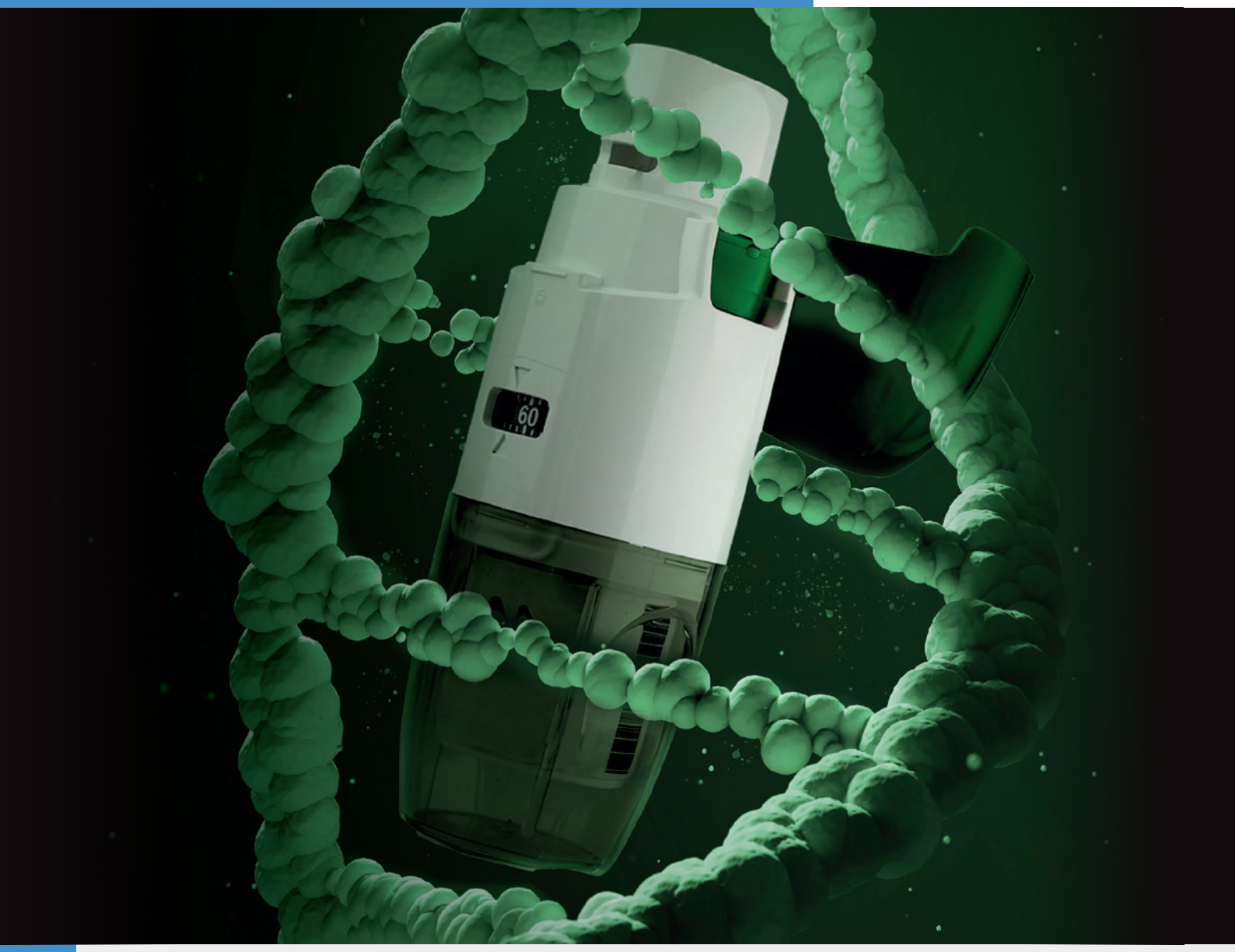
PULMONARY & NASAL DELIVERY

ON drugDELIVERY



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ONdrugDelivery Issue N° 140, November 21st, 2022

PULMONARY & NASAL DRUG 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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NASAL DELIVERY – A GALAXY NOT SO FAR AWAY... A BRIEF MARKET HISTORY OF THE NASAL DELIVERY LANDSCAPE

Here, Mark Ignaczak, Director of Innovation and Partnerships – Nasal Delivery at Catalent, provides an insight into the history of nasal drug delivery and looks at the advantages of the nasal delivery route.

The nasal drug delivery landscape has evolved tremendously since its inception several decades ago. In its early years, nasal delivery was largely confined to the administration of locally acting treatments for decongestion and rhinitis. Some of the earliest nasal sprays date back to the 1950s and 1960s, when two over-the-counter (OTC) decongestants became available for widespread use.[1] But, in fact, if we look back even further, nasal delivery of drugs dates back to ancient civilisations. Nasaya Karma is a recognised form of treatment in the Ayurvedic system of Indian medicine.[2] More recently, pharmaceutical drug developers have begun to research nasal delivery as an alternative to common routes of administration (RoA), such as oral and parenteral. In part, this is due to the high permeability of the nasal epithelium, allowing a higher molecular mass cut-off at approximately 1000 Da, as well as the rapid drug absorption rate with plasma drug profiles, which are sometimes almost identical to those of intravenous injections.[2]

> "Pharmaceutical drug developers have begun to research nasal delivery as an alternative to common routes of administration, such as oral and parenteral."

Intranasal drug delivery for systemic application is now an option for several more indications – most notably for rescue therapies because of its rapid onset of action, but also for infectious disease prevention, pain, central nervous system conditions and a variety of others. We have witnessed several first-of-a-kind nasally delivered treatments, such as: Narcan® (naloxone) for opioid overdose from Emergent BioSolutions (MD, US); an antidepressant, Spravato® (esketamine), from Janssen (J&J); a nasal diazepam for seizures, marketed as Valtoco® by Neurelis (CA, US); and, from Oyster Point Pharma (NJ, US), Tyrvaya® (vareniciline) for dry eye disease. The rate at which intranasally delivered molecules have been approved has also increased drastically over the past five years. Now, clinical research is underway to evaluate intranasal delivery as a means of delivering drugs to the brain across the blood-brain barrier, with therapies for Alzheimer's disease and other degenerative brain diseases in active development.

REGULATORY PERSPECTIVE

While the number of drugs being delivered intranasally has grown in recent years, and the acceptance of these products has advanced greatly, the requirements necessary to gain regulatory approval are still evolving. The latest approved guidance for these products was issued in July 2002.[3] This guidance, along with the requirements listed in the US Pharmacopeia, are the key points of reference for sponsors seeking to gain approval for their products. However, the chemistry, manufacturing and

> "Clinical research is underway to evaluate intranasal delivery as a means of delivering drugs to the brain across the blood-brain barrier, with therapies for Alzheimer's disease and other degenerative brain diseases in active development."

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controls provided for nasal spray drug products in the guidance document lack direction for specific unit dose delivery systems, intranasal powder delivery, controls for vaccines, and biotherapeutic modalities. As regulatory bodies look to address these new modalities, product manufacturers have needed to interpret requirements by extrapolating guidance directed at other forms of orally inhaled and nasal drug products, while still following product-specific guidances as they relate to their programme.

FORMULATION STRATEGIES

Bioavailability, solubility and viscosity are critical aspects of the formulation that must be assessed during nasal spray development. Physical barriers are also a concern, as the complex geometry of the nasal passages makes reliable and efficient delivery to the mucosal surfaces deep in the nasal cavity a challenge. Lastly, nasal clearance should be considered. The epithelium of the nasal passage is covered by a mucus layer that entraps particles and is cleared from the nasal cavity by the action of the nasal cilia, which renew the mucus every 10–15 minutes by moving it through the nose at an approximate rate of 5–6 mm/min. Drugs with poor solubility would be particularly challenged by mucociliary clearance, as they must guarantee sufficient bioavailability to achieve the desired therapeutic effect.[4]

One approach to increasing nasal residence time is through the use of muco-adhesive systems, which retain the drug solution longer in the nose. Another is the use of permeation-enhancing technologies, which facilitate both the rate and extent of absorption.[5] The development and use of permeation enhancers significantly improves the absorption of high molecular weight drugs as well. These permeation enhancers can facilitate the absorption of molecules up to 40 kDa, enabling the nasal delivery of peptides and proteins that would have traditionally had to be delivered via the parental RoA to avoid enzymatic degradation in the gastrointestinal tract.[5]

CURRENT NASAL SPRAY DEVICE LANDSCAPE

The bulk of the nasal drug delivery landscape uses three types of device: unit-dose, bi-dose and multidose; with unit- and bi-dose being used for acute/rescue indications, and multidose for chronic indications.

"The covid-19 pandemic's legacy includes an advancement in the knowledge and clinical research of nasal delivery of biotherapeutics for infection prevention, and some promising product candidates remain in development."

The allergic rhinitis market generally uses multidose nasal pumps, primed by the user and capable of delivering formulations with volumes from 25–140 µL. These devices can dose several varieties of formulations, such as solutions and suspensions for chronic indications. On the other hand, unit- and bi-dose devices are portable and can therefore easily be carried about one's person. They can be actuated easily during a crisis, and they accurately deliver necessary drug volumes at any orientation, without requiring the pump to be primed.

Factoring in the long history of nasal OTC products and their wide availability, patients have become increasingly familiar with this RoA. Ultimately, this decreases the required learning curve for new intranasal therapies in the unit- and bi-dose configurations. That said, additional verbal and written patient education is required to help ensure correct and compliant dosing.

As noted prior, the nasal market has grown significantly over the last several decades, from a market comprised of largely OTC multidose delivery to diversified offerings using specialised unit- and bi-dose devices. This evolution has also led to several advancements within nasal device technology to improve reliability over the years. These advancements, along with addressing challenges surrounding formulations to be delivered through the nasal cavity, can promote positive results.

Another reason for the growth in the unit and bi-dose segment of nasal drug delivery is the covid-19 pandemic, which fuelled vaccine development. There are over 100 vaccines or prophylactic treatments for covid-19 currently in late-stage clinical trials, some of which are being developed for intranasal administration, which aim to improve mucosal immunity efficacy and allow for faster, easier and patient-friendly global immunisation.[6] Even as covid-19 case rates decline in number and the enthusiasm to fund some of these programmes starts to wane, the pandemic's legacy includes an advancement in the knowledge and clinical research of nasal delivery of biotherapeutics for infection prevention, and some promising product candidates remain in development. Just recently, the regulatory bodies within China, India, Iran and Russia have approved the use of four intranasal covid-19 vaccines.

We now have several game-changing products, spanning a vast number of therapies, entering the space that will certainly advance the industry even further. There are currently more than 150 molecules at various stages of development within the nasal pipeline, with projections indicating the number will grow to over 195 by 2027. The development pipeline remains healthy and robust with both substantial investment in preclinical molecules and consistent maturation of programmes in the existing pipeline. The sizeable portfolio of preclinical molecules should lead to a number of commercial opportunities.

Overall, the nasal delivery market is expected to experience approximately 6% compound annual growth rates over the next decade.[7] This would drive the already significant market value of the global nasal drug delivery market from US$45 billion (£40 billion) in 2019 to an estimated $88 billion by 2030. The covid-19 pandemic aside, the growth in nasal programmes can be attributed to new disease areas and modalities using this RoA (e.g. Parkinson's disease, Alzheimer's disease, anxiety and depression), as well as increased awareness, acceptance and the benefits and ease of self-administration of nasal therapies.

In some instances, nasal delivery offers advantages over the most commonly used oral and injectable RoA, and over some less used, such as rectal administration. Unlike the oral and rectal RoA, nasal sprays avoid the biotransformation of the drug in the gut lumen prior to absorption and in the intestinal epithelium and/or liver after permeation of the intestinal mucosa but before entering systemic circulation, known as first-pass elimination.[2] Nasal delivery also provides local protection at the nasal mucosa that could potentially assist at the point of entry to defend against viruses and bacteria – an added benefit.

CONCLUSIONS

Nasal devices have proven themselves to be incredibly reliable, providing accurate dosing whether administered by the patient themselves, by a caregiver or by emergency personnel. When replacing the injectable RoA, nasal sprays or powders obviate the need for needles, bypassing injection-related phobias and, in most cases, the need for healthcare practitioner support.

It is essential that both the formulation and device are compatible if they are to support successful intranasal drug delivery. Formulation improvements, the potential use of permeation enhancers and new device technologies have led to the expansion of overall possibilities for device/formulation variations to create a successful final product with the optimal spray characteristics. Though complex, the nasal route is therefore an attractive alternative that provides access to highly vascularised mucosa, is easy to reach through self-administration and can, with the appropriate formulation and delivery system, deliver the drug dose conveniently and reproducibly while bypassing hepatic metabolism.[5]

ABOUT THE COMPANY

Catalent is a global leader in enabling pharma, biotech and consumer health partners to optimise product development, launch and full lifecycle supply for patients around the world. With broad and deep scale and expertise in development sciences, delivery technologies and multimodality manufacturing, Catalent is a preferred industry partner for personalised medicines, consumer health brand extensions and blockbuster drugs. Catalent helps accelerate over 1,000 partner programmes and launch over 150 new products every year. Its flexible manufacturing platforms at over 50 global sites supply around 80 billion doses of nearly 8,000 products annually. Catalent's expert workforce of approximately 19,000 includes more than 3,000 scientists and technicians. Headquartered in Somerset, NJ, US, the company generated nearly $5 billion in revenue in its 2022 fiscal year.

ABOUT THE AUTHOR

Mark Ignaczak's background includes extensive experience in nasal spray product development and commercialisation. He has 18 years of pharmaceutical experience and over 15 years of direct experience with nasal spray products. He has worked on more than 75 nasal programmes at varying stages of the project lifecycle, ultimately launching over 10 NDAs, some considered first-of-their-kind, best-in-class therapies. Mr Ignaczak has fulfilled various roles within bioprocessing engineering, product development, supply chain and all aspects of nasal delivery programme management and strategy. He holds a bachelor's degree in biochemical engineering from Rutgers University, New Brunswick, US.

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STEPS TO SUCCESS IN NOSE-TO-BRAIN DRUG DELIVERY

In this article Reenal Gandhi, Global Business Development Director, Prescription Division, at Aptar Pharma, and Gemma Budd, Business Development Director at Nanopharm, an Aptar Pharma company, consider the multiple hurdles associated with developing nasal drug delivery solutions, current understanding of the associated biology and the advantages of alternative device designs and state-of-the-art formulation practice.

More sophisticated product development strategies, new biologic drug molecules and drug reformulation are all defining features of the current nasal drug delivery landscape. The development of an intranasal (IN) form of naloxone, a drug traditionally delivered by injection for the emergency treatment of opioid overdose, provides a good illustration of the benefits of reformulation, and of IN drug delivery more generally. Easier and quicker to use in a crisis scenario, by a broader range of responders, this product delivers the rapid onset required to save lives; estimates indicate a global market value in excess of US$350 million (£309 million) (2021 figures).[1]

Drug reformulation has similarly delivered successful – and, in some cases, breakthrough – therapeutics for the treatment of seizures, hypoglycaemia, dry eye disease, treatment resistant depression (TRD) and migraine. But there are even bigger targets on the horizon. More effective solutions for anaphylaxis, for example, and nasal vaccines, including for covid-19, would similarly benefit from IN formats due to high patient acceptability and ease of use, alongside equivalent or enhanced therapeutic efficacy. The exponential growth of research demonstrating the viability of nose-to-brain drug delivery holds promise for efficacious treatments for disorders of the central nervous system (CNS), which would be life transforming for many.

> "Aptar Pharma has been leading the way in nasal drug delivery solutions for decades."

Products commercialised in nasal dosage forms for conditions primarily of the CNS, such as TRD, have been approved based on their systemic absorption, but there is growing evidence to suggest that their improved efficacy (as compared with traditional dosage forms) might result from some drug delivery directly into the brain. Pharmaceutical companies and researchers are expending significant efforts to understand and facilitate this pathway to address previously unmet medical needs for diseases of growing incidence, such as Alzheimer's, Parkinson's and depression.

Individually, nasal drug delivery and drug delivery to the brain both present specific challenges. Add the two together and you have an exacting and demanding task, with much of the associated knowledge base still evolving. Aptar Pharma has been leading the way in nasal drug delivery solutions for decades. Today, the company combines the widest range of proven nasal spray devices with a track record of success in supporting the commercialisation of nasal drug products targeting the CNS.

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"The nasal cavity offers a highly vascularised space for rapid absorption into the blood."

THE NOSE-TO-BRAIN DRUG DELIVERY OPPORTUNITY

Conditions such as allergic rhinitis were the earliest targets for nasal drug delivery and, in terms of volume, these topical therapeutics still dominate the market. However, there are a growing number of products that use the unique physiology of the nose to tackle very different disorders. The nasal cavity offers a highly vascularised space for rapid absorption into the blood, for systemic action. But, in addition, there is a direct pathway to the cerebrospinal fluid and brain tissues – a pathway that bypasses the blood-brain barrier (BBB).

Delivering drugs to the CNS via systemic delivery is extremely challenging. Metabolism, elimination and off-target delivery all limit efficiency, with the BBB presenting a formidable final hurdle, since transport across the BBB is largely limited to very low levels of very small lipophilic molecules. By bypassing the BBB, nasal drug delivery can result in a higher bioavailability of the drug in the brain, whilst administering lower doses and, at the same time, broadening the range of potential drug candidates. This increases the chances of achieving therapeutic efficacy with less toxicity and fewer side effects which, of course, is a major gain. The lack of any regulatory requirement for sterility is a potential additional benefit from a manufacturing perspective but can increase the complexity of formulation.

The Biology: How do Drugs Get From the Nose to the CNS and What are the Barriers?

Our understanding of how drugs travel from the nose to the brain is still advancing, but the current view is that extra or paracellular (between cell) transport, along the ensheathing channels of major nerves, is the dominant and fastest route. There is some evidence of intracellular (within cell) transport, but this appears to be much slower – a secondary mechanism that may enable the delivery of sustained therapeutic effect.

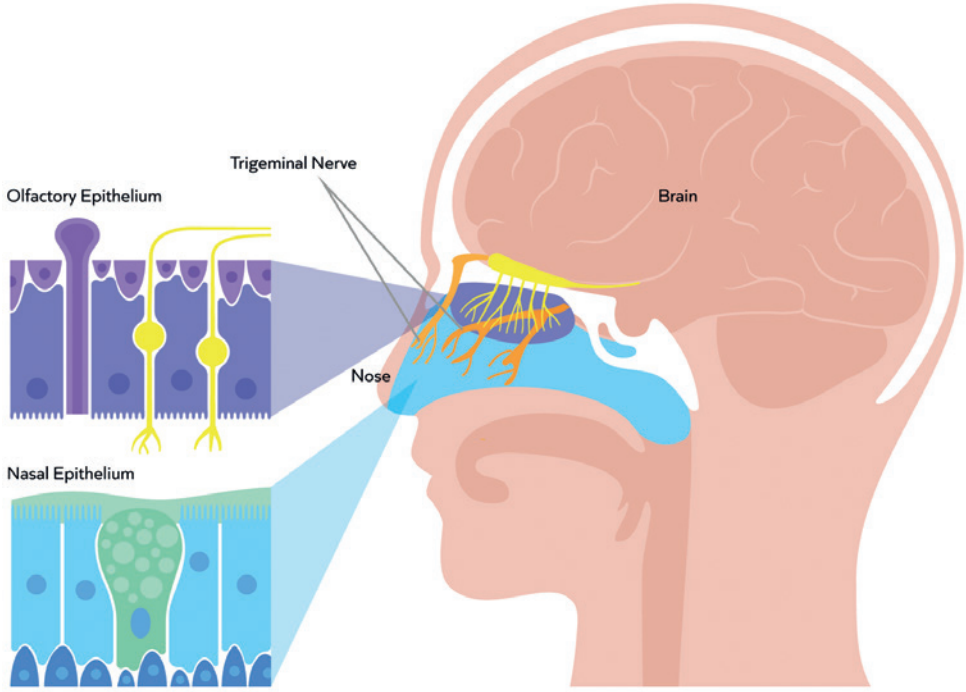

Figure 1: The exposed olfactory nerve in the olfactory region is a primary target for nose-to-brain drug delivery. The trigeminal nerve, within the turbinates, presents a larger surface area but lies behind tight cell junctions with access further compromised by mucociliary clearance.[2]

The nasal cavity offers access to two main nerves – the olfactory nerve and the trigeminal nerve (Figure 1). The olfactory nerve lies predominantly in the olfactory region – a small area deep in the roof of the nasal cavity that accounts for just 7% of the surface area of the nasal epithelia. Since the olfactory nerve is directly exposed to the local environment in this region, the primary challenge with this route is to reach and precisely target such a small area, preferably with a highly concentrated formulation to avoid spreading and off-target deposition. Penetration through the mucus is also critical to reach the interface with the neurons.

In contrast, the trigeminal nerve presents a much larger target surface area, extending through the turbinate region, which represents the majority of the nasal cavity. Since this area is subject to mucociliary clearance and the trigeminal nerve is hidden behind tight cell junctions, the defining challenge with this route is to overcome these barriers without simultaneously enhancing cellular and/or systemic uptake.

Alongside the specific challenges associated with each route, there are certain issues to address. The nasal cavity is a constrained space with a complex geometry and a narrow airflow path that contains little fluid. Reliably delivering a dose to a target site is therefore difficult, and drug dissolution (in the case of a powder) can be slow. The nose has evolved to prevent the permeation of unwanted molecules, with multiple natural defences – including the mucus barrier itself – alongside the presence of proteases and macrophages that will attempt to break down or scavenge foreign matter if countermeasures are not designed into the formulation.

"Selecting a suitable nasal spray device is a critical aspect of product development."

The Nasal Spray Device: What Factors Affect Performance and Choice?

Selecting a suitable nasal spray device is a critical aspect of product development but it is important to recognise that it is a combination of the device, formulation properties and patient technique that determines deposition behaviour. Device designs can be optimised to produce different plume geometry, angle, velocity and droplet/particle size for a given formulation to maximise deposition in the upper nasal cavity/olfactory region. With respect to patient or caregiver technique, device administration angle and spray nozzle insertion depth can both influence deposition behaviour and design features can help here too – nasal guides being a prime example. Encouraging correct device position can reduce patient influence, promoting more reliable and consistent dose delivery.

Progressing device design relies on having effective tools for assessing performance. Translational models for nose-to-brain delivery are limited, primarily due to relative differences in the size of the olfactory region between humans and animal models. Optimising the relevance and application of *in vitro* tools is therefore crucial. Aptar Pharma has developed and clinically validated an *in vitro* nasal cast model, AERONOSE® Nasal Cast (co-developed and co-owned by Aptar Pharma, Diffusion Technique Française and the University of Tours, France) to support its device and product development activities. The cast makes it quicker and easier to understand the impact of different factors on product performance and is helping to optimise device design for deposition in the olfactory region.

Figure 2 shows data from an experiment to compare the olfactory deposition performance of two configurations of the same multidose liquid pump – the standard version (blue bar) and one with a modified actuator specified for olfactory targeting (green bar). The effect of device insertion depth was also assessed with the modified actuator device (orange bar). All trials were carried out using a low-viscosity placebo (2 cP) and an administration angle of 45°.

Here we can see that modifying the actuator and inserting the spray nozzle further into the nostril – to a depth of 15 mm relative to 10 mm – are both individually and cumulatively beneficial for olfactory deposition. These results underline the importance of device design and the value of nasal guides, which can be used to promote insertion to the optimal depth.

Via studies such as these, Aptar Pharma is progressively refining device designs for targeted delivery. To date, it has reached up to 60% deposition to the olfactory region with liquids (as shown in Figure 2) and 65% deposition with powder formulations – a major advance relative to unoptimised delivery devices. Commercial prototypes with design features such as nasal guides are already undergoing trials in the clinic.

The Formulation: How Can We Optimise Deposition, Retention and Permeation to the Target Site for Different Molecules?

The starting point for formulation is detailed characterisation of the physicochemical properties of the drug molecule and identification of the mode of action. Drug molecules vary considerably with respect to their fundamental properties and need different types of "help" to reach a target site of action. For example, some are hydrophilic, others are lipophilic – polar opposites. Differences relating to nasal delivery include cell and tight junction permeability, sensitivity to enzymatic degradation (notably for biologics), sensitivity to pH, and mucosal interaction and penetration. With an understanding of the inherent properties of the drug, formulation development can proceed via a process of knowledge-led preformulation studies, typically followed by a design of experiments, because this is a complex process with multiple issues to address. The following, far from exhaustive, list gives a flavour of the issues that should be considered to reach an optimal solution:

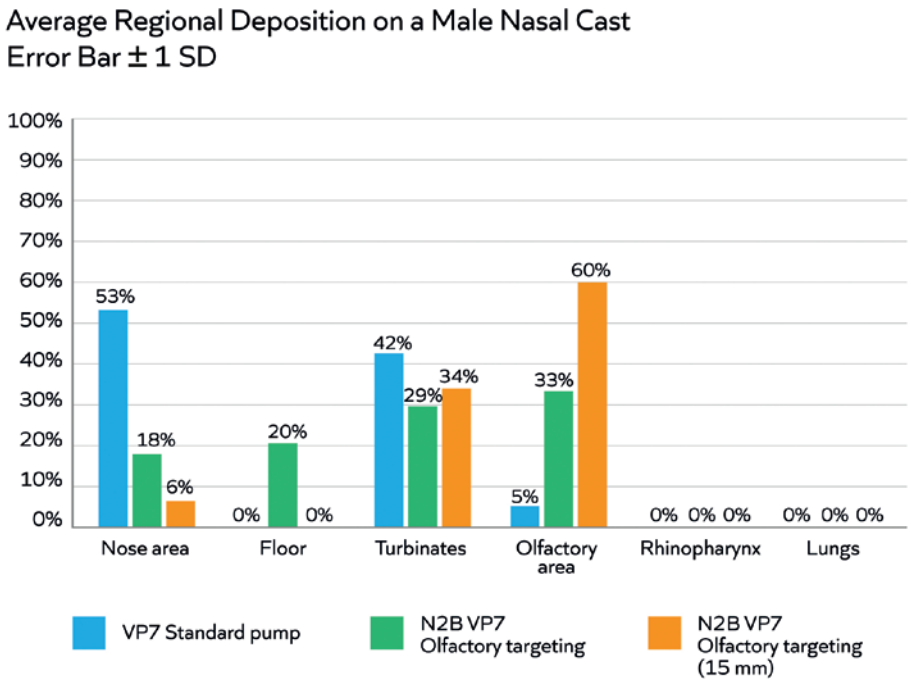

Figure 2: A multidose pump, optimised for olfactory targeting, substantially enhances drug deposition in this region relative to a standard multidose pump; increasing insertion depth to 15 mm (relative to 10 mm) is also highly beneficial.

Preservatives or Preservative Free

Non-sterile manufacture is an option for nasal sprays but preservatives are then required to deliver appropriate microbial integrity and an acceptable shelf life with a standard device. Where preservatives are used, compatibility with the drug molecule is a concern (particularly for biologics) and physiological effects, helpful or otherwise, require careful assessment. If sterile manufacture is a viable option (for example, if reformulating an injectable product, the sterile manufacturing process will already be in place), then maintaining sterility remains a challenge. Devices such as Aptar Pharma's CPS spray pump platform, which has unique features preventing microbial ingress despite multiple actuations, are essential for successful preservative-free formulation.

Osmolality and pH

In an aqueous nasal spray, incorporating excipients or selecting buffer systems to promote drug stability and delivery may impact both the osmolality (ionic concentration) and pH of the formulation. However, total flexibility in this regard, is constrained by the biology of the nose, since specific ranges of osmolality and pH are needed to avoid mucosal irritation.

Rheology and Thixotropy

Formulation rheology, including viscosity, has multiple impacts. Increasing viscosity tends to improve retention time, either by facilitating adherence to the mucus or hindering the ability of the beating cilia to clear away the drug substance. Higher viscosity can also facilitate better droplet-size control for more effective targeting to the back of the nose and olfactory region (Figure 3) and improve formulation stability, even at high drug loadings. However, device choice can be more limited for viscous formulations, and the emitted dose may emerge as a jet rather than fine droplets – giving rise to patient discomfort. A thixotropic formulation with shear-thinning behaviour can be the answer. Such formulations exhibit low viscosity

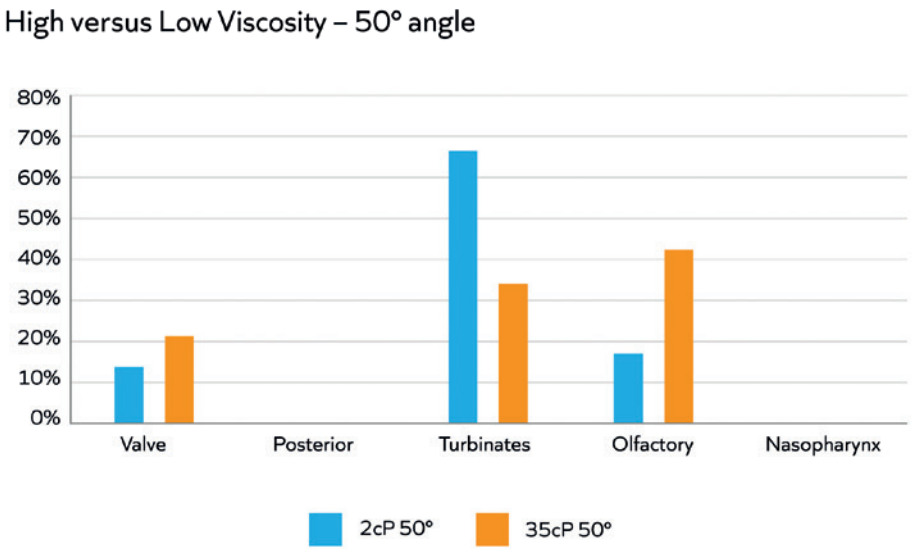

Figure 3: Higher viscosity is associated with an increase in deposition in the olfactory region in back-to-back studies.

when subject to high shear (i.e. when passing through the nasal-spray pump) but build higher viscosity upon settling, following deposition.

Formulation rheology is routinely manipulated using modifiers that often simultaneously and usefully exhibit muco-adhesive and/or mucopenetrative properties because of relationships between viscosity and cilia transport. The drug substance can also have an intrinsic effect on formulation rheology since, with some, such as biologics, viscosity increases with increasing drug concentration. These and other potentially competing effects make optimising rheology one of the most complex and critical aspects of formulation development.

Conventional Aqueous Nasal Spray or Powder Formulation

Although there are far fewer commercialised dry powder products, the benefits are, arguably, compelling, particularly for high-value or highly concentrated systems. Advantages include a longer shelf life, better retention times, potential for higher drug loadings, the ability to control aerosol properties for precise targeting and the relative ease of incorporating multiple, synergistic formulation enhancers. Set against these benefits are the drawbacks of greater manufacturing complexity, the need for drug dissolution *in vivo* and more limited device choice. Spray drying or freeze-spray drying are becoming increasingly explored for IN drug delivery. These processes allow for the use of a wide selection of formulation enhancers (e.g. co-solvents) to aid complex formulation preparations that would not be viable with a liquid system.

Muco-adhesives, Mucopenetrants and Permeation Enhancers

These excipients tackle discrete tasks but have chemical and physical properties that need to be carefully balanced in the context of other constituents in the formulation. Muco-adhesion tend to be positively charged to promote interaction with negatively charged mucins and aid retention, helping to combat mucociliary clearance. In contrast, mucopenetrants enhance permeation through to the cell surface. When targeting the olfactory nerve, rapid penetration of the mucus is the principal concern, increasing the need for effective mucopenetrants. Existing Muco-adhesives polymers are being explored for this application, along with strategies based on modification of the ionic strength of the localised environment. Where drug delivery is to the turbinates, permeation enhancers may be additionally required to, for example, disrupt tight junctions and enable access to the trigeminal neurons following successful transport to the epithelial surface.

Examples of formulation enhancers include surfactants, such as polysorbates or alkylsaccharides, polymers and oligosaccharides, such as chitosan, and cyclodextrin (CD) derivatives. Polysorbates and alkylsaccharides can have both hydrophilic and hydrophobic properties, allowing for stabilising interactions with multiple types of drug substances as well as the local nasal environment. Chitosan, on the other hand, is a cationic polymer, which means it can interact electrostatically with mucin to improve muco-adhesives, and also ionically with Ca^{2+} channels to open tight junctions and aid permeation. CD derivatives are widely used as permeation enhancers because of their ability to form inclusion complexes or nanoaggregates and the presence of both hydrophobic and hydrophilic groups in their cone structures.

Optimising the use of formulation enhancers is complex and the associated formulation science is advancing rapidly, making external advice and support in this area particularly valuable. Multiple studies are in progress to assess the synergistic effects of different combinations and ultimately this is most likely to be the most

Figure 4: Aptar Pharma has an unrivalled nasal device portfolio.

fruitful approach. A full discussion of this topic is beyond the scope of this article, but it is important to also highlight growing interest in the use of nanoparticles (NPs) for nose-to-brain delivery.

NPs typically either encapsulate or conjugate to the drug substance, shielding the molecule from the nasal environment and essentially changing its properties until it is finally released at the site of action. Some of the benefits include improving drug loading and stability, and the ability to essentially reverse the hydrophilic versus hydrophobic nature of the drug substance at different stages of the delivery process and/or to change surface charge to facilitate penetration through mucus and subsequent interaction with tight junction ion channels. Nanoparticles can protect drugs from degradation and more easily permeate through the mucus partly due to their small size, but are prone to aggregation and instability themselves, creating a new formulation challenge.

LOOKING FORWARD

The future looks bright for nasal drug delivery, which holds promise for tackling illnesses of pressing societal concern. There is considerable potential to deliver efficacious, patient-friendly solutions where there is a currently unmet medical need and to benefit from a corresponding reduction in the currently escalating costs of associated healthcare. However, realising this vision will be demanding. The development of nasal drug products for nose-to-brain delivery relies on a better understanding of the biology of the nose, enhanced device performance, advanced formulation expertise and tools to improve patient technique and compliance. Aptar Pharma is working across all these areas to help customers meet the challenge of effective nose-to-brain drug delivery (Figures 4 and 5).

> "There is considerable potential to deliver efficacious, patient-friendly solutions where there is a currently unmet medical need."

ABOUT THE COMPANIES

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 de-risk the development journey. With a strong focus on innovation,

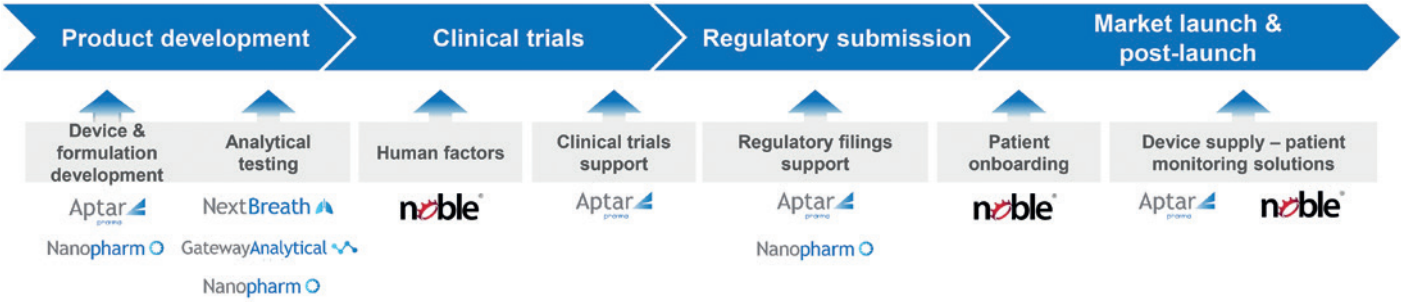

Figure 5: Aptar Pharma offers expert support from early-stage development to commercialisation.

Aptar Digital Health is leading the way in developing digital health solutions to help improve the patient treatment experience. 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.

Nanopharm, an Aptar Pharma company, is a specialist contract research organisation offering product design and development services for orally inhaled and nasal drug products. Nanopharm operates a fee-for-service model, helping its clients navigate the scientific, technical and regulatory challenges in developing nasal and respiratory drug products from discovery through to clinical investigations. It provides an integrated drug development service covering advanced materials characterisation, device and formulation development, and inhaled biopharmaceutics.

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ABOUT THE AUTHORS

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Gemma Budd is Business Development Director for Nanopharm, an Aptar Pharma company, where she is primarily responsible for developing business and collaborative opportunities for Aptar Pharma's services, solutions and technologies in the orally inhaled and nasal drug product sector. With a university degree in Biomedical Sciences, Ms Budd has more than 10 years of experience in the pharmaceutical industry in both research and commercial positions, from materials science and analytical services to formulation technology and drug delivery devices, primarily for oral and inhaled dosage forms.

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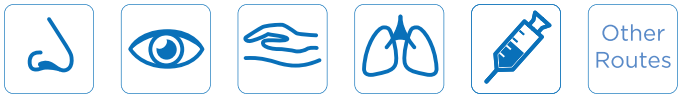

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ON drugDELIVERY

2023 EDITORIAL CALENDAR

Publication Month	Issue Topic	Materials Deadline
January	Skin Drug Delivery: Dermal, Transdermal & Microneedles	Dec 19, 2022
February	Prefilled Syringes & Injection Devices	Jan 5, 2023
March	Ophthalmic Drug Delivery	Feb 2, 2023
April	Pulmonary & Nasal Drug Delivery	Mar 2, 2023
Apr/May	Drug Delivery & Environmental Sustainability	Mar 16, 2023
May	Delivering Injectables: Devices & Formulations	Apr 6, 2023
May/Jun	Novel Oral Delivery Systems	Apr 20, 2023
June	Connecting Drug Delivery	May 4, 2023
Jun/Jul	Industrialising Drug Delivery	May 18, 2023
September	Wearable Injectors	Aug 3, 2023
October	Prefilled Syringes & Injection Devices	Sept 7, 2023
Oct/Nov	Drug Delivery & Environmental Sustainability	Sept 21, 2023
November	Pulmonary & Nasal Drug Delivery	Oct 2, 2023
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SOLVING COMPLEX FORMULATION AND DELIVERY CHALLENGES FOR INTRANASAL DRUGS

In this article, Paul Kippax, PhD, Pharmaceutical Sector Director at Malvern Panalytical, discusses the analytical techniques used for *in vitro* characterisation of nasal sprays, and how their use can accelerate and de-risk both innovator and generic nasal drug development.

Given the choice, many patients would prefer to avoid injections or other similarly invasive methods of delivering medicines. One route offering an alternative approach for a rapidly expanding range of treatments is nasal administration. As well as addressing any fear of needles and the risk of injection pain, nasal administration can enable the more rapid onset of therapeutic effects. For example, its use in vaccine delivery means less stress for the patient, reduced training requirements for administration, the potential for more relevant immune responses in the mucosal tissues where viruses enter the body and possible cold chain advantages compared with current vaccine products.

By no means can all drugs be administered this way, but intranasal delivery continues to move on from its origins in administering locally acting substances to playing an important role in a diverse range of systemic (as well as local) treatments.[1–4] Today, groundbreaking work on vaccines, prophylactics and therapeutic compounds for SARS-Cov-2 is putting the intranasal route firmly in the spotlight as researchers seek the most effective means of delivering these medicines. With nasal drug delivery on the rise, this article reviews some of the key challenges scientists face in developing the complex formulations involved, and also examines the role of physicochemical analysis in defining appropriate solutions.

NASAL DELIVERY – AN EVOLVING FORMAT

Locally acting decongestants and treatments for allergic rhinitis were among the first modern pharmaceutical formulations developed specifically for nasal delivery.[5] More recently, analgesics, anti-depressants, hormone treatments and other systemically acting drugs have joined their ranks.

The nasal cavity's large surface area and high blood flow for absorption enable direct application and rapid relief when using locally acting pharmaceuticals.[6,7] For systemic therapies, nasal delivery provides a non-invasive route that allows rapid absorption while also bypassing the gastrointestinal tract. Additionally, the possibility of direct nose-to-brain delivery opens the way for drugs unable to cross the blood-brain barrier to rapidly enter the central nervous system.[8]

The SARS-Cov-2 pandemic has heightened interest in nasal delivery. As investigators continue to explore this route for coronavirus-related vaccines,[9] as well as other therapies and prophylactic treatments,[10] pharmaceutical scientists are under increasing pressure to manage the formulation challenges effectively.

THE FUNDAMENTALS AND COMPLEXITY OF NASAL SPRAYS

While dry powder formulations are used in some applications, drug formulations for nasal delivery generally consist of an API dissolved or suspended in an aqueous formulation. The product is delivered via an aerosolisation device, such as a metered dose spray pump, to ensure easy and well-controlled administration.

Nasal drug products are classified (alongside orally inhaled preparations)

> "Nasal drug products are classified as complex pharmaceutical formulations because of the interdependence of the formulation and the delivery device."

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as complex pharmaceutical formulations because of the interdependence of the formulation and the delivery device. Successful development of a nasal drug product requires both an effective formulation and a detailed knowledge of how to deliver it consistently using a complex device. Understanding and managing the impact of both elements is essential, whether you are developing innovator or generic drugs.

The most important aspects of nasal sprays are that they must enable delivery of the drug substance to the target tissues and achieve the required bioavailability in the patient. Optimising the formulation for bioavailability and the device for delivery requires a complete understanding of how the two interact, and the impact of those interactions on delivery and efficacy. For example, the design and geometry of a spray nozzle affects the stress on the suspension and therefore impacts the resulting spray droplet size and distribution. This, in turn, influences where and how the droplets deposit in the patient's nose and, as a result, the drug's bioavailability and speed of action. Likewise, the addition of an excipient to improve nasal retention time can change the formulation viscosity and alter the pumping efficiency and "sprayability" of the product, with consequences for deposition and bioavailability.

Delivered droplet size is a critical quality attribute for nasal products, one that directly affects clinical efficacy. Correlation between the spray droplet size and *in vivo* deposition behaviour for nasal products means that particle size distribution (PSD) measurement is essential during development, manufacture and quality control. Equally, the PSD of the API within the dispersed aerosol is important in defining the efficacy of drug delivery, as well as overall bioavailability.

EXPLORING NASAL DRUG DEVELOPMENT CHALLENGES

A particular challenge when developing nasal products is that systemic drug concentration is not necessarily a good indicator of local drug concentration and therapeutic benefit. Consequently, traditional pharmacokinetic assessments of blood plasma concentration may not be relevant in determining bioavailability and equivalence. To help mitigate this, developers increasingly use *in vitro* bioequivalence (IVBE) testing – the process of using *in vitro* techniques to assess a test product's bioavailability and bioequivalence compared with the corresponding reference listed drug – to optimise and accelerate development. Underlying this trend is a recognition of the importance of the formulation microstructure in controlling drug delivery and release.

In recent years, regulators have released specific guidance on the assessment of IVBE in nasal drug products.[11] Although this has predominantly been targeted towards the rapid development of generics, it also highlights the critical material attributes (CMAs) that are important for device and formulation optimisation for innovator product research and development. Consequently, data from *in vitro* methods is helping to drive both generic and innovator product development.

Physicochemical characterisation plays a crucial role in measuring properties that are predictive of bioavailability and answering key questions about the delivery of nasal sprays. For example, "What is the spray and where does it go?" requires an understanding of droplet size, plume geometry and spray angle, whereas "How stable is the formulation?" demands knowledge of the API particle size and formulation viscosity. Among the physicochemical characterisation techniques used are laser diffraction particle size analysis for droplet size measurement, the recently developed morphologically directed Raman spectroscopy (MDRS) for API characterisation and size exclusion chromatography (SEC) to elucidate the properties of polymer excipients.

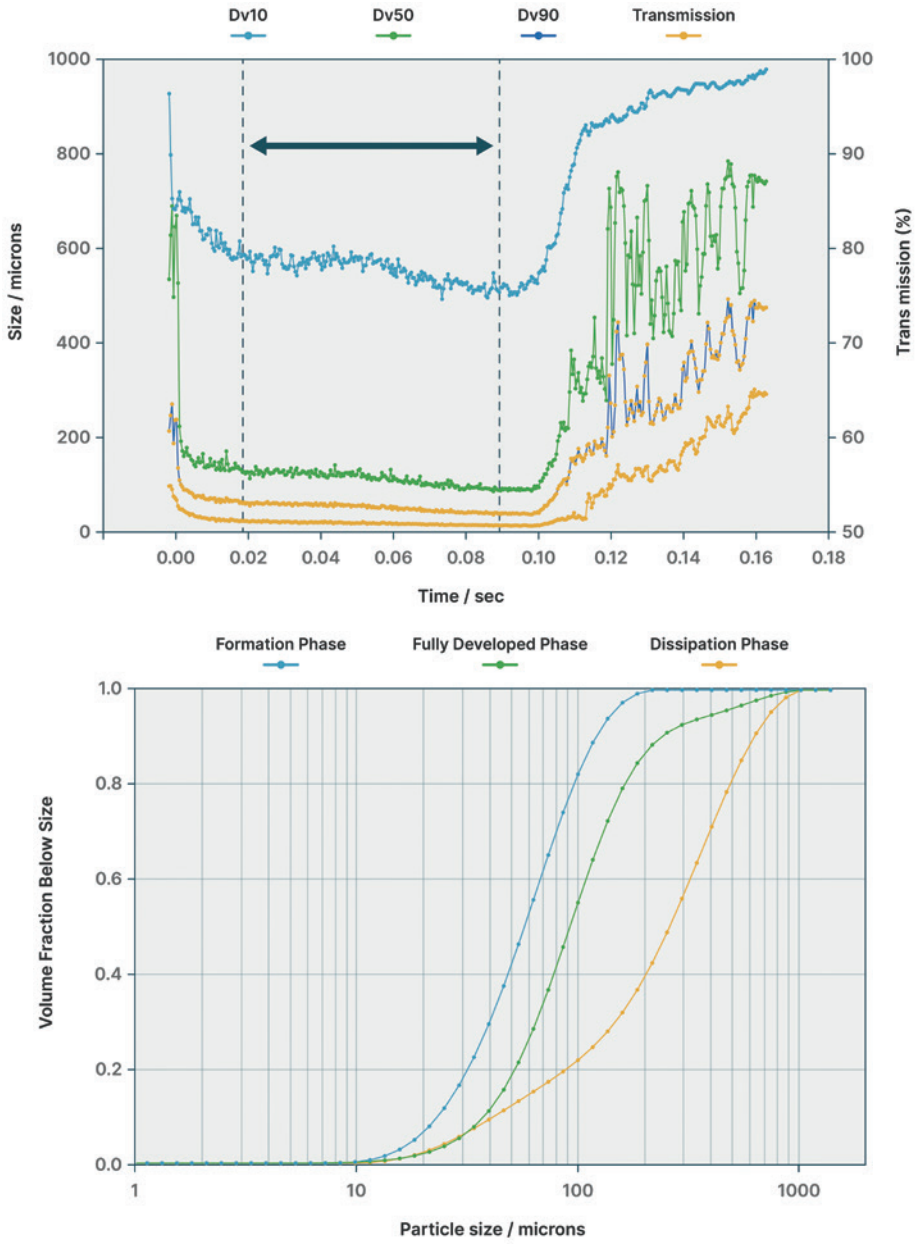

Figure 1: Understanding droplet atomisation during nasal spray delivery.

UNDERSTANDING DROPLET ATOMISATION DURING NASAL SPRAY DELIVERY

Controlling droplet size in nasal sprays is crucial to successful *in vivo* drug deposition. Nasopharyngeal deposition typically requires droplets in the range 20–120 µm. Smaller particles are likely to be deeply inhaled, while larger droplets will remain near the outside of the nose. Droplet size is a function of the formulation's physical properties (most notably viscosity), along with the mechanism and geometry of the delivery device. By manipulating formulation and device variables, developers can engineer the production of appropriately sized droplets.

Laser diffraction is the recommended technique for determining droplet size distribution in nasal sprays. Its rapid measurement capability delivers valuable information during a high-speed spray event, from device actuation right through development and then termination of the spray plume. As the following examples illustrate, understanding droplet size supports many aspects of drug and device formulation performance. It can even indicate how a product might perform in different hands. Droplet size distribution data is essential for comparing formulations in bioequivalence studies.

Figure 1 shows a set of droplet size distribution measurements that can help elucidate atomisation during a nasal spray event. Droplet size (y-axis) was measured using a laser diffraction particle size analyser designed specifically for sprays (Spraytec – Malvern Panalytical). Shown versus time are the Dv10 (the size below which 10% of the particles in the sample fall), Dv50 (the median droplet size) and Dv90 (below which 90% of particles fall), as well as the transmission level (right-hand axis). The lower the transmission, the higher the concentration of the aerosol, allowing observation of spray plume development through the droplet measurement zone. Concentration is low as actuation begins, then the main part of the spray plume moves through the measurement zone. Finally, as actuation stops, transmission rises. In the formation phase at the beginning, the droplet size is briefly relatively large, then drops in the stable phase where the plume is fully developed. When actuation ends, the droplet size increases significantly as atomisation moves out of control.

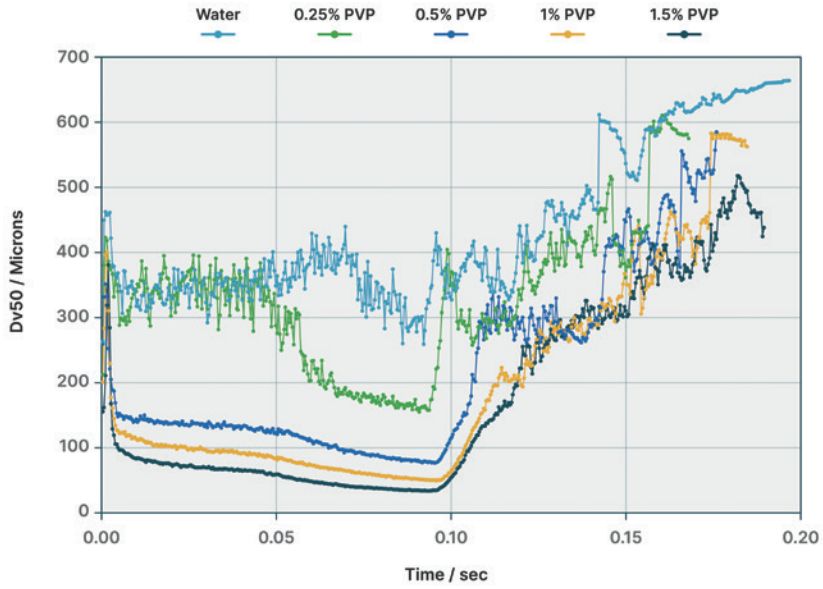

Figure 2: Linking rheology to droplet atomisation during nasal spray delivery.

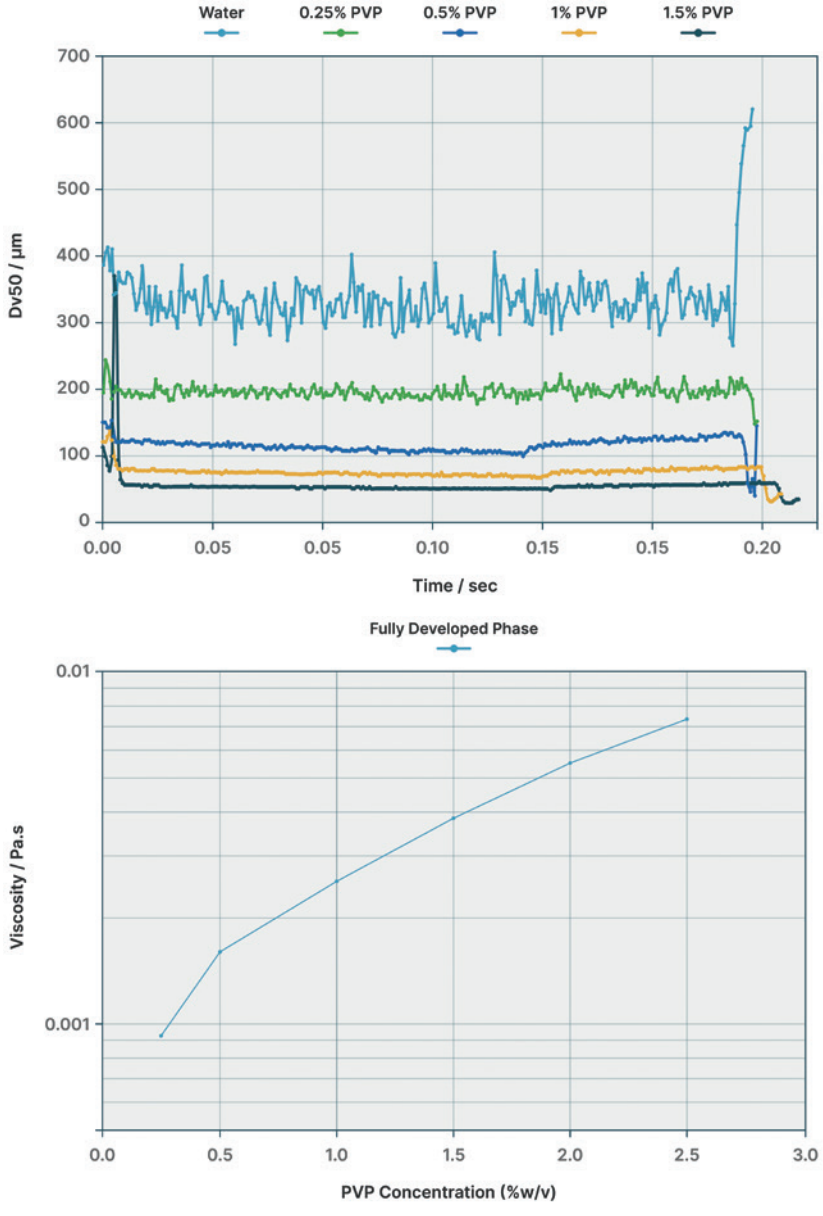

Figure 3: Linking droplet size to device selection.

Bioequivalence studies require isolation of the fully developed stage – the stage during which deposition in the nose is most likely to occur in the most controlled way – for comparison between products. Instrument software enables isolation of all phases, making this comparison straightforward.

Real-time measurement of droplet size distribution also helps quantify how variations in CMAs, such as formulation viscosity (rheology) or nozzle geometry, impact performance. Figure 2 compares the median droplet size delivered by a particular nasal spray device for formulations of different viscosities. At concentrations of 0%, 0.25% and 0.5% polyvinylpyrrolidone (PVP), the formation, fully developed and dissipation phases are all present. At higher PVP concentrations (higher viscosities), actuation is less successful, droplet size is larger and less stable, and the fully developed phase is less well defined. These profiles give an indication of how the formulation and device work together and point to where changes might be required. As shown on the right of Figure 2, the droplet size data links to other IVBE parameters, such as spray plume geometry (SprayVIEW – Proveris Scientific, MA, US. See this issue, Page 82), which in this case confirms that the device fails to atomise the high PVP concentration liquids.

Figure 3 shows results of using the same PVP formulations but a different delivery device, one which has a mechanism for storing energy that is released at the end of pump actuation. This changes the nature of the fully developed phase, giving a more stable droplet size. Although the Dv50 increases with increasing viscosity, atomisation of the liquid, even at the highest concentration, is controlled, building evidence to help match the formulation with the most appropriate delivery device.

USING API PARTICLE SIZE FOR INSIGHTS INTO BIOAVAILABILITY

API particle size gives information on the dissolution rate and the likely bioavailability of the drug. However, discriminating between API and excipient particles in nasal spray suspensions is a significant challenge. Component-specific particle size measurement using MDRS, a microscopy-based technique that combines automated imaging technology with Raman spectroscopy, delivers particle shape, size and component-specific chemical identification data.

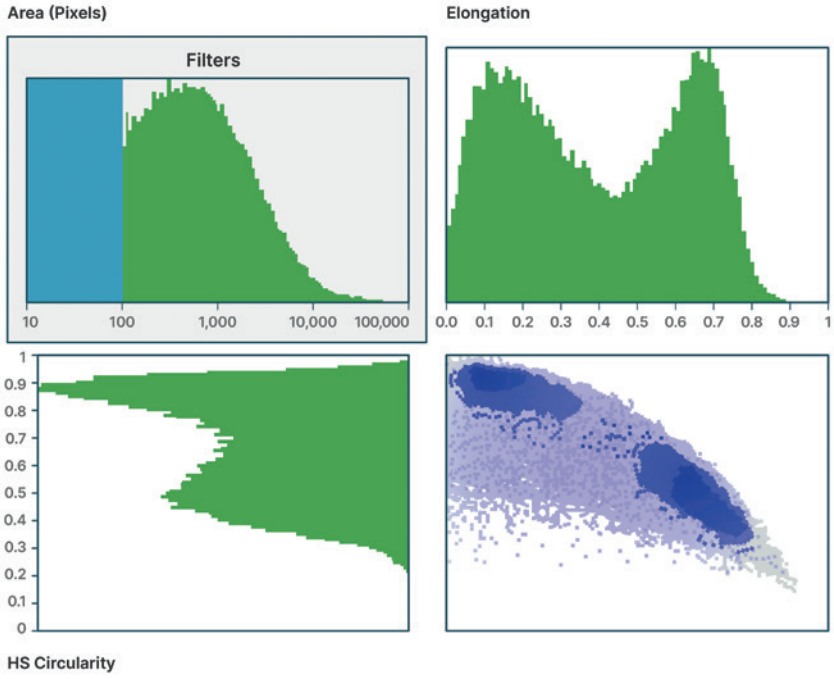

Figure 4: Selecting classification parameters for API and excipient particles.

In the MDRS workflow, particle size and shape analysis using the Morphologi 4-ID (Malvern Panalytical) helps separate excipient and API particles, as shown in Figure 4. Development of this particle size and shape classification enables targeting of the system's Raman analysis towards the groups likely to contain the API, that being particles with a low elongation ratio in this case. Raman spectroscopy is then applied to discriminate API from excipient within this particle set. Particles are classified by comparison with reference spectra, which enables the determination of API particle size distribution and comparisons with other products (Figure 5).

Third-party studies have demonstrated the correlation between MDRS data and dissolution rates and indicate that MDRS is relevant for assessing bioequivalence in nasal sprays.[12] The same studies also examine the relationship between rheological performance and spray droplet size distribution measured by laser diffraction, again demonstrating a good correlation.

GETTING A BETTER HANDLE ON EXCIPIENT BEHAVIOUR

The physicochemical properties of polymeric excipients can directly affect the clinical efficacy, safety and quality of finished

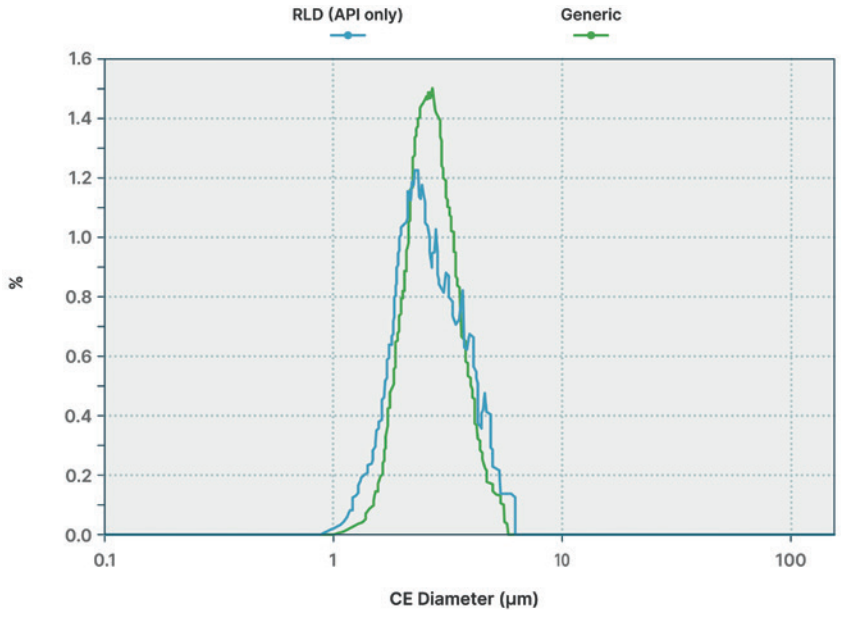

Figure 5: API component-specific particle size distribution.

pharmaceutical products, and are routinely identified as CMAs. Excipient choices make a critical difference to nasal spray performance, with polymers often used to modulate viscosity. As already discussed, this can directly impact spray droplet size distribution and affect the ultimate deposition and bioavailability of the API.

The molecular weight, molecular weight distribution and structural characteristics of such excipients define their behaviour. Here, SEC is an established technique for the measurement of these properties and plays an important role in pharmaceutical formulation. The use of multiple detectors, including for light scattering, viscosity and concentration, enables the measurement of absolute molecular weight, molecular size and intrinsic viscosity, generating information on the macromolecular structure and branching. Multiple detector systems (such as OMNISEC – Malvern Panalytical) deliver the high sensitivity needed for precise differentiation of excipient grades and offer automated and highly repeatable measurement, for efficient, high-productivity analysis.

MORE THAN A SHOT IN THE ARM

The growing appeal of nasal delivery for a widening range of pharmaceuticals puts pressure on developers to overcome the challenges of these complex formulations where drug formulation and device development must proceed hand in hand. Recognising the inseparability of these processes is fundamental to putting strategies in place to de-risk and accelerate product development.

Regulatory guidance for demonstrating IVBE in nasal spray products is benefiting developers of both generics and innovator products. It highlights the importance of formulation microstructure in controlling drug delivery and release, and points to the role of physicochemical characterisation techniques in measuring and understanding changes. Methods such as laser diffraction particle sizing and MDRS are helping developers understand product behaviour in ways that accelerate progress and support success. The use of these techniques within a range of analytical approaches makes formulation optimisation more effective, which ultimately helps to deliver a greater choice of highly effective and easier to administer pharmaceutical products.

ABOUT THE COMPANY

Malvern Panalytical is a high-precision analytical instruments and services company specialising in the chemical, physical and structural analysis of materials, which partners with numerous companies, universities and research organisations.

Malvern Panalytical provides its partners and clients with global training, service and support, including local and remote support, under a full and flexible range of support agreements, which continuously drives their analytical processes at the highest level. Malvern's worldwide team of specialists adds value by ensuring applications expertise, rapid response and maximum instrument uptime.

Malvern Panalytical is committed to "Net Zero" in its own operations by 2030 and in its total value chain by 2040. The company has 2,300 employees and is part of global precision measurement group Spectris plc.

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ABOUT THE AUTHOR

Paul Kippax, PhD, leads the business development and marketing team at Malvern Panalytical as Pharmaceutical and Food Sector Director. He has a PhD in colloid science from the University of Nottingham (UK) and joined Malvern Panalytical in 1997 – developing an in-depth understanding of how material characterisation techniques can address key industry challenges.

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TAKING THE STING OUT OF VACCINES

In this article, Heather Jameson, PhD, Senior Engineer, Juliette Ngan, Consultant Engineer, and Omar Shah, Materials Engineer, all of Springboard, discuss the potential advantages and challenges of intranasal and inhaled vaccines in the context of global respiratory pandemics.

Cast your mind into the future and imagine the world in the grip of the next global respiratory pandemic. Once again, we are presented with the monumental task of vaccinating the world against a novel pathogen. How should we achieve this?

The current default is long lines of people stood two metres apart queuing for an injection at a clinic, masked to reduce transmission of the airborne disease, with hundreds of clinical staff and volunteers trained to administer the vaccines. Furthermore, the injectable vaccines often need cold-chain transportation if they are to reach remote communities across the world.

Alternatively, what if it were possible to post an inhaler directly to people's homes? Over the past few years, there has been growing interest in inhaled and intranasal delivery of vaccines. Inhalation has several advantages over the traditional needle-based method, particularly when considering tackling the next respiratory epidemic or pandemic. This article will examine the key advantages, remaining challenges and the recent progress that has been made in this field.

KEY ADVANTAGES

No Needle

The removal of the needle improves patient comfort and safety. Needles present the risk of needle-stick injuries and needle reuse, increasing the chance of cross contamination. A trained healthcare professional is required to administer the vaccine, creating a potential bottleneck for mass vaccination campaigns, particularly in non-industrialised countries and remote areas (Figure 1). Additionally, removing the needle may reduce vaccine hesitancy and increase compliance, as up to 10% of the UK population suffers from needle-phobia[1] and the rate in other countries may be similar.

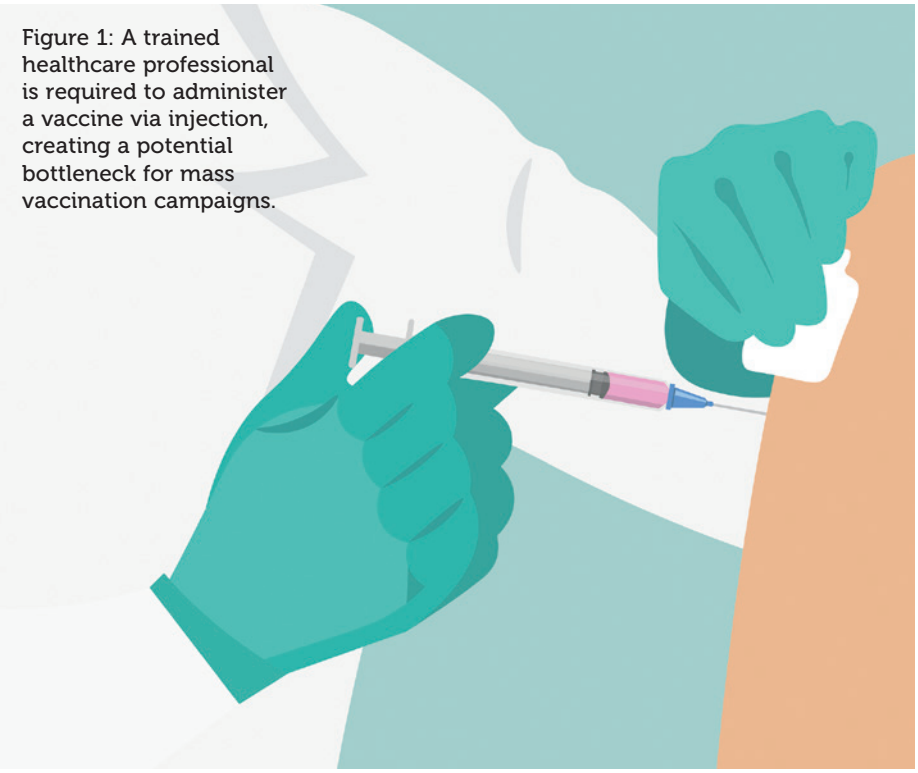

Figure 1: A trained healthcare professional is required to administer a vaccine via injection, creating a potential bottleneck for mass vaccination campaigns.

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Inhaled or intranasal delivery of vaccines could remove the need for a trained healthcare professional to be present in the majority of instances. The device could be collected from designated collection points, such as pharmacies or local grocery stores, or even delivered directly to people's homes, for self-administration at home. However, there are hurdles to achieving this idealised situation, as discussed later in this article.

Inhaled vaccines could yield sustainability improvements too. The quantity of unrecyclable, contaminated sharps generated by covid-19 vaccine syringes in the UK alone would fill around 10 double-decker buses (based on 150 million doses in 0.5 mL syringes). If a dry powder inhaler made from a few simple plastic parts could do the same job, it could easily be recycled into high-grade feedstock. Furthermore, dispensing with the cold chain, as discussed later, could have saved about 100 GJ of energy, equivalent to running a kettle every day and every night non-stop for two years (based on refrigeration power of 2 W per L).

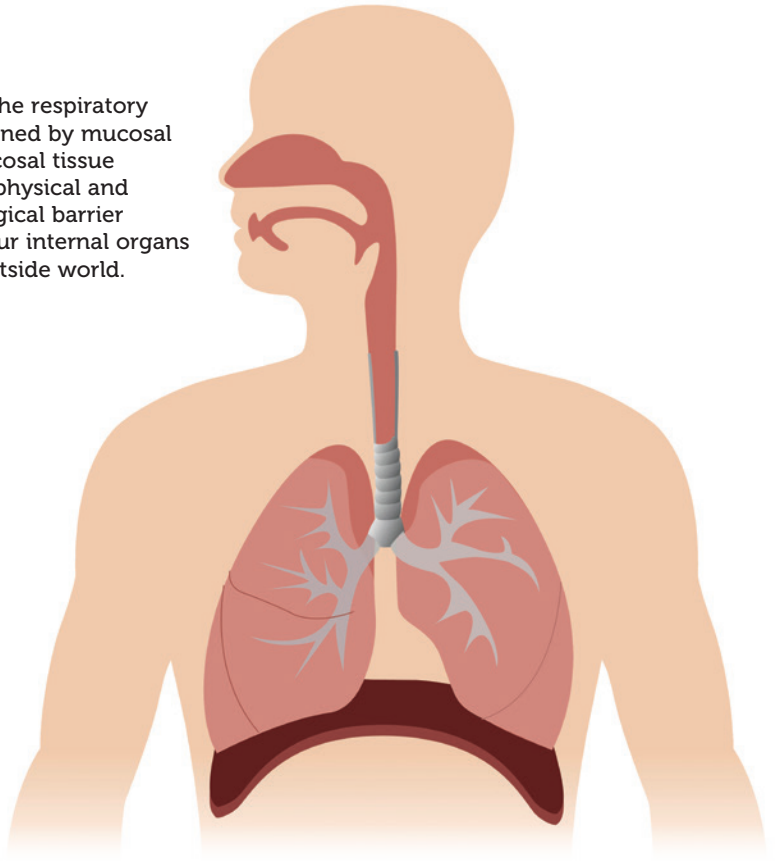

Figure 2: The respiratory system is lined by mucosal tissue. Mucosal tissue forms the physical and immunological barrier between our internal organs and the outside world.

"Inhalation has several advantages over the traditional needle-based method, particularly when considering tackling the next respiratory epidemic or pandemic."

Mucosal Immunity

Vaccines delivered via injection generally induce a systematic immune response, which is not specifically directed at the pathogen's region of infection, such as mucosal sites.[2] In contrast, nasal vaccines are able to instigate mucosal immunity directly at the site of infection (Figure 2),[3] which may provide a higher degree of protection against respiratory pathogens.

The systemic immune response induced by intramuscular vaccines provides protection to the lower respiratory tract and prevents severe complications following a respiratory infection. However, initial infection and early disease symptoms may not be prevented because the upper respiratory tract is not protected.[4] This means that the pathogens have the opportunity to invade cells, multiply and spread before they can be identified and neutralised by a systemic immune response.

In contrast, mucosal vaccines are able to induce mucosal immunity as well as systemic immunity against a pathogen. A specialised response of mucosal associated lymphoid tissue instigated by a vaccine enables pathogens to be neutralised before they can cause an infection.[2] This prevents early disease symptoms and can reduce that transmissibility of the pathogen. As has become clear during the covid-19 pandemic, reducing transmissibility is essential in slowing down the spread of a new pathogen or strain. Moreover, this additional immune response is not limited to the site of the vaccination but also offers augmented protection in adjacent or related mucosal tissues.[5] An intranasal vaccine may therefore also induce mucosal immunity in lung tissue.

Removing the Cold-Chain

Another exciting advantage of inhaled and intranasal vaccines is the option to deliver the vaccine as a dry powder, which would remove the need for cold-chain transportation and storage. Most vaccines need to be stored between 2°C and 8°C to maintain their potency. The covid-19 pandemic accelerated the progress of novel mRNA-based vaccines. These allowed for rapid development and roll-out, but with the disadvantage of extremely cold shelf-life temperature requirements. For example, the BioNTech/Pfizer covid-19 vaccine requires storage at -80°C with a shelf life up to six months.[6]

Although most can be transferred to fridge temperatures (2–8°C) for up to 30 days, the extreme cold-chain requirements of injectable vaccines can make them inaccessible for large parts of the world and can lead to vaccines being discarded, due to the time period when they can be stored above super-cooled temperatures expiring. Hence, there is interest in improving the stability of mRNA-based vaccines,[6] as well as that of traditional vaccine platforms, such as by formulation as a dry powder. Formulating complex biologics into dry powders has its own challenges, as discussed later in this article, but thin-film freeze-drying is showing promising results.

The benefits of reducing the dependence on cold-chain logistics for facilitating mass-vaccination campaigns across the globe cannot be underestimated – increasing access, reducing vaccine wastage and reducing the financial and environmental burden.

RECENT DEVELOPMENTS

To date, the only widely used vaccine delivered via the respiratory system is an intranasal influenza vaccine, known as FluMist in the US and as Fluenz Tetra in the UK (AstraZeneca). With the covid pandemic, there has been increased interest in intranasal and inhaled vaccines. According

to Nature, around 100 nasal or oral vaccines are currently under investigation.[7] Several of these have received limited approval for human use, including the CanSino Biologics (Tianjin, China) vaccine, and the Razi Vaccine and Serum Research Institute (Karaj, Iran) vaccine. Phase III trials for a number of others are underway. However, the development of the AstraZeneca vaccine as a nasal spray has hit a roadblock, with weak results in Phase I trials.[8]

The vaccines currently under research belong to a variety of different types, including viral vector, protein sub-unit and live virus, although they all appear to revolve around delivery in a spray or drops rather than a dry powder, which does not come with the benefits of removing the cold chain.

Active research into dry powder formulations of vaccines is less advanced than that of liquid formulations, although a 2019 study reported delivery of a dry powder influenza vaccine in ferrets with positive results.[9] Some dry powder inhalers already on the market, such as TwinCaps by Hovione (Loures, Portugal),[10] may be suitable for the delivery of dry powder vaccines.

Despite the recent disappointing result with the AstraZeneca vaccine, the outlook for respiratory mucosal vaccination and the untapped potential of dry powder formulations is promising for the coming years.

CHALLENGES

Formulation

The respiratory system has many defence mechanisms, such as mucociliary clearance, in place to protect us from foreign micro-organisms and particles – including the constituents of vaccines. A safe, effective vaccine must be able to bypass these mechanisms to induce the appropriate immune response, without causing severe adverse effects. In order to achieve this, the selection of vaccine platform and adjuvants, if required, must be given careful consideration.

Dry powders have stability and aerodynamic advantages but formulating complex biologics into dry powders is no easy task. Physical and chemical degradation can occur during the drying process, so the choice of technique must be carefully considered. Traditional methods include spray-drying and freeze-drying (lyophilisation). However, both have disadvantages for inhaled biologics – spray-drying uses heat, which can denature proteins, and the mechanical stresses involved in freeze-drying methods can cause protein aggregation.[11] Thin-film freeze-drying is an exciting new addition to the field[12] that has been shown to be a viable method for converting vaccines into dry powders,[13,14] giving it strong potential to become a big player.

Usability and Training

Whilst inhaled vaccines may not need a trained medical personal to be present for safety reasons, the idealised situation of self-administration at home without supervision is problematic. How do we prove that the user took the vaccine in order to authorise a "vaccine passport" or equivalent? Furthermore, how do we prove they took it correctly? Dose accuracy is inherently dependent on correct inhalation and usage by the patient for inhaled and intranasal medicines. Dry powder inhalers, for example, require a sharp intake of breath, which regular users will receive training for. A mass vaccination campaign using a dry-powder inhaler would require educating the masses effectively on the correct usage, otherwise the efficacy would be severely reduced.

Dose Accuracy

The dose accuracy will be more variable than for an injected vaccine, even if administered correctly. In addition to incorrect usage, the delivered dose could also vary due to factors such as:

- Inspiratory flow rate
- Mucosal state, such as having a cold
- Comorbidities, such as asthma
- Nasal or lung geometry
- Ambient humidity and the time taken from removing packaging to taking the drug, both of which noticeably affect dry powders due to changes in their adhesion and cohesion properties.

Furthermore, it is more difficult to measure dose accuracy for an inhaled locally acting drug.

FINAL REMARKS

Inhaled and intranasal vaccines have some key advantages over traditional needle-based methods, as highlighted in this article. However, there are challenges to overcome, if they are to be relied on for future mass vaccination campaigns.

"The dose accuracy will be more variable than for an injected vaccine, even if administered correctly."

ABOUT THE AUTHORS

Heather Jameson, PhD, 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 the University of Cambridge (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.

Juliette Ngan is a biomedical engineer at Springboard, working on projects ranging from research on biomarkers to development of drug delivery devices. She completed her MEng at Imperial College London (UK) with a focus on human-machine interfacing for rehabilitation and learning. Combining her broad academic background with creativity and industrial experience, she is able to find effective solutions to technical challenges.

Omar Shah is a multi-skilled engineer and materials scientist at Springboard, specialising in metallurgy and material processing. He has experience in corrosion, mechanical and microstructural testing, and mechanical engineering design. He completed his Master's at the University of Cambridge (UK), working with the Rolls Royce University Technology Centre developing novel titanium alloys. At Springboard, Mr Shah uses his broad knowledge base to identify and solve cross-disciplinary problems.

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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ICONOVO

WHY ARE INHALATION DEVICES SO DIFFICULT TO DEVELOP?

In this article, Orest Lastow, PhD, Chief Technical Officer at Iconovo, discusses the challenges of developing inhalation products and how best to keep costs down and prevent project delays.

Today, many conditions are managed with inhaled pharmaceuticals. The best route of administration for a pharmaceutical product is determined by the target organ for the drug and other considerations for optimal uptake of the product in the body. An inhaled drug is typically delivered to the nose, airways or lungs using an inhalation device. The main two diseases treated using this route are asthma and chronic obstructive pulmonary disease (COPD), with the drug in either a liquid or dry-powder formulation.

There are currently three main device types for inhaled pharmaceuticals – pressurised metered dose inhalers (pMDIs), dry powder inhalers (DPIs) and nebulisers. DPIs can come as either a multidose or single-dose inhaler. DPIs and pMDIs are portable inhalers, whereas nebulisers are typically stationary inhalers used in hospitals or at home. There are, however, some smaller portable nebulisers on the market. These are typically more advanced and expensive, and their market share is relatively small. What all inhalation devices have in common is that they convert a dose of formulation into an aerosol of respirable particles in the size range of 1–5 µm.

The development, manufacturing and registration of an inhalation product is associated with several major difficulties that deter pharmaceutical companies from investing in such development. There are a few major pharma companies that have a strong track record of commercialising successful inhalation products, but the list is fairly short compared with other dosage forms. This reflects how the market is structured, with a few major players dominating the market. This remains true even though the patents of many major inhaled pharmaceuticals have long since expired, presenting an opportunity for generic substitution on the market. For a new player, the threshold to enter the market is high and very few even try.

Even major generic companies, with an extensive product portfolio, find it difficult to build the very eclectic team required to successfully develop an inhalation product and bring it to market. Even for an experienced and well-equipped company, such development has proved to be costly – with lengthy development times. Perhaps the most significant deterrent is the significant risk of major delays and increased development cost.

There are four major challenges when developing an inhalation product:

- Conflicting user requirements
- Product complexity
- Inextricable performance
- The delicate balance between regulatory and manufacturing requirements.

USER REQUIREMENTS AND CONFLICTING INTERESTS

The first key challenge in the development of an inhalation product is to produce a good and balanced specification that voices the demands from users, payers, healthcare professionals and other stakeholders. The specification should be comprehensive and all the requirements must be compatible. All the implications of the requirements should be well analysed and understood. Internal company stakeholders and functions should also be

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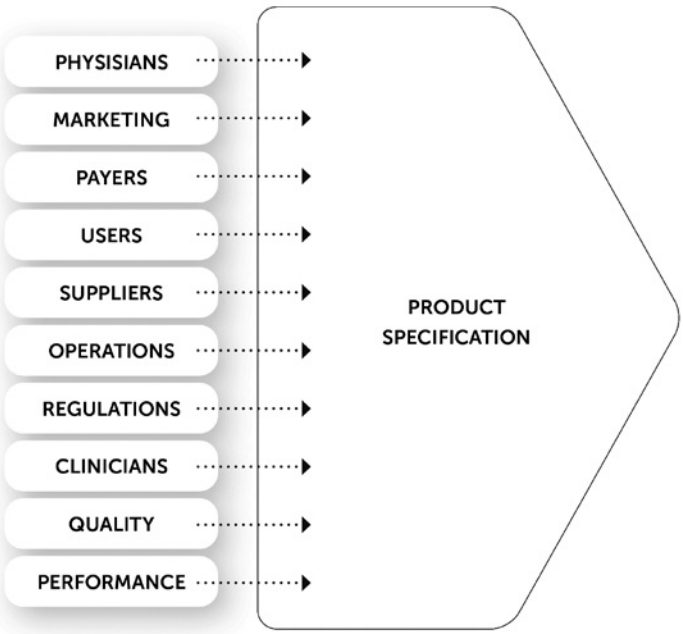


Figure 1: Requirements from users and stakeholders.

included – i.e. operations; marketing; the chemistry, manufacturing and controls (CMC) documentation team; and the clinicians that will conduct the clinical trials (Figure 1).

The different stakeholders, users and customers will, in many cases, have strongly conflicting requirements. Balancing these different needs when compiling a comprehensive specification is very demanding. When a high-level specification is drafted, several specific technical questions must be answered to select appropriate technical solutions. The questions include, for example:

- DPI or pMDI?
- Active or passive?
- Electronic or mechanical?
- Pre-metered or reservoir?
- Simple formulation or advanced formulation?
- Large dose or small dose?
- Relative humidity (RH) protection or not?
- A few user steps or many user steps?
- Dose counter or dose indicator?

These decisions will provide a foundation for future compilation of the specification.

User Studies

The next step is to map out how the patient uses the inhalation product and what drives the different aspects of use. The outcomes of user studies typically give some clear unambiguous results, however, some of these results can also be mutually conflicting. In some cases, the user has an inconsistent perception of their own personal use and preferences.

The highest ranked features are often the various feedback functions; the user requires reassurance from the inhalation device that the dose has been correctly delivered. It should also clearly show exactly how many doses remain in the device. However, some users perceive too much feedback as complicated and hard to understand, whereas others want as much feedback as possible.

The device should also be very simple, ergonomic and intuitive to use. It should provide good ergonomics for both children and the elderly. It should be safe against inadvertent opening or actuation when carried in a pocket or purse but also be easy to open and actuated by a person with impaired vision and dexterity. In general, all users agree that the operating sequence should require as few user steps as possible, ideally just open-inhale-close. There should also not be any requirement to clean the device – but it should still be simple to clean, if so desired.

"A low-cost single-use device requirement is not compatible with advanced feedback features."

Design, Cost and Lifetime of the Device

Another common requirement is that the device should be small, discrete and attractive. This clearly conflicts with the ergonomics and hygiene requirements. Furthermore, a low-cost single-use device requirement is not compatible with advanced feedback features. A disposable device is usually preferred for simplicity, but the perception of the reusable device is that it is more environmentally friendly. However, a reusable device is more complicated to use, as it needs reloading and cleaning. A reusable device is also more technically advanced – thus more expensive. The overall cost break-even point for disposable versus reusable device depends on how many times the device will be reused, which is difficult to predict. The logistics of the refills also need be factored in.

An important factor is the perception that the device is safe and reliable. A more clinical and hygienic design comes across as more reliable than a device with a more consumer-product appearance. The clinical and hygienic design is, on the other hand, less attractive. The device should preferably be attractive to all age groups, from children to octogenarians. A typical market lifetime of an inhalation device is at least 10–20 years, which means that a design should appeal to all ages and sexes over a very long period.

A typical feature sought by patients and doctors is electronic feedback and monitoring. The real benefit of this feature is, however, unclear. The device could, for example, remind the patient to take the medicine, monitor the lung function and automatically upload the data to the prescribing doctor. Although this seems to be a useful feature, it is easy to imagine the patient being annoyed by the constant reminding and seeing the data uploading as an invasion of privacy. Furthermore, not all doctors can be expected to appreciate the benefit of receiving gigabytes of patient information.

PRODUCT COMPLEXITY

When the product specification has been agreed, the multidisciplinary product development project can begin. An inhalation product is very complex and comprises multiple fundamental parts that each present their own challenges. The development of the different parts requires very different sets of skills and is often done by different teams. The number of parts can, of course, be debated but, for the purposes of this article, the product has been split into six fundamental parts (Figure 2).

The different parts are intimately interlinked, and all contribute to the function and performance of the product. The device, drug and formulation are physical parts of the product, whereas the user, operating environment and manufacturing processes are more abstract parts.

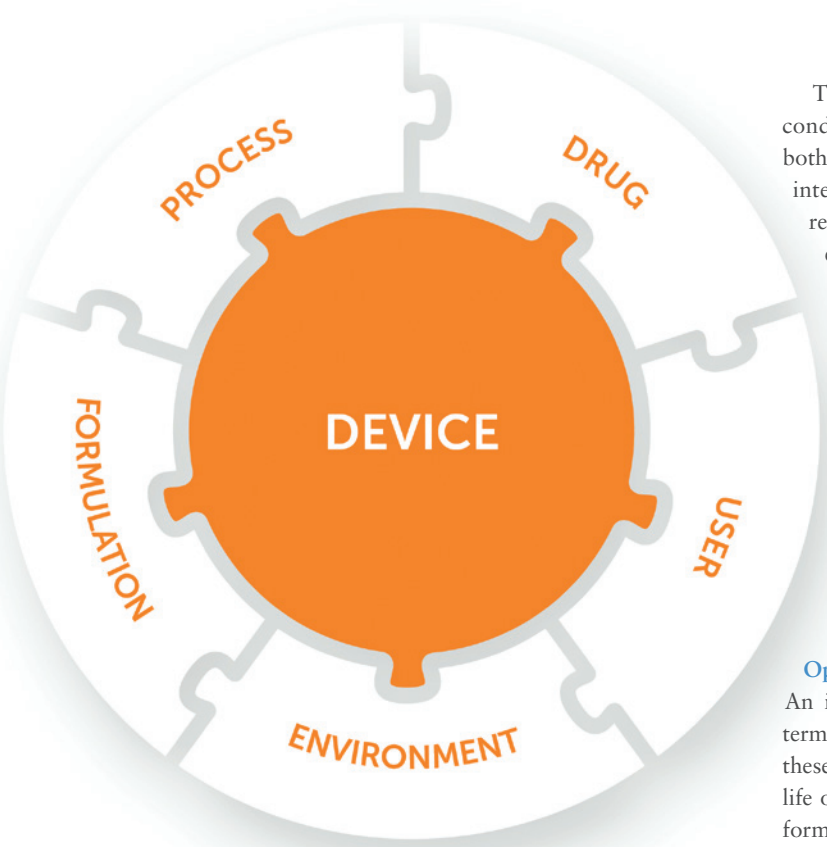


Figure 2: Parts of the multidisciplinary product development project.

Drug

The main objective of an inhalation product is to deliver the drug to the patient's nose, airway or lungs. Therefore, the drug drives many of the other features and requirements. The chemical and physical properties, together with the pharmacodynamic and pharmacokinetic properties of the drug, are the key selection criteria when developing the product. These factors also have a strong impact on the most suitable formulation and type of device. The potency of the drug drives the dose size and drug content in the formulation. The drug also dictates what kind of protection is required from the device – moisture, light, oxygen, etc.

User

Another aspect to consider is the user or patient. The patient population with diseases commonly treated by the delivery of a drug to the lungs is very heterogeneous and expected to be even more so in the future. On the one hand, patients with asthma, who are traditionally treated by inhaled drugs, often start using inhalation devices in childhood. Patients with COPD, however, are often introduced to inhaled therapy at a mature age. When developing inhalation products for this wide, heterogeneous and sometimes multi-disease patient population, patient needs and preferences must be thoroughly investigated and understood. This includes not only hard parameters like inhalation effort and inhaled volume, but also soft parameters such as handling, dexterity and user interface.

> "The device and the formulation are intimately interlinked and must be developed and optimised together."

The best way of collecting this type of information is to conduct extensive user studies. Such studies should include both practical tests of usage of different inhalation devices and interviews. The test groups must be sufficiently large and representative in terms of age, gender, disease and prior inhaler experience. The studies should preferably be conducted in all countries where the product is intended to be launched. In addition to patients, healthcare professionals should also be included to give their perspective. It is obvious that such an extensive study will be very costly and time consuming. The study can be reduced if a body of knowledge is available within the company, which has been gained by long tradition and experience from products on the market. A great deal of information can also be accessed in the literature. However, there is an obvious risk associated with a too-retrospective approach when developing new products for new patient groups.

Operating Environment

An inhalation product will be used in many different climates in terms of RH and temperature. The product will also be stored at these conditions for an extended period. Many products have a shelf life of two years and an in-use life of several months. The drug and formulation must thus be chemically and physically stable during this period and the device must provide sufficient protection from adverse environments. The question is whether the device provides sufficient humidity protection or if an additional over-wrap is required. There could even be a need for a desiccant in the device or in the wrap. A critical question is whether the device should be adapted or if the moisture sensitivity can be managed by formulation modifications.

Formulation

The formulation is, in a sense, the "blood" of an inhalation product. The function of the formulation is to enable the handling and delivery of the drug to the patient. The formulation is very sensitive to the quality of the various ingredients, the properties of the drug and the composition. The development of a formulation also includes the selection of process equipment (e.g. the mixer) and the optimisation of all the running parameters. When developing an inhalation product, the ambition is often to use the same type of formulation with many different drugs in the same device. There are many different types of formulations, and they each require the appropriate device. The device and the formulation are intimately interlinked and must be developed and optimised together.

Device

The device is what brings all the other parts together. The device should accommodate all the requirements of other parts, including ergonomics, performance, stability, robustness and manufacturing. The role of the device is to house and protect the formulation and meter-disperse-deliver the dose. The design of the device is also the user interface and defines the user sequence. Industrial design is used to develop the exterior shape, graphical design, texture, visual expression and so on. All the mechanical requirements, such as tolerances, assembly sequence, manufacturing processes and materials, are also defined by the device.

It is obvious that a thorough knowledge of all the other five parts is required in the development of the device. Developing a device includes all the traditional mechanical design tasks that are common

to all complicated plastic devices. However, in an inhalation device, several tasks and challenges are added. Things like flow resistance, drug retention on the surfaces and fluid dynamics must be included and addressed. To succeed with such a multidisciplinary development, a very eclectic team must be formed

Manufacturing Process

When the formulation is put into the inhalation device, filling equipment is always needed. The filler must be compatible with both the formulation and the device. It should also be compatible with variations of the formulation for when a different drug is used. The filling, and other processes like heat sealing, will be a strong contribution to the manufacturing yield and capacity.

The total cost of the product is also strongly dependent on the manufacturing processes and the process equipment. Much of the CMC documentation is related to the various processes that require extensive validation and verification. Due to the high cost of development, the same inhalation device and manufacturing equipment is often intended for many different drug products. This gives another layer of complexity to the development.

A major challenge is the journey from simple bench-top technical equipment used during development to the GMP equipment used to produce the clinical trial supplies – and, finally, to high-capacity commercial equipment. It is a delicate task to balance development risk against financial risk. From a development point of view, it is advantageous to scale up the process as soon as possible to reduce the risk. From a financial point of view, it is preferred to delay the investment as much as possible to reduce the financial risk.

INEXTRICABLE PERFORMANCE

The different parts discussed above interact and together give the performance of the product. The interaction between the physical product parts is very complex and their individual contributions to the performance are inextricable. On top of which, the interaction with the user is an additional factor – pharmaceutical products are highly regulated, and the inhalation product must deliver the same performance independently of the user's inhalation effort and inhalation profile.

The dose from an inhaler can be described in terms of delivered dose, respirable dose and respirable fraction. To maintain the same respirable fraction, the particle-size distribution must be the same for every dose. To achieve consistent particle-size distribution, the formulation must be consistent and the device geometry variations very small. To have a high delivered dose uniformity, the properties of each individual dose must be the same for each inhalation, each patient and each manufactured batch. It must also remain the same over time, independent of the storage conditions. When an inhalation device is intended as a platform for many different drug products, the performance should be the same for all drugs and all dose strengths. Needless to say, it is extremely challenging to meet all these performance requirements – and performance testing is the most labour-intensive task during development.

REGULATORY VERSUS MANUFACTURING REQUIREMENTS

The regulatory requirements have a strong focus on patient safety and consistency of performance. The patient should always get the same dose, irrespective of how the inhalation product is used and how it has been stored. The regulatory requirements drive the complexity and quality standards of the inhalation product. When designing the mechanics of an inhalation device, there are two sets of regulatory requirements.

One set is the functional requirement – i.e. the mechanical function of the device. This requirement has the nature of pass or fail – either the inhalation device fits together and works according to specification or it does not. If the design fails these tests, the product cannot be approved and launched. The mechanical function can be tested and verified without the formulation. The design should be robust enough to be able to accommodate small dimensional variations without failing. The allowed dimensional variations are defined as tolerances. To reach a high yield or process capability (Cpk), which is desirable from a manufacturing and cost point of view, the tolerances should be as wide as possible.

The other set of requirements is the performance requirements. Performance requirements must be tested with the formulation and include delivered dose uniformity, fine particle dose, chemical stability and physical stability. The actual value in the requirement is not absolute and is a matter for clinical trials and discussions with regulatory agencies. There are guidelines to adhere to, but many performance requirements are not covered in the guidelines.

There is a conflict emanating from the two sets of requirements. For instance, some dimensions in the inhalation device require one tolerance for the mechanical function and a different tolerance for the performance. As an example, the functional tolerance could give a high Cpk of 1.8. This is the process capability of a mechanically functioning inhalation device – i.e. no formulation included and no pharmaceutical performance tested. This variation in dimension could, however, lead to a high variability in performance.

This could, for example, be the gap between two parts forming a duct. The duct has no mechanical function but governs the dispersion of the formulation and the inhalation resistance. To achieve acceptable performance uniformity, this tolerance must be tighter. However, the new tolerance will decrease the Cpk to, for example, 1.5. It could then be the case that the uniformity could be improved even more, decreasing the Cpk to 1.0. A low Cpk will lead to a high manufacturing cost. The increased manufacturing cost will, in the end, reflect on the price and profitability of the product. The higher cost will eventually be covered either by a lower profit margin for the producer or a higher cost for the payer. The sponsor is facing a delicate trade-off between performance and cost.

"A key challenge is to set up a relevant and comprehensive product specification for the inhalation product."

CONCLUSION

The development of an inhalation product poses many serious challenges. Most of the challenges have their origin in the complex interaction between the different parts of the inhalation product. To keep down the development costs and minimise project delays, it is important to have a thorough understanding of the inhalation product. This requires an eclectic combination of skills, including pharmacy, engineering, chemistry and physics. A good understanding of the regulatory requirements, together with clinical and pharmacological experience, is also very valuable. This required skill base should be considered when forming project teams.

A key challenge is to set up a relevant and comprehensive product specification for the inhalation product. It is time well spent to have a thorough analysis of the various consequences of each requirement. An incompatible or over-ambitious set of requirements can have tremendous ramifications on the development. The consequences may not become obvious until late in the development and then lead to extensive redesign and delays.

ABOUT THE COMPANY

Iconovo develops novel inhaled pharmaceutical products in collaboration with international pharmaceutical companies. The company provides several types of patent-protected inhalers, with significant commercial opportunities in the development of novel pharmaceuticals and in patent expirations for established pharmaceuticals. Iconovo has in-house capabilities in the development of inhalation products – design tools for inhalers, and dry-powder formulation equipment for measuring and mixing, and characterisation testing using next-generation pharmaceutical impactor and high-perfomance liquid chromatography methods. Possessing a unique combination of engineering and pharma expertise, Iconovo can provide the optimal combination of customised inhalers and tailored formulations.

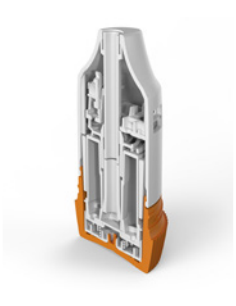
ABOUT THE AUTHOR

Orest Lastow, PhD, has more than 30 years' experience in inhalation development, mainly at AstraZeneca. He has invented more than nine different inhaler devices and been involved in the development of 13 different inhaler devices. Dr Lastow has also made more than 40 patent applications and has published several research articles and books. He also co-authored the ISO standard for inhaler devices and is frequently an invited speaker at inhalation conferences. Dr Lastow founded Iconovo in 2013.

2023 EDITORIAL CALENDAR

Publication Month	Issue Topic
January	Skin Drug Delivery: Dermal, Transdermal & Microneedles
February	Prefilled Syringes & Injection Devices
March	Ophthalmic Drug Delivery
April	Pulmonary & Nasal Drug Delivery
April/May	Drug Delivery & Environmental Sustainability
May	Delivering Injectables: Devices & Formulations
May/June	Novel Oral Delivery Systems
June	Connecting Drug Delivery
June/July	Industrialising Drug Delivery
September	Wearable Injectors
October	Prefilled Syringes & Injection Devices
October/ November	Drug Delivery & Environmental Sustainability
November	Pulmonary & Nasal Drug Delivery
December	Connecting Drug Delivery

Iconovo brings inhalation expertise to your business



We are enabling our partners to develop complex generics and novel pharmaceuticals as inhaled therapy for a global market. An integrated development process of the inhaler and formulation is crucial for a successful completion of an inhalation product and reduces lead time, cost and risk.

ICONOVO

THE INNOVATIONS THAT ARE HELPING TO TACKLE CHALLENGES AND MAXIMISE OPPORTUNITIES FOR INHALATION SOLUTIONS

Here, Marco Franza, Sales and Business Development Director – Global Inhalation & Medical Devices, and Nadine Khoury, Senior Strategic Marketing Manager Healthcare, both at Berry Global, look at how the latest digital technologies, manufacturing techniques and advances in packaging materials are combining to take the manufacture of inhalers to a new level in terms of the patient experience, financial improvements and sustainability gains.

The fast-track introductions of the various vaccines during the covid-19 pandemic has highlighted how the pace of drug development has increased significantly in recent years. Today, pharmaceutical and healthcare companies can bring many types of treatment to market more quickly.

At the same time, the drugs now being developed are becoming ever more sophisticated, in terms of their overall effectiveness and how they can be closely targeted to different patient groups. This enables the provision of more individualised care for patients, tailored to their specific needs and medical history. According to a Euromonitor report on the future of personalised healthcare, this patient-tailored approach is expected to reduce trial-and-error treatments and improve outcomes and healthcare cost effectiveness.[1]

The report also identifies how personalised healthcare systems are being driven by strong biotech and R&D sectors that are helping to speed up the development of these new solutions, combined with the experience of the pharmaceutical industry, which brings them quickly to manufacture and commercialisation.

Alongside this, the introduction of these precision medicines has been supported by the move to eHealth, telemedicine and remote diagnostics – a trend that was accelerated by the pandemic. Through the use of information management and information and communication technology, diagnoses can be carried out remotely, and care and treatment integrated into patients' daily lives. Carers can also share relevant information more easily, and data can be analysed as part of disease management or a clinical trial.

In this way, patient engagement can be enhanced and improved, encouraging positive behaviour and ensuring greater adherence and compliance to treatments (Figure 1).

Figure 1: A new generation of inhalers with digital technology is seeking to improve inhaler adherence and technique.

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"A new generation of models, which incorporate digital technology, is able to improve adherence and monitor treatments more effectively to greatly enhance patient outcomes."

Such sophistication presents additional challenges in terms of how these treatments are packaged, dispensed and administered. Each format needs to meet the precise requirements of the particular drug while also delivering the appropriate patient experience so that the drug can be taken easily and intuitively to maximise its effectiveness.

In its ongoing development of solutions to deliver drugs effectively to the lungs, the medical device sector is no stranger to innovation. The first pressurised metered dose inhaler was introduced in 1956 and, since then, we have seen continual enhancements and improvements to the technology, as well as the introduction of dry powder inhalers.

Much of the success of today's inhalers is a result of the advanced manufacturing techniques that have been introduced over the years (Figure 2). High-precision moulding and assembly are required for the complex and technical parts, some of which are microdimensional. Internal coatings must deliver product protection and stability.

It is therefore quite sobering to learn that, despite these many advances since 1956, the number of inhaler errors caused by inadequate adherence and technique has hardly changed at all during this time. Specifically, up to 94% of patients still make critical mistakes using their inhalers.[2] Another study found that adherence to asthma and chronic obstructive pulmonary disease treatments was as low as 32%, meaning two out of three people were taking their medicine incorrectly.[3]

It is this problem that the latest technical inhaler innovation is seeking to overcome. A new generation of models, which incorporate digital technology, is able to improve adherence and monitor treatments more effectively to greatly enhance patient outcomes.

Figure 2: Advanced manufacturing techniques are critical to the capabilities of the latest inhalers.

The new inhalers incorporate built-in sensors with digital capabilities that allow them to track inhaler use. This information is shared with a companion app, which then provides personalised guidance to each patient. The use of the app reminds patients when to take a dose and provides tips to help them self-medicate more effectively. Patients can also share their data with healthcare providers, either remotely or in person, to enable data-driven treatment adjustments.

A typical app is able to track when and how a patient inhales a dose and provide an alert if a dose is missed. It can monitor inhaler orientation during inhalation and capture estimates of inhalation parameters. Through this, personalised learning content can be prepared with health forecasts and insights. Patients can build better inhalation techniques, learn to identify and avoid what triggers their symptoms and track their breathing to identify signs of improvement or worsening of their condition.

- At study end, **84% patients** in the digital medicine group had their **asthma partially or well controlled.** On average, asthma control **scores improved by 5.9**
- Asthma control levels were linked to cost data, with **average annual cost reduced by 72% (p=X.X)**

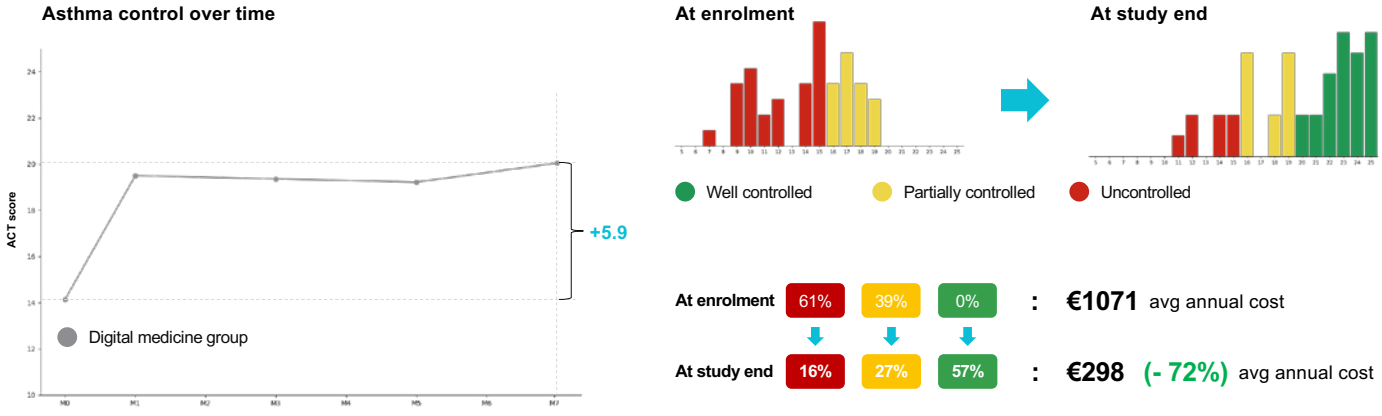

Figure 3: Positive improvement in asthma control scores in a trial of the Amiko Respiro™ app.

For one app already on the market, the Amiko (Milan, Italy) Respiro™, a seven-month randomised control trial generated a 43% improvement in medication adherence, a 61% reduction in inhaler technique errors and a +5.9 improvement in asthma control (Figure 3).

Importantly, these digital features can be introduced without compromising on the technical design and intricate manufacture of the inhalers. This ensures that they retain both their ability to dispense the medicine accurately and their user-friendly features, particularly in terms of suitability for all age groups.

While these benefits are primarily focused on improving patients' quality of life, they have equally important financial implications. A recent study by York Health Economics Consortium and The University of London's School of Pharmacy estimated that the resulting net benefit associated with greater compliance for asthma treatment was £2,250 per patient, leading to savings of £90–130 million per year.[4]

Similarly, Health-monitoring.com estimated the costs associated with imprecise dosing of medicines to be around US$765 billion (£680 billion), which represents some 30% of total spend on healthcare.[5]

Alongside these continual improvements in design and technology, the drive for more sustainable solutions is also becoming a critical factor in inhaler design.

This is not to say that this is something completely new to medical devices. The lightweighting of products to reduce the amount of material required to produce them has long been a key factor in new inhaler designs. Here, the critical consideration has been to lower the weight of the dispenser while ensuring that it remains fully functional and user friendly, and continues to deliver the best patient experience.

Another important consideration for any product design has been to improve its recyclability. This has led to the development of more mono-material solutions, made in materials such as polyethylene (PE) and polypropylene (PP), both of which are now widely recyclable.

Alongside this has been the introduction for pharmaceutical and healthcare applications of ISCC Plus certified packaging and plastic components that contribute to a circular economy approach.

ABOUT THE AUTHORS

Marco Franza is Sales & Business Development Director – Global Inhalation & Medical Devices, at Berry Global Healthcare. He was previously Director, Sales, Marketing and Key Accounts at Plastiape, until it was acquired by Berry in 2019. Mr Franza has extensive experience in the commercial side of the drug delivery industry, having held roles related to sales, business development and marketing. His roles have had a particular focus on inhalation devices, which are both key growth factors for the company as well as a passionate personal interest.

Nadine Khoury is the Senior Strategic Marketing Manager for Berry Global Healthcare. She joined the company in 2016. Ms Khoury started her career as a designer and digital marketer and has since then held roles in product management, marketing research, communications and brand management. Ms Khoury holds a masters in Marketing Management from ESADE Business School in Spain and a bachelor's degree in Graphic Design and Advertising from the Lebanese American University, Lebanon.

"Alongside these continual improvements in design and technology, the drive for more sustainable solutions is also becoming a critical factor in inhaler design."

ISCC is a globally applicable sustainability certification system, covering all sustainable feedstocks, including agricultural and forestry biomass, circular materials and renewables, based on advanced recycling mass balance. Mass balance is an accepted and certified protocol that documents and tracks recycled content from supplier through to final delivery to customers.

The availability of this advanced recycled resin in both circular PP and PE, which is free from harmful contaminants and therefore suitable for food and pharmaceutical applications, provides the opportunity for the development of solutions for drug delivery applications that contain a high percentage of recycled material, from 30% to 100%. Crucially, these can be for products where this has been difficult to achieve previously.

Increased consumer spending on healthcare, demand for customised services and an ageing population are all driving demand for personalised healthcare services. For inhalation treatments, the transition to precision medicine and to outcome-based care provides great opportunities to improve patient technique and adherence through the adoption of digital technologies, and the health and financial benefits that this can bring are plain to see. And by focusing on both human- and environmental-centred design, the medical device industry can devise solutions that benefit both people and the planet.

ABOUT THE COMPANY

Berry Global Group creates innovative packaging and engineered products that it believes makes life better for people and the planet. Berry does this by leveraging its global capabilities, sustainability leadership and deep innovation expertise to serve customers of all sizes around the world. Harnessing the strength in its diversity and industry-leading talent of 47,000 global employees across more than 300 locations, the company partners with customers to develop, design and manufacture innovative products with an eye towards the circular economy. The challenges and innovations it solves and pioneers benefit its customers at every stage of their journey.

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CREATING A PLATFORM FOR **NEBULISATION** OF A WIDE RANGE OF DRUG TYPES AND FORMULATIONS

In this article, Elijah Nazarzadeh, PhD, Chief Executive Officer, and John Pritchard, PhD, Chairman, both of Acu-Flow Limited, discuss the potential of the inhalation route for both treating respiratory disorders and systemic delivery, consider the limitations of current inhalation technologies and introduce Nebu~Flow – a novel nebuliser technology that represents a major step in the ability to deliver drugs efficiently to the lungs.

According to the WHO, respiratory diseases, such as asthma and chronic obstructive pulmonary disease (COPD), are the leading causes of death and disability in the world.[1] The British Lung Foundation estimates that one in every five people in the UK will be affected by a lung disorder during their life, with staggering annual cost of £11 billion, while it is estimated that more than 200 million people suffer from COPD globally, from which about 3.2 million die each year.[1–3] Furthermore, the covid-19 pandemic, which has claimed more than 4.5 million lives, mainly due to respiratory causes, has highlighted the importance of healthy lungs for fighting respiratory infections.[3]

These disorders are usually treated by the inhalation of aerosols, where the effective delivery of medication is crucially dependent upon the droplet size distribution and inhalation pattern.[4–5] It is generally believed that droplets larger than 10 µm are caught in the nose and throat, while droplets larger than 5 µm can reach the upper airways. Only droplets smaller than 5 µm can reach the small bronchi and alveolar regions, where the chances of drug adsorption are higher.

> "Drug delivery via inhalation can be an alternative to the oral and parental drug delivery routes, with the advantages of bypassing gastrointestinal and hepatic metabolism and reducing the side effects."

In addition, there is growing interest in exploiting the large surface area of lungs for systemic drug delivery. It has been shown that drug delivery via inhalation can be an alternative to the oral and parental drug delivery routes, with the advantages of bypassing gastrointestinal and hepatic metabolism and reducing the side effects.[6] The alveolar region of the lungs provides a large surface area (up to 75 m^2) with a long residence time and a higher chance of uptake of the drug to the blood stream, making it an ideal target for systemic drug delivery.[7] However, current devices have limited ability to generate aerosols smaller than 2 µm, which are necessary to target the alveolar region.

INHALATION DRUG DELIVERY DEVICES AND UNMET NEEDS

Current inhalation drug delivery devices are mainly categorised as either inhalers or nebulisers. Inhalers are small, portable devices that normally contain one month's therapy, whereas nebulisers are relatively larger devices, dispersing liquid formulations from a unit dose package in the form of an aerosol.

Correct use of inhalers requires specific manipulation and breathing techniques, which results in a high degree of misuse amongst patients, especially for those of older ages.[8–9] On the other hand, nebulisers can aerosolise and deliver medication during tidal breathing, providing an easier drug delivery method that does not require patients to be trained in a special inhalation technique.

Furthermore, nebuliser drug delivery provides an easier formulation step, where the drug dose can be easily adapted during the dose-ranging studies. This is of significant importance in the early stages of

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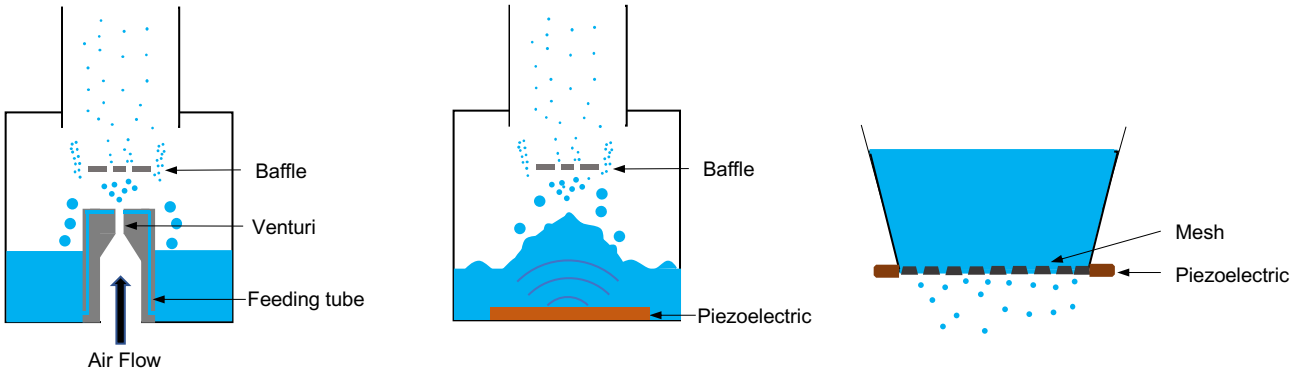

Figure 1: Schematics showing the working principles of current nebuliser technologies – jet nebuliser (left), ultrasonic nebuliser (middle) and mesh nebuliser (right).

"Despite advances in current nebuliser technologies, including jet and mesh systems, existing state-of-the-art devices still have some limitations."

drug development, accelerating clinical trials and regulatory approvals. The use of nebulisers in clinical trials has increased in recent years and has played an important role in enabling new drugs for covid-19 treatment; 69 of the clinical trials started in 2020–21 for the treatment of SARS-CoV-2 used a nebuliser, compared with only 16 drugs trialled using an inhaler.[10]

Because of the significant variability in nebuliser performance between different makes of device, regulators treat a new drug-nebuliser formulation as a combination product, granting market authorisation for the drug to be administered only using that specific device. This means that drugs nearing the end of their patent life can be repurposed as nebulised treatments and still retain a degree of market protection. It should be noted that the market protection of such a combination product can be enhanced by the intellectual property protection of the nebuliser device. It has also been shown that the development and launch of a new drug in a nebulised form before that of an inhaler can have a significantly better return on investment.[11]

A search of clinical trials in 2020–21 showed that almost 54% of clinical trials used a nebuliser, compared with the historic average of 25%. Also, the market trend shows that the number of doses of drug delivered by nebulisers has increased by 6%, compared with only a 3% increase for the number of doses delivered by inhalers.[11]

However, despite advances in current nebuliser technologies, including jet and mesh systems, existing state-of-the-art devices still have some limitations, namely:

- Limitations on controlling the aerosol particle size
- Sub-optimal performance
- Poor user experience
- Limited range of acceptable formulation properties (e.g. viscosity, surface tension).

This article provides an overview of current nebuliser technologies on the market and their limitations. This is followed by an introduction to the Nebu~Flow® surface acoustic wave (SAW) nebulisation technology, which is the most recent development in the field, and some its advantages over current devices.

Jet Nebulisers

Jet nebulisers have been in use since the 1850s and have the highest share of the market. They are developed based on the Venturi principle, using a high-pressure flow of air (or oxygen) through a nozzle to aerosolise liquids. At the Venturi, air pressure drops and the gas velocity accelerates. This generates a negative pressure that sucks the liquid from the reservoir to this point and breaks it into the form of droplets (Figure 1, left). The generated aerosol has a range of large and small droplets, with the large ones captured by a baffle and recirculated into the reservoir and the smaller ones leaving the area for inhalation. The aerosol droplet size from a jet nebuliser varies highly with the design of the system, which results in a significant variability in jet nebulisers from different companies.[10]

The use of high-pressure air and multiple passes of the liquid through the Venturi makes this system unsuitable for a range of formulations. For example, formulations of fragile biologic drugs can be degraded through the multiple passes, while formulations with a surface-active molecule usually result in foaming in the chamber and cannot be nebulised efficiently.[12]

Jet nebulisers are usually inefficient and have a high residual drug volume that cannot be aerosolised (>0.5 mL).[13] This, combined with the noise from the pump and cleaning procedures, makes them an unfavourable device for patients.

Ultrasonic Nebulisers

The first use of ultrasonic nebulisers can be dated back to 1950s. They employ the energy from an ultrasonic beam to disperse liquids in form of aerosols. The wave of ultrasound is produced by rapid vibration of piezoelectric crystal, which transfers its energy to the liquid. The piezoelectric crystal is usually placed at the bottom of the liquid reservoir, forming a crest from which droplets are detached (Figure 1, middle). Like jet nebulisers, large droplets are captured by a baffle and recirculated within the liquid reservoir.

Ultrasonic nebulisers usually employ frequencies in the range of up to few megaHertz, which can generate cavitation and increase the temperature of the liquid significantly. The excessive heat can denature

the API, especially with macromolecules. Additionally, suspension formulations usually settle at the bottom of the reservoir and cannot be dispersed as an aerosol. These technical challenges have resulted in limited use of ultrasonic nebulisers, which are mainly used for the nebulisation and delivery of saline solutions.

Mesh Nebulisers

Mesh nebulisers were first developed in the early 1990s. Early mesh nebulisers were based on a technology originally developed for ink-jet printing, where the liquid was actuated indirectly. In one of the first designs, piezoelectric crystals vibrate around a feeding tube, which forces liquid through a mesh (pore size of 5 µm), which then creates an aerosol. Later forms of mesh nebuliser, where the piezoelectric crystal vibrates the mesh directly, are known as vibrating mesh nebulisers (Figure 1, right).

In general, the orifice sizes of current mesh nebulisers are in the range of 2–5 µm. The small orifices of mesh nebulisers result in a number of inherent technical limitations. As these orifices are very small, they tend to get blocked easily and cannot disperse suspension formulations when the particle in suspension has the same size as the orifice. Also, formulations with low surface tension usually drip through the orifices and flood the system, resulting in inefficient nebulisation. Finally, the passage of fragile biologics through the small orifices, combined with their lengthy exposure to the vibration within the drug reservoir, can denature these macromolecules.

While mesh nebulisers have increased the overall use of nebulisers, their inherent limitations in the delivery of different formulations results in a limited availability of drugs for patients. Also, the main patents for mesh nebulisers are expiring, which may discourage their adoption in the development of new drug-nebuliser combinations.

Unmet Needs

Despite the ongoing developments of nebuliser technologies, there are still significant unmet needs. As discussed, not only may complex formulations lose potency, the output rate and droplet size of nebulisers depends in large part on the physical properties of the formulation, such as viscosity and surface tension.[14] Furthermore, suspension formulations are unsuitable for ultrasonic nebulisers and may block the micron-sized pores in mesh nebulisers.[14]

In addition, the droplet size is a fundamental function of the design of a nebuliser and can be difficult to change, which can clearly impact the likely efficacy of the product by targeting the wrong location in the lungs.[15] A tuneable nebuliser would offer significant advantage in

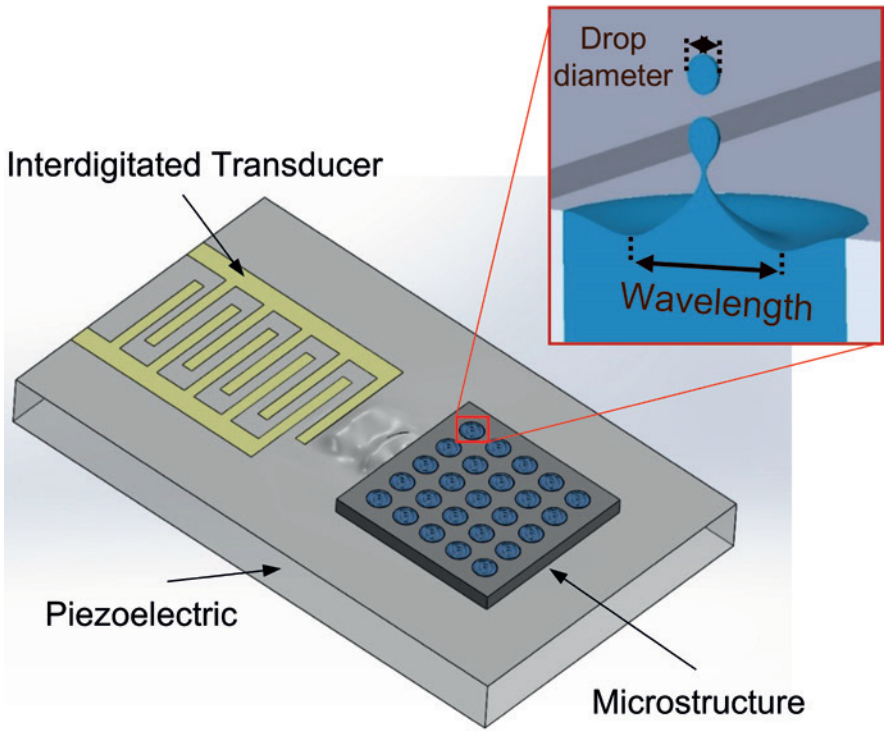

Figure 2: Schematics showing the working principles of Nebu~Flow technology. Inset shows confinement of liquid within the microstructure, which controls the largest capillary wave on the surface of liquid and generated droplet size (droplet size is proportional to capillary wavelength).

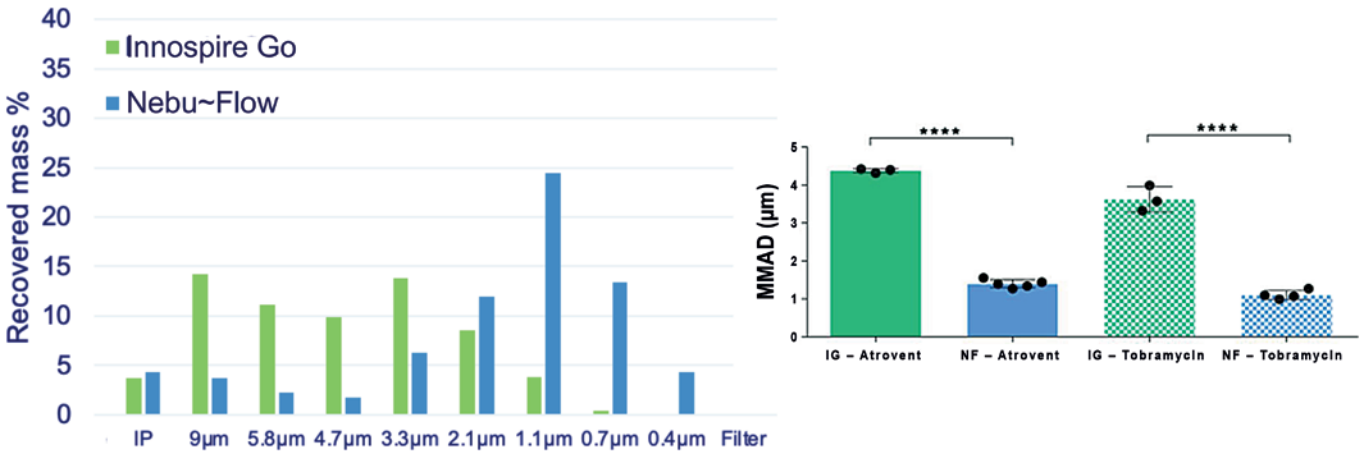

Figure 3: Cascade impaction measurement comparison of aerosols generated by Nebu~Flow (NF) and InnospireGo (IG) mesh nebuliser. A representative aerosol distribution of Atrovent (250 µg/mL ipratropium bromide) nebulisation with both Nebu~Flow and InnospireGo (left); MMAD of aerosols generated using Atrovent and Tobramycin (40 mg/mL) from Nebu~Flow and InnospireGo (right). Aerosols from Nebu~Flow have smaller sizes with MMAD in range of 1 µm, ideal for deposition in the alveolar region.

optimising the efficacy and safety profiles of a new drug. Finally, there is still room to improve the patients' burden of disease when it comes to factors such as cleaning and treatment time.[16] Thus, there has been ongoing research to find novel ways to create droplets of a size and output rate suitable for application as a nebuliser.

NEBU~FLOW TECHNOLOGY

One of the leading contenders to overcome the challenges of current nebuliser technologies is surface acoustic wave (SAW) atomisation. The SAWs are generated by an interdigitated transducer on the surface of a piezoelectric crystal, creating a Rayleigh wave with a nanometer amplitude, which travels on the surface of the material. These SAWs can transfer their energy (in the form of mechanical energy and acoustic pressure) into the liquid on their propagation path,[17] dispersing the liquid in the form of aerosols.

The use of SAWs as a means of nebulisation was first reported by Kurosawa et al in 1995, promising development of a pocket-size nebuliser.[18] However, although SAW-based nebulisation has been the focus of many research activities,[19,20] no commercial product has yet been developed. These studies have proven that the use of SAWs is a "soft" method for nebulisation of fragile biologics, such as plasmid DNA and siRNA, which retain their biological activity post-nebulisation.[20,21] However, for one design of a SAW nebuliser, studies showed that only 7%–10% of the loaded API reached the lungs.[22]

The main challenge of nebuliser technologies is controlling the aerosol droplet size for efficient drug delivery. The Nebu~Flow technology controls the aerosol droplet size by confining the liquid and surface waves in an array of microstructures.[20] Nebu~Flow's work has shown that the aerosol droplet size is proportional to the capillary wavelength on the surface-actuated liquid. Using a microstructure prevents formation of large capillary waves and consequent large droplets, working as a low pass filter (Figure 2).

The Nebu~Flow technology controls the aerosol droplet size by employing microstructures in the range of hundreds of micrometres. This technology can generate aerosols with mass median aerosol diameters (MMADs) well below 5 µm, enhancing the aerosol drug delivery and increasing the fine particle fraction (Figure 3). For example, a salbutamol solution for nebulisation was delivered from microstructure arrays of 200 and 400 mm in diameter, resulting in an approximate doubling of droplet size (Table 1). This approach also has the potential to tailor the droplet size through the choice of different driving parameters. Furthermore, the technology can generate aerosols within milliseconds, providing a great platform for breath-actuated nebulisers. Additionally, the large microstructures cannot be easily blocked and can be easily cleaned, making it an easier platform to maintain.

Microstructure	400 µM	200 µM
MMAD (µM)	2.2 + 0.5	1.0 + 0.2
GSD	1.8 + 0.1	1.6 + 0.1
FPF (%)	86.5 + 1.5	93.7 + 5.4

Table 1: Performance of Nebu~Flow technology for a wide range of formulations. The same platform was used in all experiments, without further modification. Characterisation carried out by an Andersen cascade impactor at 30 L/min. The concentrations of placebo formulation models were measured by addition of Allura Red dye.

	Solution	MMAD (µm)	GSD (µm)	FPF (%)	Flow rate (µL/min)	Viscosity (cP)	Surface tension (mN/m)
Surrogate formulation models	1% Sodium sulfate	1.1	1.8	73.6	200	1.1	69
	1% Sodium chloride	1.4	1.9	83.1	200	1.0	72
	50% (v/v) Ethanol	**1.6**	**1.8**	**81.3**	**170**	**2.0**	**27**
	2.5% SDS	0.9	2.9	53.5	320	1.3	31
	2 % Tween 80	1.9	2.2	77.5	100	1.2	33
	10% PEG 400	2.4	1.6	44.3	100	1.56	55.7
	10% Glycerin	2.0	1.8	45.6	120	1.4	50
	2% Dextran	2.7	3.3	26.6	60	1.66	68.5
Generic drugs	Amikacin 50 mg/mL	1.3	2.0	42.7	90	N/A	N/A
	Tobramycin 40 mg/mL	1.1	1.7	83.7	210	N/A	N/A
	Ipratropium bromide 0.25 mg/mL	1.4	1.8	88.1	100	N/A	N/A
	Ipratropium bromide 0.25 mg/mL	1.7	1.9	83.4	300	N/A	N/A
	Salbutamol 2 mg/mL	1.6	2.0	84.4	300	N/A	N/A

Table2: Control of salbutamol droplet size in a Nebu~Flow, using microstructures with sizes of 400 and 200 µm. MMAD: mass median aerodynamic diameter; GSD: geometric standard deviation; FPF: fine particle fraction as percentage emitted dose; SDS: sodium dodecyl sulfate. Characterisation carried out by an Andersen cascade impactor at 30 L/min.

Nebu~Flow technology has been used successfully to nebulise a range of placebo and commercially available formulation types with a wide range of physical properties, including those with very low surface tension (<30 mN/m) and high viscosity (2 cP), as shown in Table 2. Nonetheless, while this is a broader range of physical properties than mesh nebulisers can accommodate, there is still some dependency of output rate on these physical properties. However, in these studies, the Nebu~Flow technology was able to generate droplet sizes around half of those achieved by conventional technologies (Figure 3), indicating the rate of individual droplet creation is an order of magnitude greater.

Beyond this, one of the major advantages of the Nebu~Flow technology is its ability to aerosolise biological entities without denaturing them. Acu-Flow has tested this with a range of biologics, including Herring sperm DNA and siRNA.[22]

SUMMARY

Inhalation drug delivery is the primary route for treatment of respiratory disorders and also shows a great potential for unlocking needle-free systemic drug delivery, while reducing side effects. The main challenges of this route are the technical limitations of current inhalation technologies; for example, the development of inhalable biologics has been delayed due to the lack of optimal devices for delivery.

Nebu~Flow technology provides a platform that can deliver a wide range of formulations with different physical properties, as well as the ability to deliver fragile biologics. The further ability of the technology to control the aerosol droplet size for deep lung deposition, with an MMAD in the range of 1 µm, can provide significant improvement for efficient inhalation drug delivery, as well as unlocking systemic drug delivery via deposition of drugs in the alveolar region. A combination of technical capabilities and patent protection makes Nebu~Flow an outstanding platform for the development of tailored drug-nebuliser products.

"A combination of technical capabilities and patent protection makes Nebu~Flow an outstanding platform for the development of tailored drug-nebuliser products."

"Nebu~Flow technology has been used successfully to nebulise a range of placebo and commercially available formulation types with a wide range of physical properties, including those with very low surface tension and high viscosity."

ABOUT THE COMPANY

Acu-Flow Limited (trading as Nebu~Flow) is a start-up medical device company, developing the Nebu~Flow technology in the form of a user-friendly nebuliser for efficient inhalation delivery of a wide range of formulation types. Nebu~Flow technology can be tailored for delivery of specific drugs, enabling development of multiple drug-nebuliser products. The company is currently developing the product and seeking collaborators for product development.

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ABOUT THE AUTHORS

Elijah Nazarzadeh, PhD, is the Chief Executive Officer of Acu-Flow Limited (trading as Nebu~Flow). In this role, he is responsible for business and technical developments. Dr Nazarzadeh has a PhD in Fluid Mechanics from King's College London (UK). During his career, he has provided scientific consultation services to a number of companies in the field of emulsions and multiphase systems. Since 2015, he has worked as a postdoctoral researcher at the University of Glasgow (UK), where he developed the Nebu~Flow technology and led the commercialisation activities, founding Acu-Flow Limited in 2019. Dr Nazarzadeh received a Lee Lucas Award from the Institute of Physics (UK) for his exceptional efforts in development of Nebu~Flow® technology.

John Pritchard, PhD, Chairman of Acu-Flow, is a private consultant specialising in strategic approaches to developing respiratory devices, drugs and digital health. At different stages in his career across three major pharmaceutical companies, he has been associated with the launch of 11 major products and, at the Respiratory Drug Delivery conference in April 2018, Dr Pritchard received the Charles G Thiel award for outstanding research and discovery in respiratory drug delivery. He has published widely in the field, as well as having served as a board member on various scientific and industry bodies. He is currently a member of the UN Committee that makes recommendations on the essential uses of propellants.

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DELIVERING BIOLOGICS WITH SOFT MIST INHALERS – A MARKET POISED TO EXPAND

In this article, Philippe Rogueda, PhD, Co-Founder and Chief Business Officer of Merxin, discusses the inhalable biologics market, including its successfully approved and marketed products, how the introduction of soft mist inhalers represents a significant opportunity for new and old therapeutics alike, and how the market is poised for a major expansion in therapeutic application, size and value.

A frequently discussed segment of the pharmaceutical market is the rapidly growing area of biopharmaceutical therapeutics. This covers a broad range of molecules and a wide variety of disease areas. Biologics are typically more fragile than traditional small molecules, being highly unstable under adverse conditions, and the optimal way to deliver them remains an open question.

Biologics have primarily been the purview of parenteral delivery due to the need to avoid the harsh conditions of the gastrointestinal tract, which many biologics are unable to weather. Another factor is that the synthesis of biologics typically yields aqueous "brews", which makes liquid formulations much more attractive. However, the issues with regular injections of biologics are well documented, with formulations struggling to keep to acceptable volumes and viscosities. Therefore, there is significant interest in finding alternative ways to deliver biotherapeutics, particularly via the inhalation route.

A PROVEN MARKET

It is easy to see why delivering biologics to the lungs is an attractive option for drug developers – inhalation offers numerous advantages compared with oral and parenteral delivery routes. The inhalation route is non-invasive and needle-free, making it naturally more patient-friendly; is suitable for both local and systemic delivery, giving it potential for a wide array of therapeutics; and most inhalers are highly portable and suitable for at-home use, supporting current drives to move care out of the clinic and into patients' homes. Additionally, the inhaled route also has pharmacokinetic responses aligned with the parenteral route, further easing a shift from one to the other.

Taking these various advantages into consideration, it is not surprising that a popular pharma market database reports that there are over 700 companies that have had at least one inhalable biologic project in their pipeline, ranging from

> "It is important to remember that delivery of biologics via inhalation is not a new idea; in fact, it has been around for decades."

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small biopharma start-ups to major pharmaceutical companies. Similarly, one has only to look to find a wealth of discussions, reviews and research articles concerning inhalable biologics in current scientific literature. The potential is clearly there for a major expansion in this market.

However, it is important to remember that delivery of biologics via inhalation is not a new idea; in fact, it has been around for decades. To date, there have been four inhalable biologic products approved and marketed:

- Survanta (beractant) by AbbVie – launched 1991
- Pulmozyme (dornase alfa) by Roche – launched 1993
- Afrezza (insulin) by MannKind Corporation – launched 2014
- Exubera (insulin) by Pfizer – launched 2017.

These approvals demonstrate that regulatory pathways exist for inhaled biologics to reach the market. With three of these products still going strong, coupled with recent advances in inhalation technology and the recent flourish of new biomolecules, this proven market is poised to expand – all it will take is the right product in the right device.

THE RIGHT PRODUCT IN THE RIGHT DEVICE

Of the currently marketed inhaled biologics, two use an inhalation delivery device: Afrezza is delivered via a single-dose capsule-like dry powder inhaler (DPI) and Pulmozyme via a nebuliser. However, a survey of inhalable biologic development programmes from 2020/2021 literature shows a clear bias towards nebulisers as the delivery device of choice (Figure 1).[1–3]

While nebulisers have their advantages, especially in a clinical setting and for emergency care, it is difficult to justify them as the optimal choice for the current market, due to their limited intellectual property (IP) protection, high interchangeability, long dosing times and a high level of drug wastage, which is of particular concern for expensive biologic therapies.

This poses an obvious question: if other delivery devices are better suited to chronic at-home use, why are nebulisers so popular in early-phase clinical trials? The answer is simple – convenience and availability. The majority of biologics are synthesised as an aqueous or ethanol solution, and so are easily formulated for nebulisation. Additionally, some of the disadvantages of nebulisers for a marketed product are obviated – or turned into strengths – at the clinical trial phase. This makes nebulisers the default choice for drug developers whose priority is to get their therapeutic into trials as soon for as possible for a quick clinical signal.

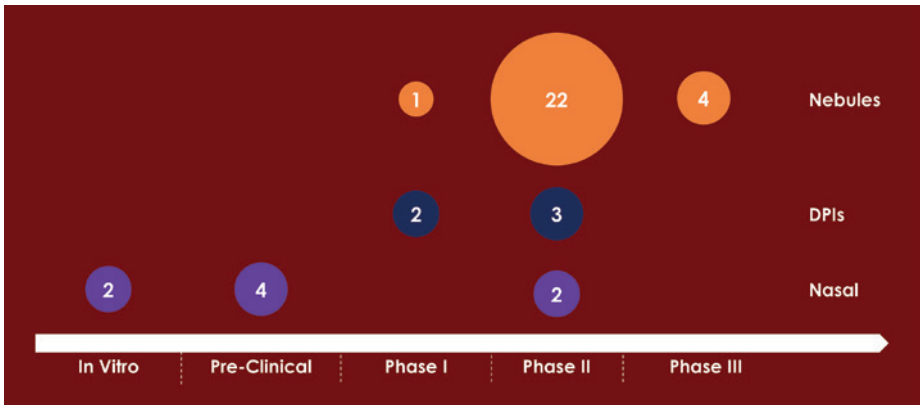

Figure 1: A survey of 40 inhaled biologic development programmes from 2020/2021 literature.

The allure of nebulisers for clinical trials becomes even clearer when the difficulty of formulating a biologic for a DPI is considered. Preparing a dry power formulation for a biologic is far from trivial. The challenges include the need to process the biologic molecules into a powder form without damaging them, keep them in humidity-controlled storage and avoid electrostatic charging within the primary packaging and the device, among other key considerations.

However, despite this perceived convenience, going into clinical trials with a nebuliser is often a strategic error. As a project progresses through the clinical trials process with a nebuliser, it is going to encounter a dilemma – do you go the whole way with the nebuliser and go to market with a suboptimal drug-device pairing? Or do you pick a point to throw out the progress made with the nebuliser and start from scratch with a DPI?

As such, it is not surprising that other potential delivery devices are becoming the preferred choice. The ideal device should have strong market protection, be suitable for delivering sensitive biologics in aqueous or ethanol-based solutions and have proven patient usability and acceptability. There has been some interest in the nasal route, but it is not a substitute for delivery to the lungs. Nasal delivery's strengths lie in one-off acute and emergency treatments,

> "SMIs offer the advantages of both DPIs and nebulisers, without the drawback of having to formulate the drug as a dry powder, or the inconvenience and lack of protection of nebulisers."

where pure simplicity in delivery is a major concern, rather than delivering medication for chronic indications, where patients have more time to learn and become accustomed to the device.

But if not DPIs, nebulisers or nasal delivery, what? Recent years have provided the answer to this question with the development of a new inhaler device category that fits the bill perfectly – the soft mist inhaler (SMI).

SOFT MIST INHALERS – UNLOCKING THE POTENTIAL OF INHALABLE BIOLOGICS

When developing a biologic for inhalation, SMIs offer the advantages of both DPIs and nebulisers, without the drawback of having to formulate the drug as a dry powder, or the inconvenience and lack of protection of nebulisers. With SMIs, the term "soft mist" refers to both the aerosol-generation mechanism and the quality of the aerosol itself; SMIs are functionally non-pressurised metered dose inhalers that use a mechanical power source, such as a compressed spring, to push a liquid formulation through a microfluidic nozzle to create a fine, slow-moving aerosol suitable for inhalation, allowing for easy delivery in distinct,

metered doses.[4] Due to their use of liquid formulations, SMIs are readily suitable for aqueous and ethanol-soluble biologics in the same way that nebulisers are. Having significant advantages at both the clinical and market stages, SMIs are poised to be a game changer for inhalable biologics.

Similar to DPIs, SMIs are portable, pre-dosed, do not require patients to handle the formulation, offer strong IP protection and do not require an external power source. From the nebuliser side, SMIs use a solution formulation and are relatively quick to get to clinical trials. SMIs are accurate and capable of reliable deep-lung drug deposition; by changing the size of the pores in the mesh, it is possible to control the size of the droplets delivered to the patient and therefore the region of the lungs in which most will be deposited.

Another advantage of SMIs is the high fine particle fraction (FPF) they can achieve. This means that a significantly greater proportion of the drug can reach the target region of the lungs compared with other inhalation devices. Therefore, less drug is required to achieve the same therapeutic effect and less overfill of the device is required, which is a significant benefit when dealing with expensive biologic molecules.

The first SMI to reach the market was Boehringer Ingelheim's Respimat®, which is now used to treat a variety of respiratory indications, including asthma and chronic obstructive pulmonary disease (COPD). The success of Respimat has demonstrated that there is an appetite for SMIs across the market, with approval from regulators and a positive response from patients and healthcare providers.

Figure 2: Merxin's MRX004 soft mist inhaler (www.mrx004.com).

"With the breadth of interest in inhalable biologics, there is little doubt that an SMI such as MRX004 will be a boon to the drug development process, covering all development stages with a single device."

With Respimat's patent expiring, there is now a prime opportunity for a massive expansion in SMI use as competitor devices enter the market, giving drug developers more device options to choose from to differentiate their drug and optimise its delivery. With inhalation device specialists able to offer generic and customised SMIs, the potential of this device category is ready to be unlocked.

Leading the way in the expansion of SMIs is Merxin, which has developed the MRX004 SMI (Figure 2). Initially, MRX004 has been developed and optimised for tiotropium olodaterol formulations for the maintenance treatment of COPD. However, the potential of MRX004 is far greater than COPD alone; it is ideal for both new molecules and lifecycle management of existing inhalable products. For example, Merxin has formulated Pulmozyme for the MRX004 and achieved a 60% FPF (<5 µm), demonstrating that it is an ideal candidate for reformulation for an SMI (Figure 3), as well as nicotine for nicotine replacement therapies and cannabidiol.

With the breadth of interest in inhalable biologics, there is little doubt that an SMI such as MRX004 will be a boon to the drug development process, covering all development stages with a single device – from *in vitro* screening to clinical trials and

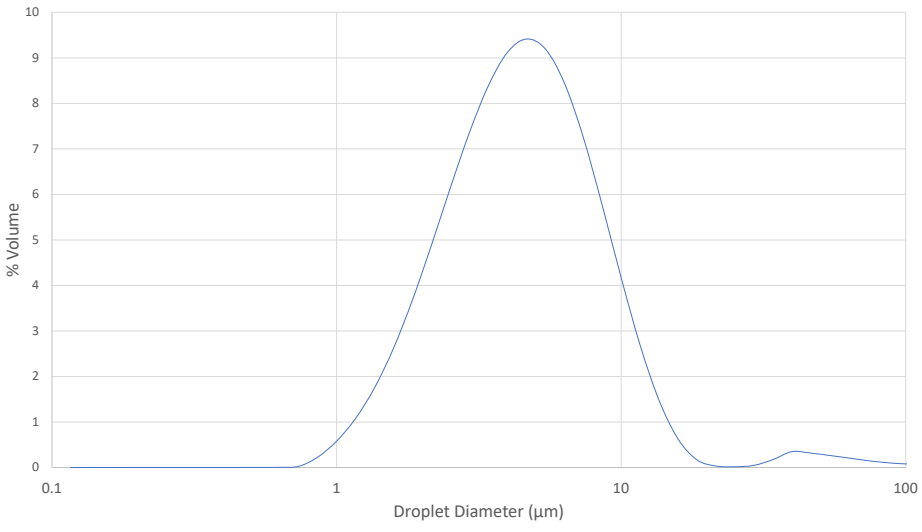

Figure 3: Average droplet size distribution of dornase alfa formulated for MRX004.

commercialisation. An SMI can be used from the first clinical signal to the final product, meaning that there is no concern about duplication of effort or the need to choose the right time to switch devices.

Partnering with a device expert enables projects to unlock the potential of their formulations by ensuring that they are paired with the optimum device. Merxin helps guide its partners through the device selection process, such as determining if the best option is a generic device or one specifically customised to the drug, in order to meet their development goals.

POISED TO EXPAND

With new device players ready to increase the presence of SMIs, the market for inhaled biologics is poised to expand significantly in both size and value. Inhaled biologics have enormous potential for the treatment of respiratory diseases, such as asthma, COPD and covid-19, as well as exciting prospects for a variety of systemically acting therapeutics, such as insulin, antibiotics, anti-infectives and vaccines.

Because of this diversity, it is challenging to make any firm predictions of how the market will grow and where the largest emphasis will be. It can be expected that, once its expansion gets underway, the inhalable biologics market will borrow growth from other sectors, and as the advantages become more self-evident, an increasing number of products will gain regulatory approval as patients come to favour the ease and convenience of inhaled therapies over their parenteral competition.

For both biopharma companies developing new molecules and established brands looking for lifecycle management options for their existing products, SMIs represent a major opportunity. As patient friendly devices that are easy to formulate for and offer strong patent protection, SMIs stand out among the inhalation device competition as the go-to device for inhaled biologics.

To make the most of the opportunity that SMIs and the upcoming expansion of the inhaled biologics market offers, it is important to partner with a device specialist to ensure that the optimum drug-device pairing is made. With a proven track record in both generic and custom devices, including single- and multidose DPIs and its MRX004 SMI, Merxin is ideally placed to provide the technology and expertise that an inhaled biologic development project needs to succeed.

ABOUT THE COMPANY

Merxin designs and supplies generic and customised inhaler device platforms, including multidose DPIs, capsule DPIs, SMIs, no-heat no-propylene-glycol vaping devices and devices tailored to cannabinoid delivery to the lungs. Customers combine Merxin devices with their drug formulation to make final dosage forms that are supplied to users and patients. Merxin is certified as meeting the requirements of ISO 13485:2016 for the design, development and supply of inhalers. Merxin accesses manufacturing expertise across the globe, an international client base and is adding more products to its portfolio as it rapidly expands. See more at www.merxin.com and on Merxin's LinkedIn blog.

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ABOUT THE AUTHOR

Philippe Rogueda, PhD, Co-Founder and Chief Business Officer of Merxin, is a Fellow of the Royal Society of Chemistry and orally inhaled and nasal drug product expert with an accomplished track record delivering technology and global projects across R&D and commercial industrialisation. Dr Rogueda has held a number of positions in the inhaled drug delivery field, starting as a formulation scientist in the pMDI formulation labs of AstraZeneca; as a principal scientist at Novartis designing DPI, nasal and nebulised inhaled therapies; as an Executive Director of Inhaled Products R&D at Actavis/TEVA; before founding Merxin to make inhaler technology accessible to a wider audience. Dr Rogueda is Principal Consultant at Aedestra, founder of Inhalation Asia, and of Anthocan a company dedicated to the formulating of inhaled cannabis therapies.

AN AIRLESS SPRAY NOZZLE TO PRODUCE A FINE AND SOFT MIST

In this article, Claire Authesserre, PhD, R&D Fluidics Manager, and Florian Corne, PhD, R&D Fluidics Engineer, both at EVEON, discuss the current challenges faced by the topical spray-based delivery of therapeutics and how the company's Ad-Mist™ spray nozzle overcomes these challenges to harness the potential of this delivery route.

SPRAY DELIVERY AS A NEW ROUTE OF ADMINISTRATION

Over the past decades, drug delivery has evolved and new routes of administration have emerged. When one thinks of drug administration, one usually thinks of swallowing pills (oral administration) or getting an injection (parenteral administration). However, drugs can also be delivered via other routes, such as the enteral route through tubing in the gastrointestinal tract, inhalation to the lungs via the mouth or even the topical route via the skin (cutaneous, transdermal) or a mucosa (intranasal, buccal, auricular, ophthalmic, etc).

The choice of delivery route for a drug depends not only on the site of desired action, but also on its properties – its absorption by the body and the environment in which it will be administered. Compared with the conventional oral and parenteral routes, it is claimed that topical administration offers the advantages of being non-invasive and avoiding first-pass metabolism in the liver by enabling the drug to enter directly into the circulatory system. This is an advantage when rapid drug absorption and onset of action are desired.

Depending on the route of administration, the formulation and the dosage, a delivery device may be needed to properly administer the drug. Over many years, a variety of spray devices have been developed, such as nasal or buccal sprays, inhalation systems and even spray-on bandage devices. Indeed, spray- or mist-based delivery presents many advantages over conventional methods:

- Delivery to areas with limited access
- Delivery in any patient posture, in particular, in any patient's head position for intranasal, buccal or auricular administration
- Overdose-free and high surface coverage – precise delivery of a small dose to a large surface area – increasing the drug's bioavailability
- Safety – non-contact, non-invasive and needle-free delivery
- Convenient and easy to use.

CHALLENGES IN SPRAY DELIVERY

Atomisation of Highly Viscous Formulations

High-viscosity formulations have become increasingly prevalent over the last few years in the pharmaceutical industry. This new paradigm could be attributed to several key factors. The first one is the significant growth of biologics. Monoclonal antibodies (mAbs) are expected to reach combined global sales of US$150 billion (£134 billion) by 2022. Biosimilars have also entered the market, creating a highly competitive landscape.

The second key factor is the increasing development of sustained/controlled release formulations. These long-acting formulations are intended to reduce the required dosing frequency of a therapy, improving patient compliance and reducing impact on healthcare costs. There are several technical strategies that can be used

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"As the biologic and controlled-release formulation markets grow, there is a huge need to overcome high-viscosity formulation challenges with specific spray devices."

to develop a controlled release formulation, but the main challenge is that they could be difficult to deliver. For example, they could include high molecular weight polymers or other vehicles, increasing the viscosity of the entire formulation. As the biologic and controlled-release formulation markets grow, there is a huge need to overcome high-viscosity formulation challenges with specific spray devices.

Airless and Propellant-Free Spray Delivery

The use of compressed gas or propellant can facilitate the atomisation of a liquid, especially when it is highly viscous. However, the contact of the drug with air can lead to oxidation of the drug and can increase the risk of microbial contamination. Therefore, the challenge is to develop an airless spray nozzle for drug preservation and sterility, and propellant-free devices to provide a more eco-friendly alternative to existing products.

Fine and Soft Mist

For pharmaceutical applications, delivering a fine mist improves the efficacy of the delivered formulation by improving the topical absorption of the drug by the tissue. Additionally, a soft mist is important for minimising the pain or discomfort felt by the patient. In industries other than pharmaceuticals, such as cosmetics, fine and soft mist delivery is required to improve the user experience.

Figure 1: Ad-Mist nozzle.

DEVELOPMENT OF A SPRAY NOZZLE

EVEON has designed and patented a spray nozzle, the Ad-Mist™ nozzle (Figure 1), requiring neither air nor propellant, that overcomes these spray delivery challenges. Different versions of the nozzle have been designed, based on the same technology, to adapt to the requirements in terms of flow rate, droplet size, inlet pressure and spray angle, among others.

Viscosity & Viscoelastic Properties

The Ad-Mist nozzle can adapt to a large range of viscosities, including highly viscous formulations. For example, the Ad-Mist nozzle is capable of spraying a gel with a viscosity of 8,000 Pa·s at $0.1s^{-1}$ with a shear-thinning index of <0.1. However, it is critical that the inherent properties of the formulation, such as the viscoelasticity, are not altered by the spraying mechanism.

To evaluate the impact of the spray on the gel structure, viscoelastic properties of the gel were characterised on a rheometer and a comparison delivery between the gel deposited on the rheometer plate with a cannula and the gel deposited by the spray device (Figure 2). With the spray, a small relaxing time can be observed but, in less than 200 s, the gel regains its original rheological properties – equivalent to standard, non-spray, cannula deposition. This demonstrates that the Ad-Mist nozzle developed by EVEON enables proper conservation of the viscoelasticity properties.

Particle Size

The droplet size of the mist produced by the Ad-Mist nozzle has been characterised using a laser diffraction system (Spraytec – Malvern Panalytical, Malvern, UK, see this isssue, Page 18) with several formulations having viscosities from 1 to 14 cP. The measurement was performed at 2 cm and 15 cm from the nozzle outlet; Figure 3 shows the results obtained at 2 cm. Whatever the viscosity, the mean droplet size was around 20 µm, with 90% of the droplets below 45 µm in diameter. Fewer than 10% of droplets were below 10 µm in diameter, limiting the amount of mist reaching the lungs. The mean droplet size measured at 15 cm was around 40 µm.

Surface Covering

The Ad-Mist nozzle is capable of delivering a homogenous distribution of droplets

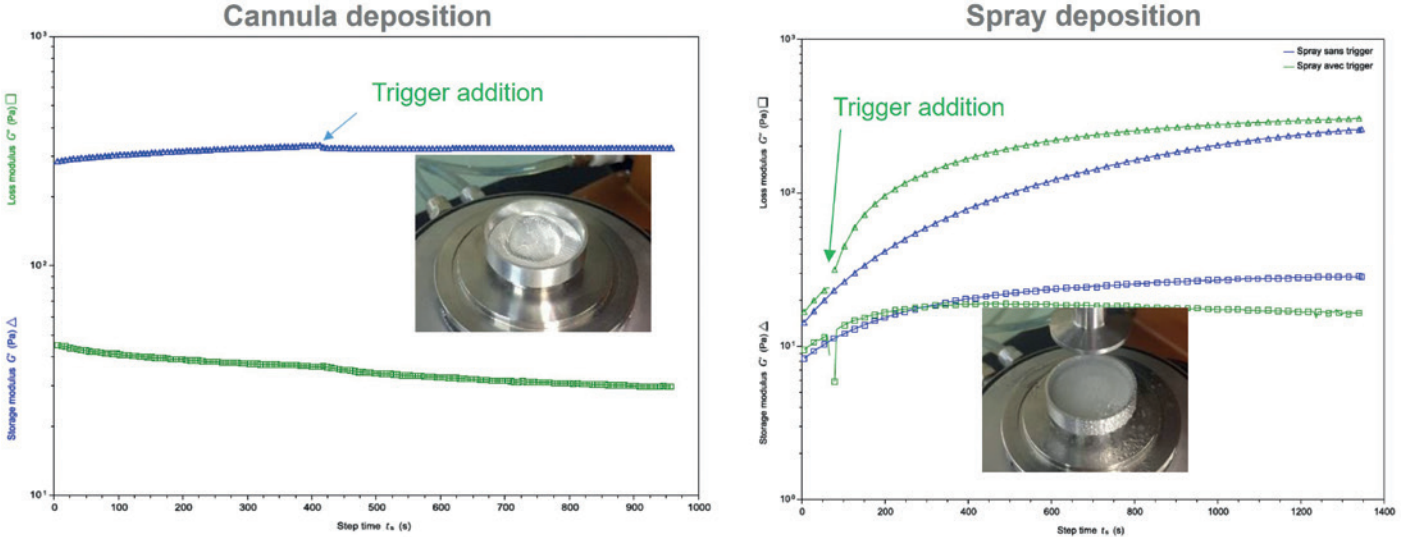

Figure 2: Conservation of visco-elastic properties after spraying with the Ad-Mist nozzle.

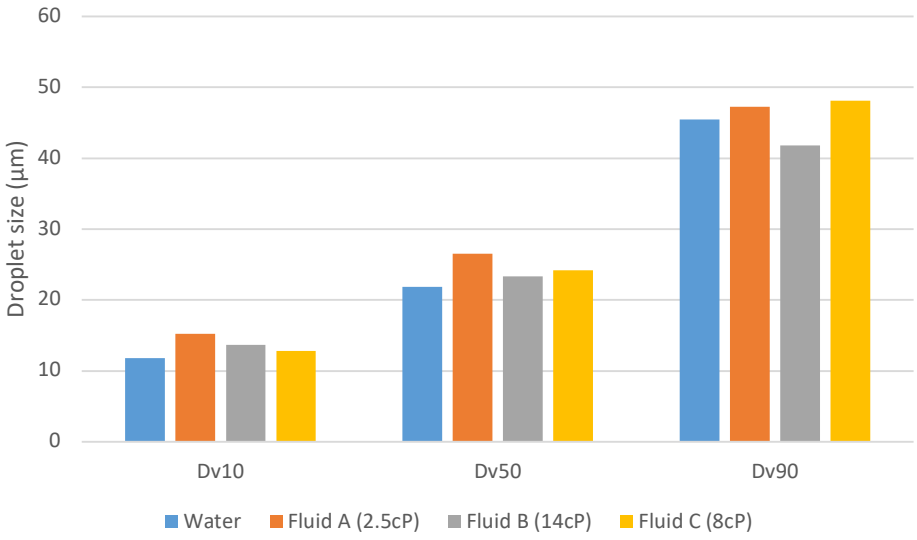

Figure 3: Droplet size of the mist produced by the Ad-Mist nozzle.

to a surface. The area covered by the mist directly depends on the spray plume geometry, which can be tailored with the nozzle fluid path geometry and flow rate between 25° and 60°. For example, a spot size of 1 cm is obtained with water at a distance of 2 cm from the surface. With a continuous delivery using a flow rate of 0.15 mL/s, the Ad-Mist nozzle can cover a 100 cm^2 area within 15 s.

Low-Impact Pressure

In collaboration with its sister-company ALPAO (Montbonnot-Saint-Martin, France), EVEON was able to measure the impact pressure generated by the Ad-Mist nozzle thanks to an optical system based on ALPAO's deformable mirror core technology. During a topical administration, Ad-Mist's droplets impact a surface at 2 N/m^2 when sprayed 2 cm away from the administration site. This is comparable with the impact of a fly landing on a stamp. The low-impact pressure generated by the Ad-Mist nozzle provides significant potential for administration to strongly innerved or sensitive areas.

"EVEON's Ad-Mist spray nozzle is a versatile platform that can be integrated in a broad range of devices and adapted to the required use gesture and user experience."

DEVELOPMENT OF SPRAY DEVICES

EVEON's Ad-Mist spray nozzle is a versatile platform that can be integrated in a broad range of devices and adapted to the required use gesture and user experience – usability being a key factor for device acceptability on the part of the user. EVEON is used to working with ergonomists and designers to take human factors into account, right from the first steps of device design, to ensure that the device design is appropriate to the target user population and easy to use.

The Ad-Mist nozzle can be used with a standard syringe thanks to a Luer connection for a continuous and manual administration of the drug (Figure 4). The nozzle can be connected to a syringe as simply as a needle would be. It is the easiest way to produce a spray when there is no specific dosage requirement and the viscosity allows for a reasonable force to be applied to the syringe plunger.

"Designed for a precise dose administration, EVEON's Intuity® Spray is capable of delivering doses from 15 µL to several millilitres with 1 µL accuracy."

If precise control of the administration and spray quality are required, this spray nozzle can also be integrated into the Intuity® Spray platform (Figure 5). Due to its unique electronic and fluidic features, this tailored, easy-to-use medical device offers controlled flow rates and dosages. The mist can be delivered with a highly controlled flow rate between 0.1 and 1 mL/s, as either a continuous or a dose delivery due to the integration of a micropump specifically developed by EVEON.

Designed for a precise dose administration, EVEON's Intuity® Spray is capable of delivering doses from 15 µL to several millilitres with 1 µL accuracy. The spray quality is highly reproducible; the standard deviation of the mean droplet size between two sprays is less than 1 µm. Therefore, by using Intuity® Spray in combination with the Ad-Mist nozzle, the mist administration can be standardised.

Figure 4: Ad-Mist nozzle for syringe – easy mist delivery.

Figure 5: Intuity Spray – highly controlled mist delivery.

CONCLUSION

Administering drugs in the form of a spray, particularly for topical administration to the skin or mucous membranes, is a major trend in the pharmaceutical industry. Sustained market growth is expected, with an annual growth rate of +7.3% between now and 2026 for mucosal administrations. Compared with parenteral routes, sprays offer undeniable advantages; as an easy-to-use, non-invasive medical device, they can improve therapeutic adherence, particularly for self-administration.

EVEON is the right partner to build custom airless spray nozzles for gels, and highly viscous and non-viscous solutions, suitable for standard primary containers and adapted to the intended usage.

ABOUT THE COMPANY

EVEON is an ISO 13485-certified company that designs and manufactures safe, connected and automatic medical devices for the preparation and delivery of therapeutic treatments to improve patient quality of life. EVEON places the needs of patients and healthcare professionals at the heart of its development by designing simple, intuitive devices to improve therapeutic performance, compliance and the conditions of at-home care. The company's expertise has been recognised by *Forbes*, which ranked EVEON as the third most inventive company in France in the category of medical technology in 2019.

ABOUT THE AUTHORS

Claire Authesserre, PhD, graduated from ESPCI Paris (France) and Imperial College London (UK) where she obtained an MSc in Biomedical Engineering in 2013. She then completed a PhD in microfluidics at CEA-Leti (Grenoble, France) in the Department of Microtechnologies for Healthcare and Biology. In 2017, Dr Authesserre joined EVEON as R&D Fluidics Manager, leading a team of fluidics engineers and technicians, working very closely with both the Mechanical & Plastics and Digital teams, to design medical devices with optimised performances to fit with customer and patient needs.

Florian Corne, PhD, completed a Process Engineering PhD in the nuclear field with a specialisation in microfluidics, reactive liquid-liquid extraction and computational modelling at the CEA Marcoule (Chusclan, France). From 2020 to 2022 he held a postdoctoral position in the radiochemistry programme at the University of Nevada, Las Vegas (US), under the supervision of Dr Artem Gelis. During these two years, he had the opportunity to implement and lead the microfluidics activity of the radiochemistry programme. In mid-2022, Dr Corne joined EVEON as an R&D Fluidics Engineer to bring his microfluidics knowledge to medical devices.

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A ROADMAP FOR DRUG-NEBULISER COMBINATION PRODUCT DEVELOPMENT

Here, Edgar Hernan Cuevas Brun, Business Development Manager & Scientist, Aerosol Drug Delivery, and Yuan-Ming Hsu, PhD, Research and Development Director, both at HCmed Innovations, lay out the company's roadmap for the development of drug-nebuliser combination products.

To ensure the efficient drug delivery of inhaled formulations, extensive research and development of drug-device combination products is required to address diverse aspects from both elements. Research has shown that accurate and efficient delivery of an API to the correct airway section is as important as its dosage and efficacy, making delivery a crucial factor for the success of an inhaled product.

> "A surge in the number of novel inhaled biologics has also directed focus towards the use of mesh nebulisers as one of the primary delivery platforms."

In recent years, the inhalation therapy field has seen an increasing demand for combination products when it comes to the use of nebulisers. This demand, driven by requirements for predictable and consistent delivery performance in particular, has received further stimulus from regulatory authorities, which has promoted updated guidelines to incentivise the development of combination products. Moreover, a surge in the number of novel inhaled biologics has also directed focus towards the use of mesh nebulisers as one of the primary delivery platforms.[1]

As biologic drugs are more susceptible to losing their therapeutic effect when exposed to hazardous conditions, such as high shear forces and high temperature, mesh nebulisers have been recognised as suitable delivery platforms. Mesh technology is commonly associated with only a minimal increase in temperature and shear force exposure when aerosolising liquid formulation.[2]

As a result of this increased demand, the necessity for a clear understanding of drug-nebuliser combination products has paved the way for the establishment of contract development and manufacturing organisations (CDMOs) that can support pharmaceutical partners with their desired expectations for device performance and the development and the selection of appropriate formulations and nebuliser platforms for the development of new inhaled treatments.

DRUG-NEBULISER COMBINATION PRODUCTS

The realisation of a drug-nebuliser combination product is the result of harmonising both elements. The liquid formulation and the nebuliser device both contribute to the expected therapeutic effect; therefore, optimisation of their interaction is critical. On the formulation side, understanding the physicochemical properties of the liquid, which could be either a solution or a suspension, is part of the background information required to initiate the combination pairing. Regarding delivery with mesh nebulisers, high viscosity and very low surface tension can influence

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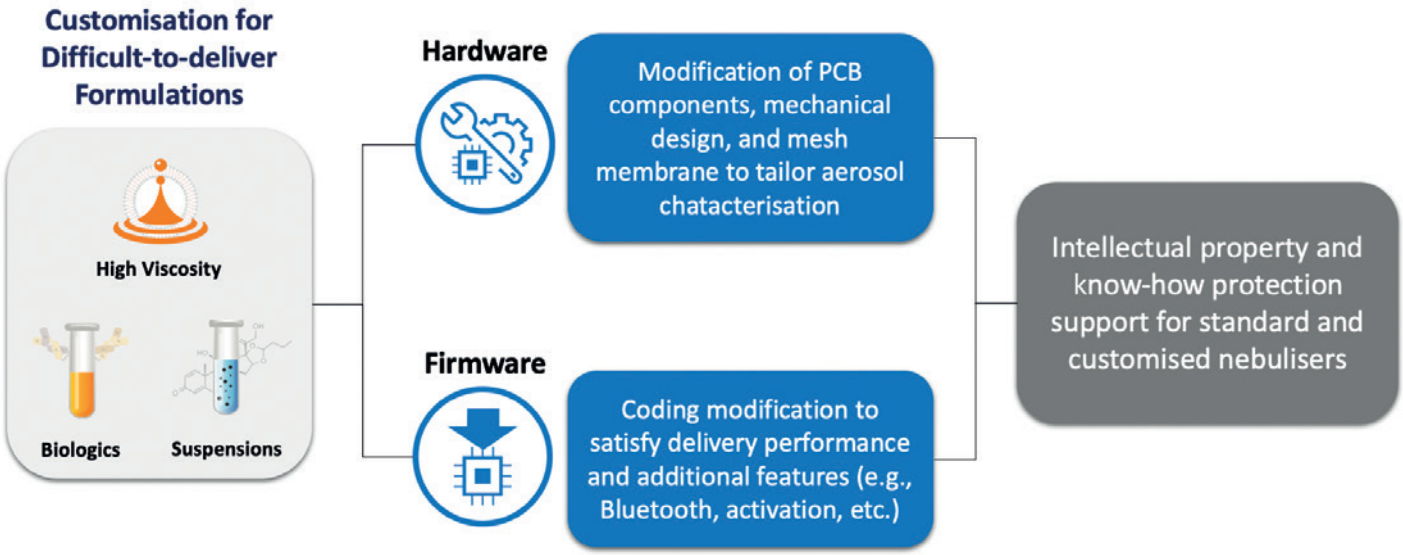

Figure 1: Device customisation scope for drug-nebuliser combination development.

the delivery rate.[3] Furthermore, the involvement of biologic drugs introduces additional concerns, such as their stability and activity post-nebulisation, which could be significantly reduced when aggregation or structural unfolding occurs.

The selection of excipients plays another important role on the formulation side. The addition of appropriate excipients can support the aerosolisation of formulations, avoiding undesirable reactions that could otherwise lead to coughing or irritation of the airways. The purpose of these excipients extends from modifying the properties of the formulation to protecting the API. It has been documented that small amounts of polysorbates can be used to decrease the viscosity of a formulation, while lysine and arginine can be used to tailor aerosol characterisation performance.[4]

> "The addition of appropriate excipients can support the aerosolisation of formulations, avoiding undesirable reactions that could otherwise lead to coughing or irritation of the airways."

Alternatively, customisable mesh nebulisers, such as the AdheResp platform from HCmed Innovations, allow a wide range of modifications, including hardware and firmware. Hardware components can be modified to satisfy requirements related to loaded volume, indicators, device structure, user interface, connectivity and even the mesh component itself. This last one permits the adjustment of aerosol characterisation performance to identify the most suitable mesh membrane for the liquid formulation in the combination product. Similarly, the firmware can also be modified to define aerosolisation periods that are more effective for a specific formulation, as well as the delivery needs of a specific patient population or user behaviour requirement. Moreover, enabling and disabling Bluetooth and activation functions based on the requirements for the combination product enhances the flexibility of the platform firmware (Figure 1).

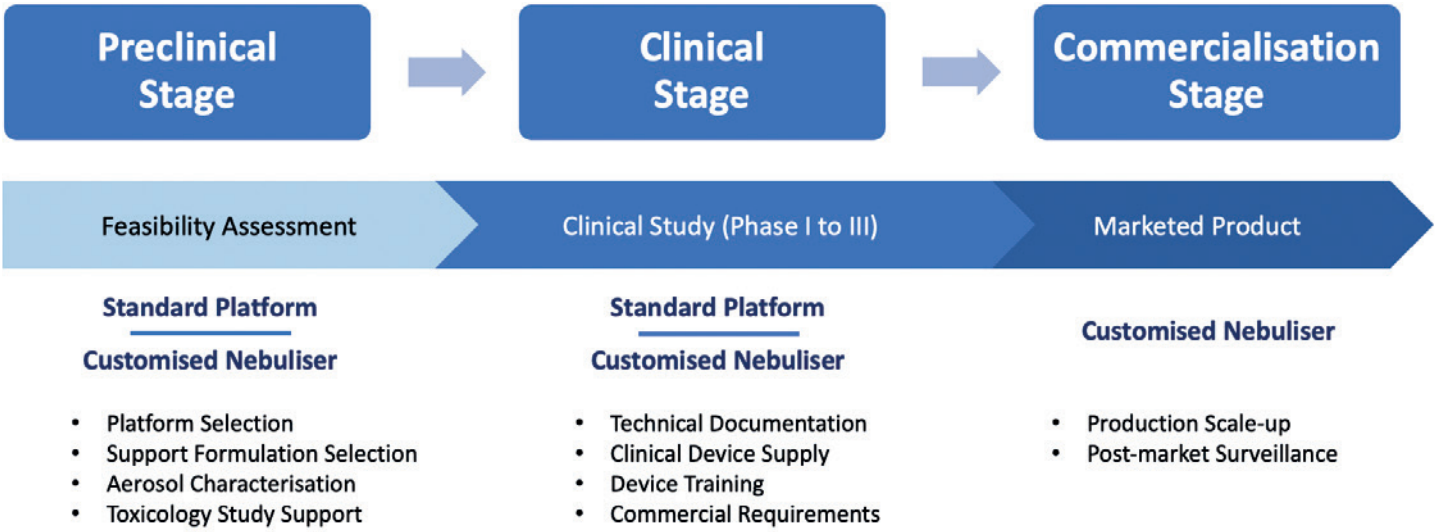

Figure 2: Drug-nebuliser combination CDMO services throughout the development stages.

Ultimately, the optimal matching of the nebuliser and formulation factors can define the efficacy of the final combination product.

DRUG-NEBULISER COMBINATION CDMO

The scope for combination product development begins prior to a feasibility study. The value of a CDMO working on drug-nebuliser development can be clearly seen at the initial stage when comparing direct assessments of over-the-counter nebulisers with customisable platforms. While the former is only likely to provide *in vitro* data of the tested nebulisers, the latter could provide a comprehensive set of data with points to optimise delivery performance in the following stages, guaranteeing a higher success rate, and thus offering a more methodical approach.

At HCmed Innovations, which is focused on the development of drug-nebuliser combination products, the entire development is a well-rounded process that provides support to pharmaceutical partners at all stages, from preclinical and clinical stages to commercialisation (Figure 2) – a fully integrated path supported by HCmed's proprietary mesh technology.

The expectations for the development at each stage could be summarised as follows:

Preclinical Stage

Nebulisation of formulations can vary significantly due to each formulation's distinctive properties. Furthermore, the requirements of aerosol characterisation (e.g. mass median aerodynamic diameter, fine particle fraction, geometric standard deviation) and delivered dose are equally important, as they are selected based on the indication (e.g. chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, cystic fibrosis, pulmonary arterial hypertension, etc.) to be treated and the patient population. It is for this reason that selecting the correct platform from an early stage can greatly facilitate the development process.

The two main categories of mesh nebuliser platform can be classified as continuous output and breath-actuated. As their names suggest, a continuous output nebuliser generates aerosol continuously throughout the whole treatment, whereas a breath-actuated device aerosolises the formulation based on a triggering mechanism that allows generation during a specific phase of inhalation.

> "By generating data, assessing performance and customising the platforms in parallel, a reduction in cost and time is attainable."

Depending on the requirements for delivery, it would be expected that treatments that prioritise delivery time over a high-dose delivery would be more suitable for a continuous output mode platform. Conversely, a breath-actuated nebuliser would be the preferred choice when prioritising the delivered dose and reduction of fugitive aerosols.

The user interface also plays a major role when establishing design requirements, such as user feedback. For that reason, distinguishing these requirements at an early stage is helpful for ensuring smooth project development. Furthermore, the security provided by a strong intellectual property portfolio for standard and customised nebulisers, along with the corresponding freedom to operate in the selected countries and territories, enhances the value of the device for the combination product.

Once the platform is selected, an understanding of the formulation and nebuliser interaction is indispensable, and it is here that a supportive team of experienced professionals in the aerosol delivery field is essential. The team at HCmed Innovations, which is formed of experts in the field, can offer suggestions that extend beyond device customisation to the point of tapping into formulation comprehension. The benefit then lies in recommending a customisable version of the device based on the pre-formulation assessment and, therefore, assisting with the formulation selection and the most suitable nebuliser.

To support the selection and testing process, HCmed works with a state-of-the-art *in vitro* laboratory that is equipped with analytical capabilities and a group of testing engineers and knowledgeable scientists familiar with the nebulising platforms used. Aerosol characterisation via laser diffraction particle size analysers and cascade impactors, as well as delivered dose assessment with breath simulators, are some of the studies that HCmed conducts at the development stage. By generating data, assessing performance and customising the platforms in parallel,

a reduction in development cost and time is attainable. Moreover, HCmed's installations not only cover testing of continuous mode devices but also of breath-actuated platforms with the addition of mixing inlets, which can help accelerate initial development stages. Last but not least, for biologic drugs, the aerosol performance analysis of a biologic compound's stability and activity post-nebulisation must also be covered within the scope of the feasibility study.

To complete the activities of the preclinical stage, toxicology research is also performed, at which point receiving support for the toxicology study setup is extremely valuable.

Clinical Stage

When entering the clinical stage, device documentation compliant with the regulatory standards of different health authorities plays a major role. Although standard platforms come with corresponding technical documentation packages, newly customised nebulisers also require equivalent documentation.

The HCmed team ensures that the device development process complies with all the aspects needed to satisfy regulatory requirements, including device risk assessment, chemical risk assessment, process failure mode effects analysis, design failure mode effects analysis, device verification and validation documentation, among others. This process guarantees the safety and efficacy of the nebuliser, which is part of the requirement for the clinical trial applications. Moreover, GMP-compliant device supply and training for each trial are part of HCmed's services.

In some instances, the use of standard platforms, such as HCmed's Pulmogine (continuous output – Figure 3a) or AdheResp (breath actuated – Figure 3b), may be suggested for a Phase I trial, leaving the customised nebuliser for later clinical phases. This type of development strategy can ensure reliance on the same technology, which simplifies the transition to a customised version in later stages.

Consequently, collaborating with a trusted partner at the clinical stage is a critical point when taking into consideration the length and cost of clinical trials. This is the stage at which a company such as HCmed can provide strong support and reliability.

Commercialisation Stage

Quality assurance for the production scale-up of the nebuliser is the pillar for the commercialisation stage, along with an already evaluated and guaranteed freedom-to-operate status. However, the work goes beyond this point and covers extensive post-market surveillance to monitor the performance of the marketed device and offer assistance on any issue that may arise from the use of the product. HCmed's driven motivation and key goals as a CDMO partner are always to ensure patients' comfort, safety and treatment efficacy for the drug-nebuliser combination product.

CONCLUSION

Recent advancements in inhalation therapy have created demand for the use of nebulisers in novel drug-device combination products, establishing a market for services that can be fulfilled by companies that provide a fully integrated development path. Although it is suggested that this path be adopted from early-stage development, its integration can bring wide-ranging benefits for pharmaceutical companies at any stage. The objective is to facilitate the development process and increase the likelihood of originating new treatment options for a significant number of diseases that could use the respiratory route to achieve the desired therapeutic effect.

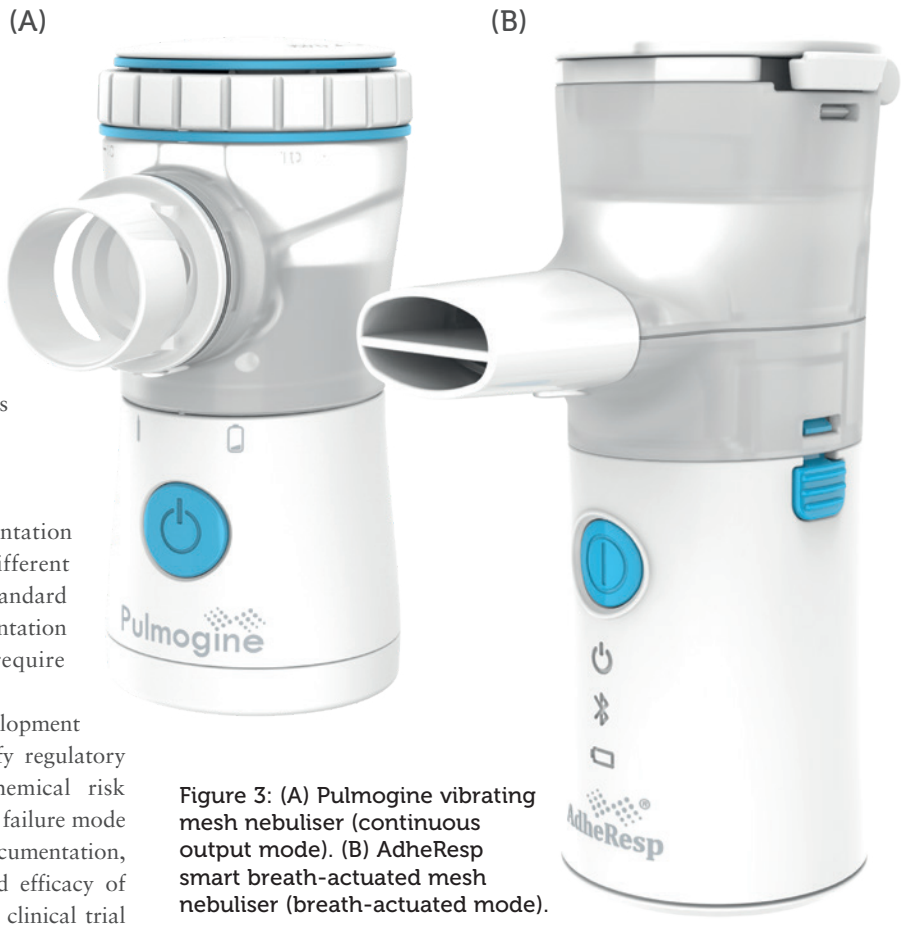

Figure 3: (A) Pulmogine vibrating mesh nebuliser (continuous output mode). (B) AdheResp smart breath-actuated mesh nebuliser (breath-actuated mode).

To summarise, the development of a drug-nebuliser combination product is a lengthy process that requires constant interaction and input from both parties to tailor both the formulation and nebuliser, aiming for an optimal match. The role of a CDMO supporting this process is to provide a roadmap from conceptualisation to commercialisation to support pharmaceutical partners with experts at each stage, shortening development timelines and reducing development risks to create an optimal combination.

ABOUT THE COMPANY

Founded in 2014, HCmed Innovations is a contract development and manufacturing organisation that provides high-quality and cost-effective vibrating mesh nebuliser technology and services to support global pharmaceutical partners in the development of drug-nebuliser combination products for inhalation therapy. HCmed offers mature customisable mesh nebuliser platforms to enhance drug delivery. This technology enables efficient and reliable nebulisation of different types of medication, ranging from small molecule synthetics to large molecule biologics, as either solutions, suspensions or even difficult-to-deliver high-viscosity drugs. The latest platform includes the incorporation of breath-actuation and connectivity features to enhance drug delivery and monitor patience adherence.

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Hernan Cuevas Brun is Business Development Manager of HCmed Innovations. He has over eight years of experience in the drug delivery field and holds a BS in Biomedical Engineering from National Tsing Hua University (Taiwan) and a Master's degree in business administration. He is responsible for expanding and co-ordinating the establishment of new partnerships with global pharmaceutical companies, while also supporting the development of drug-nebuliser combination products. Moreover, he is involved in the development of connected devices, assisting in the company's programmes and establishing alliances with new partners to expand into digital health.

Yuan-Ming Hsu, PhD, is R&D Director of HCmed Innovations. He is responsible for new product development and existing product customisation for drug-nebuliser combination products. He holds a PhD in Biomedical Engineering from National Yang-Ming University (Taiwan). Additionally, he has worked as a researcher at a medical centre in the field of regenerative medicine and controlled-release drug delivery systems. Dr Hsu also gained experience in animal and clinical studies while he was the R&D supervisor in a pharmaceutical company. In the medical device field, he has more than seven years of experience of developing class II and III products and clinical trials, including drug-device combination products.

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CLIPhaler – INHALATION DEVICE DESIGN REDUCED TO THE MAXIMUM

In this article, Klaus-Dieter Beller, PhD, Inventor and Consultant, discusses the advantages of the inhalation route of administration, how his principle of design simplicity has informed the design of novel inhalation devices and introduces CLIPhaler, his latest and simplest device.

POTENTIAL OF INHALATION AND NASAL ADMINISTRATION

While a significant majority of therapeutic agents remain administered either orally or via injection, the inhalation route remains a key delivery pathway for a number of therapeutics, especially when treating diseases of the lung. Worldwide, the most important indications for inhaled drugs are asthma and chronic obstructive pulmonary disease (COPD). Over 70% of the inhalers on the market are used for these two conditions (Figure 1). On the other hand, nasal drug delivery – both in powder and liquid form – accounts for less than 5%.

The pharmacological potential of the inhalation and nasal routes of administration is far from being fully realised. The well-vascularised mucosal membranes of the pharyngeal region and the nasal area are easily accessible, and yet relatively few delivery methods and therapeutics have been developed to target them. Furthermore, the inhalation route only becomes more relevant as an increasing number of patients develop a fear of injections and the oral route becomes increasingly difficult for newer, more sensitive drugs due to maldigestion, malabsorption and swallowing difficulties. This unmet need should be closed, or at least addressed, by new drug product developments.

Some novel devices have been developed in the sector, including the mucosal atomisation device by Teleflex (NC, US) and the Adapplicator "spraying ampoule" by Köhler Pharma (Alsbach-Hähnlein, Germany) – one of the author's inventions. There have also been promising results from nanopatch microprojections, with recent studies showing a 10-fold increase in

> "Inhalation and nasal administration offer a number of advantages, including relative ease of use and improved patient acceptance compared with injectable administration."

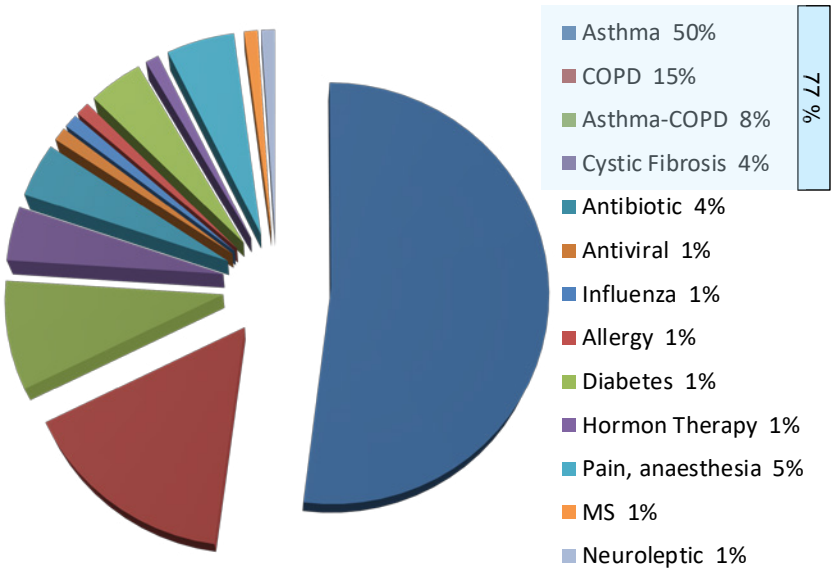

Figure 1: Breakdown of inhalation market share by indication.

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immunisation by vaccines when applied through micro-array patches. From an immunological perspective, oropharyngeal application is particularly interesting, given its access to immunologically important transdermal cells. The Waldeyer's pharyngeal ring or lymphatic pharyngeal ring plays a dominant role here.

Inhalation and nasal administration offer a number of advantages, including relative ease of use and improved patient acceptance compared with injectable administration. For sustained injectable use, pharmacovigilance must always be considered; injectable applications are associated with higher risks, such as needlestick injuries and misinjection, and side effects. In contrast, inhalation and nasal applications are noninvasive and not subject to first-pass metabolism. Furthermore, it has been demonstrated that nasal application is capable of directly reaching the central nervous system and bypassing the blood-brain barrier. Additionally, in many cases, mucosal applications have shown a faster onset of action and are suitable for both local and systemic treatments.

WHY IS THIS POTENTIAL NOT USED?

Inhaler development and production is complex, expensive and time-consuming. This is true for both passive and, to an even greater extent, active systems. Inhalers are usually quite complex in design, consist of several parts and frequently have complicated manufacturing processes. The expense and risk inherent in developing an inhalable therapeutic can only be justified if significant sales are expected, whether due to a high individual unit price or it being necessary for long-term maintenance.

The author has set himself the goal of meeting this unmet need by developing a simple, inexpensive and user-friendly dry powder inhaler (DPI). The stated objective was to keep the design as minimalistic as possible to expand its potential therapeutic areas and applications and make inhalation and nasal administration affordable for emerging economies. The motto for this project was "Reduce to the maximum". In contrast to common DPIs, these minimalistic inhalers are designed to consist of only a few components to minimise tool, material and assembly costs. Over many years, the author has developed a number of inhalers according to this principle, such as the VALVEhaler (developed with Braunform, Endingen, Germany), PERLAMED - BLISTair (Perlen Packaging, Perlen, Switzerland), Papillon (Hovione, Loures, Portugal) and CLIPhaler.

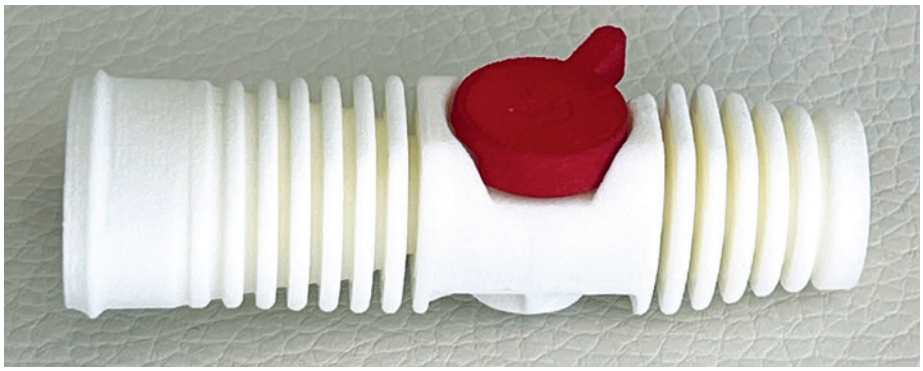

Figure 2: The VALVEhaler and DRUGpod.

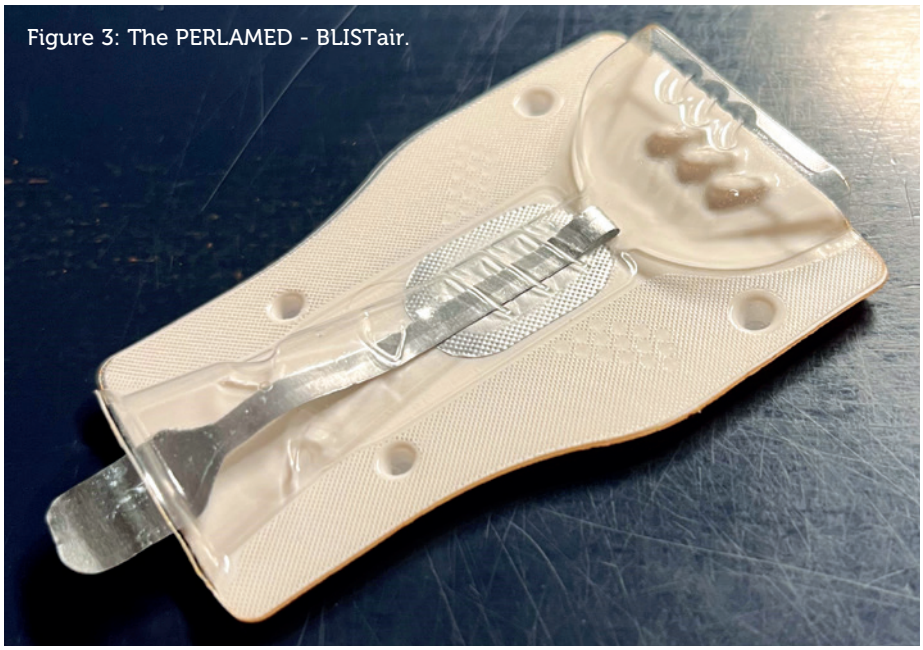

Figure 3: The PERLAMED - BLISTair.

VALVEhaler

The VALVEhaler is a two-part DPI in which the powder carrier – the DRUGpod – is contained within a rotatable and exchangeable cylinder (Figure 2). The system is activated by rotation or pressure. The DRUGpod defines the requirements, such as deagglomeration, airway resistance and turbulence via its "interior life". The dosing quantity can be adjusted via the height and diameter of the DRUGpod. The VALVEhaler can be designed for single use or with exchangeable cartridges for multiple use. Tandem or triple function can be realised by simple design modifications to the DRUGpod.

PERLAMED - BLISTair

The world's first cost-effective disposable inhaler, the PERLAMED - BLISTair is manufactured using a thermoforming process rather than the usual injection-moulding process. The BLISTair represents a new class of DPI:

- It can be manufactured and filled in a single manufacturing process without assembly
- The tacked manufacturing process is based on standard blister manufacturing and filling procedures
- The upper part (inlet and mouthpiece) can be formed from low-cost standard films, although laminates with a high barrier to water and/or oxygen must be used for the lower part with the powder chamber.

BLISTair can also be easily adapted to different requirements; by changing the relatively simple format parts, BLISTair can be adapted to different powder formulations and doses. Necessary changes to the functional geometry, such as resistance to

airflow or bypasses, can also be introduced into the format parts. Operation of the device is extremely simple – with a simple pull on the peeling foil tab, the dosing chamber is opened and the BLISTair is ready for inhalation (Figure 3).

PAPILLON

The innovative single-dose, multi-use blister-based DPI Papillon represents a paradigm shift in inhaler development. Because it consists of a single, reusable plastic part, Papillon can achieve competitive single-dose costs at a fraction of the development cost and without the development risks inherent to complex, multi-part inhalers. The Papillon inhaler is extremely user-friendly; the patient inserts the blister, closes the device and inhales the dose. During this process, the prefilled blisters are automatically pierced. Due to its one-piece design, the Papillon can be adapted to a wide range of inhaled drug doses (Figure 4).

CLIPhaler

The minimalist DPI CLIPhaler is a novel, patent-protected invention that contains no moving parts to assemble and consists of only one injection moulded part (Figure 5). CLIPhaler is extremely user-friendly; the user inserts the blister, unclamps the inhaler and the device automatically pierces the prefilled blisters. The inhaler is then ready for use. The transparent blister is always visible to the user, so the patient can easily check if they have taken the entire dose of their medication. If this is not the case, the patient can inhale again to ensure that they take their entire dose. This increases phamacovigilance and patient safety.

Due to its one-piece design, CLIPhaler can handle a wide range of inhalable drug dosages in different formulations. Necessary changes to the functional geometry (breathing resistance, flow changes, bypasses) can be introduced easily, quickly and cost-effectively with only two mould inserts. This means that the interaction between powder and device can be quickly tested in the early development phase.

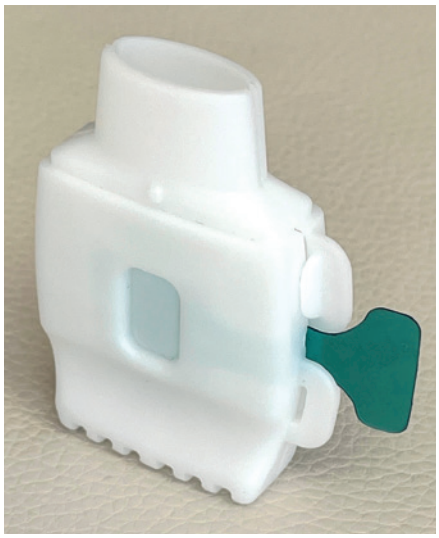

Figure 4: The Papillon inhaler.

One of the mould inserts determines the orientation of the blister, while the fork shape defines the circumference and outer contour of the blister. The blister can have round, oval or asymmetrical shapes and be equipped with guides for positioning or fixing. The reusable-disposable function can also be defined via the fork-shape insert.

In addition to the piercing function, the second mould insert characterises the aerodynamic function of the spikes. The specially developed piercing mandrels not only enable debris-free piercing of the aluminium foil, but also create a unique swirling effect in the blister due to special design features. The blister therefore forms a functional part of the deagglomeration and aerosolisation of the inhaled powder.

The multi-edged hollow mandrels modulate the flow energy and flow directions depending on the grind, orientation and angular degrees. This is reminiscent of turbines and drive blades. The fluid flow is deprived of part of its internal energy by the laminar flow around the spikes, which is then transferred to the powder present in the blister. This improves deagglomeration and turbulence. Depending on the size of the CLIPhaler, up to two mandrels can be integrated in the inlet area. Additionally, depending on if the running directions of the guide vanes are oriented in the same or opposite directions, fundamental differences can be induced in the flow pattern. The use of moulded inserts allows the mandrels to be designed as conical worm threads (cyclone, helix). Finally, the airway resistance can be regulated by the design of the spikes.

The design and volume of the blister is integrated into the aerodynamic function by imprinting an internal structure on the blister. The deagglomeration process can be further modulated by this structuring of the blister.

A series of internal tests with reference substances have shown that 100% emitted mass and an effective drug separation mechanism are achievable. The following test substances were transferred by hand into CLIPhaler blisters and sealed, then tested with third-generation CLIPhaler prototypes:

- Seebri Breezehaler (Novartis, Basel, Switzerland): capsule containing 44 µg glycopyrronium
- Rolenium (Elpen Pharmaceutical, Attica, Greece): blister containing 50 µg salmeterol and 250 µg fluticasone propionate
- Spiriva (Boehringer Ingelheim): capsule containing 18 mg tiotropium

> "Due to its one-piece design, CLIPhaler can handle a wide range of inhalable drug dosages in different formulations."

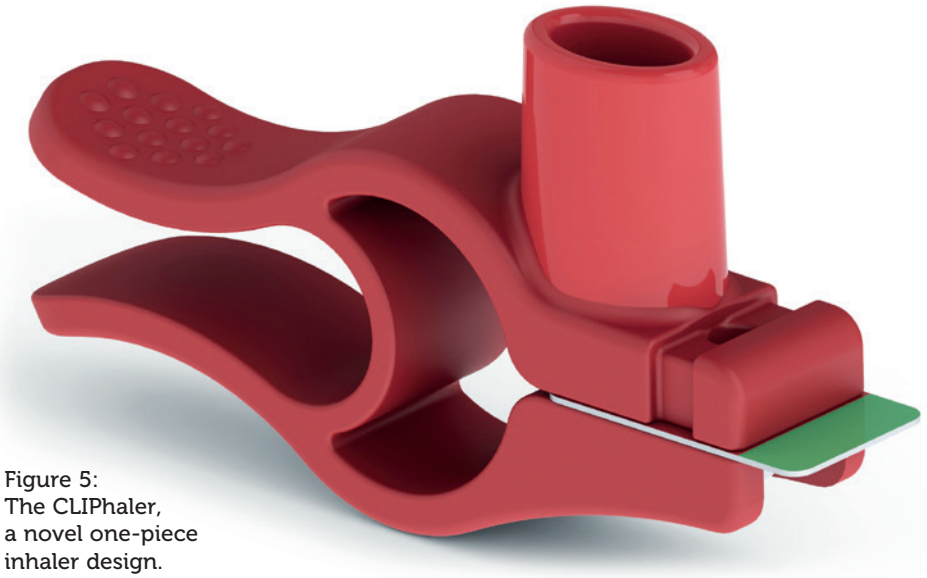

Figure 5: The CLIPhaler, a novel one-piece inhaler design.

- Diskus Viani (GSK): blister containing 50 µg salmeterol and 250 µg fluticasone propionate
- AirFluSas Forspiro (Sandoz, Basel, Switzerland): blisters containing 50 µg salmeterol and 500 µg fluticasone propionate.

For non-respiratory indications, the strictly defined fine particle fraction (FPF) of 3–5 µm does not play a decisive role; instead, uptake via the well-vascularised mucosa in the pharynx is sufficient. To reach the transdermal cells in Waldeyer's pharyngeal ring or the lymphatic pharyngeal ring, an FPF of 1–10 µg should be sufficient. Current respiratory inhalers are designed for respiratory patients with impaired respiration; however, inhaled drug delivery for non-respiratory patients can assume that patients will have good-to-very-good lung function. These patients will be able to generate higher inhalation energy and can therefore better deagglomerate the drug.

Like most DPIs on the market, the CLIPhaler is "passive" – it has no additional energy source. However, an "active" function can be adapted for the CLIPhaler. Such an active function was already considered for the metered dose inhaler "Penhaler" (developed by the author and Braunform) in a similar way.

The unique technical possibilities and commercial advantages for CLIPhaler include:

- Simple, easy design and development process
- Low-cost prototyping and production
- No need for assembly, reducing the effort required for quality assurance and management
- Single component means low production costs – CLIPhaler is much cheaper than currently marketed asthma inhalers, which can consist of up to 23 components.

Furthermore, CLIPhaler is strongly patent-protected, and so represents an excellent opportunity for market differentiation. The author's patent portfolio covering CLIPhaler is currently available for sale and the author is seeking interest in bringing CLIPhaler to market.

The development of simple and cost-effective DPIs, capable of delivering a wide range of formulations and dosage volumes are indicative of the interest in using the inhalation route in new therapeutic areas. In addition to the classic respiratory indications, minimalistic inhalers, such as CLIPhaler, represent a real alternative to oral and parenteral drug delivery. Innovative new APIs and formulations are leading to an increasing interest in using inhalers for new indications. For example, currently, inhaled nanocarriers are being developed for targeted lung cancer therapy. Since nanocarriers can easily overcome mucosal barriers, their use as an inhaled medication also has great potential for treating other diseases, especially in the immunological field.

CONCLUSION

In summary, CLIPhaler presents an interesting option for both new and old drugs. Current considerations around drug repurposing are looking to develop more therapeutic options for both common and rare diseases, often by changing their delivery route. Given the potentially lower development costs and development times, drug repurposing has seen increasing levels of interest in recent years. CLIPhaler is well positioned to help realise the full potential of this movement. Perhaps in the foreseeable future, injections and tablets can be replaced with cheaper inhalable alternatives, and necessary and life-saving medicines can be made available in economically weak regions and areas with less-developed infrastructure.

The CLIPhaler has been designed for easy, intuitive use with maximum effectiveness and a minimum of components using only standard production processes and materials. The simplicity of CLIPhaler offers the possibility of use as an innovative disposable or reusable inhaler. CLIPhaler can also be easily adapted for new indications and therapeutic areas that require much higher delivery doses than respiratory indications.

CLIPhaler has been designed for nasal use, with compliance and human factors at the forefront of its design. Simultaneous inhalation of different active ingredients (tandem inhalation) is easy to realise. Additionally, CLIPhaler's low material usage per inhaler and its monomaterial design supports environmental sustainability. CLIPhaler represents the full realisation of the ideal "Reduce to the maximum".

The CLIPhaler patent portfolio is currently available for sale, please contact the author for further information.

ABOUT THE AUTHOR

Klaus-Dieter Beller, PhD, is an independent inventor with extensive experience in the respiratory field. He is a graduate of the Karlsruhe Institute of Technology (Germany) and the inventor of multiple novel inhalation devices with an emphasis on promoting simplicity, including the VALVEhaler, PERLAMED - BLISTair, Papillon and CLIPhaler. Dr Beller is currently seeking buyers for his latest inhalation device, CLIPhaler.

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GETTING A GRIP ON FRICTION – A CRUCIAL CONSIDERATION FOR INHALER DESIGN

In this article, Bryan Deacon, Global Marketing Manager, Celanese, discusses the importance of considering friction when developing a new inhaler design, providing an overview of some of the basic considerations friction raises, as well as highlighting how optimising friction early with the aid of a materials expert can reduce risk, lower cost and lead to a better product overall.

WHY CONSIDER FRICTION?

There are always a wide variety of factors to consider for any design project, and inhalers are no exception. At the outset of a device design project, friction may seem like a safe factor to overlook as low priority and leave for later, to only deal with if and when it becomes a problem. However, to do so is to set the project up for expensive and time-consuming problems down the road when it becomes a fundamental flaw in the design, requiring late-stage redesigns and specialty materials to resolve.

Friction is not a trivial matter and is fundamental to the function and quality of an inhaler, be it ensuring the accuracy of a dose counter or guaranteeing that the complex mechanisms in a dry powder inhaler (DPI) work smoothly throughout their lifespan, from the first dose to the last. As such, it is important to develop a solid understanding of how friction will affect a design as early in the development process as possible in order to avoid expensive mistakes down the line. Partnering with a materials specialist like Celanese from the start can enable a simpler bill of materials, help avoid expensive mistakes, improve product quality and de-risk the whole development process.

> "It is important to develop a solid understanding of how friction will affect a design as early in the development process as possible in order to avoid expensive mistakes down the line."

Getting friction right isn't just a question of making sure the mechanisms move as intended, but of ensuring that the end product is easy to use and of high quality. This is important for a multitude of reasons. For example, chronic obstructive pulmonary disease (COPD), one of the major indications treated by respiratory medication, primarily affects older patients, who may not have the strength to actuate their inhaler if the mechanism is too stiff or tends to exhibit stick-slip.

Friction affects not just the physical performance of a device but also its perceived quality. Sub-optimal friction pairings can make a device seem cheap and poorly made, potentially leading patients to lose confidence in its ability to deliver their treatment reliably and negatively impacting their compliance. It may even lead them to ask their healthcare provider for an alternative if they are especially dissatisfied.

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Figure 1: Key friction interactions for single-dose DPIs, multidose DPIs and pMDIs.

Celanese can provide the expertise necessary to avoid the pitfalls of friction and ensure that a development programme progresses smoothly, using the right materials in the right way to achieve the functionality and quality required. This article covers some of the basic considerations of friction, providing insight into some of the questions that need to be answered during the development process to produce a device that stands out on the market.

KEY FRICTION INTERACTIONS IN INHALATION DEVICES

The friction interactions that will need to be optimised very much depend on what sort of device is being developed (Figure 1). The considerations for a single-dose DPI where the patient loads a capsule before each actuation are going to be different from those for a multidose DPI with a blister strip running over geared rollers, with the considerations for a pressurised metered dose inhaler (pMDI) being very different again. Knowing which mechanisms will be most impacted by friction is key to optimising the inhaler design.

Single-Dose Capsule DPIs

Nearly all capsule-based DPI devices incorporate a manually operated spring-returned piercing mechanism. This piercing mechanism is critical for device function, so the design will need to be robust enough to guarantee that the mechanism works every time from the first to the last. Optimised friction in the mechanism can allow for the use of less stiff springs, an important factor in ensuring useability for those with impaired hand function. Lastly, the hinge should be considered as a point of quality – it neither wants to be too stiff, making it difficult to open, nor squeak, which can give the patient a poor impression of the device's quality.

Multidose DPIs

Multidose DPIs are often based on complex gear trains to enable the peel and open/pierce mechanisms that move and open the blister strip. Failure in these mechanisms compromises the functionality of the device, be it by the mechanism jamming or slipping, leading to incorrect dose delivery. Understanding the friction at play in these gear mechanisms is therefore essential for ensuring that the device operates as intended. Friction must also be considered for dose counters, failure in which could, at worst, lead a patient to mistakenly believe that they have medication available when their device is empty, posing a significant risk to their health.

pMDIs

As with multidose DPIs, a key area of consideration for pMDIs is the dose counter. Ensuring that the dose counter is accurate is necessary for the device to achieve regulatory approval and guarantee patient safety. Additionally, advanced pMDIs may contain additional mechanisms where friction plays a critical role, breath-actuated pMDIs being a prime example. For a breath-actuated pMDI to function as intended, the friction in the release mechanism must be precisely calibrated so that the device activates with the force of the patient's inhalation – too weak and it will activate at the incorrect time, too strong and it won't activate at all.

THE FRICTION-WEAR-NOISE TRIANGLE

Friction, noise and wear are all interlinked aspects of the operation of an inhaler, and understanding how they interact is key to understanding how a device will function over the long term (Figure 2). To begin with, friction, at the most basic level, comes from the interaction of intermolecular forces. The source of friction of primary interest in inhaler design is that which occurs between two surfaces as different parts of the device interact. Friction in this context considers how smoothly two surfaces move against each other and how much force is required to do so, as well as how those surfaces deform as they interact with each other.

Wear naturally occurs over time as a result of friction acting on the parts of a device, be it from fatigue, corrosion or fretting. For plastic contact, wear comes in two major types, abrasive and adhesive – scuffing and sticking. Abrasive wear reduces the friction between parts, which can impair functionality as parts cease to hold in place properly, slipping past each other when they shouldn't. Conversely, adhesive wear means that parts stick together more strongly than they should, which can lead to jamming and increased stick-slip effects.

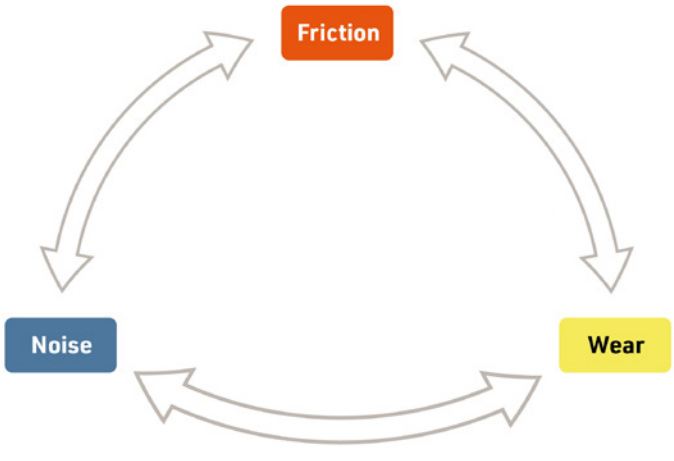

Figure 2: The friction-wear-noise triangle.

The third corner of the triangle is noise. There are two primary types of noise to consider here, squeaking and knocking. Squeaking is a result of the slip-stick effect. A completely smooth motion does not produce a squeak, whereas if the motion of one plastic surface over another is stop-start, with one surface sticking, then jumping forward, sticking again and repeating the process, it creates an audible squeak. Knocking, on the other hand, comes from mechanical interactions causing two parts to strike each other repeatedly.

Putting these three aspects together, noise can be viewed as an indication of unwanted friction within the device, which then results in unnecessary wear, which leads to more noise. Inhalers are rarely single-use devices, so controlling these three factors is key to producing a device that retains its functionality for its full lifespan and inspires confidence in its users – a patient might be unaware of the wear and friction happening inside a device, but they will certainly know if it starts making unwanted noise!

UNDERSTANDING THE SYSTEM AS A WHOLE

To master the friction-wear-noise triangle, it is crucial to understand how friction acts upon a system as a whole (Figure 3). A fundamental aspect of this is a solid foundation in materials – knowledge of how different materials interact with each other and themselves is key to success. A good rule of thumb is to use dissimilar materials in combination for the best results, but the best and easiest approach is to engage with experts, such as Celanese, and make use of their existing knowledge base.

Even relatively simple systems will be dealing with multiple materials and a wide array of interactions. A brief list of key considerations for each of those reactions would include:

- Total sliding distance
- Contact force
- Sliding speed
- Type of interaction (e.g. continuous, oscillating, fretting)
- Surface finish
- Interaction environment (e.g. temperature, humidity, contaminants, etc).

To characterise and understand each of these aspects, it is necessary to perform tests. If friction considerations are ignored until a full prototype is developed, resolving friction-related issues can prove to be an expensive exercise, as part sizes may need to change or alternative specialist materials with the precise properties required need to be sourced. If, instead, friction is considered from the start, testing can be performed using more standard materials to determine ahead of time which is the best fit for the device. To ensure the best results, either the same or the closest possible analogue material is used, which is facilitated by partnering early with a materials specialist.

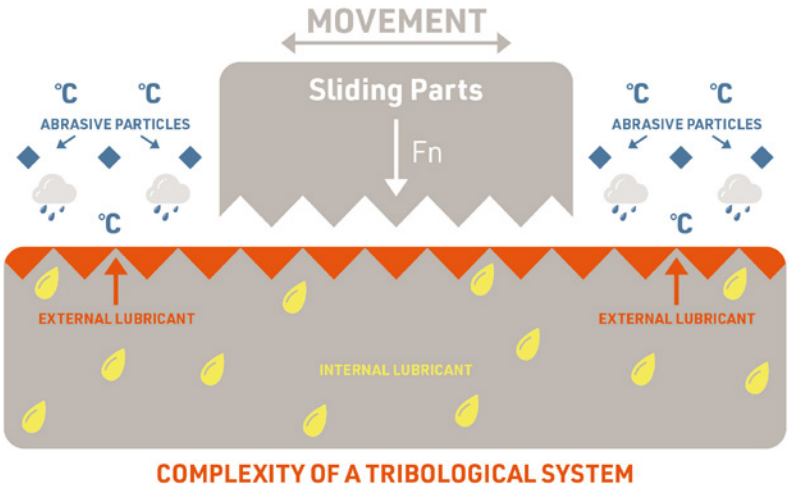

Figure 3: The total friction system.

> "If friction considerations are ignored until a full prototype is developed, resolving friction-related issues can prove to be an expensive exercise, as part sizes may need to change or alternative specialist materials with the precise properties required need to be sourced."

Additionally, testing will be necessary to characterise breakaway forces and long-term wear. Breakaway friction plays a large part in how much force is needed to actuate the device, and so is especially important when designing a breath-actuated inhaler. Long-term testing characterising wear is necessary to ensure that the device will work as intended for its full lifespan. Both of these testing processes are easier and cheaper to complete if friction is considered early in the development process.

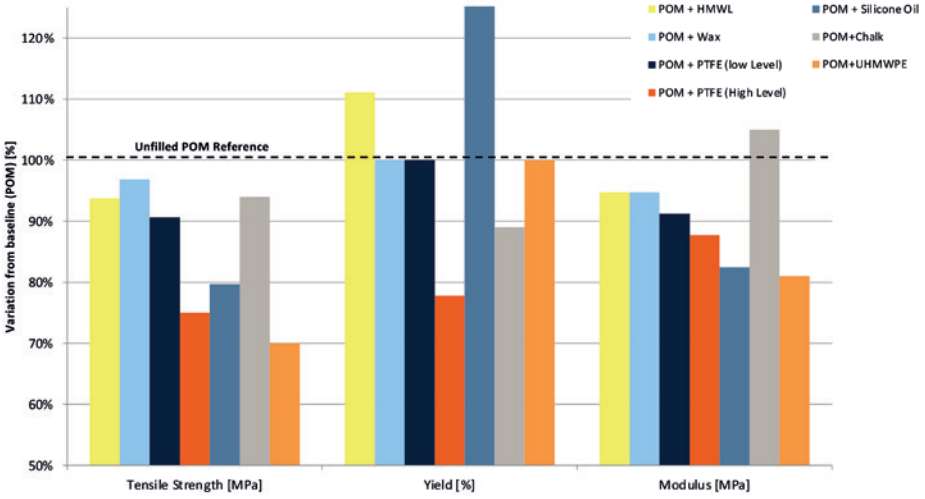

Figure 4: The effects on mechanical properties of various internal lubricants.

"Choosing the correct lubricant system for a given application requires understanding their various methods of action, strengths and limitations."

LUBRICANT SYSTEMS

Even with careful selection of the most appropriate materials for an inhaler design, over the many times it will be used it is inevitable that some wear will occur. As such, it is important to consider how lubricant may help minimise the effect of that wear on device functionality. There are many lubricant systems available, including wax, chalk, silicone oils and polytetrafluoroethylene (PTFE), all with their own advantages and disadvantages (Figure 4). Choosing the correct lubricant system for a given application requires understanding their various methods of action, strengths and limitations. Here, making use of expert knowledge can be crucial for optimising device functionality, reducing risk and minimising cost.

Immediate Versus Wear-Based Lubrication

The first big consideration when choosing a lubricant system is whether the lubrication needs to occur immediately from the first use of the device or be steadily introduced over time as the parts wear. Immediate lubrication provides its full benefit up front, but will diminish over time. This can be very useful if a little wear is needed to achieve the desired level of friction, while the initial use is too stiff. Wear-based lubricant, on the other hand, provides little to no immediate benefit, but instead is released as the parts wear. This means that lubricant is replenished at the point of interaction over time, providing a consistent force profile throughout the device's lifespan.

Internal Versus External Lubrication

Another significant dichotomy when it comes to lubrication systems is internal versus external. External is the simpler option, whereby a layer of oil or grease is applied to a surface at the point of friction during assembly, which can make the friction of the interaction largely independent of the materials. However, external lubricant is very susceptible to migration and can spread throughout the inhaler in undesirable ways, so thorough quality assurance testing is required to ensure that this is minimised.

In comparison, internal lubrication systems consist of small particles of lubricant contained within the material itself that are released as friction acts upon them. This means that internal lubricant systems are more easily controlled, but the cost of employing them can be greater than external systems. Which is more appropriate for a given application is therefore highly contextual. Developing a holistic understanding of how friction acts upon the system as a whole, along with the costs involved for both materials and testing, is absolutely necessary to optimise device design and assure regulators of its long-term functionality.

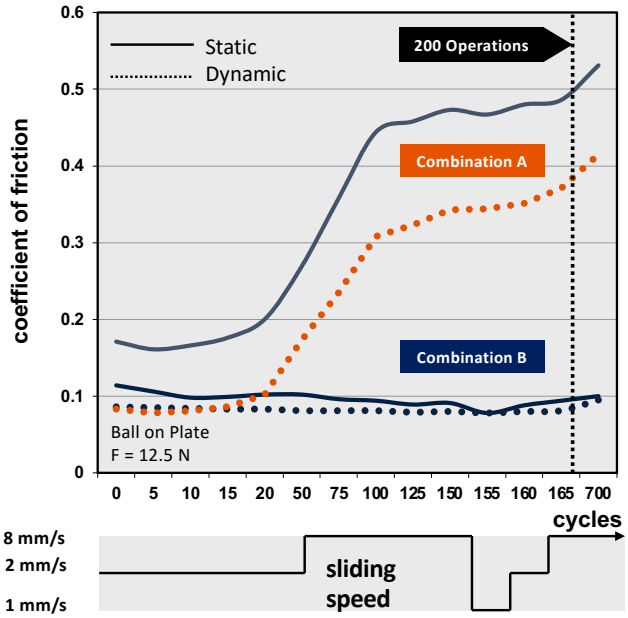

Figure 5: Development of friction over multiple movement cycles, as tested on an oscillating slip-stick tester.

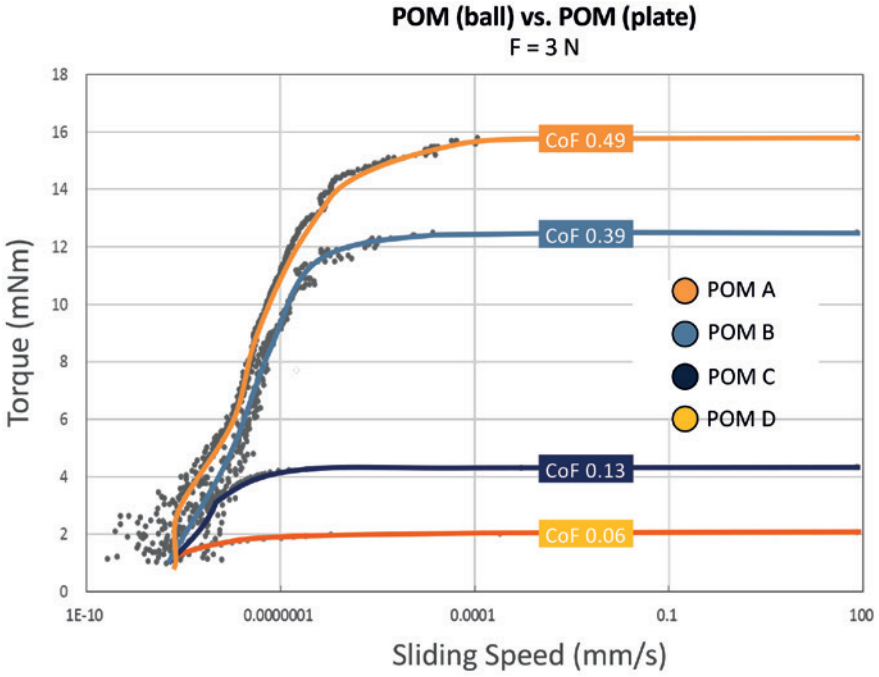

Figure 6: Initial breakaway friction and torque, as tested on a rotary MCR multi-tester.

CHANGES IN FRICTION OVER TIME

As has been discussed thus far, many factors affect the friction in any given material pairing. One of the most critical of these factors is the distanced travelled (or the number of cycles) an interaction will see – the balance between friction, wear and noise can vary significantly as sliding distance increases. As shown in Figures 5 and 6, while friction may stabilise during initial breakaway, it can change

> "Working with an established expert in materials with a proven track record in tribology is the easiest and most effective way of capitalising on the advantages of optimising friction in your device."

dramatically as the number of operations increases. Understanding the development of friction over time is specifically important in mechanisms such as dose counters and actuation triggers.

CONCLUSION – OPTIMISE EARLY

Whether it's acknowledged or not, friction plays a major role in every inhaler development project. Understanding and optimising it early leads to reduced cost, lower risk and smoother regulatory approval. Working with an established expert in materials with a proven track record in tribology is the easiest and most effective way of capitalising on the advantages of optimising friction in your device.

As such an expert, Celanese can help ensure success. Using its broad portfolio of established medical grade materials, Celanese can help with materials testing, making sure tests are conducted with either the same material or the closest possible analogue to that intended for prototyping and production tooling. Furthermore, Celanese can assist in resolving problem interactions in the design, potentially offering modified polymer grades if required to achieve success.

Late-stage changes to inhaler design due to friction-related problems are costly to fix, often requiring multiple part changes, alternative materials or both. As such, partnering with an expert supplier early provides key benefits and expertise to the design process, helping generate designs that make the most of their materials and ensuring that the right questions are asked and answered before they become costly mistakes. Friction problems can easily sneak through the early stages of the development process, so getting a grip on friction reduces risk, lowers cost, improves quality and goes one step further to make sure an inhaler stands out against its competition.

ABOUT THE COMPANY

Celanese Corporation is a global chemical leader in the production of differentiated chemistry solutions and specialty materials used in most major industries and consumer applications. Celanese's businesses use the full breadth of the company's global chemistry, technology and commercial expertise to create value for its customers, employees, shareholders and the corporation. As Celanese partners with its customers to solve their most critical business needs, it strives to make a positive impact on communities and the world through The Celanese Foundation.

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The company's high-performance polymers and thermoplastics unlock design opportunities for your products to improve patient care.

ABOUT THE AUTHOR

Bryan Deacon is a Global Marketing Manager for Celanese, specialising in the drug delivery device area. Over the past two decades, in various roles, he has supported the development of some of the world's most successful drug delivery devices, working across the value chain to help end users bring their products to market. Mr Deacon holds a BEng in Mechanical Engineering/Computer-Aided Engineering from Heriot-Watt University in Edinburgh (UK).

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HIGH-PRECISION INJECTION MOULDS FOR INHALERS: CHALLENGES AND SOLUTIONS

In this article, Rob Doorakkers, Chief Innovation Officer, and Erwin van Huijksloot, Senior Sales Manager, both at IGS GeboJagema, discuss the challenges and solutions of engineering and manufacturing high-precision injection moulds for inhalers.

The goal of an inhaler is simple: to reliably and efficiently deliver medicine. Efficient drug delivery makes treatments more effective and thus allows patients to extract more successful dosages from a single canister.

> "Whether inhalers accurately deliver drugs is largely determined by the precision of the moulded actuator."

Whether inhalers accurately deliver drugs is largely determined by the precision of the moulded actuator. Small differences in the geometry of the actuator can drastically change the medicine's spray behaviour, also known as bloom. The bloom determines where the medicine is applied in the mouth, which is an important factor in how effective a drug is. For example, some drugs are most effective when administered to the roof of the mouth, while others should reach the back of the throat to be inhaled deep into the lungs (Figure 1).

IGS GeboJagema has engineered and manufactured injection moulds for inhalers for more than 20 years. In fact, the first inhaler mould the Eindhoven company delivered is still active today. In this article,

Figure 1: Some drugs must be administered through the roof of the mouth, while others must reach the back of the throat.

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Figure 2: More than 20 years of experience.

the authors will discuss the challenges in realising the required degree of precision, as well as some of the most effective solutions developed by the IGS GeboJagema engineering team (Figure 2).

CRITICAL COMPONENTS: THE STEM FIT AND THE ORIFICE

To understand the challenges in manufacturing inhalers, it is first necessary to take a closer look at how these devices are constructed. The device has a right-angled design. The canister is placed in the body of the device, while the medicine is administered through the mouthpiece (Figure 3).

Two components are absolutely critical for accurate drug delivery: the stem fit and the orifice. The stem fit is where the medicine canister and the plastic device connect. The orifice is the opening through which the medicine is sprayed into the patient's mouth.

The geometry of the stem fit and orifice determine the device's bloom. Consequently, this is where all IGS GeboJagema's injection mould expertise can be found. For example, during the validation phase, the IGS GeboJagema team extensively tests the bloom of different device dimensions. Ink is placed in the device, which is then sprayed at a "dartboard" to confirm that the drug will reach the correct location in the mouth (Figure 4).

Having determined which device dimensions are necessary for accurate drug delivery, the next step is to create an injection mould for the device. Over the past two decades, IGS GeboJagema has developed a range of solutions for common challenges and client requirements in this process.

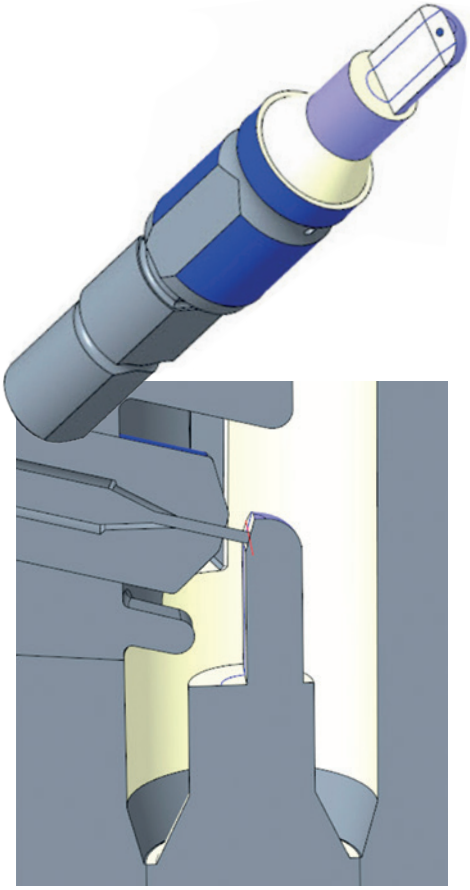

Figure 3: The stem fit.

1. Fast Stem Fit Variations for Optimal Uptime and Higher Mould Output

The stem fit is of vital importance for accurate drug delivery. It must be perfectly in line with the body and mouthpiece to create the optimum spray direction. If this is not the case, the "aim" will be off and medicine will be unnecessarily lost. Moreover, the geometry of the stem fit affects the bloom of the medicine. So, by using a different stem fit, a different bloom can be realised.

During the injection-moulding process, a stem fit insert is used to mould this part of the plastic product. In what could be called the standard injection mould for inhalers, it is possible to change the stem fit insert. However, the process is time consuming, as the mould must first be removed from the moulding machine. For contract manufacturing organisations (CMOs) that produce limited variations of their product, this is not an issue.

> "Applying too much pressure on the orifice pin will cause it to deform."

But for medical device manufacturers that need to produce many different variations, a better solution is necessary.

For these clients, the engineering team at IGS GeboJagema created a solution where the stem fit insert can be removed while the mould is still on the machine. Via the side of the mould, a system can be activated to remove or mount the stem fit insert. This easy system saves a lot of time and improves the uptime of the mould, which allows for higher mould output.

2. Orifice Precision to Avoid Flash in the Shut-Off Area

The orifice is the opening in the mouthpiece through which the medicine passes. It is, of course, essential that this opening remains perfectly "clean". For example, no plastic film (also known as "flash") must be left behind in the orifice. IGS GeboJagema has developed a special technique to mould the orifice. In its moulds, a spring keeps sufficient pressure on an "orifice pin" in order to realise a clean "shut-off area": the area where the stem fit insert and the orifice pin meet. This prevents flash in the orifice, which could otherwise potentially be inhaled by the patient.

This technique requires a high degree of precision. Applying too much pressure on the orifice pin will cause it to deform and result in a "mushroom effect". Moreover, placing too much pressure on the orifice pin will also create an indent on the stem fit insert, which can also create flash. As a solution, in the past, hard materials were used for this component. But, as these hard materials proved susceptible to breakage, today IGS GeboJagema uses a tough steel-grade component with a carbide centre in the shut-off area.

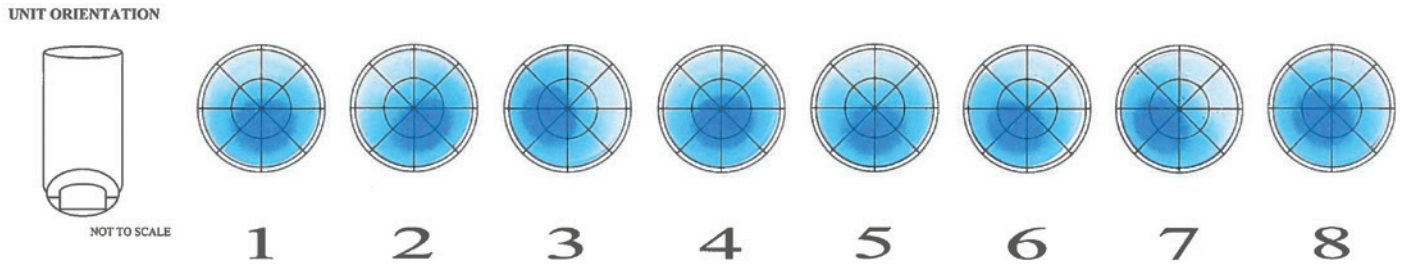

Figure 4: The tests of the bloom during the validation phase.

3. Flexible Orifice Moulds for Improved Uptime and Mould Output

As discussed, the bloom of an inhaler can be modified by changing the stem fit. However, for some devices it is necessary to change the orifice as well, as different drugs require a different orifice length and diameter. For these projects, IGS GeboJagema has implemented a quick-change system that allows replacement of the orifice pin while the mould is mounted on the injection-moulding machine. As with the system to quickly change stem fit inserts, this saves time and improves the uptime of the mould – and thus optimises mould output. For even more switching speed, the engineering team at IGS GeboJagema developed a second solution, which gives CMOs the option to adjust the jet length of the orifice in seconds using a control built into the mould.

4. Long-Life Orifice Pins for Highly Reliable Product Quality

The orifice diameter is usually between 0.2 and 0.5 mm. The orifice tends to have a length between 0.2 and 1 mm. That means the orifice pin required to mould this component will be very thin as well. Considering the large amount of pressure placed upon the orifice pin during the moulding process, it should be no surprise that these pins are at risk of bending or breaking over time. The bending of the pin is a particularly pernicious problem, as it can slowly affect the accuracy of the actuator and thus the bloom. Considering the trend of orifice diameters becoming smaller and smaller, this could become a more prevalent issue for medical device manufacturers if no countermeasures are taken.

The root cause of these problems is the force released when the injection mould closes and opens again. This force causes the orifice pin to move slightly which, over time, can cause the issues described above. To prevent this, IGS GeboJagema developed a solution where a servo-driven system retracts the orifice pin to a safe position before the clamp is released and the mould is opened. The system then returns the orifice pin to its original position once the mould is closed again and the clamp force has already been applied. This solution extends the lifetime of the pin and prevents bending and breaking problems.

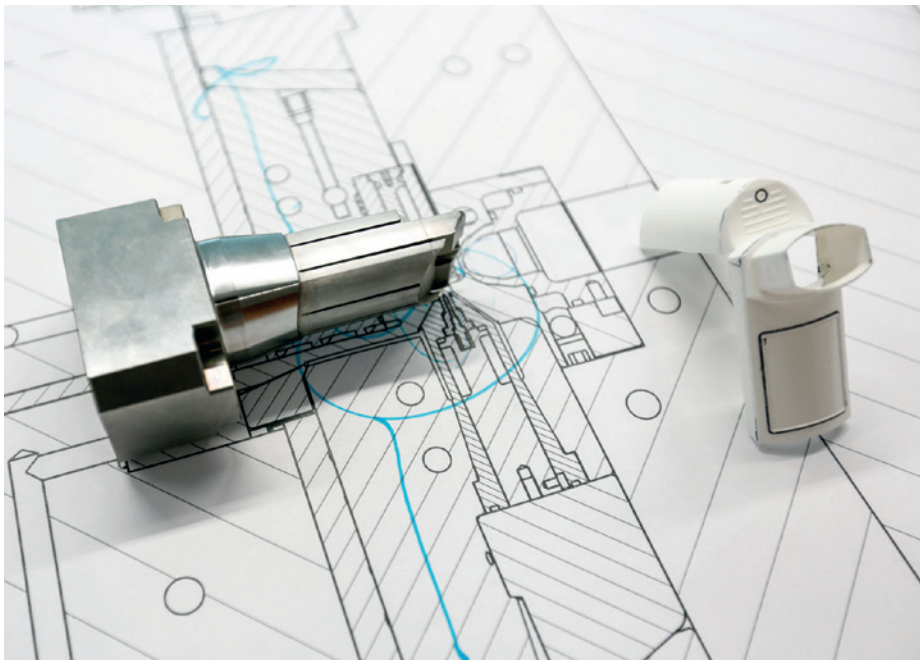

Figure 5: Innovation through passion.

> "The ideal mould design depends on a project's exact requirements."

A PASSION FOR PRECISION

This article has presented several solutions that the engineering team at IGS GeboJagema has developed over the past two decades. Of course, the ideal mould design depends on a project's exact requirements. The mould features described in this article can help to meet those project requirements through greater uptime, fewer problems and a lower total cost of ownership (Figure 5).

Through smart technical solutions, moulds can minimise loss of medicine in the device. It allows patients to rest assured that exactly the right amount of medicine is being administered. It is just one example of how IGS GeboJagema's passion for precision touches billions of lives every day.

ABOUT THE COMPANY

IGS GeboJagema is a high-precision mould maker, headquartered in the Netherlands. The company designs, manufactures, validates and maintains moulds for products where extreme precision is vital: from glasses and contact lenses to asthma inhalers, insulin pens and blood diagnostic devices. IGS GeboJagema specialises in collaborating with medical original equipment manufacturers early in the product lifecycle, allowing its engineering team to develop innovative moulding solutions.

ABOUT THE AUTHORS

Rob Doorakkers is Chief Innovation Officer at IGS GeboJagema, where he focuses on optimising production processes, continuously improving product quality and finding innovative solutions to solve the most challenging technical challenges. Mr Doorakkers has over 30 years of experience in the injection moulding and manufacturing industry.

Erwin van Huijksloot is Senior Sales Manager at IGS GeboJagema, responsible for the commercial relationship with healthcare customers, with a focus on partnership and long-term customer relations. He has more than 20 years of experience in sales in the injection-moulding industry and has worked for IGS GeboJagema since 2010.

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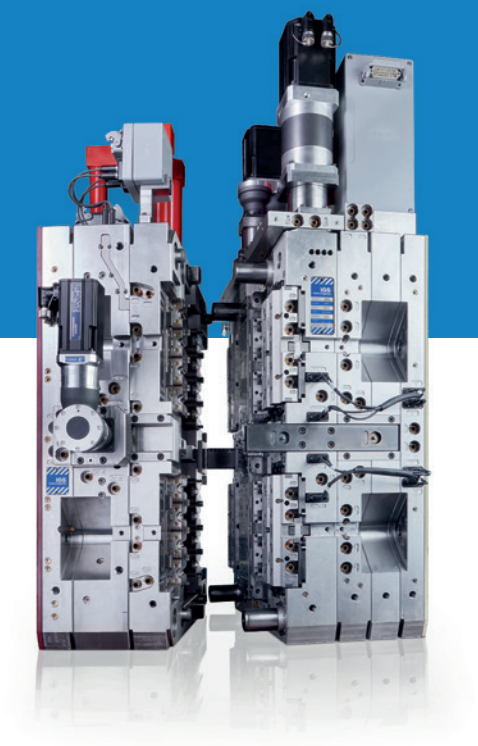

IGS GeboJagema combines unrivalled technical expertise, smart innovations and rigorous testing with the latest technology and the highest specifications of materials. By working closely with medical OEMs early in the product life cycle, we allow our clients to take full advantage of our engineering power. It's how we deliver unique, innovative solutions that give our clients an edge over their competitors.

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ENGINEERING EXPERTISE: DESIGN FOR EXCELLENCE

Here, Drew Jelgerhuis, Business Development Manager, Medical, at Scherdel Medtec, looks at how a design-for-excellence (DFX) systematic approach can help manufacturers achieve their objectives.

STORY OF REGRET

Explosions, batteries overheating and burns were just some of the issues with a recent mobile phone product launch failure. According to *Time* magazine, this popular brand recalled 2.5 million of its new devices just weeks after it launched.[1] Maybe your product launch has not been "burnt" in this way; however, not attending to design with all the factors associated with the product at the start could lead to similar failures. This major electronics company made mistakes in the product launch phase by not fully attending to design issues that became manufacturing issues both inside and outside the company.[2] The reason for sharing this story of regret is to highlight the importance of design and using the design for excellence (DFX) systematic approach to achieve your objectives. This might include assembly, manufacturing, safety, cost and sustainability, to name those important to the market sector.

> "The wide range of specialised fields of engineering makes it nearly impossible to contain all the relevant knowledge that a subject matter expert can bring to bear to a design concept."

Figure 1: Springs represent a crucial and yet complex component in inhalers and many other categories of drug delivery device.

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"In recent years, sustainability has become a higher priority during the design phase."

THESIS FOR DFX

Building DFX into your product development process provides a means for subject matter experts to offer valuable knowledge early enough in the design phase to reduce future risk, cost, time and failures. Many developers and designers in search of expertise will rely on specific design guidelines. Although much value can be derived from these guidelines, the wide range of specialised fields of engineering makes it nearly impossible to contain all the relevant knowledge that a subject matter expert can bring to bear to a design concept. During a recent design review with a customer focusing on multiple springs for an autoinjector platform, one of the developers said, "Springs are one of the hardest components to fully understand because of the depth of their technical complexity in a drug delivery device." This applies in numerous categories of delivery system, including pulmonary (Figure 1), nasal, injectables (including wearables), and others, where springs play a crucial role, and is enough reason to engage expert spring designers early and throughout the development project using excellent simulation software.

WHAT IS DFX?

DFX is a systematic approach embedded in the product development cycle that requires a cross-functional team of experts to evaluate a product design focusing thoroughly and methodically on targeted objectives or characteristics. The chosen characteristics and objectives are represented by "X" and often focus on safety, cost, manufacturing and assembly. In recent years, sustainability has become a higher priority during the design phase, as well. A couple of specific "X" focuses are:

1. Design for assembly (DFA) provides a method for simplifying the product design by minimising assembly operations and reducing components. The goal is to reduce assembly complexity, thereby improving throughput and reducing variation.
2. Design for sustainability (DFS) focuses on material, processes, resources used and environmental impact, to name a few areas methodically evaluated and considered for changes to improve wholistically the sustainability of a product (Figure 2).

Scherdel Examples

Scherdel has been designing and manufacturing springs and precision stampings for over 130 years and has an extensive engineering team and technical resources. This depth and breadth of expertise that Scherdel can provide early in the development phase will reap great benefits in the later phases of launch of the product. Some examples with recent customer developments include automated assembly, part-design input to minimise quality issues, patient requirement characteristics affected by part-process tolerances and part-handling considerations for high-volume production. Using DFA as the focus, here are four relevant examples.

"Scherdel has been designing and manufacturing springs and precision stampings for over 130 years and has an extensive engineering team and technical resources."

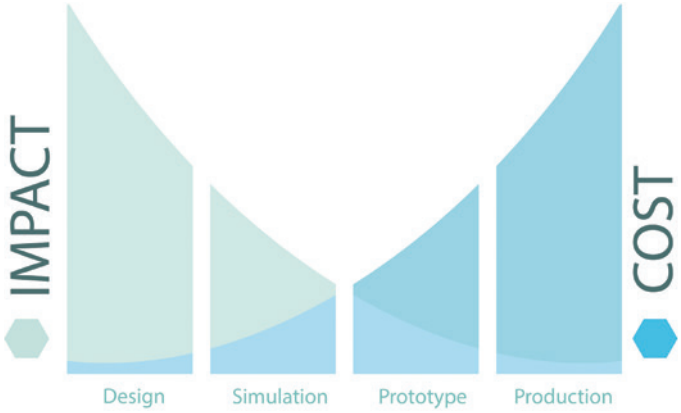

Figure 2: Impact cost diagram.

The first example is for a current customer that is producing low-volume product manually and is ramping up production with projections for significant volume increase in the coming years. Due to Scherdel's experience in both high-volume spring production and automation equipment, the company worked closely with this customer on various concepts for automation that would significantly reduce labour, improve quality and reduce material cost with minor design changes. After several iterations, the companies were able to agree on a concept that reduced labour by more than 75%, paid off the automation in under 18 months and provided upwards capacity from the current 100,000 parts per year to over 1.2 million per year.

Another example involved redesigning two parts to be identical and symmetrical about a central axis. This allowed the part to be bowl fed in one bowl instead of two and picked up by the same robot gripper, and eliminated a costly and timely vision system that would have been necessary to identify the two different part designs. Had this DFA been conducted before the part was designed and tooled for injection moulding, it would have saved the company around US$30,000 (£26,500) in tooling cost and $15,000 per year in labour.

A third assembly related example involves working with a start-up in the drug delivery business. This customer is designing a novel delivery device that requires multiple springs. Scherdel conducted multiple design review sessions focusing on the specified force to meet the delivery needs of the drug in various viscosities while still meeting patient safety and comfort characteristics. The design was optimised by designing both right- and left-hand wound springs to balance the torque load during deployment of the drug. By designing the ends of the springs and the corresponding component they nest in with error proofing features, the parts could not be assembled incorrectly and yet can be fed with automation and no tangling issues often associated with springs that are fed automatically.

A final assembly example involves a combination device that required several different springs. Scherdel's design engineer engaged in many design review sessions focusing on eliminating grinding,

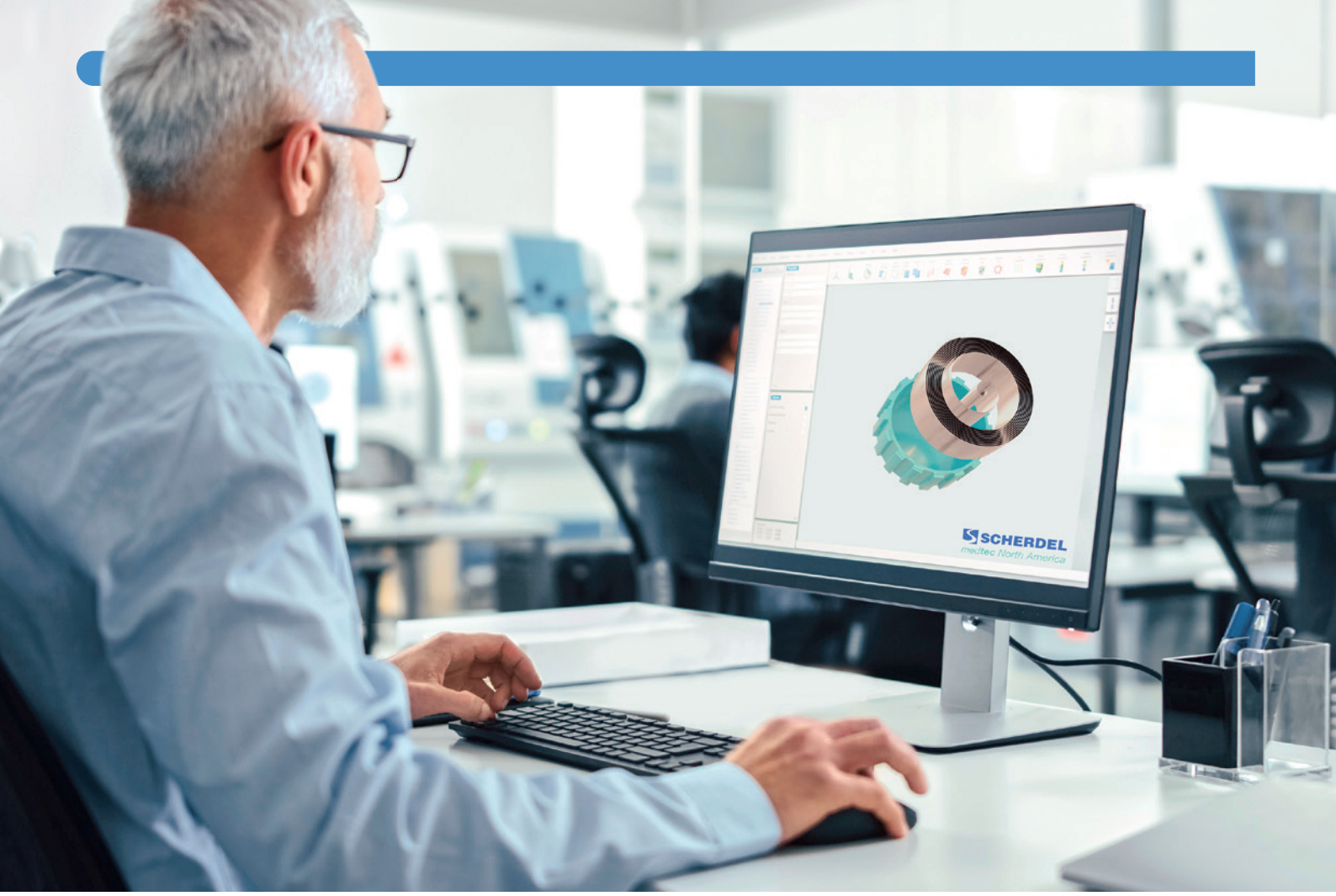

Figure 3: Scherdel's design team provides inputs supporting concepts, simulation, prototypes, testing, tooling and automation, all based on experience gained from serial production of hundreds of millions of drug delivery springs and stampings.

tangling and tight tolerance issues. The grinding that was initially required was eliminated by suggesting square wire in place of round and a redesign of the mating component. The tangling issue was resolved by including an innovative spring redesign that did not impact the component characteristics. The tolerancing concern would have required a slower process and higher-cost in-line inspection but, by changing the design, the tolerance could be opened and not affect the very critical free length specification.

BENEFITS OF DFX

As evidenced by the examples, the cost-benefit ratio is much greater the earlier Scherdel's design team can engage with the product development team. This involvement early on with subject matter experts, such as design engineers, can arguably reap, as an MIT research paper suggests, 50%–65% savings.[3] Certainly, the company has specific examples where savings of the spring or stamping component was reduced by at least this amount when redesigned. In addition to the assembly examples shared, Scherdel can also bring its subject matter expertise to bear on safety, material and sustainability topics related to product design (Figure 3).

Scherdel provides best-in-class design input in the form of concepts, simulation, design, prototypes, testing, tooling, automation and, of course, serial production of hundreds of millions of drug delivery springs and stampings. Scherdel leverages its team to drive significant cost out of your product while improving quality, safety and environmental impact.

ABOUT THE COMPANY

Scherdel Medtec is part of the Scherdel Group. With about 5,800 employees at 32 locations worldwide, the Scherdel Group is a family-owned, leading company in the field of metal forming, with core competence in the production of engineering springs, stamping parts and assemblies for the pharmaceutical market as well as vehicle components.

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ABOUT THE AUTHOR

Drew Jelgerhuis is the Business Development Manager, Medical, for Scherdel Medtec North America. With over 15 years of business development experience in the medical device sector, Mr Jelgerhuis leads the North American Medtec team growth in co-operation with the other global Medtec leaders. Mr Jelgerhuis holds a BSc in Mechanical Engineering from Dordt University (IA, US) with a minor in Business Administration. He enjoys solving technical problems for customers by providing solutions for their medical device component requirements.

POWDER CHARACTERISATION FOR DPI PERFORMANCE IN CAPSULE-BASED INHALERS

In this article, Salvatore Pillitteri, PhD, Particle Scientist and Aurélien Neveu, PhD, Particle Scientist, both of Granutools, and Sarah Zellnitz-Neugebauer, PhD, Senior Scientist at Research Center Pharmaceutical Engineering, discuss the analysis of three powder blends of salbutamol sulphate with distinct lactose grades, using tapped density and rotating drum methods.

Respiratory diseases are commonly treated with orally inhaled drugs – via dry powder inhalers (DPIs), for example. DPIs typically consist of the micronised API in the size range 1–5 µm, blended with a larger inactive carrier material.[1] But such small API particles often have poor flowability and high cohesion, which makes handling difficult.[2,3] Moreover, they rarely exhibit the expected performances in terms of aerosolisation and absorption. Consequently, their properties must be improved with the addition of larger carrier particles to reach the required performance.

Lactose is often used, and the large variety of available grades allows for designing the DPI according to the requirements.[1] However, it remains difficult to predict the behaviour of the blend. The fine particle fraction and the fine particle mass (FPM) are quantities measured via impaction to evaluate the *in vitro* aerosolisation performance of the API. Since this measurement is cumbersome and time consuming, simple methods to evaluate DPI performance based on bulk powder characterisation are necessary. Therefore, different studies have focused on the investigation of measurement methods for DPI characterisation.[3]

In this study, Granutools and Research Center Pharmaceutical Engineering (RCPE) characterised three powder blends of salbutamol sulphate (SBS) with distinct lactose grades using tapped density (GranuPack, Granutools) and rotating drum (GranuDrum, Granutools) methods. Their usability has been evaluated by correlating the bulk powder properties with the *in vitro* performance when the mixtures are delivered with a capsule-based inhaler.

MATERIALS

Three binary powder blends were analysed in the study. Three lactose grades were used to compose the different blends: DuraLac® H, FlowLac® 90 (both MEGGLE, Wasserburg, Germany) and Respitose® SV003 (DFE Pharma, Goch, Germany), shown in Figure 1. Each was mixed with 2% of micronised SBS (DV0.5 = 1.43 ± 0.04 µm) in a low-shear tumble blender (TC2, Willy A Bachofen Maschinenfabrik, Basel, Switzerland) for 90 minutes at 62 rpm.

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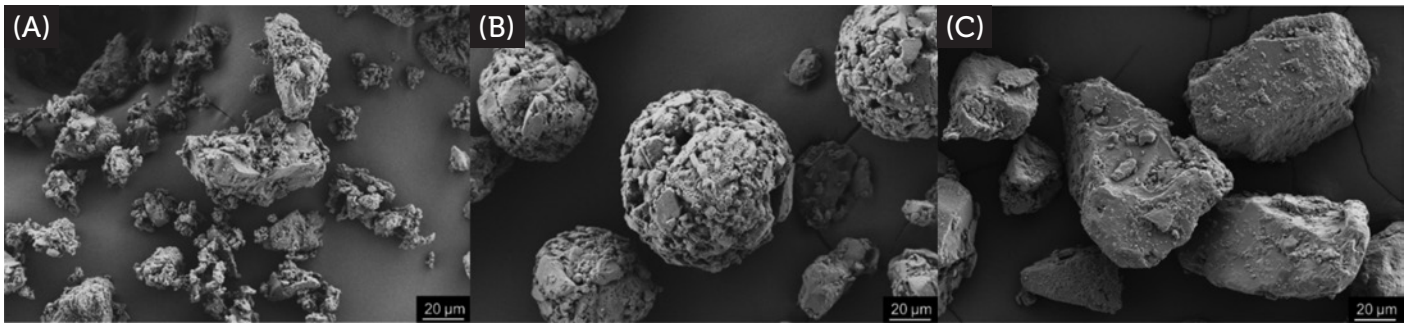

Figure 1: Scanning electron microscopy images of the different grades of lactose: (A) DuraLac® H, (B) FlowLac® 90 and (C) Respitose® SV003.

EXPERIMENTAL METHOD

The bulk properties of the blends were characterised by two instruments from Granutools: the GranuPack and the GranuDrum.

GranuPack

The GranuPack conducts an automated tapped density measurement characterising the packing dynamics of a powder. It consists of a steel cylindrical cell, 26 mm in diameter and 100 mm in length, in which a narrower tube, open on both sides, is initially inserted. Once the powder is poured inside (about 35 mL), the narrower tube is moved upward at a low and constant velocity of 1 mm/s. This initialisation protocol allows a reproducible initial granular pile and reduces operator errors.

After initialisation, the cylindrical cell containing the powder performs a succession of free falls, called "taps". After each tap, the powder densifies and the bulk density is measured. In this study, each measurement lasted 1,500 taps. The initial and final tapped density, $\rho(0)$ and $\rho(1{,}500)$, were obtained and the Hausner ratio $Hr=(\rho(1500))/(\rho(0))$ was calculated. This number characterises the flowability of the powder. The larger it is, the lower the flowability. A high Hausner ratio can come from strong particle interactions, indicating high cohesion, since these interactions tend to decrease the initial density.

GranuDrum

The GranuDrum carries out an automated powder flowability measurement. It consists of a cylinder with transparent sidewalls, called a drum, half filled with approximately 55 mL of powder. The drum can rotate at different speeds, from 2 to 60 rpm, and a charge-coupled device (CCD) camera takes 40 pictures of the powder interface, each separated by 1 s. The powder interface is detected by an algorithm and averaged over the 40 pictures. The fluctuations around the average interface define the dynamic cohesive index (σ_f), related to the cohesiveness of the powder. The larger this index, the more cohesive the powder and consequently the lower its flowability.

> "When the aeration increases, the powder increases its volume, due to the integration of air in the powder during the flow."

Information about σ_f at different speeds is useful for highlighting rheological behaviours. For example, if σ_f decreases when the rotation speed increases this indicates shear-thinning and, conversely, σ_f increasing with increasing rotation speed points to shear-thickening. In addition to the measurement of σ_f, GranuDrum can measure powder aeration index during the flow. This index is the ratio between the estimated volume of the powder's volume and the volume at the lowest speed. When aeration increases, the powder increases due to the integration of air.

Aerosolisation performance was quantified *in vitro* with a next-generation impactor (NGI) by Pinto et al and a Cyclohaler® capsule-based inhaler.[3] For three airflows (100, 60 and 28 L/min), FPM was measured by filling about 40 mg of blend in a capsule and discharging it into the NGI. In this study, each measurement was repeated three times.

RESULTS AND DISCUSSION

Table 1 presents the results obtained with the GranuPack.

The DuraLac® blend had the lowest initial density $\rho(0)$, followed by the FlowLac® blend and then the Respitose®. However, the DuraLac® blend had the highest final density $\rho(1{,}500)$, resulting in a higher Hausner ratio than the other two. This indicates that the DuraLac® blend had a higher cohesion index than the FlowLac®

Name	ρ(0) (g/mL)	ρ(1,500) (g/mL)	Hr
DuraLac® H	0.586 ± 0.009	0.843 ± 0.003	1.439 ± 0.018
Respitose® SV003	0.679 ± 0.002	0.784 ± 0.002	1.156 ± 0.003
FlowLac® 90	0.644 ± 0.003	0.744 ± 0.005	1.155 ± 0.003

Table 1: Parameters obtained with the GranuPack for three powder blends: initial density ρ(0), final density ρ(1,500) and Hr (three tests, mean±SD).

Name	D_{50} (µm)	Fraction < 10 µm (%)
DuraLac® H	52.89 ± 7.10	13.48 ± 1.76
Respitose® SV003	60.26 ± 3.76	3.34 ± 0.07
FlowLac® 90	73.44 ± 2.96	0.54 ± 0.045

Table 2: Particle characteristics for three raw lactose powders DuraLac® H, Respitose® SV003 and FlowLac® 90 (three tests, mean±SD).

"Fine particles have the ability to fill the voids between larger ones, which tends to increase the density."

and Respitose® blends. Particle analysis of the raw powders, shown in Table 2, revealed that DuraLac® had the broadest size distribution with a larger proportion of fine particles compared with the two other lactose powders.

Since fine powders are known to be more cohesive than powders with larger particles, this could explain the lower density of the DuraLac® blend. Indeed, a high cohesion index means strong interactions between grains that can support the weight of several neighbours, which leads to a large number of voids and therefore a low density, compared with a non-cohesive powder. On the contrary, fine particles have the ability to fill the voids between larger ones, which tends to increase the density and could explain the larger final density of the DuraLac® blend. The voids generated by high cohesion can be rapidly filled by fine particles when successive taps move these particles and densify the system. Regarding the Respitose® and FlowLac® blends, the Hausner ratios are too close to each other with overlapping error bars to be able to differentiate the cohesiveness of the two powders.

The results from GranuDrum are presented in Figures 2 and 3. Figure 2 shows σ_f as a function of rotating drum speed. At low speed, one observes that the DuraLac® blend is the most cohesive powder as indicated by the Hausner ratio. This result is consistent since the measurement of σ_f is close to a quasi-static condition as undergone by the powder with the GranuPack. The three powder blends can be ranked from the most cohesive to the least cohesive as follows: DuraLac® > FlowLac® > Respitose®.

Conversely, at higher rotation speeds, between 45 and 60 rpm, the DuraLac® blend is observed to be the least cohesive. Indeed, the powders exhibit different rheological behaviours: while the DuraLac® blend shows shear thinning, the FlowLac® blend exhibits shear-thickening behaviour, and the Respitose® blend shows a constant cohesion, changing the classification that

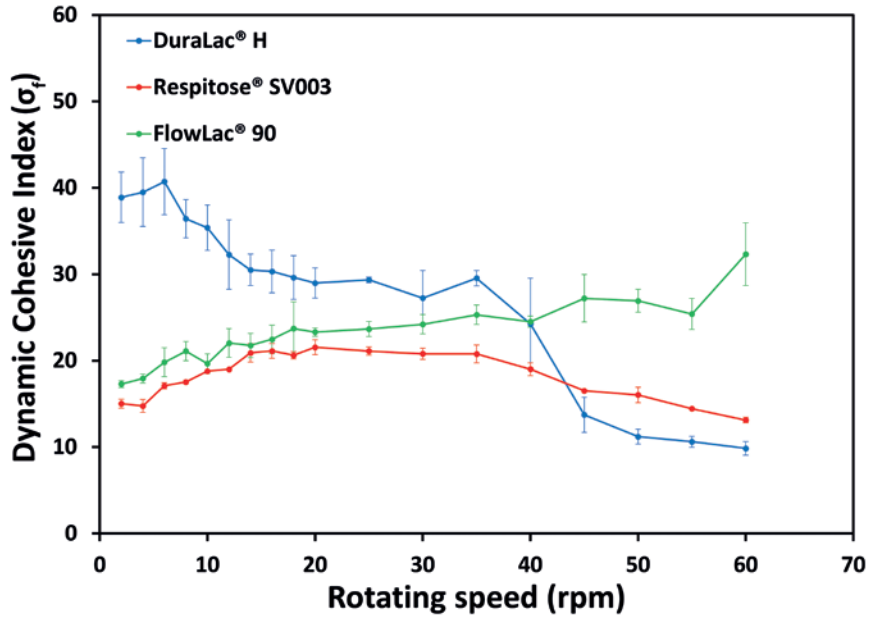

Figure 2: Dynamic cohesive index as a function of the rotating drum speed for the three powder blends.

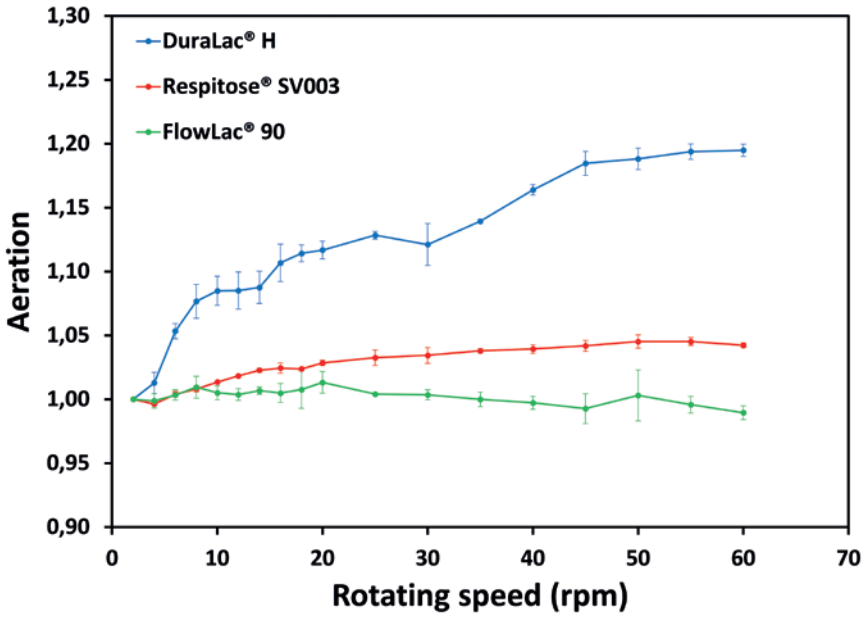

Figure 3: Aeration index as a function of the rotating drum speed for the three powder blends.

"The shear-thinning behaviour observed for the DuraLac® blend could come from its larger proportion of fine particles."

can be made at low-shear stress conditions. From the most cohesive blend to the least cohesive, one has: FlowLac® > Respitose® > DuraLac®. The shear-thinning behaviour observed for the DuraLac® blend could come from its larger proportion of fine particles (Table 2). Indeed, fine particles are known to increase cohesion but it has also been observed that a small number of fine particles in the presence of larger ones can lead to shear-thinning behaviour.[4]

In Figure 3, aeration index as a function of rotating drum speed is presented. For the DuraLac® blend, a large increase in aeration index versus rotation speed can be seen, compared with the Respitose® and FlowLac® blends. Air incorporated in the DuraLac® blend due to mechanical

Name	100 L/min	60 L/min	28 L/min
DuraLac® H	0.80 ± 0.10	0.72 ± 0.01	0.62 ± 0.01
Respitose® SV003	0.74 ± 0.02	0.60 ± 0.04	0.38 ± 0.01
FlowLac® 90	0.20 ± 0.06	0.13 ± 0.02	0.01 ± 0.00

Table 3: Fine particle mass of SBS, determined with the NGI at different flow rates (three tests, mean±SD).

agitation could decrease the amount of contact and and the number of interactions between particles, which could also explain the decrease in cohesion of this blend. Both aeration and fine particles may play a role in the shear-thinning behaviour of the DuraLac® blend. One can see that the Respitose® blend has an intermediate ability to be aerated, while the FlowLac® blend presents the worst propensity to be aerated, particularly at higher speeds, where the aeration ratio is gently decreasing with the rotation speed.

The FPM of the DuraLac®, Respitose® and FlowLac® blends was investigated and the results are presented in Table 3.

It can be seen that airflow has an impact on FPM. Indeed, higher airflow leads to higher FPM. The DuraLac® blend has the highest FPM, followed by Respitose®, while the FlowLac® blend had the lowest FPM.

The quasi-static measurements are not able to predict the performance of the powder blends. Based on the measurement of the Hausner ratio, a differentiation is not possible between the Respitose® and FlowLac® blends, while a clear difference can be observed between these two blends in terms of FPM. Likewise, the measurements recorded by the GranuDrum at low speeds rank the powder blends from the most cohesive to the least as follows: DuraLac® > FlowLac® > Respitose®. This does not correlate well with the performance classification given by FPM, from the highest to the lowest: DuraLac® > Respitose > FlowLac®. On the contrary, the cohesion characterisation made at high rotating speeds allows correlation between σ_f and FPM. The DuraLac® blend is observed to be the least cohesive powder at high rotating speed and has the highest FPM. On the other hand, the FlowLac® blend shows the highest cohesiveness with the lowest FPM, and the Respitose® blend exhibits intermediate behaviour in terms of cohesiveness and FPM.

Moreover, considering that in a capsule-based inhaler the powder is released by a pierced capsule rotating at high speed (around 1,000 rpm),[2] one could legitimately suppose that a measurement made at high shear stress, as performed by the GranuDrum at high rotating speeds, is more relevant than a measurement made at low shear stress, as performed by quasi-static measurements. While quasi-static measurements are generally used for powder characterisation to predict DPI performance, complex rheological behaviours, such as shear thinning, exhibited by the DuraLac® blend, or shear thickening, exhibited by the FlowLac® blend, completely reverse the classification that can be made under quasi-static conditions. In this study, the lower the cohesion, the higher the FPM.

CONCLUSION

Three powders composed of a mixture of SBS with different lactose grades were analysed in this study regarding rheological properties and *in vitro* aerosolisation performance. The Hausner ratio, generally used to classify powder in terms of cohesiveness, is unable to differentiate between the Respitose® and FlowLac® blends in terms of cohesiveness, and the dynamic cohesive index at low rotating speeds is not well correlated with the FPM, representing the DPI performance.

However, it was highlighted with the GranuDrum that the three powder blends exhibit different rheological behaviours: shear-thinning for the DuraLac® blend, shear-thickening for the FlowLac® blend and a constant cohesion for the Respitose® blend. Considering σ_f at higher rotating speeds, classification of the blends in terms of cohesion is completely different from that obtained from quasi-static measurement. With dynamic measurement performed by the GranuDrum at a high rotating speed, closer to the shear state that a powder can undergo during aerosolisation, one obtains a classification in terms of cohesiveness that can be correlated with the FPM obtained with the NGI. These results have demonstrated that measurements in a dynamic state can be more relevant than quasi-static measurements.

> "Measurements in a dynamic state can be more relevant than quasi-static measurements."

ABOUT THE COMPANIES

Granutools combines decades of experience in scientific instrumentation with fundamental research on powder characterisation to develop and manufacture instruments that measure physical powder characteristics such as flow, static cohesion, dynamic cohesion, tapped density and tribo-electric charge.

The Research Center Pharmaceutical Engineering (RCPE) is a global leader in pharmaceutical process engineering, supporting its partners in developing and manufacturing innovative medicines. RSPE's science enables tomorrow's medical discoveries and improves the lives of patients around the world.

The experience of its multidisciplinary teams and unique capabilities in simulation, artificial intelligence, material science, process design and quality control redefine the boundaries of what is possible and provide scientific solutions tailored to its partners' needs.

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ABOUT THE AUTHORS

Salvatore Pillitteri, PhD, studied Physics at the University of Liège (Belgium). He completed his PhD thesis on granular compaction under the supervision of Professor Nicolas Vandewalle and developed expertise in the field of granular materials. His work is part of the European project PowderReg. The aim of this project was to boost the competitiveness and attractiveness of the Grande Région (Großregion) and is part of a plan to optimise processes applicable to industrially relevant powders within the highly developed sectors such as agrifood, chemicals, pharmaceuticals and construction. After his thesis defence, Dr Pillitteri started a career at Granutools as a Particle Scientist to apply his knowledge in granular science to industrial problems.

Aurélien Neveu, PhD, focuses his research activities mainly on the understanding of granular materials at different scales. During his PhD he developed discrete numerical models to describe the fragmentation mechanics of cohesive granular materials by taking into account the complex micro-properties of the grains. He then moved to a larger scale to study segregation in gravity-driven rapid flows as well as aeolian transport of granular materials, with huge implications for natural disasters. Dr Neveu is now working as a Particle Scientist at Granutools, performing research into powder characterisation.

Sarah Zellnitz-Neugebauer, PhD, is a pharmacist by training. During her PhD at Graz University of Technology (Austria) she focused on glass beads as new model carriers in DPIs and gained expertise in particle engineering via surface modification and detailed material characterisation. She currently holds the position of Senior Scientist at Area II Advanced Products and Delivery at the Research Center Pharmaceutical Engineering in Graz (Austria). Her work centres on tailoring DPI formulations via mechanistic understanding of the interplay of material properties, formulation properties, adhesive-cohesive force balance and drug detachment. Recently, she also took up the field of co-processing of API combinations for inhalation therapy.

ADVANCING THE SCIENCE: EXPLORING NEW ALTERNATIVE *IN VITRO* TESTS TO HELP DEMONSTRATE BIOEQUIVALENCE IN INHALATION PRODUCTS

Here, Proveris Scientific looks at recent advances in *in vitro* testing in inhalation products to demonstrate bioequivalence and discusses the company's INVIDA platform that replicates human usage of the device.

REGULATORY LANDSCAPE

The first pressurised metered dose inhaler (pMDI) was invented by Charles Thiel and developed by a small team at Riker Laboratories (MN, US) back in 1956 to treat asthma.[1] Since then, pMDIs have become the preferred delivery system for the treatment of lung diseases, including chronic obstructive pulmonary disease, emphysema and chronic bronchitis, because "small doses of drug are delivered directly to the site of action, leading to an onset of actions and a low incident of side effects".[2] In addition, innovation in pMDI development has led to newer delivery systems, such as dry powder inhalers (DPIs) and soft mist inhalers (SMIs), each with their own unique delivery mechanisms and benefits for patient usage and formulation compatibility (Figure 1). Furthermore, research is now underway to apply the delivery mechanisms to other therapeutic areas, such as vaccine delivery and biologics.

With the long history of generic drug approvals in parenteral and oral dosage forms, it might be expected that inhaled therapies would easily follow suit. However, due to the complexity of the relationships between device performance, formulation and patient usage, this has not been the case. Currently there are only a small handful of approved generic inhaled therapies in the US. With the approval of the first generic version of ProAir HFA

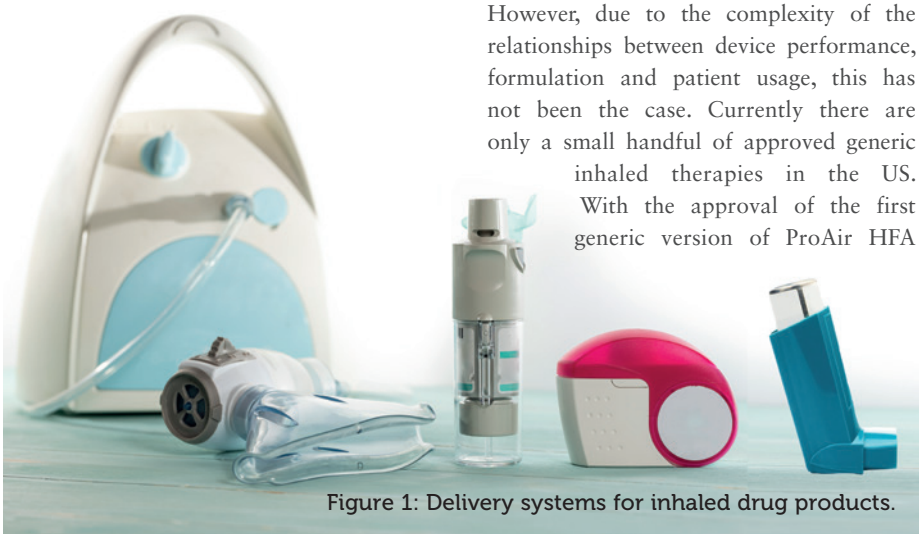

Figure 1: Delivery systems for inhaled drug products.

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(albuterol sulfate) from Teva (Tel Aviv, Israel) in February 2020, US FDA commissioner Stephen Hahn stated:

"Metered dose inhalers like these are known as complex generics, which are traditionally harder to copy because of their complex formulation or mode of delivery. As a result, many complex drugs lack generic alternatives even after patents and exclusivities no longer block generic approval. Supporting development and approval of generic copies of these complex medicines so that these products can get to patients has been a major focus of our efforts to improve competition and access and to lower drug prices. Getting more generic copies of complex drugs to the market is a key priority for how we'll help bring new savings to consumers."[3]

In accordance with this statement, there has been a dramatic shift in the regulatory landscape, allowing for more of a defined roadmap to generic approvals.

In 2007, the FDA first introduced the idea of Product-Specific Guidance (PSG), which provides specific recommendations on individual drug products as a framework to guide developers towards successful market approval. In 2017, with the release of the Generic Drug User Fee Amendments, it increased the commitment, issuing PSGs for ~90% of the non-complex new chemical entities (NCEs) that were approved on or after October 1, 2017. In addition, it offered a commitment to provide future PSGs for complex products as scientific recommendations become available. As of June 1, 2021, approximately 1,900 PSGs have been released.

For inhalation products, typically these PSGs have listed several commonly accepted *in vitro* tests that data must be provided for in a submission package for an ANDA.[4] Traditionally, these have included tests such as:

- Single actuation content through container life
- Droplet size distribution by laser diffraction
- Aerodynamic particle size distribution by cascade impaction
- Drug particle size by microscopy
- Spray pattern
- Plume geometry
- Priming and repriming.

However, as recently as May 2019, the FDA has shown a commitment to expanding this list of tests and has tasked the industry with exploring new alternative approaches to the comparative clinical endpoint bioequivalence study.[5] Some of these new tests that Proveris Scientific focuses on include characterisation of spray-velocity profiles, spray duration, propellant evaporation rates and the use of more human-realistic mouth-throat models and breathing profiles for drug deposition tests.

Figure 2: SprayVIEW measurement system SFpMDI configuration, Vereo® SFMDx and NSx automated actuators – the technology used to perform PFV, spray duration and evaporation rate measurements for pMDIs and SMIs.

PFV AND SPRAY DURATION ACHIEVED WITH THE SPRAYVIEW® MEASUREMENT SYSTEM

Proveris Scientific's SprayVIEW measurement system has long been the industry standard for measuring and analysing the spray pattern and plume geometry of spray and aerosol devices. With the addition of spray velocity and evaporation rate to the list of proposed *in vitro* tests, the technology has been adapted to perform these measurements on the same common platform. For plume front velocity (PFV), the set-up can be achieved using a standard method set-up for a plume-geometry measurement for both the SprayVIEW for pressurised metered dose inhalers (SFpMDIs) and for oral sprays (OSP) configurations shown in Figure 2.

PFV is currently available as a contract service through Proveris Laboratories and can be performed on a customer's SprayVIEW measurement system with the recent release of Viota® software at Revision 9.0. The measurement itself is

"Proveris has built into the PFV measurement the ability to calculate the spray duration of the product using the average image-intensity data for each spray."

achieved by using an image-processing algorithm to track the leading edge of the plume as it is emitted from the mouthpiece of an inhaler using image-intensity data. For each image that is taken with the camera, the system will produce a series of data points consisting of distance and time components until the plume has exited the field of view (Figure 3a). Therefore, to maximise the amount of data collected per spray, it is important to adjust the method to maximise the field of view. Once the raw data is collected, a curve fit equation can be applied to the data (Figure 3b). This allows the user to interpolate and solve for velocity at any distance or time they wish. This new functionality allows users to easily generate PFV data according to the methodology listed in the November 2020 Tiotropium Bromide PSG for SMIs.[6]

In addition, Proveris Scientific has built into the PFV measurement the ability to calculate the spray duration of the product using the average image-intensity data for each spray. The system uses an automatic algorithm to detect the start and stop times for the spray based on the image intensity (Figure 4). Alternatively, the user can switch to manual mode and drag the cursors to set the duration before saving the measurement.

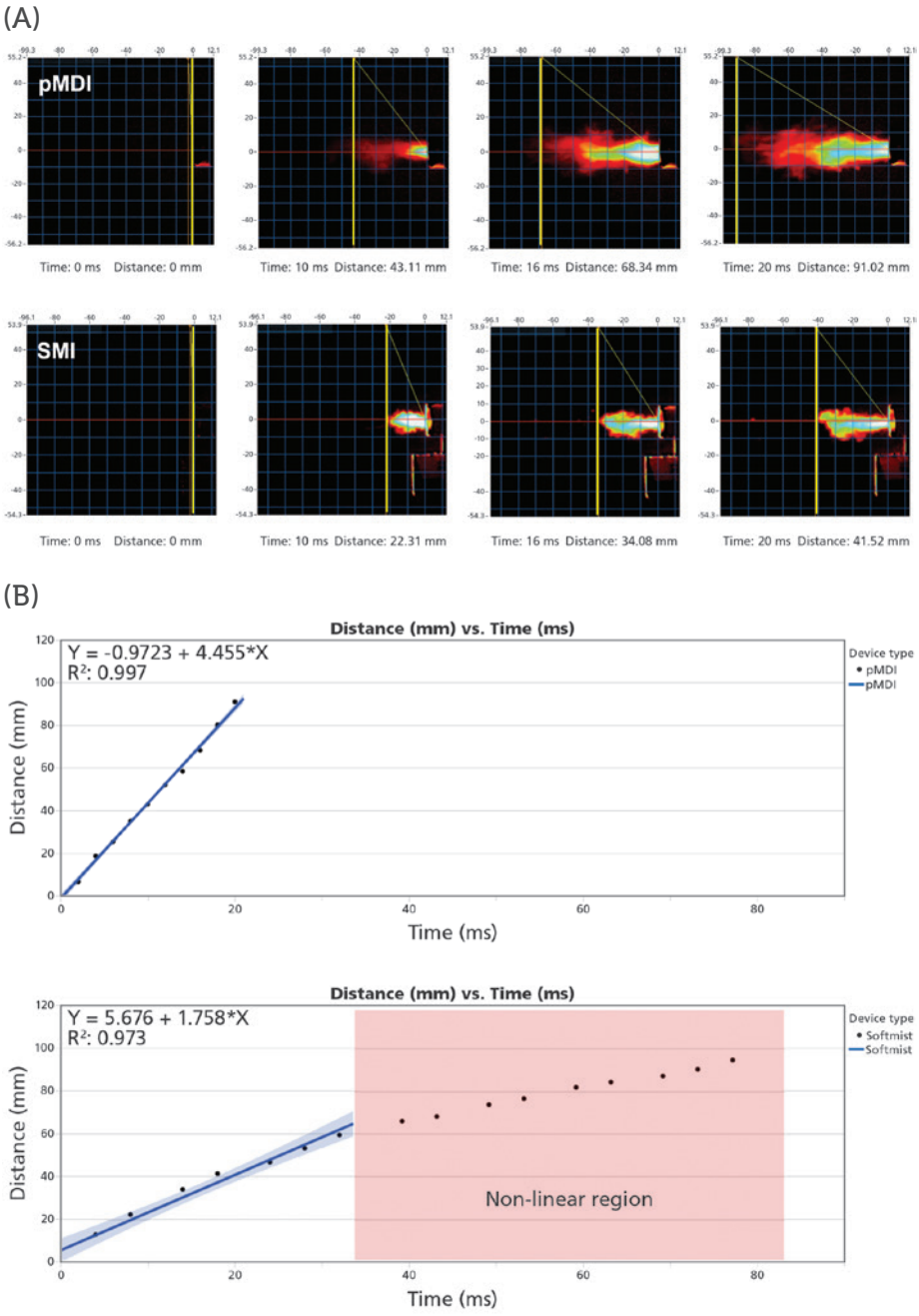

Figure 3: (A) Image captures taken with the SprayVIEW measurement system camera produce a series of data points consisting of distance and time components until the plume has left the field of view. (B) Graph plots of the distance versus time data points based on calibrated, time-synchronised plume sequence analysis.

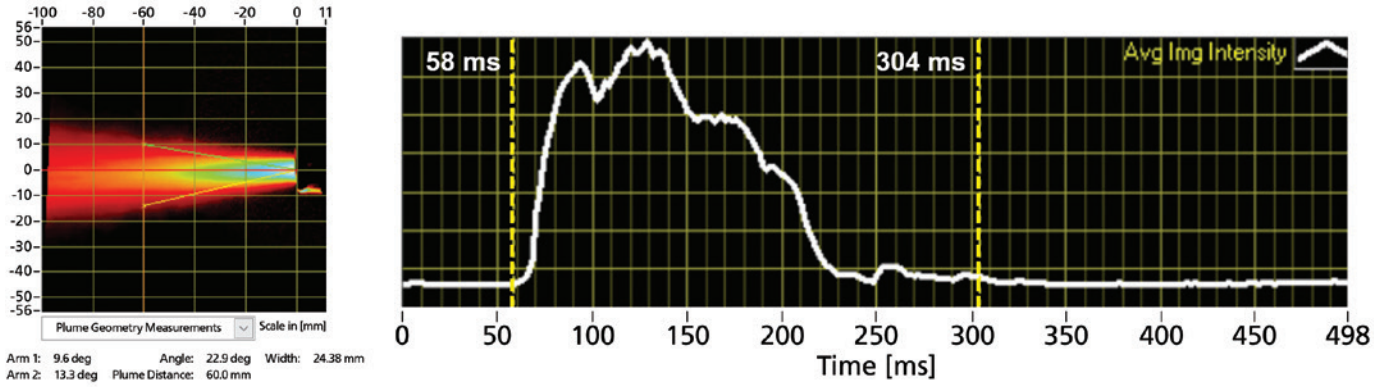

Figure 4: An example of time-averaged plume results (left) with time-synchronised intensity profile (right, white curve) indicating the spray duration (58–304 ms).

"The INVIDA platform has the potential to accelerate product development and approvals by providing the information necessary for predictive clinical outcomes and bioequivalence."

EVAPORATION RATE

Evaporation rate studies are currently offered exclusively through Proveris Laboratories as a contract service. The evaporation fraction represents the relative amount of aerosol that has evaporated at specified distances from the mouthpiece of the product. The evaporation rate is simply defined as the rate of change in the evaporation fraction with respect to time.

The methodology includes taking spray pattern images at defined distances from the mouthpieces (usually 10, 20, 30 and 60 mm). By calculating the area under the curve of the image intensity picked up by the SprayVIEW's high-speed camera, Proveris Laboratories can correlate through proprietary algorithms how much of the bulk mass of the spray has evaporated (Figure 5). This technique has proven highly informative for several customers to support their development process.

PROVERIS'S INVIDA™ PLATFORM

The INVIDA platform represents a new paradigm for *in vitro* analysis of aerosol products. By incorporating human-realistic mouth-throat models and a novel breathing simulator capable of creating complex programmable breathing profiles, both quantitative and qualitative insights into a product's performance are provided. The INVIDA platform has the potential to accelerate product development and approvals by providing the information necessary for predictive clinical outcomes and bioequivalence. This innovative technology measures the aerosol dispersion and regional deposition of inhaled drugs under simulated human-realistic conditions, enabling scientists to better understand their product's performance through visual mapping within the respiratory tract and quantitative measurements of drug deposition that are more predictive of *in vivo* performance.

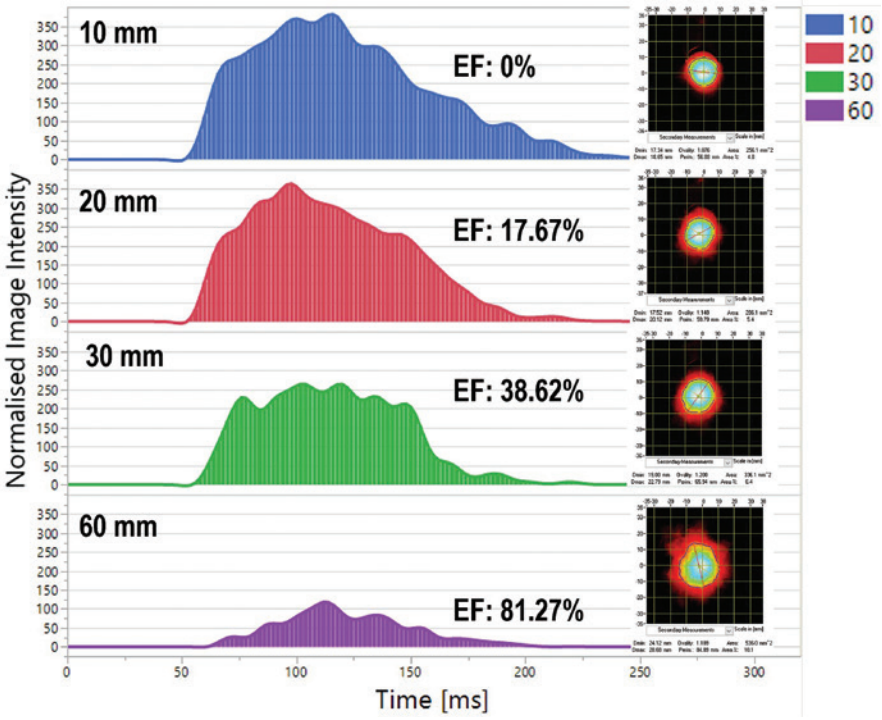

Figure 5: The area under the curve (AUC) indicates the drug mass at a certain distance from the pMDI mouthpiece: the AUC decreases as the spray aerosol moves further away from the mouthpiece because of drug mass loss due to evaporation.

The platform consists of human-realistic mouth-throat models that are capable of being swapped out for other geometries. A Vereo automated actuator is mated to the mouth to fire the drug under controlled and repeatable parameters. Downstream from the throat, there is an optical flow cell where the flow of the drug can be visualised using similar technology to the SprayVIEW system. This allows for qualitative visualisation of the aerosolisation characteristics, providing key insight into its performance throughout the entire breathing cycle. This aspect of the system can be valuable as a comparative tool when evaluating different formulations or device types.

Downstream from the flow cell is a filter, or series of filters depending on the configuration, allowing for capture of the drug product. In addition, all pieces of the mouth-throat assembly are specially coated to promote drug adherence and mimic conditions inside the lung. Humidity and temperature control of the INVIDA system replicate the high humidity conditions within the human respiratory tract. All parts in the assembly are easily disassembled and can be assayed separately to obtain a full mass balance for quantitative deposition of the API(s) in question. This data provides the development team with localised deposition of the active drug under human-realistic breathing conditions to better assess performance and complement approaches for *in vitro-in vivo* correlations.

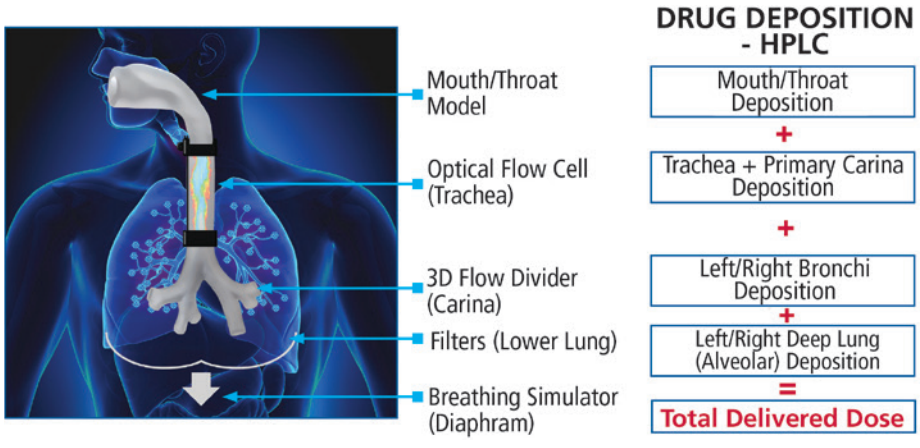

Figure 6: Schematic of Proveris Scientific's INVIDA platform.

The INVIDA system can achieve fully programmable complex profiles, including flexibility to control inhalation, hold times and exhalation, offering the ability to perform a wide range of tests. In addition, there is capability to simulate disease states including left/right lung imbalances.

When experiments are performed early in the development cycle, INVIDA can offer valuable insight into the performance of a product, allowing critical decisions to be made that could save time and money over the course of a project (Figure 6). Compared with cascade impaction, the platform offers significant potential in terms of pharmacokinetics correlation due to the human-realistic nature of the set-up.

CONCLUSION

The performance of orally inhaled and nasal drug products is affected by a combination of formulation, device and patient usage. The Proveris Scientific and Proveris Laboratories approach closely follows the approach recommended by the FDA and can save both time and resources while accelerating the time to market of these products. Alternative *in vitro* tests that are human-realistic can enable companies to make data-driven decisions and expedite product development and approval while saving time and resources. The Proveris Scientific *in vitro* testing platform INVIDA is built to replicate human usage of the product (in terms of breathing profile, respiratory geometry and environment), while minimising the gap between *in vitro* and *in vivo* performance to predict true product performance.

ABOUT THE COMPANY

Proveris Scientific Corporation delivers innovative technologies, services and expert product knowledge to a worldwide customer base of branded and generic pharmaceutical companies, device manufacturers, CDO/CRO/CMOs and regulatory agencies working with orally inhaled and nasal drug products (OINDPs). Its team of engineers, scientists and service professionals has developed a more complete understanding of the critical quality attributes affecting the performance of OINDPs, effectively controlling them from a testing and patient usability perspective.

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EXPANDING THE DESIGN OF CHARACTERISATION STUDIES FOR ACCURATE HANDLING-ERROR ASSESSMENT

In this article, Yannick Baschung, PhD, Team Leader of OINDP Development and Analytical Services at Solvias, discusses the importance of a comprehensive and accurate assessment of patient handling errors when it comes to inhaled product development.

Up to 87% of inhaler users are not using their inhaler properly.[1] Generally, simple, easy-to-use, breath-actuated dry powder inhalers (DPIs) are handled better by patients than metered dose inhalers (MDIs), which require shaking and breath-actuation co-ordination. However, the diversity of DPIs with respect to design, operating principles, order of handling steps, exact adherence to the order of handling steps and feedback to the patient means that there is significant complexity and the potential to confuse patients.

Effectively and representatively establishing the link between *in vivo* action and *in vitro* performance for orally inhaled products can represent a major challenge, as lack of treatment adherence, incorrect breathing techniques and misuse of inhalers by patients can critically affect the delivered dose and the lung deposition – and therefore the success of the treatment.

Several studies exist in which the prevalence of human error for each type of inhaler and category is described. However, the actual impact of some of these handling errors on the effective dose delivered to the patient by the inhaler remains unclear, as only common respiratory and handling errors are evaluated *in vitro*. For the prescriber, easy access to comprehensive information about device specific critical handling errors is often missing – complicating effective inhaler patient training.

HUMAN CAPABILITIES AND LIMITATIONS

When evaluating an inhaler device, the design of the product's user interface should be assessed in human factors (HF) studies, which evaluate the ability of the patient to perform critical tasks and to understand the information presented to them by the packaging and labelling, such as product labels or instructions for use, and how that informs the patient's actions – factors that are critical to the safe and effective use of the device. Consistent with a risk-based design and development paradigm, HF studies should identify critical tasks that, if performed incorrectly or not performed at all, would or could cause harm to the patient or user, where harm is defined to include compromised medical care.[2]

"For the prescriber, easy access to comprehensive information about device-specific critical handling errors is often missing."

Validated HF studies should demonstrate that the final finished device's user instructions maximise the likelihood that the product will be safely and effectively used by patients, for the intended uses in the intended use environments. Moreover, in situations where understanding the information provided by the device labelling is critical for using a product safely and effectively (for example, the user's understanding of the diagrams), a study to assess the user's understanding of such information – a knowledge task study – is appropriate.

An appropriate HF development programme will maximise the likelihood that the device's user interface is safe and effective for use by patients in the intended use environments. However, HF studies are frequently limited to assessing the device only in the context of the intended use and use environment and are not sufficient to establish the reliability of the device instructions in real-world use. Therefore,

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Step	HandiHaler Checklist Item	Item Score
1	Open top cover	100.0
2	Open mouthpiece	91.7
3	Peel open strip with capsule	76.6
4	Put capsule in inhaler	93.3
5	Close mouthpiece until click is heard	88.3
6	Perforate capsule with mouthpiece facing upward	68.3
7	Release the perforation button	75.0
8	Exhale to residual volume, not in mouthpiece	75.0
9	Mouthpiece between teeth and lips	95.0
10	Inhale slowly and deeply to make capsule vibrate	23.3
11	Hold breath for several seconds	28.3
12	Remove empty capsule	83.3
13	Close inhaler	81.7

Table 1: Patient score (percentage of patients performing the checklist item correctly) of relevant HandiHaler checklist items.

additional *in vitro* product characterisation studies (PCSs) are necessary to support the robustness and performance of the device and its labelling.

THE LIMIT OF CHARACTERISATION STUDIES AND INSTRUCTION LEAFLETS

PCSs are required by regulatory agencies for all MDIs and DPIs to characterise the optimum performance properties of a drug product and to support appropriate labelling statements, thereby contributing to patient compliance. For DPIs, alongside various stability, storage and environmental simulation studies, regulators require data on device performance for specific handling and breathing situations, such as flow-rate variation and device orientation.

Determining the emitted dose (ED) and aerodynamic particle-size distribution of the ED as a function of different flow rates at constant volume can help to evaluate the device's sensitivity to the differences in breathing profiles between patients of different age, gender and severity of disease. However, the outcome of such studies is often limited by the narrow range of flow rates tested and by the restriction to a constant volume.

Device orientation studies aim to demonstrate the performance of a DPI across various dosing orientations. However, these tests are generally limited to the likeliest scenarios of device orientation variations – +45° and -45° – and omit scenarios where severely ill and bedridden patients use their devices in vertical positions.

Handling errors common to most of the bestselling devices – such as failure to properly close the DPI before actuation, failure to release the piercing button while actuating, double piercing the capsule before actuation or shaking the loaded device – are often addressed in the device's instruction leaflets. However, their impact on product performance is rarely investigated as part of PCSs. Selestini *et al*[3] reported in their study on prescription bias and factors associated with improper use of inhalers that only 66% of DPI users received at least some instruction from their healthcare provider, regardless of whether the prescribing physician was a generalist or a pulmonologist. However, DPI users had more often read the instruction leaflet accompanying their inhaler compared with MDI users (72% and 55%, respectively), possibly to compensate for the lack of instruction by their physician.

However, the benefit of providing information, including written instructions, without any form of "hands-on" demonstration has been shown to be similar to that of not providing any information at all. Significant improvements in DPI handling technique were only observed when the educational intervention included a practical demonstration, which requires the prescriber to have a comprehensive knowledge of the device. On the other hand, poor inhaler technique, due to either a lack of instruction or leaflet reading, has been associated with more frequent hospital emergency visits, presumably reflecting a poorer control of the underlying respiratory disease.

"Poor inhaler technique, due to either a lack of instruction or leaflet reading, has been associated with more frequent hospital emergency visits."

ASSESSING THE POTENTIAL IMPACT OF HANDLING ERRORS

Van der Palen *et al*[4] evaluated patient compliance to a purpose-designed checklist specific to HandiHaler® (Boehringer-Ingelheim) after patients had received only written information. As can be seen in Table 1, breathing-related handling instructions scored the lowest, followed by failure to orient the device properly while piercing the capsule.

While these errors are usually considered by the PCS, the impact of other handling errors that could potentially impact the performance of the device, such as improper closing of the mouthpiece or not releasing piercing button, remains generally unknown. Moreover, the score for typical DPI handling errors, such as shaking the device with the capsule loaded or double piercing the capsule, were not evaluated in this study and their impact on the *in vitro* performance, which are presumably device specific, are also often unknown.

To investigate these unknowns, a study was undertaken to reproduce the respiratory and handling errors listed in Table 2 *in vitro*. The standardised HandiHaler *in vitro* testing flow rate of 39 L/min and volume of 2 L were used as a reference. Six replicate determinations were performed per ED determination and collected in a dosage unit sampling apparatus (DUSA).

Test parameter n°	Reproduced errors	*In vitro* parameters
1	Forcefully and deeply inhale through the device	Inhalation flows : 10 – 20 – 100 L/min Inhalation volume: 2 and 4 L
2	Not closing the device correctly	Device remains slightly open (no "click" sound) during actuation
3	Double piercing	Capsule pierced twice before actuation
4	Shake prior to use	Device shaken (one up-and-down movement) before and after capsule piercing
5	Maintain the piercing button	Not releasing the piercing button during actuation
6	Incorrect inhaler position	DUSA positioned vertically (90° and -90°) during actuation

Table 2: Reproduced *in vivo* handling errors and *in vitro* corresponding parameters.

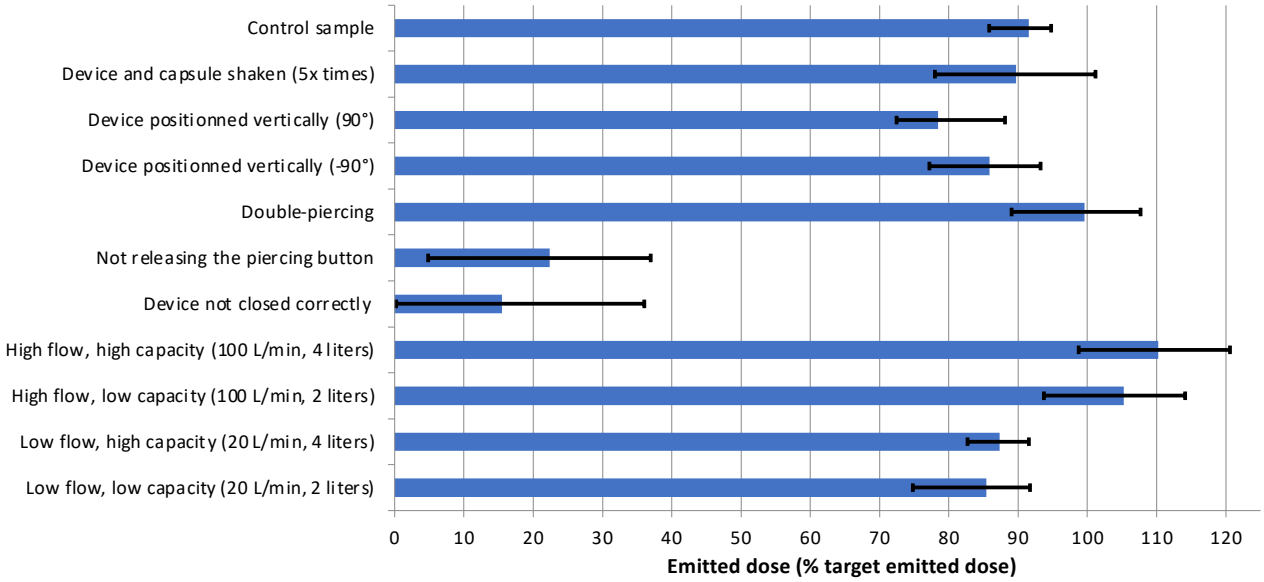
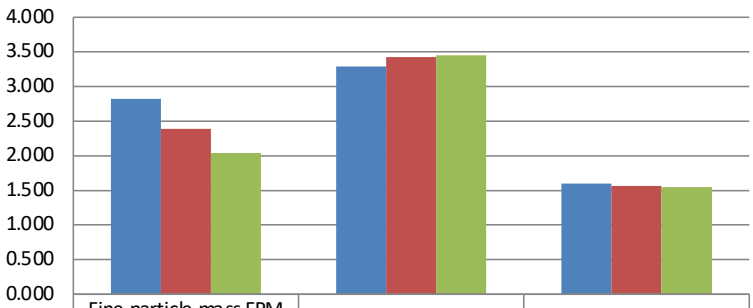


Figure 1: Impact of various handling and breathing errors on the performance of HandiHaler.

All determinations were evaluated by reversed-phase high performance liquid chromatography (HPLC). ED results were reported in percentages against the target delivered dose (TDD) of 10.4 µg reported in the Spiriva HandiHaler prescribing information.

The results of the simulations are summarised in Figure 1. A significant increase of the ED can be observed with increasing flow rate. Varying the volume of air drawn in the device from 2 L to 4 L does not significantly impact *in vitro* performance. However, tests performed at 10 L/min have shown a dramatic fall of the DPI performance (<0.4 µg ED, not shown in Figure 1). These data are illustrative of the stable performance of DPIs once critical flow of the device has been reached but also underline the critical need to monitor seriously ill patients' and children's inhalation strength when using DPIs. This aligns with the hypothesis made in Selestini's study that DPIs were less frequently prescribed to patients with severe obstruction because of physicians' fear that such patients would be unable to generate the inspiratory flow rate required for effective aerosolisation.

Among the different handling-specific errors that were reproduced, "not releasing the pressed piercing button" and "device not closed correctly" had the most significant impact on the delivered dose. The ED of these two handling errors was reduced



	Fine particle mass FPM (µg/cps)	MMAD (µm)	GSD
Control	2.825	3.29	1.60
Shaking prior piercing	2.388	3.42	1.57
Shaking after piercing	2.044	3.45	1.55

Figure 2: APSD performance of HandiHaler with a shaken capsule (one up-and-down movement) prior to and after piercing.

Risk matrix		Impact on device performance			
		Minor	Moderate	Major	Critical
		0–25%	26–50%	51–75%	76–100%
Likelihood of occurence	76–100%	3	4	4	5
	51–75%	2	3	4	4
	26–50%	2	2	3	4
	0–25%	1	2	2	3

Table 3: Handling error risk matrix.

to 22.4% ($p<0.01$) and 15.5% ($p<0.01$) of the TDD, respectively. This represents a drastic decrease that could negatively impact the efficiency of the patient's treatment, considering that these handling errors are made by up to 45% of DPI users (up to 25% for HandiHaler).[5] The ED obtained from an upright (+90°) position of the device also shows a 10% ($p=0.01$) decrease in the ED, while shaking of the loaded device before use (five up-and-down movements) and downward (-90°) actuations did not yield significantly different results from the control sample ($p>0.05$).

While the ED obtained from the control and the shaken device were comparable, the effect of the capsule being shaken prior to and after piercing led to a significant difference in the fine particle dose (FPD) delivered by the device, as summarised in Figure 2. The FPD decreased after a single up-and-down movement by 15% ($p=0.05$) prior to capsule piercing and by 28% ($p<0.01$) after capsule piercing. The significant decrease in the number of fine particles below 5 µm observed after a single up-and-down movement potentially highlights the role played by electrostatics when DPIs are erroneously manipulated and further shows the importance of controlling both the performance of the total dose delivered and the fine particle dose delivered to the lungs *in vitro*.

Overall, the results of thorough *in vitro* simulation of handling errors as part of a well-designed PCS can show the potential impact of patient non-adherence to the handling instructions presented in DPI leaflets. Although proper breathing techniques are important to achieve accurate and reproducible delivered doses, failure to meet specific items on the DPI handling checklist can lead to a drastic decrease in device performance, potentially affecting the chances of success of the treatment. Applicants or market authorisation holders should consider expanding the design space of *in vitro* testing during PCSs to cover all – or at least the most relevant – manipulation errors, as well as various respiratory capacities to obtain an accurate assessment of the impact of HF on device performance.

Usage data from HF and clinical studies allows for further assessment of the likelihood of non-adherence or manipulation errors. An evidence-based correlation of such data on likelihood and the potential impact of handling errors and variations via a risk impact matrix, as illustrated in Table 3, could drive a thorough understanding of associated risks for therapeutic effectiveness. Identifying the most critical device-handling steps can inform better instruction for patients and prescribing physicians on key handling errors, facilitate effective patient training and, ultimately, improve therapy outcomes.

"Failure to meet specific items on the DPI handling checklist can lead to a drastic decrease in device performance."

ABOUT THE COMPANY

Solvias is a world leader in contract research, development and manufacturing, providing integrated analytical services and solutions to the pharmaceutical, biotech and medical device industries. The Solvias OINDP analytical testing portfolio provides expert support across the entire OINDP development cycle on a wide range of products, such as pMDIs, DPIs, nebulisers, nasal sprays and soft mist inhalers. Comprehensive services offered by Solvias range from analysis of early-stage candidate formulations and device selection studies to bioequivalence and comparability studies, full-scale analytical chemistry, manufacturing and control programmes, including stability studies, and commercial batch release.

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ABOUT THE AUTHOR

Yannick Baschung, PhD, has more than eight years of experience in chemistry, manufacturing and controls activities, including five years in orally inhaled and nasal drug product (OINDP) development and analytical services. Currently, he is the head of the OINDP analytical services team at Solvias, where he has accompanied several products from early clinical phase to successful commercial launch. Dr Baschung is a member of the EDQM inhalation working group and holds a master's degree from the University of Bordeaux (France) and Uppsala University (Sweden), and a PhD in Biomedical Mass Spectrometry from the University of Rostock (Germany). His interests include formulation, aerosol science and drug-device combination products.

THE INFLUENCE OF UNCERTAINTY ON CHEMICAL CHARACTERISATION

In this article, James Silk, Senior Analytical Chemist at Medical Engineering Technologies, discusses the importance of accounting for uncertainty when characterising the extractables profile of a medication, with particular reference to the ISO 10993 standard.

INTRODUCTION

As is true of any measurement or experiment, analytical chemistry has uncertainties. For example, when you use the bathroom scales to weigh yourself, does the screen oscillate between two values or the arrow on the dial point between two numbers? If so, which number is correct? There is an uncertainty in the measurement of your weight to the tune of 5 g. Equally, when we say that there are 10 µg of phthalate in your sample, depending on the accuracy of the equipment and other relevant factors, we might actually be saying that it is somewhere between 9.5 µg and 10.5 µg. The ISO 10993-18 standard compels us to consider this in our analyses.

ISO 10993-18 – UNCERTAINTY FACTOR

The quantification of extractables is performed using screening methods, which need to be able to detect a large variety of possible extractables. The accuracy of the estimated concentrations can vary depending on the quantification method used. Quantification methods that use internal standards assume that all analytes give similar responses to each other, and therefore all respond in a similar way with respect to those internal standards. If this assumption is true, the estimated concentrations for all analytes will be very accurate. However, if this assumption is false – i.e. the response factors are not similar for all analytes – the accuracy of the estimated concentration will vary depending on the proportional difference in the response factor of the analyte to the response factor of the internal standard.

> "The quantification of extractables is performed using screening methods, which need to be able to detect a large variety of possible extractables."

> "The variation in response factors of extractables and internal standards is accounted for in the calculation of the AET."

There are, however, other quantification methods that provide accurate estimates for concentrations. Calibration curves can be generated for expected extractables, using the same screening method, by injecting standards over a range of known concentrations. These will give a very accurate quantification if the same compound is found in the extracts.

Another quantification method is a hybrid of the previous two, where relative response factors are obtained for expected extractables. The relative response factors are the ratio of the standards over a range of known concentrations versus an internal standard, which produces another calibration curve. This calibration curve adjusts for the variation in response factors of extractables compared with internal standards.

The variation in response factors of extractables and internal standards is accounted for in the calculation of the analytical evaluation threshold (AET). The AET is the threshold used to determine whether a chemical detected in the test sample is of a high enough concentration to be reported. The AET is only applicable to screening methods such as gas chromatography-mass spectrometry (GC-MS) and high-performance liquid chromatography-mass spectrometry (HPLC-MS). The AET should not be

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used for methods designed to identify and quantify highly toxic extractables in a cohort of concern. The following formula, taken from ISO 10993-18 Annex E, is used to calculate the AET:

$$AET = \frac{DBT \times \frac{A}{BCD}}{UF}$$

Where:

- **A** is the number of medical devices extracted to generate the extract
- **B** is the volume of the extract in mL
- **C** is the number of devices a patient would be exposed to in a day under normal clinical practice
- **D** is the concentration or dilution factor
- **DBT** is the dose-based threshold (such as the threshold of toxicological concern or the safety concern threshold) in µg/day
- **UF** is an uncertainty factor that accounts for the analytical uncertainty of the screening methods used to estimate the concentration of extractables in an extract.

Each of the variables that make up the formula for calculating the AET are easily determined when preparing the extraction, except for the uncertainty factor, which must be calculated or justified beforehand. As shown by the formula for the AET, the uncertainty factor and the AET are inversely proportional to each other – a larger uncertainty factor will give a smaller analytical evaluation threshold and vice versa. A small uncertainty factor is desirable, because it shows that the variation in response factors is low and therefore suitable for reporting data, which is the foundation of a toxicological risk assessment.

For analytical methods, where the variation in response factors of the expected extractables, applied internal standards and targeted extractables using qualified methods are all known to be acceptably low, an uncertainty factor of one can be justified. An uncertainty factor of two can also be justified for screening methods that use gas chromatography-flame ionisation detection (GC-FID) or GC-MS, as the response factors of extractables detected by these methods are deemed to be somewhat consistent. For other screening methods, such as HPLC-MS, no guidance is given by ISO 10993 for a specific uncertainty factor.

"Rather than assuming and justifying the value of the uncertainty factor to be one, two or another number, the uncertainty factor can be calculated for a specific method, which gives a more accurate value of the AET."

However, rather than assuming and justifying the value of the uncertainty factor to be one, two or another number, the uncertainty factor can be calculated for a specific method, which gives a more accurate value of the AET and, therefore, a more reliable threshold to exclude or include peaks when reporting data to be assessed in a toxicological risk assessment for that specific analytical method. To facilitate this, ISO 10993-18 has recently had an amendment on how to determine the uncertainty factor by using the following formula, which assumes a Gaussian distribution of response factors (which is not the case for all chromatographic detection methods):

$$UF = \frac{1}{(1 - RSD)}$$

Where UF is the uncertainty factor and the RSD is the relative standard deviation of the response factors from the reference database.

The reference database is an internal record of response factors specific to the analytical method that the uncertainty factor is being calculated for. These response factors are the peak areas or heights for each compound at a known concentration. One analytical method for an extractables and leachables study should have as many response factors in the reference database as there are screening methods. The RSD of a response factor can be obtained from the repeatability section of a method validation. To obtain the combined RSD for all of the compounds in the reference database, the RSDs for all of the compounds should be summed in quadrature.

The size of the uncertainty factor must not be too large or too small, as this indicates that the method being used is not suitable. A large uncertainty factor (e.g. >10) shows that the method is inaccurate and, therefore, should not be used as the basis for a toxicological risk assessment. In addition, a large uncertainty factor could give an AET that is so small that it would not be detected by the analytical method, due to it being smaller than the method's limit of detection. If this occurs, the method should be improved before it is used as the foundation of a toxicological risk assessment.

When the RSD is greater than or equal to one, which occurs when the standard deviation is greater than or equal to the mean, the uncertainty factor will equal infinity or a negative number. An analytical method with this much variation of response factors is obviously not suitable to be used as the foundation of a toxicological risk assessment and the method should be improved.

Screening for extractables and leachables is usually done using orthogonal and complementary analytical methods, such as GC-MS and HPLC-MS. This use of multiple techniques can be used to decrease

"Screening for extractables and leachables is usually done using orthogonal and complementary analytical methods, such as GC-MS and HPLC-MS."

the response factor variation and can be considered in the determination of the uncertainty factor, which is then applied to all of the complementary methods. Alternatively, a separate uncertainty factor can be calculated for each method and applied to each individual method, which gives a more accurate and specific AET than combining all of the techniques for each analytical method. Whichever is chosen, the use, value and means of calculation of the uncertainty factor used should always be justified for each analytical method used.

CONCLUSION

The purpose of chemical characterisation is to ascertain if a device is likely to be toxic or have negative effects when given to a patient, and ideally obviate the need for biological testing. The data from such an analysis is frequently used by a toxicologist to ascertain this. They will need to know how accurate the data is in relation to the AET in order to form conclusions. Here, we have shown how to quantify this as required by ISO 10993-18.

ABOUT THE COMPANY

Medical Engineering Technologies (MET) is the destination for medical and combination device batch release and design validation testing. Clients from across the globe have found the company's laboratory services to be rapid, precise and extremely effective. MET has successfully delivered testing to medical device and pharmaceutical companies in over 20 countries across Africa, Asia, Australasia, Europe and the US. MET knowledgeably, reliably and effectively delivers medical device and packaging validation, and is a world-leading CRO for combination device and prefilled syringe testing.

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ABOUT THE AUTHOR

James Silk is Senior Analytical Chemist at Medical Engineering Technologies. Mr Silk is a subject matter expert in extractables and leachables based on ISO 10993 standards, designing studies on a broad range of medical devices. He is also passionate about statistics and has become the subject matter expert in uncertainties, calculating uncertainties for analytical methods used for the identification and quantification of materials released by medical devices. Mr Silk has two years' experience at MET in performing studies measuring volatile organic compounds released by medical devices following ISO 18562-3. He obtained his Chemistry Degree at Cardiff University.

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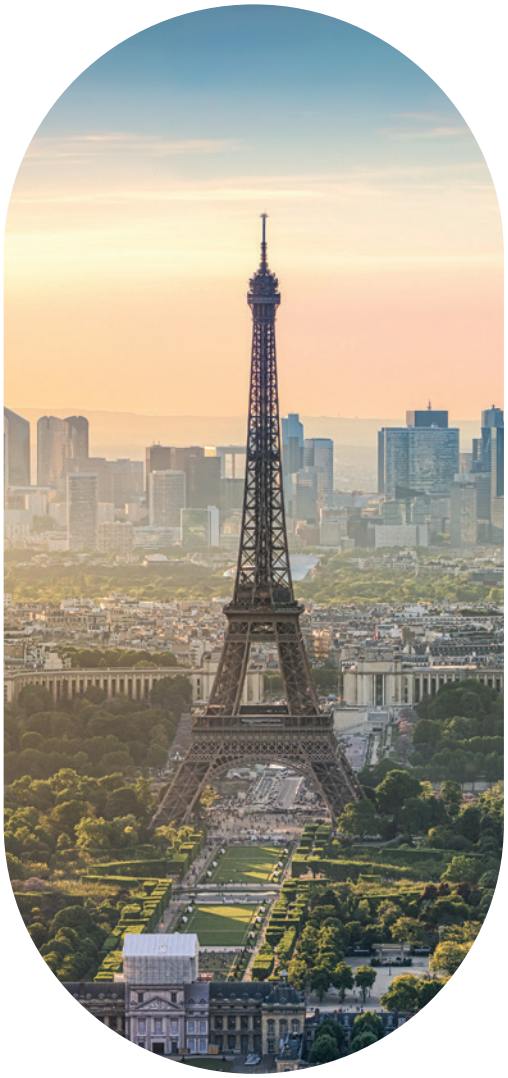

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