ABOUT THE COMPANY

Vectura is a leading specialist inhalation contract development and manufacturing organisation that provides innovative inhaled drug delivery solutions that enable customers to bring their medicines to patients. With differentiated proprietary technology and pharmaceutical development expertise, Vectura is one of the few companies globally with the device, formulation and development capabilities to deliver a broad range of complex inhaled therapies. Vectura has 13 key inhaled and 11 non-inhaled products marketed by partners with global royalty streams, and a diverse partnered portfolio of drugs in clinical development.

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ABOUT THE AUTHOR

Daniel Lock joined Vectura in 2010 and is a pharmaceutical development specialist, working on a wide array of product and technology development workstreams – from DPI generic programmes to cross-platform *in-vitro/in-vivo* correlation. Recently, he has been working with the Inhaled Product Solutions group as a Team Leader, bringing experience in early-phase development with the FOX® smart nebuliser. In 2022, he has resumed technology development and innovation workstreams relating to cross-platform understanding of formulation/device interactions to optimise performance.

ON drugDELIVERY

2022/23 EDITORIAL CALENDAR

Publication Month	Issue Topic	Materials Deadline
April/May 2022	Drug Delivery & Environmental Sustainability	Deadline passed
May	Delivering Injectables: Devices & Formulations	Deadline passed
June	Connecting Drug Delivery	May 12, 2022
July	Novel Oral Delivery Systems	Jun 2, 2022
August	Industrialising Drug Delivery	Jul 7, 2022
September	Wearable Injectors	Aug 4, 2022
October	Prefilled Syringes & Injection Devices	Sep 1, 2022
Oct/Nov	Drug Delivery & Environmental Sustainability	Sep 15, 2022
November	Pulmonary & Nasal Drug Delivery	Oct 6, 2022
December	Connecting Drug Delivery	Nov 3, 2022
January 2023	Skin Drug Delivery: Dermal, Transdermal & Microneedles	Dec 1, 2022
February	Prefilled Syringes & Injection Devices	Jan 12, 2023
March	Ophthalmic Drug Delivery	Feb 2, 2023
April	Pulmonary & Nasal Drug Delivery	Mar 2, 2023

DO SOFT MIST INHALERS HOLD THE KEY TO FASTER INHALATION DRUG DEVELOPMENT?

Here, Wilbur de Kruijf, General Manager and Chief Technology Officer, and Bernhard Müllinger, General Manager and Chief Operations Officer, both at Resyca, a joint-venture between Recipharm and Medspray, discuss the the market requirements for new inhalation options and the benefits of soft mist inhalers.

The rise of the biopharmaceutical segment has increased the value of the inhalation sector, with more and more drug developers exploring inhalation as an alternative delivery mechanism to the parenteral approach traditionally used for biologics.

While inhalation is an ideal delivery pathway for a wide range of drugs, pharmaceutical companies face a range of challenges when developing effective inhalation drug products. In fact, the cost and complexity of developing and customising inhalation devices and formulations are often too high for biologics or drug products requiring large dosages.

Soft mist inhaler (SMI) technology has evolved in recent years alongside traditional inhalation device technologies with a range of different technical capabilities. Does SMI technology offer the opportunity to address this issue and support the expansion of the inhalation segment?

THE MARKET NEED FOR NEW INHALATION OPTIONS

Managing respiratory illnesses has reached an annual cost of US$81.9 billion (£61.8 billion) in the US[1] and $110 billion in the EU.[2] Respiratory diseases are the third leading cause of death in EU countries, accounting for 8% of all deaths in 2017 alone.[3]

With this burden on the healthcare system set to continue, biopharma companies are under continued pressure to respond to the increase in global diagnoses of acute respiratory conditions.

Biopharma companies are also becoming aware of the potential of inhalation as a delivery route for more short-term treatments. Inhaled antibiotics have been developed for treatment of acute bacterial infections in patients with cystic fibrosis (CF), non-CF bronchiectasis and ventilator-associated pneumonia.[4] Studies have also been conducted that examined inhaled therapies for the treatment of cardiovascular diseases, such as paroxysmal atrial fibrillation, and diseases affecting the brain, including acute repetitive seizures.[5]

> "Innovations in orally inhaled delivery devices are essential to meet these rising demands while ensuring that delivery is efficient, effective and patient-friendly."

Direct delivery to target sites within the respiratory system, rapid onset of action and a reduced risk of systemic side effects are significant advantages of inhalation compared with oral therapies.[6] With such advantages in mind, it is no surprise that inhalation is being considered for a wider array of drug formulations.

Advances in drug development are resulting in inhaled therapies that are longer-acting, require smaller doses or are intended to treat non-chronic conditions.[7] Consequently, devices designed for short-term use to deliver these drugs are becoming increasingly sought after.

Innovations in orally inhaled delivery devices are essential to meet these rising demands while ensuring that delivery is efficient, effective and patient-friendly. Throughout development of these new products, it is essential that developers remain aware of the sustainability, cost and complexity involved in manufacturing devices.

UNDERSTANDING SOFT MIST INHALERS

Drug delivery device innovations have led to the development of SMIs, a liquid-based inhaler capable of producing a

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"For paediatric and geriatric patients, who may have difficulties with inhalation technique, SMIs may simplify treatment administration, thereby improving deposition in the lung."

slow-moving aerosol cloud. These devices provide convenient, optimal drug delivery to the lungs while reducing the need for patient co-ordination and inspiratory effort. SMIs are designed to be hand-held devices, further offering ease of use for patients. In contrast to conventional liquid delivery systems, such as nebulisers, SMIs allow integration of the drug product's container closure system into the SMI. This allows distribution of the device in combination with the drug product and locks the two together (creating a closed system). As a result, their use has recently been approved in treatments for a variety of respiratory diseases.[8] They also have great potential to be used to administer treatments that require shorter-term care.

How SMIs Work

Drugs in SMI devices are formulated in liquid formulations, as opposed to a powder (as in dry powder inhalers), and stored within a drug cartridge or syringe. This offers advantages for APIs that are readily available in liquid formulations. By formulating in solution, for example, problems with moisture adsorption and subsequent agglomeration can be avoided. Jet-milled powder used in some inhalers is extremely cohesive and prone to strong agglomeration due to the electrostatic charge and increase in surface energy.[9]

As opposed to other technologies that use propellants, such as inspiration or electrical energy, aerosol formation in SMIs is powered by mechanical energy, such as that from a compressed spring or other simple robust mechanical system. Patients trigger the release of the drug (e.g. by pushing a button) whereupon the mechanical energy is used to transfer a predefined metered volume of the drug from the cartridge. This ensures that the dose delivered with each actuation remains uniform.

The mechanical energy pushes the liquid drug formulation through a silicon chip with micro-nozzles. The nozzles form liquid jets that break up into small respirable droplets. As a result, a slow-moving mist with a high fine particle fraction is produced.

The size of the pores or channels in the nozzle determines the droplet size, which will impact the area in the lung that the drug is deposited. By synchronising the patient's breathing with the actuation, the droplets can mix with the inhalation air stream to form a slow-moving cloud of soft mist. Inhalation of a slow-moving cloud means that less of the dose is deposited at the back of the throat, and a higher proportion of the drug is deposited in the lung.[10]

SMIs are both environmentally friendly and have a long spray duration, making it easy for patients to co-ordinate their breathing. Correct inhaler technique is important for optimal delivery of the drug to the lungs and peripheral airways. For paediatric and geriatric patients, who may have difficulties with inhalation technique, SMIs may simplify treatment administration, thereby improving deposition in the lung.

UNDERSTANDING PREFILLED SYRINGE INHALERS

Prefilled syringe inhalers (PFSIs) are one type of soft mist inhaler. In these devices, the formulated drug solution is stored within a prefilled syringe (PFS). When actuated, the syringe plunger is pushed forward, applying pressure in the PFS, which forces liquid to flow to the spray nozzle unit where it is aerosolised and inhaled by the patient. To avoid inconsistent dosing, this pressure must be applied in a controlled way. This can be achieved with spring-loaded devices that apply pressure smoothly and accurately over time.

Although PFSI devices are not yet available on the market, they offer exciting opportunities for the future. PFSIs have the advantage of being potentially available as both single-use and reusable devices. To reuse, the PFS can be simply switched out for a new one and the mouthpiece disposed of and replaced. As a result, they are ideal for use in clinical environments, clinical trials for investigational drug products and single dose treatments.

"It is clear that SMIs offer a number of distinct advantages for patients, including ease-of-use, portability and high percentage of lung deposition."

WHERE SMIs CAN ADD VALUE

It is clear that SMIs offer a number of distinct advantages for patients, including ease-of-use, portability and a high percentage of lung deposition. Using SMIs can also be advantageous when developing drugs compared with other devices.

Suitable for Biologic Formulations

Most biologic drugs currently in clinical development are in liquid form to streamline formulation processes. As a result, SMIs offer distinct advantages for many biologic drugs requiring delivery to the lungs. Using a fill-finish platform of glass PFSs with the soft mist nozzles already mounted in, PFSI manufacturing can also offer good stability of the drug formulation and improved shelf-life, even for complex biologic drugs. In addition, SMIs allow the effective aseptic filling required for biologic products.

Increased Drug Delivery Potential

Many COPD sufferers rely on multiple medications, each requiring its own delivery device. SMIs can be used to deliver multi-API drug formulations, easing administration of multiple medications and potentially improving patient compliance. However, drug formulation for solutions containing multiple APIs can be challenging.

Although conventional SMIs are generally suited to low doses, PFSIs can also be used to deliver both low and high doses, further increasing their potential.[11,12]

Gentle Aerosolisation for Sensitive Drug Products

SMIs can present an alternative to certain types of nebulisers for the delivery of biologics. The ultrasound, vibration and cavitation methods used in nebulisers to create aerosols can damage proteins, such as antibodies and lipid-based nanoparticles, and lead to shear degradation.[13] SMIs can be designed with specialised nozzles that limit shear forces and are gentle on fragile formulations.

"SMIs such as PFSIs offer sustainability as they can be reused – drug storage modules (syringes) can be easily switched out or refilled."

Sustainability

SMIs such as PFSIs offer sustainability as they can be reused – drug storage modules (syringes) can be easily switched out or refilled. This means the device could be used for the administration of multiple therapies.

CONSIDERATIONS FOR CUSTOMISING SMIs

Despite the benefits SMIs offer, there is still a need to overcome certain challenges in development, particularly surrounding formulation and optimisation for device compatibility. For different drugs, SMIs will need to be carefully customised to deliver efficient treatment. Maintaining sterility in the container throughout repeated use without using preservatives is also a challenge for liquid systems when compared with dry powder inhalers.

Formulation Development Considerations

Ensuring dose uniformity is particularly challenging for drug products delivered via the inhalation route. Inhaled delivery of aerosols is generally influenced by the patient's inhalation flow and the consistent release of a predetermined volume not of the drug but of the drug formulation.

To minimise dosing variability, care must be taken to avoid blocking the nozzle, which could impact the particle size and mist formation. This can occur as a result of irreversible agglomeration or caking of particles in solution due to inadequate formulation. As the API would no longer be evenly distributed in the solution, this could be further detrimental to dose uniformity.

Device Considerations

The aerosol particle size characteristics of the aerosolised drug will affect the amount of drug that reaches the lungs, and therefore the efficacy achieved. By adapting the method used to generate fine particles and their size, drugs can be delivered more precisely. For example, drug particles with a diameter of 2–5 µm will more likely be deposited in the peripheral airways and small bronchioles, whereas larger particles will be deposited in the upper airways.

Additionally, lung deposition when using certain SMIs has been shown to be significantly higher at a slow flow rate with a larger particle size compared with high flow rate with a smaller particle size. As a result, the flow rate is also important to consider when optimising delivery and should be considered in conjunction with particle size.

By engineering the nozzle to optimise particle size distribution, adjusting the nozzle pore size and selecting a suitable built-in flow limitation for the device, efficient delivery to specific areas of the lungs can be achieved.[14]

"The inhalation drug market is growing quickly, with many inhalation products currently in development or at clinical trial."

WHAT'S IN STORE FOR THE INHALATION SEGMENT?

Advancements in inhalation product design and engineering have improved the precision and accuracy of dosing while enabling delivery of a wider range of drug formulations. Consequently, the inhalation drug market is growing quickly, with many inhalation products currently in development or at clinical trial.

Furthering this growth relies on cost-efficient and effective drug delivery devices. SMIs represent an ideal solution with several advantages over traditional inhaler devices and have the potential to make inhalation a viable option for a wider range of drugs than ever before.

ABOUT THE COMPANY

Resyca is a joint venture between Recipharm and Medspray (Enschede, the Netherlands) and a sister company to Recipharm, forming part of Recipharm's Advanced Delivery Systems business unit.

Resyca acts as a single hub to deliver next-generation SMI devices that are ideal for the delivery of both small and large molecules, and designed to optimise lung deposition whilst minimising oropharyngeal deposition.

Resyca's innovative SMI technology platform consists of both PFSI devices and clinical devices that can be filled on the spot, speeding up clinical investigations. Development, manufacture, filling, assembly and packaging take place within Recipharm Group.

Recipharm is a leading contract development and manufacturing organisation in the pharmaceutical industry employing almost 9,000 employees. Recipharm offers manufacturing services for pharmaceuticals in various dosage forms, production of clinical trial materials and APIs, pharmaceutical product development, and development and manufacturing of medical devices. The company manufactures several hundred different products to customers ranging from big pharma to smaller research and development companies and operates development and manufacturing facilities in France, Germany, India, Israel, Italy, Portugal, Spain, Sweden, the UK and the US, and is headquartered in Stockholm, Sweden.

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ABOUT THE AUTHORS

Wilbur de Kruijf is General Manager and Chief Technology Officer at Resyca, based in Enschede, the Netherlands. Mr de Kruijf has a background in medical product design and human factors engineering. Prior to joining Resyca, he held a role at Medspray for 15 years, developing micro-spray nozzles and aerosol devices based on that technology. Mr de Kruijf has experience working with design consultancy firms developing a range of medical devices, such as wheelchairs, hospital beds, x-ray scanners and drug delivery devices.

Bernhard Müllinger is the General Manager and Chief Operations Officer of Resyca and is based in Munich, Germany. Mr Müllinger has experience with smart nebuliser devices and has worked in this industry for most of his career. He has extensive knowledge in medical device development and clinical development of combination products. Prior to joining Resyca, Mr Müllinger worked at Vectura (Chippenham, UK), Activaero (Gemunden, Germany), which was acquired by Vectura in 2014, Inamed-CRO (Munich, Germany), Asklepios Clinic (Hamburg, Germany) and Helmholtz-Zentrum (Neuherberg, Germany).

USING QUALITY BY DESIGN TO OPTIMISE THE COMBINATION PRODUCT JOURNEY

In this article, Justin Lacombe, PhD, Chief Scientific Officer at Experic, and Julie D Suman, PhD, President, Scientific Affairs at Next Breath, explain how applying quality by design principles to combination products improves development efficiency, aligns with design controls, and maximises product safety and efficacy.

With the shift from quality by test (QbT) to quality by design (QbD) principles in drug development and manufacturing, drug and device developers have adopted a flexible approach that allows them to determine the root cause of a quality issue more quickly and adjust accordingly. Applying QbD principles to combination products is especially valuable due to the complexity inherent in both clinical and commercial manufacturing. Following a QbD approach helps developers identify quality issues earlier in the development process, which helps streamline the path through clinical trials to regulatory approval and commercial release.

WHAT IS QUALITY BY DESIGN?

As applied to pharmaceutical development and manufacturing, QbD refers to a systematic approach that is based on predefined objectives, emphasises product and process understanding and control, and is based on sound science and quality risk management. QbD has been part of ICH guidance since 2005 for drug product development, and has since been extended to include drug substance and analytical method development.

As outlined by the ICH guidance, QbD includes the following elements:

- A thorough identification of the definition of a product through its critical quality attributes (CQAs)
- A systematic evaluation, understanding and refining of the formulation and manufacturing process, including:
  - Identifying (through, for example, prior knowledge, experimentation and risk assessment) the material attributes and process parameters that can have an effect on CQAs
  - Determining the functional relationships that link material attributes and process parameters to product CQAs
- Using the enhanced product and process understanding in combination with quality risk management to establish an appropriate control strategy which can, for example, include a proposal for a design space(s) and/or real-time release testing.

QbD combines the target product profile with quality requirements to arrive at a quality target product profile (QTPP). The objective is to bring together ICH quality risk management, regulatory requirements and design of experiments to arrive at robust products and processes, with the end goal of more efficient design, development and manufacturing.

WHY TAKE A QUALITY BY DESIGN APPROACH?

Combination products, including prefilled syringes, autoinjectors, infusion systems and dry powder inhalers (DPIs) have advanced dramatically over the past several years. Within this context, DPIs – as systems to deliver drugs via inhalation to the lungs – require a deep understanding of the complex formulation-device-patient interplay.

A methodical, focused approach is critical for developing products that are consistently safe and effective for their intended patients. DPIs, for example, require the formulation and device to work in concert to deliver

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the inhaled dose. Development for DPIs and other combination products includes the integration of QbD principles with process development, design controls and human factors (HF).

Because QbD is a systematic approach that builds quality into product design and development, it enhances development capability and speed, as well as formulation design. As a proactive rather than reactive process, QbD allows product developers to identify issues earlier than they could under a QbT approach, increasing efficiency by focusing on the most important interactions – a priority for all stages of combination product development and manufacturing. QbD also benefits later stages of development as, with an improved understanding of product and process, manufacturers can scale up more easily and efficiently.[1]

However, successful combination product development and manufacturing using a QbD approach requires varying and advanced expertise. It brings together pharmaceutical science and regulatory disciplines, all related to both drug formulation and device performance, to optimise drug delivery and achieve the best outcome for a development programme.

QUALITY BY DESIGN AND GMP COMPLIANCE

QbD for combination products aligns with good manufacturing practice (GMP) requirements for drug products, as well as the following medical device GMP requirements per 21 CFR Part 820:

- **Management responsibility**: senior-level oversight of the process from development through to validation
- **Corrective and preventative action (CAPA)**: procedures for implementing CAPAs
- **Purchasing controls**: quality agreement between supplier and sponsor with well-defined change controls
- **Design controls**: process for confirming that there is no negative interaction between the drug and device.

DESIGN CONTROL: BRINGING DRUG AND DEVICE TOGETHER

The design and development of a medical device or its constituent parts is performed under the rigorous structured framework of the design controls process. The process involves several steps, starting with identifying patient needs, which is arguably the most important step in the process.

Once the patient needs have been identified, the process continues by translating these needs into design and engineering requirements. These requirements feed into the design process to create a prototype with controlled specifications (i.e. outputs).

Next, developers determine whether the product meets CQA and other design aspects through a verification process, often carried out with support from a device supplier. The finished combination product then goes through a rigorous validation process that includes clinical trials and HF (summative) studies. The primary question to answer during these studies is "Does this combination product address the patient needs set out in step one?"

Following a QbD process aligns well with the medical device design controls process. This, in turn, allows more development activities to occur in parallel than under QbT. Risk management, which takes place throughout the development process, can then encompass and inform both the drug and device development processes (Figure 1).

HUMAN FACTORS: A STUDY IN PERFORMANCE

HF studies relate to safety and efficacy but primarily focus on how the patient (or user) interacts with the combination product. HF studies help sponsors uncover the cause of issues that arise during use. Over the past five years, the US FDA has taken a stronger interest in HF studies, issuing guidance on HF information for combination products in 2016.

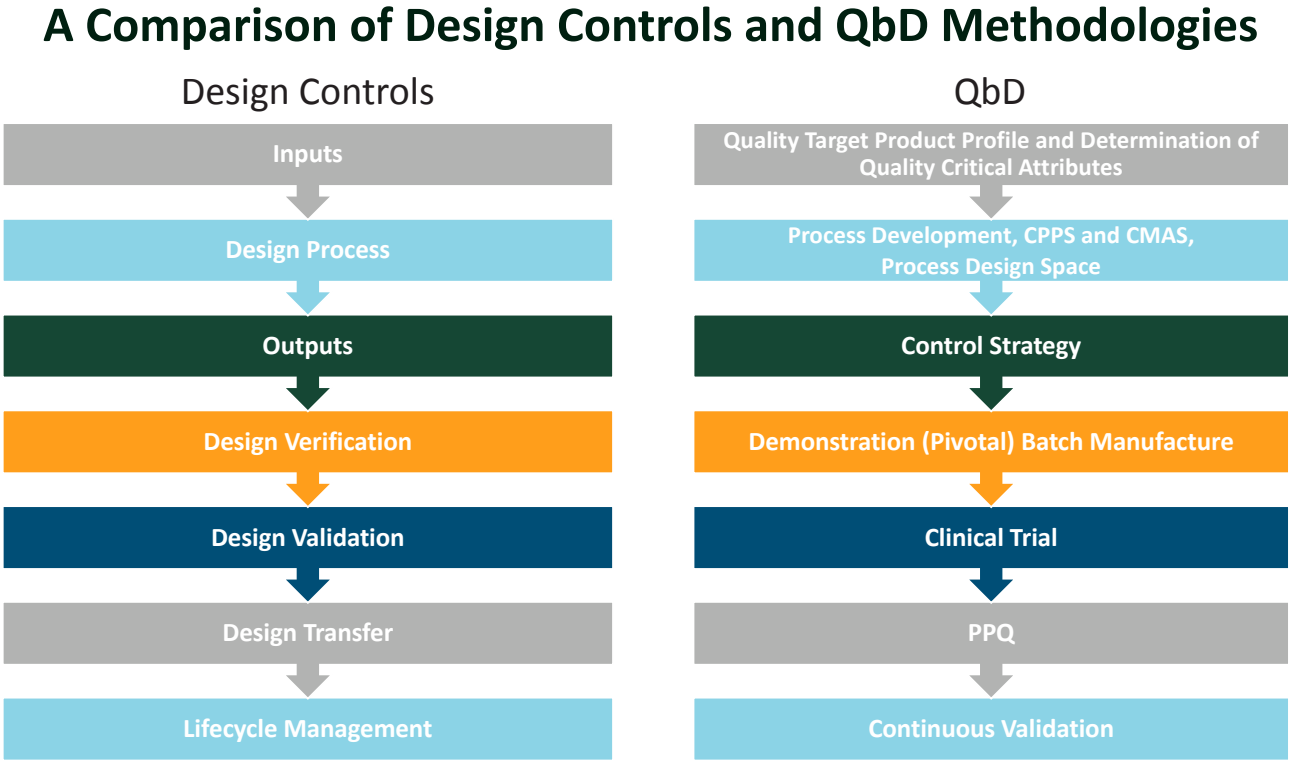

Figure 1: A comparison of traditional and QbD design controls.

> "Combination product developers must prove that all the tasks involved in a combination product allow patients to use the product safely and effectively."

When conducting HF testing for combination products, defining the patient and patient needs is critical. The patient's age; whether they will use the product at home, in the doctor's office or the emergency room; and whether the patient, a caregiver or a physician will administer the product all play a role in HF study design.

HF also considers the patient experience, which differs from traditional oral drug products. Rather than simply swallowing a pill, tablet or liquid, the patient performs several tasks to administer the product – for example, inserting a cartridge, removing a cap, turning on a device, pressing a button, stopping delivery and so on. DPIs that incorporate digital technology (e.g. smart inhalers) may be tailored to patients' breathing patterns and add additional features to address handling errors.

Failure to correctly perform any of the tasks necessary to administer the drug increases the risk that the patient will not receive the intended dose. Combination product developers must therefore prove that all the tasks involved in a combination product allow patients to use the product safely and effectively.

POINTS TO CONSIDER BEFORE MEETING WITH A CDMO

Clinical and commercial manufacturing of a combination product involves multiple interrelated steps. In addition to formulation, filling and testing, manufacturing these products involves component design, assembly and labelling. These processes interact with one another, multiplying the complexity. When meeting with a contract design and manufacturing organisation (CDMO) for the first time, keep these complexities in mind. Any outsourcing of manufacturing or certain processes to a moulder, product design firm, analytical laboratory or other third-party vendor also increases the complexity of managing the project.

When using a QbD approach, keep the following practices in mind for a more efficient sponsor-CDMO relationship:

Determine Responsibilities

Which part of the assembly process will the CDMO handle versus an outside vendor? Using CDMO-approved vendors instead of a sponsor's own may require more extensive release testing.

Prepare for Additional Labelling Requirements

When moving a combination product through clinical trials, sponsors may have more extensive labelling requirements. A multidose device, for example, may include labelling for the device itself, the device packaging and the carton it's transported in.

Define Process Requirements

Manufacturers must determine processes for formulations, filling, assembly, labelling, sampling and inspection. If filling takes place at a different site, sponsors will need to think about shipping steps, storage containers, packaging conditions and allowable hold times. With moisture-sensitive or potent materials, sponsors will also need to consider what part of these processes need to occur within these protected environments. Do operators need protection from highly potent materials? What parts of the system need low relative humidity?

Establish Formulation and Filling Processes

For combination products, manufacturers will need to know both occupational exposure limits and permitted daily exposure limits, as well as formulation method and parameters, and filling mechanisms and limits. Manufacturers also need to be aware of interactions between performance and filling requirements.

Understand Component & Sub-Assembly Requirements & Specifications

Sponsors must prepare well-defined documentation requirements that include all relevant certificates and inspections. Where applicable, include Transmissible Spongiform Encephalopathy and Bovine Serum Albumin certificates. Sponsors will also need to know the function of each component within the combination product and its level of risk. They must also outline and understand which components the CDMO will want to inspect.

Plan for Analytical Testing Requirements

A combination product like a DPI requires extensive testing as part of the QbD process. This includes aerosol performance, microbiological testing, leachables, and physical and chemical attributes. Sponsors should allocate sufficient material to meet the testing and stability requirements for these drug products.

THE MEETING: A RISK-BASED APPROACH TO PROCESS DEVELOPMENT FOR SPONSORS AND CDMOS

Meeting with a CDMO for the first time requires learning and patience on both sides. When preparing to manufacture a combination product, share all processes, requirements and specifications necessary so the CDMO can manufacture the product with consistency and accuracy.

Process development is one of the more involved elements of the CDMO-sponsor relationship. In terms of mitigating risk, process development informed by risk analysis and QbD is one methodology sponsors can use to determine risks involved in certain parts of the manufacturing and development processes. The more information obtained during process development, the better the yields and the higher the quality that can be achieved. As the product moves through development, sponsors will find fewer unknown quality issues during GMP manufacturing.

Applying QbD to process development requires the establishment of an acceptable quality target product profile (QTPP). Establishing a QTTP is achieved by defining product attributes and patient needs (CQAs). These needs are mapped to critical

> "Applying QbD principles to combination products not only improves efficiency by identifying quality issues early, it also helps maximise product safety and efficacy, and aligns it better with design controls."

material attributes (CMAs), evaluating the quality impact of critical process parameters (CPPs), and evaluating both metrics together. Risk analysis occurs during process development. Using a QbD approach, sponsors should consider using a risk analysis tool such as failure mode and effects analysis in conjunction with a decision tree to identify the highest risks.

ABOUT THE AUTHORS

Justin Lacombe, PhD, is Chief Scientific Officer at Experic, leading the pharmaceutical development and engineering teams to provide expertise, insights and solutions that address many of the technical challenges pharmaceutical companies encounter during drug and combination product development. With a focus on scale-up and process development using QbD and design controls principles, Dr Lacombe has expertise in manufacturing, combining small-volume dosing technology for rheologically complex powders, primary packaging development and formulation optimisation. He received his MSc and PhD in chemical engineering from Rutgers University (NJ, US) and has presented extensively on manufacturing drug product interaction, process development optimisation and drug-device combination products.

Julie D Suman, PhD, is Co-founder and President of Next Breath, an Aptar Pharma company. The contract research organisation is dedicated to the development and analytical testing of nasal, inhalation and injectable delivery systems. Dr Suman also supports Scientific Affairs for Aptar Pharma. She holds a BSc in pharmacy from Duquesne University (PA, US) and a PhD in pharmaceutical sciences from the University of Maryland, Baltimore (US). Dr Suman is a co-editor for Respiratory Drug Delivery Proceedings, an international symposium. She is also an affiliate assistant professor in the Department of Pharmaceutics, School of Pharmacy, Virginia Commonwealth University (VA, US). Dr Suman is the past-chair of the AAPS Inhalation Technology Focus Group.

BRINGING IT ALL TOGETHER

Applying QbD principles to combination products not only improves efficiency by identifying quality issues early, it also helps maximise product safety and efficacy, and aligns it better with design controls. Now that regulatory agencies encourage a QbD approach, it's more important than ever to build quality into the process. Connect QbD principles with design control and HF testing to arrive at combination products that bring the most benefit possible to the patients who need them.

ABOUT THE COMPANY

Experic, a CDMO and pharmaceutical supply services company, supports every phase of a product's lifecycle from clinical to commercial scale, across a range of dosing and packaging formats, including capsule filling, powder and pellet dosing (including DPI), and autoinjectors and pen assemblies. Using cutting-edge Harro Höfliger (Allmersbach im Tal, Germany) equipment in its state-of-the-art Class A GMP facility and build-to-suit suites, the company manages global delivery of the highest quality products, even for expedited projects, while providing unparalleled knowledge, expertise and customer service.

Next Breath is a speciality company of Aptar Pharma and a cGMP compliant analytical laboratory located in Baltimore, Maryland (US). Next Breath is viewed as an intellectual leader in the field of inhalation and nasal spray development, testing and regulatory strategy. Since inception, it has collaborated with over 65 pharmaceutical companies and contributed to several successful regulatory submissions in domestic and international markets. Its expertise and results have been used in NDAs, ANDAs, 510(k) studies and BLAs. In addition, Next Breath's FDA-inspected laboratory performs commercial batch release and stability studies for the US market.

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Solid Dose Solutions

MANUFACTURING DPIs: AN ENGINEERING PERSPECTIVE

In this article, Pietro Pirera, Product Manager for Capsule Fillers at IMA Group's IMA Active division, discusses the optimal process parameters for microdose dry power inhalers achieved by dosator technology.

When developing new dry power inhalers (DPIs), industrial manufacturing aspects must be considered from the very beginning to speed up the scale-up and optimisation of the final manufacturing process, as well as to achieve a more efficient and cost-effective production. Precise microdosing, weight control and ease of device assembly are all issues that must be faced at an early stage.

IMA draws on its extensive expertise to provide the most advanced solutions for DPI processing and assembly. Direct weight control performed in line on each single capsule or device, both before and after filling, for example. No mechanical powder compression – for improved airway intake. And accurate microdosing, as well as automatic feedback and adjustment.

This study investigates optimal process parameters for microdose DPIs achieved by dosator technology. The study proves that a major advantage of using this technology for processing DPIs is that the dosators can be accurately adjusted without any need to compress or aspirate the powder. Maintaining the free-flowing properties of the dispensed powder within the capsule better ensures the release of powder from the capsule into the inhaler when the capsule is pierced, thereby better controlling both the emitted dose and the fine particle fraction of the dose discharged from the DPI.

INTRODUCTION

In 1948, the first commercial DPI was launched on the market. This first technology seems archaic by today's standards: a deep inward breath would cause a ball to strike a cartridge containing powder and shake the powder into the airstream. Since then, changes in the drug delivery market and regulatory pressures have driven DPI innovation. It is estimated by the WHO that, worldwide, some 300 million people suffer from asthma and 240 million people suffer from chronic obstructive pulmonary disease (COPD). DPIs represent 50% of the total asthma/COPD market by value worldwide.

> "Patients and pneumologists are now increasingly focusing on convenience and ease of use, favouring a compact design."

The latest patient-focused studies using DPIs indicate that the expectations regarding this technology have evolved. Patients and pneumologists are now increasingly focusing on convenience and ease of use, favouring a compact design. Indeed, DPIs have shown great promise in their ability to deliver drugs reliably and effectively, and novel designs can ensure that future cost, compliance and safety challenges are overcome.

Some of the performance characteristics essential to DPIs are related to dose delivery, fine particle fraction content and performance levels at varying airflows. These characteristics can differ from one powder formulation to another, and some fine tuning of either device or formulation

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Figure 1: Minima tabletop capsule filler.

Figure 2: Adapta high-speed capsule filler.

> "Some of the performance characteristics essential to DPIs are related to dose delivery, fine particle fraction content and performance levels at varying airflows."

– or a combination of both – may be necessary to achieve optimal performance. Microdosing DPIs take this challenge to extremes. IMA Active (Bologna, Italy) and Medochemie (Limassol, Cyprus) have joined forces to achieve optimal microdose DPIs by combining dosator technology and the direct net weight control in a tabletop device and in an industrial-production-scale capsule filler.

STUDY AIM

The aim of the study was to explore the best process parameters to achieve the 5.5 mg dose of a powder mix, including a first lactose type as carrier and a second one (4% in concentration by weight) of microfine lactose as an API simulator. The process was carried out first in a tabletop capsule-filling device (Minima, IMA) and then scaled up to an industrial-production-scale capsule-filling machine (Adapta with 100% gravimetric net weight control, IMA). Two types of lactose were compared from different suppliers.

MATERIALS

Components of the tested formulations are:

A. Blend of placebo powder composed of InhaLac 251 (Meggle, Germany) and 4% in concentration of Lactochem microfine lactose (DFE, Germany).

B. Blend of placebo powder composed of Respitose (DFE, Germany) and 4% in concentration of Lactochem microfine lactose.

For the execution of the tests, HPMC capsules size 3 were used (Table 1).

METHODS

The Minima and Adapta capsule fillers are designed to process microdose DPIs. Minima (Figure 1) is a tabletop capsule filler designed to dose solid products in hard capsules. Extremely precise and with a single dosator, Minima can be equipped with the same dosing devices applied on IMA production machines. Minima comes factory preset for use with DPIs, thus being an efficient system for inhalation product research, development, optimisation and protocol validation.

The Adapta capsule-filling machine (Figure 2) covers medium and very high-speed production requirements and features exceptional design flexibility. Fitted with the 100% gravimetric net weight control (Figure 3), Adapta ensures maximum dosing precision and reliability even at very high speed. On the Minima machine, the target dosages of 5.5, 15 and 25 mg were achieved with both formulations.

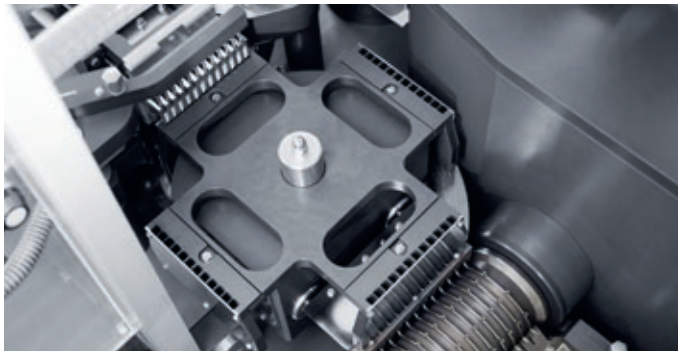


Figure 3: Adapta 100% gravimetric net weight control.

Each lot consisted of 20 samples. Reliability and consistency were assessed by replicating the acquisitions three times for each lot. The second step of the study was to scale up the experience gained on the benchtop machine to the production equipment. Since the target dose was 5.5 mg, the main work was concentrated on this target with both preparations. A total of 100,000 capsules were produced with Adapta with 100% gravimetric net weight control for each blend.

To determine the net weight of the samples dosed with Minima, the macro-analytical electronic scale Sartorius was used. Weighing range: 220 g, accuracy: 0.1 mg. To check the net weight of the samples dosed with the capsule-filling machine, the total filling control system of Adapta was used.

EXPERIMENTAL PART

In Tables 2 and 3, the experiments of the Minima first screening are reported, including machine setting, real weight achieved, tolerances, range between minimum and maximum sample weight obtained and relative standard deviation.

Table 4 summarises the final results of the Adapta with 100% gravimetric net weight control: the powder mixtures and

> "A major advantage of using dosator technology for processing low-dose DPIs is that the system can dose very small amounts of powder into capsules."

Powder mix	Bulk density (g/mL)	Tapped density (g/mL)	Car Index (%)	Loss on drying (%)
InhaLac 251 + 4% Lactochem microfine lactose	0.593	0.780	23.9 (poor flowability)	0.04
Respitose SV003 + 4% Lactochem microfine lactose	0.658	0.812	18.9 (fairly good flowability)	0.08

Table 1: Technological characteristics of the two kinds of powder mixes – InhaLac 251 and Respitose with 4% Lactochem microfine lactose each.

Average net weight (mg)	Doser internal diameter (mm)	Dosing chamber position (mm)	Powder layer height (mm)	Min-max weight sample deviation (mg)	Tolerance obtained (%)	Relative Standard Deviation (%)
25.9	3.0	4.1	15	1.48	+3.3 to -2.3	2.03
14.6	2.5	3.7	15	0.74	+1.6 to -3.4	1.48
5.4	2.0	2.4	10	0.70	+8.0 to -6.1	3.0

Table 2: InhaLac 251 + 4% Lactochem microfine lactose, Minima trials.

Average net weight (mg)	Doser internal diameter (mm)	Dosing chamber position (mm)	Powder layer height (mm)	Min-max weight sample deviation (mg)	Tolerance obtained (%)	Relative Standard Deviation (%)
25.5	3.0	4.2	15	1.75	+3.4 to -3.4	2.24
14.6	2.5	3.8	15	0.46	+1.5 to -1.6	0.90
5.5	2.0	2.2	10	0.67	+4.8 to -8.1	2.9

Table 3: Respitose SV003 + 4% Lactochem microfine lactose, Minima trials.

Lactose kind	Average net weight (mg)	Doser internal diameter (mm)	Dosing chamber position (mm)	Powder layer height (mm)	Relative Standard Deviation (%)	Machine speed (caps/h)
InhaLac 251 + + 4% Lactochem microfine lactose	5.5	2.0	2.13	10	2.52	85,000
Respitose SV003 + + 4% Lactochem microfine lactose	5.5	2.0	2.18	10	2.52	85,000

Table 4: Powder mixtures Adapta with 100% gravimetric net weight control trials.

machine settings are reported, including real weight achieved and relative standard deviation for an easy evaluation.

Figures 4 and 5 show the net weights of all 24 dosators of the Adapta with 100% gravimetric net weight control for both powder mixes.

RESULTS

The tests on Minima demonstrated that both formulations gave good results in terms of workability and tolerance obtained. No significant differences were observed by the operator. Both formulations demonstrated good behaviour, even on the machine Adapta with 100% gravimetric net weight control: no seizing and no empty capsules produced. It was confirmed that for 5.5 mg dosing, the range between the minimum and maximum weight value in the tabletop capsule filler was always lower than 1 mg. The results obtained once formulations were tested in the production-scale capsule-filling machine were even better: for both formulations, the relative standard deviation was confirmed below 3%.

DISCUSSION AND CONCLUSION

As proven by this study, a major advantage of using dosator technology for processing low-dose DPIs is that the system can dose very small amounts of powder into capsules. This powder-dosing technology does not require powder compaction to transfer the powder to the capsule. This ensures that the powder within the capsule is less likely to form aggregates and is maintained as a free-flowing powder.

Maintaining the free-flowing properties of the dispensed powder within the capsule better ensures the release of powder from the capsule into the inhaler when the capsule is pierced, thereby better controlling both the emitted dose and the fine particle fraction of the dose discharged from the DPI.

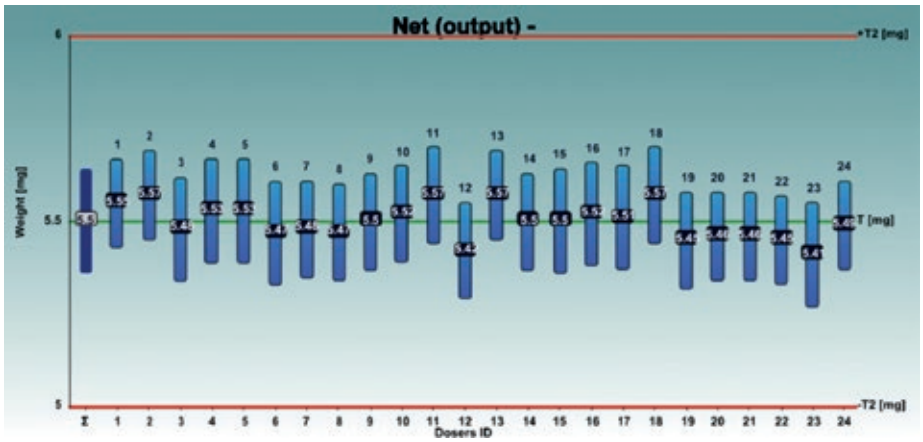


Figure 4: InhaLac 251 + 4% Lactochem microfine lactose, behaviour of the 24 dosators on Adapta with 100% gravimetric net weight control.

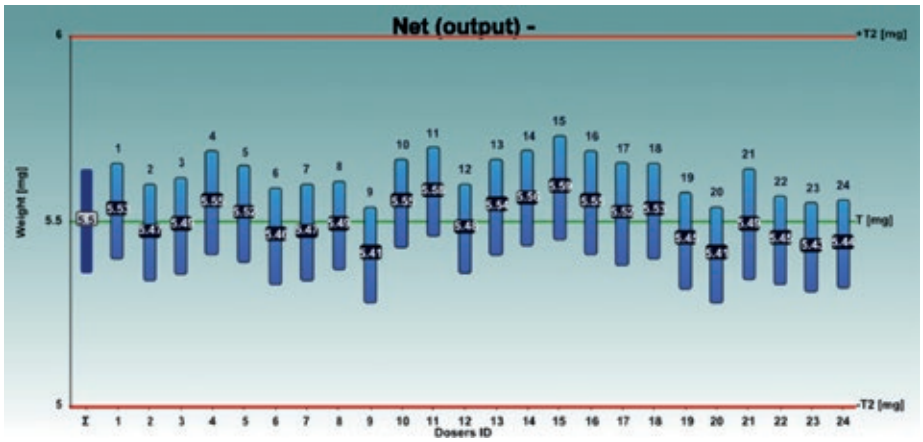


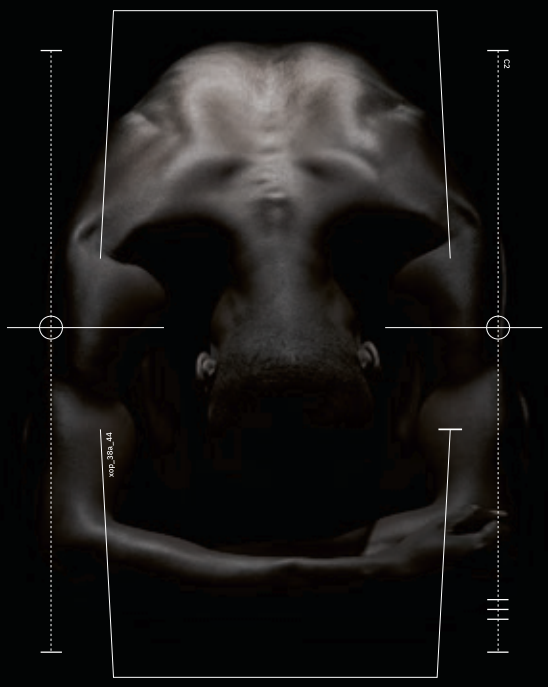
Figure 5: Respitose SV003 + 4% Lactochem microfine lactose, behaviour of the 24 dosators on Adapta with 100% gravimetric net weight control.

ABOUT THE COMPANY

IMA Group is a world leader in the design and manufacture of automatic machines for the processing and packaging of pharmaceuticals, cosmetics, tea, coffee and food. IMA Active, one of the three pharmaceutical divisions of IMA Group, partners with pharma for each solid-dose processing phase: granulation, tableting, capsule filling and banding, weight checking, coating, handling and washing.

ABOUT THE AUTHOR

Pietro Pirera is Product Manager for Capsule Fillers at IMA Active. He graduated with a degree in Mechanical Engineering from the University of Bologna (Italy) and has been working in the field of solid-dose processing and manufacturing for more than 20 years. He is an expert in pharmaceutical engineering and the processing of microdosing DPIs.



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CAPSULES FOR DRY POWDER INHALATION – A COMPLETE PRODUCT

Here, Anita Solanki, Lead – White Papers, Formulation R&D; Jnanadeva Bhat, Vice-President and Head of R&D; and Justin Kalafat Head of International Scientific Business Development, all at ACG Capsules, discuss capsules for dry powder formulation and consider their potential as a dosage form for patients with respiratory conditions and systemic illnesses.

There has been a substantial rise in the prevalence of chronic respiratory diseases globally[1] and chronic obstructive pulmonary disease (COPD) is now the third leading cause of death worldwide.[2] This growth trend, combined with advances in applications of systemic pulmonary drug delivery for non-respiratory conditions, means that inhalation drug delivery is an increasingly important area for research and development, and there is a clear need to develop better, more effective and affordable inhalation methods.[3]

> "The inhalation route has numerous benefits over the conventional oral route, such as lower doses, matchable therapeutic efficacy and reduced side effects."

The inhalation route has numerous benefits over the conventional oral route, such as lower doses, matchable therapeutic efficacy and reduced side effects.[4] Extremely sensitive molecules, potent molecules and larger molecules, such as proteins and peptides, can be delivered via inhalation.[5] For systemic delivery, the higher vascular nature and larger surface area of the lungs mean that drug absorption into the patient's systemic circulation is effective and without first-pass metabolism.

The efficiency of drug delivery to the patient by inhalation ranges between 12% and 40%[6] of the dose inhaled. The remainder is expelled or deposited in the upper respiratory tract. However, in the treatment of respiratory diseases and other conditions affecting the lungs, the drug is being targeted to the site of action, meaning that a lower dose can be administered than would be required if it were taken orally, resulting in fewer side effects. For example, the oral dose of salbutamol (albuterol) is 2–4 mg, whereas the inhaled dose ranges from 0.2–0.4 mg, which is one-tenth of the oral dose. Additionally, the onset of effect is often faster when drugs are inhaled compared with oral administration. With an oral solid dose of salbutamol, the onset of effect is about 30 minutes, whereas with inhalation it is about five minutes. These clear benefits contribute to the growth in popularity of the inhalation route.

Nebulisers, pressurised metered dose inhalers (pMDIs) and dry powder inhalers (DPIs) are the three primary types of inhalation drug delivery system.[7] As well as the devices, the formulations used are different for each type.

Nebulisers are used mostly in hospital settings and often require the supervision of healthcare personnel. Due to this and their size, nebulisers are not frequently used for the routine treatment of chronic respiratory diseases.

In pMDIs, the drug is dissolved or suspended in a propellant. When the device is activated, the drug aerosolises and is deposited in the lungs. The propellants in pMDIs have caused concern regarding environmental damage. Early devices used chlorofluorocarbons (CFCs), which damage the ozone layer. In response, pMDIs with hydrofluorocarbon (HFC) propellants that do not damage the ozone layer were developed. However, the HFCs being used were found to be greenhouse gases.[8] Less harmful HFC propellants are being developed and beginning to reach the market.

Other potential challenges arising with pMDIs include non-uniformity of emitted dose if patients are not given correct use guidelines,[9] and the requirement for the patient to co-ordinate actuation of the device using their hand with their inhalation of the drug.

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DRY POWDER INHALATION

In ACG's opinion, dry powder inhalation technology is the most promising approach for numerous future applications both in the treatment of a range of respiratory conditions and other diseases affecting the lungs, and for systemic drug delivery via the lung. DPIs are already an incredibly important method of drug administration. Since the restriction of CFCs in the late 1980s, DPIs have become the most frequently used type of inhaler, and the preferred inhalation device technology in many European nations.[10]

Both single- and multidose DPIs are available in the market. The global DPI market is projected to rise to US$1.3 billion (£991 million) by 2031, growing at a compound annual growth rate of 7.2% (2021–2031). The market is predicted to generate opportunities of approximately $458 million in the next 10 years. DPIs account for more than 35% of the global inhaler market.[11] Capsule-based inhalers are likely to lead the market due to a rise in the number of companies offering inhalation products and the increase in acceptance of these devices by healthcare personnel and patients.

Capsule-based DPIs (cDPIs) are the most popular method of administration as they are propellant-free, provide uniform dose delivery and offer patient-centric portability and ease of operation.[12] The effective performance of products is dependent on the capsule, inhalation device, formulation and attributes such as particle size, distribution, shape and surface properties. As breath-device co-ordination is not required, cDPIs are suitable for patients of all ages and respiratory abilities.

CAPSULES FOR DRY POWDER INHALERS

cDPIs are portable, easy to use and control, cost-effective, painless and, most importantly, patient-friendly. Capsules for DPIs are specifically designed for this application and are different from regular oral capsules. Different process parameters, including environmental conditions and additives, are employed during the manufacture of inhalation capsules because the capsule, as the primary container of the formulation, contributes to powder aerosolisation of the micronised drug from the carrier during inhalation. Critical attributes of this type of capsule are low residual lubricant (for lower powder retention), microbial limits and capsule-device compatibility (Figure 1).

Residual lubricant in the capsule is one of the key factors that must be managed to ensure low powder retention in the capsules after the formulation is inhaled via the device. Therefore, the edible lubricant used on the capsule pin bars during manufacture is optimised and the quantity is controlled. The quantity of powder retained inside the capsule is dependent on the interaction between the inner surface properties of the capsule and the characteristics of the powder formulation. Conventional oral capsules do not have optimised or controlled lubricant content, hence the powder retention is higher than in capsules for DPIs (Figures 2 and 3).

With inhalation, the microbial limit is an essential criterion in capsule manufacturing. The respiratory tract is susceptible to contamination and subsequent infection, unlike oral delivery where harsh gastric acid helps prevent certain infections. This is why the acceptable microbiological limits for DPI capsules are more stringent than for oral capsules and should be no more than 100 CFU/g.[13]

Figure 1: Capsule for dry powder formulation.

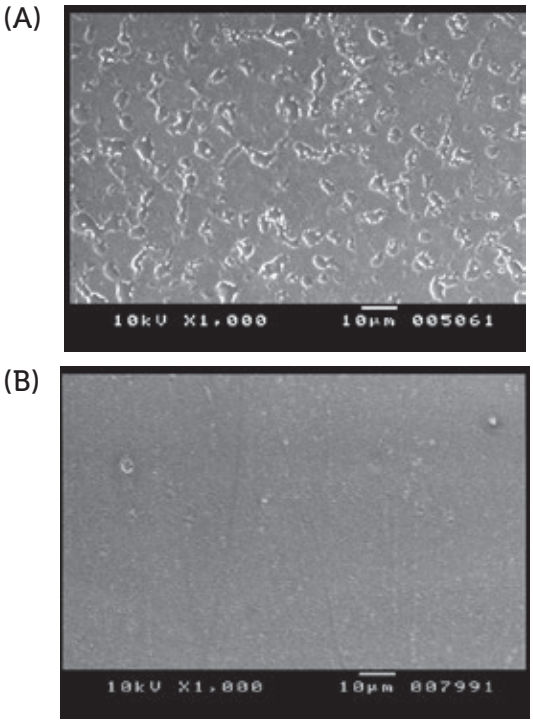

Figure 2: Scanning electron microscopy imaging of internal surface of capsules. (A) Conventional oral capsules show larger lubricant globules. (B) cDPI uniform layer of lubricant (no large globules).

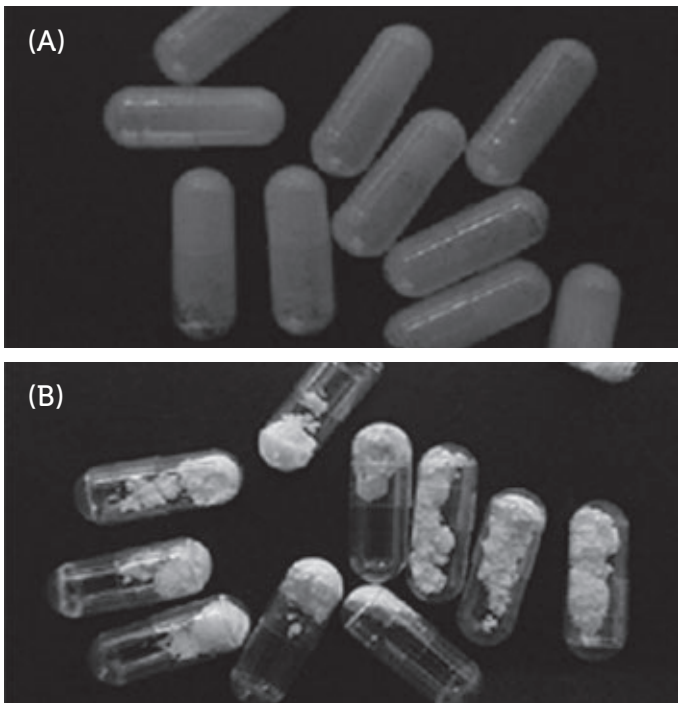

Figure 3: (A) Powder stuck to inner surface of oral capsules. (B) Free flowing powder in cDPI.

HPMC CAPSULE SUITABILITY FOR INHALATION APPLICATION

Two-piece hard capsules are manufactured from either gelatin or hydroxypropyl methylcellulose (HPMC) – also known as hypromellose. Both the polymers have different characteristics that can impact the performance of the finished product. Globally, the most widely used capsule size for commercial products is size 3. Sizes 2 and 0 are also being taken into consideration in the development cycle for new products. cDPI capsules are partially filled (Figure 4).

HPMC capsules have an inherently lower moisture content of about 3%–8% w/w while gelatin capsules have around 13%–16% w/w. The puncturing properties of HPMC capsules are better over a wider range of relative humidity than gelatin capsules because HPMC capsules are more resistant to deformation.[14] HPMC polymer capsules are stable, inert and flexible; thus they do not face brittleness challenges when being punctured. HPMC capsules have exhibited outstanding properties in the stability of formulations due to lower moisture content and aerosolisation.[15]

Figure 4: Partially filled cDPI.

DRY POWDER INHALATION FORMULATION

Commonly, dry powder inhalation formulations are a mixture of the micronised drug and a carrier, for example, inhalation-grade lactose. Carrier particles are used to improve flow, dosing accuracy and overall fill weight for low doses. This facilitates manufacturing processes by improving the handling and encapsulation of the powder formulation.

For the drug component, potential critical attributes include particle size distribution, moisture content, bulk density, flow properties, morphic form (e.g. amorphous, crystalline, hydrate), the morphology of drug particles (e.g. shape, texture, surface area) and impurities.

Pertinent properties for consideration while selecting carriers during product development include the ratio of drug to carrier, compatibility and particle size distribution. Inter-particle interactions between the drug, carrier and device constituent, as well as cohesive and adhesive forces, surface area and static charge properties of the formulation, are also important. If not properly managed, these properties may affect uniformity, flow property and dose delivery.

"HPMC polymer capsules are stable, inert and flexible; thus they do not face brittleness challenges when being punctured."

The drug particles are adsorbed on the carrier surface and then detached by the inhaled air stream. Inhaled air energy is greater than the adhesion forces between the drug and the carrier particle causing deagglomeration.[16] The turbulent airflow then leads to the deposition of the drug in the lungs. The aerodynamic diameter of drug particles controls the drug deposition. Generally, particles with aerodynamic diameters between 1 and 5 µm are more likely to deposit in the lungs effectively.[17]

"Hard gelatin capsules and HPMC capsules act as pre-metered unit-dose systems, and both offer easy encapsulation for formulations."

INHALATION DEVICE COMPATIBILITY

Device design is fundamental to effective drug delivery for cDPIs. It is critical that the patient can produce adequate air flow to inhale the drug from the capsule, to deliver it to the lungs and achieve the desired therapeutic effect. An ideal inhaler would provide uniform dosage and be easy for patients to use and carry. As devices may come into direct contact with the formulation, they have the potential to affect product safety and performance. For instance, drug particle-surface interactions, such as the adhesion of a drug to the surface of the mouthpiece, can affect the emitted and delivered dose. Therefore, the properties of the device material are important. The design and dimensions of the device's components can also influence the resistance, air flow, shear and turbulence generated within the device and, therefore, impact drug delivery.

Hard gelatin capsules and HPMC capsules act as pre-metered unit-dose systems, and both offer easy encapsulation for formulations. Capsule activation can be achieved by twisting open the cap and body to release the formulation into the chamber of the device or by puncturing the capsule on the cap and body with pins. The puncturing technique is the more frequently used device system to release powder from the capsule. Puncturing can either be from the top (dome of cap and body) or the side of the capsule (Figure 5).

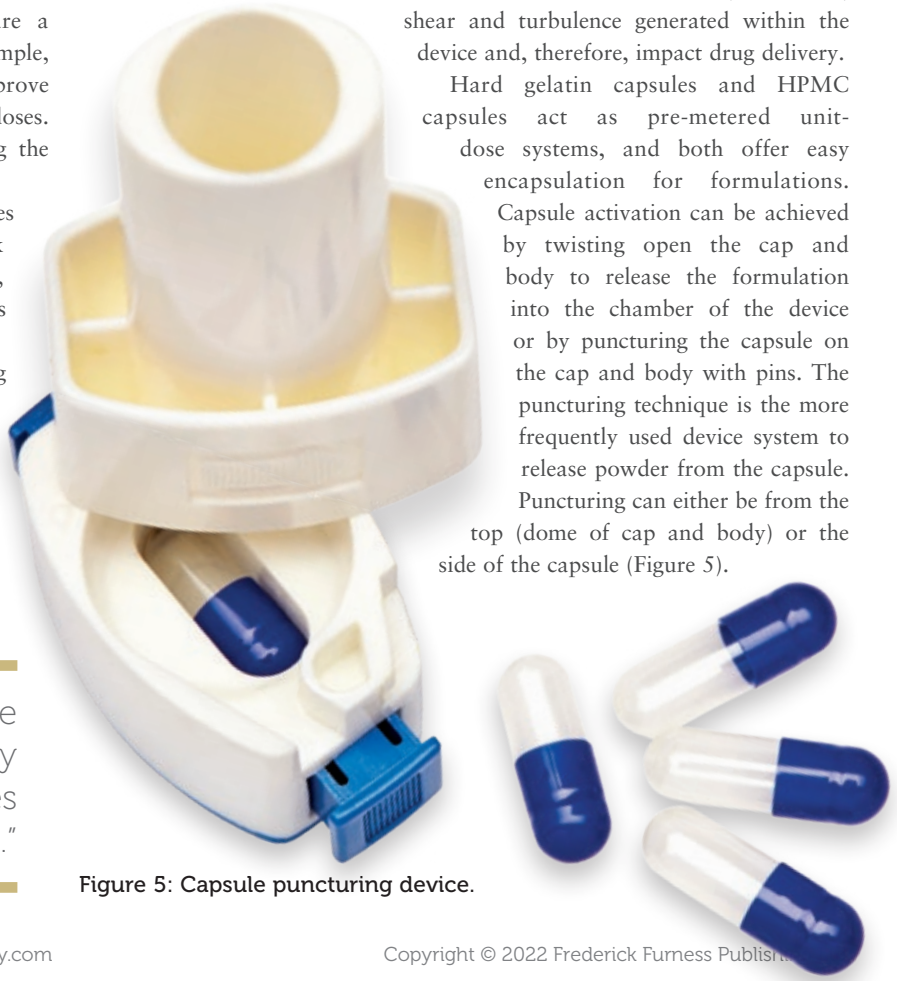

Figure 5: Capsule puncturing device.

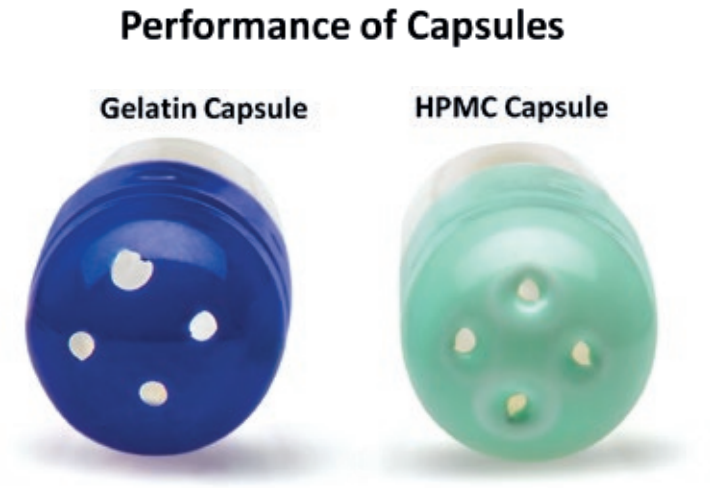

Figure 6: Gelatin capsules with uneven punctures. HPMC capsules with even punctures and no fragmentation.

Although the puncturing behaviour under normal storage conditions has been proven acceptable for both HPMC and gelatin, HPMC capsules exhibit better performance under dry conditions. No fractures or particles from the shell are observed, and they exhibit better flexibility compared with gelatin capsules (Figure 6).

NOVEL THERAPEUTIC SEGMENTS IN INHALATION ROUTE VIA CDPI

After the US FDA and the EU EMA approved the first inhaled therapeutic macromolecule for systemic delivery, human insulin, scientific researchers began exploring other opportunities for patients to benefit from inhalation delivery.[18] In contrast to injection, inhalation is not associated with pain, giving the potential for improved patient compliance and, in turn, improved treatment outcomes too.[19]

Now, other lung diseases, such as cystic fibrosis, lung cancer, and respiratory infectious diseases, as well as systemic disorders, including diabetes, Parkinson's disease, migraine and cancer, are being considered for treatment by dry powder inhalation drug delivery. It is not only new therapeutic segments that are being targeted but also old molecules, such as ciprofloxacin, vancomycin and sumatriptan, that could be administered via inhalation for new applications.

CONCLUSION

Already, cDPIs are demonstrating great success as a dosage form to treat patients with respiratory conditions, as well as systemic illnesses. Their potential is likely to continue to increase with new drug developments, particularly as capsules for inhalation administration are an effective and affordable option for dry powder formulations.

> "The future development of cDPI formulations and devices must focus on newer therapeutic segments and newer molecules to be delivered via inhalation."

Soon, this dosage form will become more prevalent and will help in the treatment of a wide range of diseases. The future development of cDPI formulations and devices must focus on newer therapeutic segments and newer molecules to be delivered via inhalation.

ABOUT THE COMPANY

ACG has been delivering solutions to the global pharmaceutical and nutraceutical industry for more than 60 years, across six continents and in a hundred countries. ACG is the world's only integrated pharma manufacturing solutions company with products ranging from capsules to films & foils, to engineering equipment, and inspection systems, all meeting international regulatory requirements. Collaboration is at the core of ACG's ethos of finding innovative solutions to the world's greatest health challenges.

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ABOUT THE AUTHORS

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COLLABORATION AIMS TO ACCELERATE DEVELOPMENT PROCESS IN DPI FORMULATION

Here, Harry Peters, Senior Product Application Specialist (Inhalation) at DFE Pharma, explains how the collaboration between DFE Pharma, Hosokawa Micron and Harro Höfliger can help manufacturers save time and money in the development process for dry powder inhalers, enabling them to tackle unmet needs and unleash the potential of the significant market opportunity presented by dry powder inhalers.

Lactose-based dry powder inhaled (DPI) formulations are well established in the market for the treatment of respiratory diseases, such as asthma and chronic obstructive pulmonary disease (COPD). There is now a growing trend towards developing DPI formulations that are ternary mixtures including magnesium stearate as well as lactose and APIs. However, the development process for such formulations is complex.

Successful delivery of an API into the lungs depends on many interconnected factors during the production process. The smallest change in the formulation can have a major effect on the end result. DFE Pharma, Hosokawa Micron (Doetinchem, Netherlands) and Harro Höfliger (Allmersbach im Tal, Germany) have joined forces to set up a multidisciplinary study to generate valuable data-driven insights as the basis for offering better advice and support to pharmaceutical companies.

COMPLEX OPPORTUNITIES

Lactose-based DPI formulations are in growing demand. The worldwide prevalence of asthma, which is primarily treated with DPIs, appears to be rising.[1] Increasingly, doctors are using inhaled medications to treat the symptoms of covid-19.[2] Both conditions are global health issues, and neither is going away any time soon. As such, drug developers and generics manufacturers are increasing their focus on DPIs in a bid to tackle this unmet medical need.

DPIs allow patients to inhale an aerosolised powder into their lungs. Formulation considerations include how the powder properties blend with the API, as well as how they affect device filling and the deposition of the API into the lungs.

Most DPI formulations consist of an active ingredient, micronised to a size suitable for inhalation and blended with a

> "How excipients behave in the final formulation depends on all manner of variables. For example, previous studies in fine particle fraction and dosing have shown an increase in lactose fine particles also increases fine particle fraction."

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"This 'magic triangle' collaboration links global expertise in formulations, excipients, powder processing and manufacturing technology."

larger excipient, usually lactose. They tend to be based on carrier principles – the drug is blended with the lactose, which helps to improve the handling and the dosing of the API into the device. The lactose also helps to de-agglomerate the cohesive particles, so that individual particles can be inhaled and enter the lung, as well as enabling the right flowability of the formulation for release from the device.

Of course, how excipients behave in the final formulation depends on all manner of variables. For example, previous studies in fine particle fraction and dosing have shown an increase in lactose fine particles also increases fine particle fraction. This presents developers with a challenge of trial and error when selecting the right lactose for their product. Formulators will test the effect of different grades and blending processes on metrics such as filling, performance and delivery, until they find the right one for them.

JUMPSTARTING DPI DEVELOPMENT

DFE Pharma's joint research project with Hosokawa Micron and Harro Höfliger aims to overcome this time- and resource-hungry trial-and-error step, thus accelerating the development of much needed new DPI products. This "magic triangle" collaboration links global expertise in formulations, excipients, powder processing and manufacturing technology. It expands on the findings of previous work exploring the influence of differing qualities and concentrations of graded powders on the capsule-filling and dosing process with and without magnesium stearate.

By sharing the data-driven insights of the three-phase study, the research team aims to help generic players stay ahead of the curve and tap into the growing DPI market.

- **Phase I:** Establish baselines by blending varying fine lactose samples without the addition of magnesium stearate
- **Phase II:** Blend samples coated with magnesium stearate and compare the results to baseline
- **Phase III:** Blend samples with active ingredients and compare results.

Thus far, the team have completed and published the results of Phase I. Phase II data will be published in the coming months.

THE STORY SO FAR

In Phase I of the study, the team focused on understanding the impact of the addition of fines on flow properties and filling consistency, using different filling techniques. It was found that, as fines concentration increases, cohesivity also rises in all different grades of lactose. However, different fines grades have different impacts on Q4.5 (particles below 4.5 µm), Q30 (particles below 30 µm) and the flow of powders. There was also a strong relationship between lactose Q30, flow properties and filling.

The drum filler showed the lowest variation in terms of fill weight and relative standard deviation (RSD). As such, the team concluded that it was a robust system for a wide range of powders with respect to flowability. Additionally, flow function showed good correlation to mean fill weight.

Powder characteristics had a strong influence on the filling results of the membrane filler, with percentage compressibility showing good correlation to mean fill weight. The team concluded that permeability should be higher than 6 mbar at 15 Kpa to ensure low RSD values that can be controlled by lactose Q30. The team also found that dosator filling results in good filling consistency with respect to RSD, though high RSD was observed in lactose grades with a high concentration of fines.

In the second phase of the study, trials were conducted using different grades of lactose fines with different mixing/blending speeds and times, and both with and without a magnesium-stearate coating. While the analysis is being finalised, the team can already conclude that the addition of magnesium stearate to lactose changes the flowability.

The study is now moving into its final phase, which will be conducted at Harro Höfliger's state-of-the-art facility using DFE Pharma's lactose and Hosokawa Micron's powder mixing technology. APIs will be added to formulations using high-shear blending. The result will be analysed for flow properties, blend uniformity, assay, emitted dose and aerodynamic particle size distribution. The team, who are expected to publish their results later this year, will also carry out short-term stability studies.

"By sharing the data from this project, DFE Pharma, Hosokawa Micron and Harro Höfliger hope to help the sector leapfrog the costly, time-consuming trial-and-error part of the formulation process and carve out a shorter path to market."

ENRICHING THE KNOW-HOW ON DPI FORMULATION TO ACCELERATE THE DEVELOPMENT PROCESS

DPI formulations hold life-changing potential for patients the world over. Tackling the unmet need triggered by the increasing prevalence of conditions such as asthma and covid-19 is a huge opportunity for the pharma industry. By sharing the data from this project, DFE Pharma, Hosokawa Micron and Harro Höfliger hope to help the sector leapfrog the costly, time-consuming trial-and-error part of the formulation process and carve out a shorter path to market. The results from this research will strengthen the understanding of the coating process and the correlation between lactose quality, blending, flowability and dosing, as well as provide practical advice for pharmaceutical companies.

ABOUT THE COMPANY

DFE Pharma is a global leader in pharmaceutical excipient solutions. The company develops, produces and supplies high-quality functional excipients for use in the pharmaceutical, biopharmaceutical and nutraceutical industries for respiratory, oral solid dose, ophthalmic and parenteral formulations. The company's excipients are used in numerous medicinal and nutraceutical products, including covid-19 vaccines and treatments.

DFE Pharma's excipients play an essential role as fillers, binders and disintegrants, as well as in stabilising active ingredients for release in a predictable and effective manner into the patient's system. With over a century of experience and more than 450 people worldwide in over 100 countries serving more than 5,000 customers, DFE Pharma is committed to supporting (bio)pharmaceutical and nutraceutical companies in their journey to improve patients' lives.

ABOUT THE AUTHOR

Harry Peters has been working as a specialist in the use of lactose in pharmaceutical applications for more than 15 years. In the last six years at DFE Pharma, he has further specialised in the dry powder inhalation field. Mr Peters is Senior Product Application Specialist (Inhalation), having started working as R&D manager and Product Application Specialist for inhalation grade lactose. He advises formulators of dry powder inhalers about the use of inhalation grade lactose.

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