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EDITORIAL:

Guy Fumess, Proprietor & Publisher E: guy.fumess@ondrugdelivery.com

CREATIVE DESIGN:

Simon Smith, Creative Director (Freelance) E: simon.smith@ondrugdelivery.com

SUBSCRIPTIONS:

Audrey Furness (subscriptions@ondrugdelivery.com) Print + Digital subscription: **£99/year + postage**. Digital Only subscription: free.

ADVERTISING:

Guy Fumess (guy.fumess@ondrugdelivery.com)

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CONSIDERATIONS WHEN SWITCHING FROM CURRENT pMDI PROPELLANTS TO NEW LOWER-GWP PROPELLANTS

In this article, Mark Parry, Senior Scientific Director at Intertek, discusses the considerations that need to be made when switching from current pressurised metered dose inhaler propellants to new alternatives with lower global warming potential, including formulation, regulatory and analytical standpoints.

INTRODUCTION

As climate change continues to drive political and legislative action, many organisations are striving to achieve net zero greenhouse gas emissions. For manufacturers of inhaled medicines, this means exploring more sustainable inhaler propellants. Switching from current pressurised metered dose inhaler (pMDI) propellants to new propellants with lower global warming potential (GWP) could help to reduce the carbon footprint of pMDIdelivered medicines significantly.

The Montreal Protocols1 in the 1990s drove the migration from chlorofluorocarbons (CFCs) to hydrofluorocarbons (HFCs) to address the critical need to move away from ozonedepleting chemicals - but also started a move to lower-GWP fluorinated-gas (F-gas) propellants. Evolution of these regulations with the Kigali amendment¹ aims to further reduce the use of higher-GWP F-gas propellants and promote the development and adoption of new low-GWP propellants. The structure of these targets is phased over time and across different regions but targets an 80% reduction in the use of current pMDI propellants in the EU by 2030, providing a strong incentive to migrate to these newer low-GWP options.

DEVELOPMENT APPROACH

Addressing the Carbon Footprint

pMDIs represent a significant portion of carbon emissions in the medical sector,

with an estimated 3.1% of emissions being due to these products, according to the UK NHS.² Migration to alternative device technologies, such as dry powder inhalers (DPIs), has been suggested as a route to mitigate these risks. However, it should also be understood that the vast majority of emissions from pMDI devices are due to the propellant and reformulation to low-GWP propellants could potentially close, or even beat, the gap between pMDIs and their DPI and soft mist inhaler (SMI) alternatives.²

Understanding the overall carbon footprint of an inhaler is also more complex than just the choice of propellent gas, and companies looking to address their corporate social and environmental responsibilities need to look at the whole product lifecycle. This includes considering the production and transport of all the constituent device and formulation components, as well as distribution and disposal of the finished product. For example, inhalers make significant use of virgin-plastic materials and lack widescale recycling support. Some companies are making efforts to address this, such as Boehringer Ingelheim's development of a reusable version of its Respimat device platform, and it is important to look at the full context and complete lifecycle of a product.

Propellent Availability

The use of F-gases for pMDI products represents around 2.3% of F-gas contributions to greenhouse gas emissions,³ with the use of F-gases as a refrigerant

"pMDIs represent a significant portion of carbon emissions in the medical sector, with an estimated 3.1% of emissions being due to these products, according to the UK NHS."



Mark Parry Senior Scientific Director T: +44 1763 261 648 E: inhalation@intertek.com

Intertek Melbourn

Saxon Way Melbourn Hertfordshire SG8 6DN United Kingdom

www.intertek.com



Propellant	Structure	Ozone Depleter	GWP (CO ₂ = 1)	Atmospheric Lifetime	Boiling Point °C	Density g/mL	Dipole Moment	Solubility of Water ppm	Flammable Range	Ignition Energy (mJ)
CFC 11		Yes	4,660	55 years	23.7	1.49	0.45	100	Non- flammable	N/A
CFC 12	F F	Yes	10,800	113 years	-29.8	1.33	0.51	90	Non- flammable	N/A
HFA 134a	F F F-C-C-H F H	No	1,300	14 years	-26.2	1.23	2.06	2,200	Non- flammable	N/A
HFA 227a		No	3,350	31-42 years	-16.5	1.41	1.46	610	Non- flammable	N/A
HFA 152a	F	No	138	51.45 years	-24.7	0.91	2.26	2,200	3.7-18%	0.38
HFO1234ze	F F F	No	<1	18 days	-18.9	1.29	1.44	225	8-8.5% @30°C 5.7-11.3% @60°C	61,000

Table 1: An overview of the primary historic, current and future propellants of interest for pMDI formulations.^{3,4}

by far the most dominant use. This could suggest that continued use of these gases for medical purposes may be supported within the global targets; however, the availability of high-purity, pharma-grade propellants at reasonable prices is a result of the large-scale production of these gases to support their use as a refrigerant. As production volumes reduce, the costs and availability of pharma-grade gases will increase significantly and so, regardless of a company's broader carbon-reduction strategies, addressing the migration away from current HFA propellants will have both regulatory and commercial drivers.

Propellent Choice

Table 1 illustrates the key propellants under discussion. HFA 134a and HFA 227a are the propellants currently in widespread use for pMDI products, with HFA 134a representing the major proportion of current usage. HFA 152a and HFO1234ze are the primary new low-GWP propellant options being used in the development of new and reformulated pMDI products. Both new options provide physical properties that suggest some compatibility with the current HFA propellants – indeed, both are being used successfully by companies such as Chiesi (Parma, Italy) and AstraZeneca. The question of flammability, however, should be addressed.

HFA 152a is classified as an extremely flammable gas, with a minimum ignition energy within the range of a typical static discharge from a human. The concentration range needed for flammability does mean the risk is likely not significant for a patient in normal use, but it does present new challenges for identifying, assessing and managing the risk involved in handling the raw material and manufacturing the drug product. HFO1234ze is technically classified as non-flammable, however, it does have a flammability range at elevated temperatures and is generally classified as mildly flammable in its widespread use as a refrigerant.

While the incorporation of ethanol in existing HFA 134a-based formulations has presented some flammability challenges for current pMDI products, the particular challenges of HFA 152a may mean that significant investment in redesigning or upgrading manufacturing facilities is required to ensure that it can be handled safely. "Whichever propellent is selected, despite the somewhat similar physical properties, reformulation of existing products may not be as simple as a drop-in replacement of the new propellent."

Formulation

Whichever propellent is selected, despite the somewhat similar physical properties, reformulation of existing products may not be as simple as a drop-in replacement of the new propellent. The general principles of pMDI formulation still apply, with solution and suspension formulations achievable and currently used excipients still applicable if required.

Considering suspension formulations, it may be possible to maintain the engineered API particle size across a change in propellant. However, the stability and performance of the suspension formed will depend greatly on the physicochemical properties of the propellent, such as its density and how it interacts with the surfaces of the micronised API. Examining the sedimentation stability of salbutamol sulphate suspensions in HFA 134a, HFA 152a and HFO 1234ze showed sedimentation rates of 188±26, 226±136 and 60±24 mm/hr respectively, while HFA 227a showed creaming behaviour with the API not fully settling, likely due to the propellant's higher density.⁵

Looking at solution formulations, the produced particle size from the device will depend more significantly on the characteristics of the aerosol spray, such as droplet size. Factors like the evaporation rate, solubility and density will all have an effect and research has shown differences in droplet size and spray stability when looking at both placebo and model formulations.6 The change in propellent can also influence the API solubility and may require changes in the co-solvent levels if migrating a solution formulation. The work referenced looked also at salbutamol sulphate and beclomethasone dipropionate solubility in HFA 134a, HFA 227a, HFA 152a, and HFO 1234ze.5 Salbutamol showed no solubility in any of the propellants, while the solubility of beclomethasone dipropionate in HFA 152a was 400 µg/mL - more than twice the concentration observed with HFA 227a and three times the concentration observed with HFA 134a and HFO 1234ze.

When considering new chemical entities (NCEs), incorporating these new propellants into formulation development should be reasonably straightforward – provided that the development facilities address the increased handling risks. For reformulation projects, neither of the new propellants provide complete equivalence with those currently in use, and so a broader formulation development design should be considered to understand the specific behaviours and interactions between the API and the propellants.

REGULATORY APPROACHES

For NCE products, incorporating these new propellants into product development should be more straightforward through the relevant NDA and marketing authorisation application (MMA) routes. Some work regarding the toxicology and safety of the new propellants will need to be incorporated, and the manufacturers of these propellants are working to support these studies and establish the drug master files to support their integration.⁷

Reformulating Products

When considering the reformulation of existing products, the regulatory approach is more complex. There is no specific guidance directing the industry on how to approach these reformulation projects; however, two main approaches present themselves – either treating it as a generic or as an NDA.

Approaching as a "hybrid" generic product via a US FDA Accelerated NDA 505(j) application seems logical, as the objective is likely to replicate the current product with the new propellent. This may prove appropriate, however, modern expectations for bioequivalence have continued to develop and expand since some of the original products were developed.⁸

The successful approval of inhaled generic products continues to prove challenging for the industry with only a handful of generic pMDI products on the market, highlighting the difficulty of demonstrating equivalence even without a change in one of the key formulation elements. With the major formulation component - the propellant - changing to a new material, the generic-like approach is potentially a significant challenge, due to the evolving toxicological and safety positions for these new propellants, the likely need to change other elements of the formulation to provide clinical equivalence and the likely change in spray characteristics that may impact in vitro equivalence.

Approaching the product as an NDA is likely to be the more prevalent approach for these products, even though the API has an established safety and clinical data profile. Looking back to the CFC-to-HFA migration that started in the 1990s, this was generally the approach taken for those products. This provides the space to address more significant changes in formulation, while still using data from the existing approved product; however, it does mean a significant increase in expected costs and timelines overall.

The ecological urgency that drove migration away from CFC use is less prominent here and, even then, full replacement of the CFC pMDI market in the US took until 2014 to complete⁹ – 25 years after the initial experiments with HFA-based formulations and 18 years after the 1996 target in the Montreal Protocol for the end of all non-exempted use. The regulatory

"Engaging early with the relevant regulatory parties and understanding the likely scope of the changes that are needed for a given product will be a key factor in ensuring that the development process is as focused, pragmatic and efficient as possible."

position surrounding these reformulation projects is still evolving but, given the targets of the latest amendments to the F-gas regulations, it is likely regulators will continue to take a measured, but conservative, approach to reviewing these products. Engaging early with the relevant regulatory parties and understanding the likely scope of the changes that are needed for a given product will be a key factor in ensuring that the development process is as focused, pragmatic and efficient as possible.

ANALYTICAL CONSIDERATIONS

When looking at the reformulation of an existing product, there is also a need to review the analytical methodology and overall chemistry, manufacturing and controls approach. Even if there are no significant changes in the analytical strategy, improvements in technology may yield improvements in method reliability, consumable use and overall turnaround time that can have a significant positive impact on the costs of the analytical activity.

With changes being made to the formulation, a suitable validation gap analysis of methods will be required, even if no changes are made to the procedures. These methods will underpin the generation of significant volumes of data, such as product characterisation, stability and *in vitro* bioequivalence work, so any validation should be addressed early in the process. Depending on the development and regulatory approach taken, it may be possible to use data from the existing product; however, care should be taken to ensure these data are evaluated against the current regulatory expectations.

Generics and In Vitro Bioequivalence

Whether or not a generic approach to the regulatory pathway is taken, understanding the current expectations and techniques used for building a strong understanding of *in vitro* bioequivalence is valuable. Current regulations still have an understanding of emitted dose and aerodynamic particle size at their core, but also include expectations for equivalence in priming and re-priming behaviour, spray pattern and plume geometry, which may prove more challenging to meet with a change in propellant.

Beyond the core regulatory expectations, considerable work has been undertaken to expand the range of analytical tests addressing in vitro-in vivo correlation, with the aim of both de-risking and reducing the need for clinical studies for generic product developments. Even if the generic approach isn't being followed, these can provide additional insight into product performance during development and how the product might perform in the clinical setting. For pMDIs in particular, the use of spray pattern/plume geometry testing,¹⁰ as well as plume velocity and actuation force measurements,11 can generate key insights into aerosol and device performance.

Other developments, such as the incorporation of physiologically relevant throat models and breathing profiles, as well as the use of morphologically directed Raman spectroscopy,¹² have provided key advances – in particular for DPI products – that may also provide useful insights here.

CONCLUSION

There is a combination of environmental, regulatory, commercial and ethical drivers pushing the industry towards adopting lower-GWP propellants for pMDI products as part of the overall management of their carbon footprint. The availability of new propellants, such as HFA 152a and HFO 1234ze, is scaling up with new

ABOUT THE AUTHOR

manufacturing plants for both coming online in the last year. Both are well positioned for broad market adoption, although the handling risks of HFA 152a in particular will need to be addressed to incorporate these into existing manufacturing facilities safely.

Work looking to formulate products using these new propellants has shown them to be viable replacements, but also highlights that there will be development challenges to address in migrating existing products. The regulatory position is still developing for these reformulation projects, and collaboration and consultation between regulators and businesses will be important in developing best practices and expectations in this area, and ensure the commercial feasibility of an important legislative drive to tackle climate change.

ABOUT THE COMPANY

With 30 years of experience in supporting clients' orally inhaled and nasal drug product development, Intertek provides support for small and large molecules across all respiratory delivery technology platforms from its GMP-compliant laboratories. With continual investment, Intertek has focused on expanding its analytical capabilities, integrated with formulation development and stability studies, to help enable its clients' key decisionmaking activities throughout the product development lifecycle. Intertek offers formulation development, including particle engineering approaches, with specialist support for biologics and DNAbased medicines, clinical manufacturing, independent device screening/selection, CMC package support, ICH stability testing, QC and GMP batch release testing, in vitro bioequivalence studies and GMP IV-IVC tools (MDRS, inhaled dissolution, idealised inlet models and realistic breathing profiles for impaction testing).

Mark Parry has worked with Intertek for over 20 years since graduating from Cambridge University (UK) and currently works as the Senior Scientific Director, supporting the wide range of analytical, formulation, product development and research activities across the company. Mr Parry has worked in a range of pharmaceutical analysis and formulation development areas, with a particular focus on inhaled and nasal drug products. Mostly working in the pre-approval stages, Mr Parry's background includes extensive experience with product and formulation development, as well as method development and validation, stability studies and pharmaceutical development activities for a wide range of clients across the pharmaceutical industry.

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NAVIGATING pMDI REFORMULATION 2.0

In this article, Chris Baron, Director of Business Development at Aptar Pharma, and William Ganley, PhD, Head of Computational Pharmaceutics at Nanopharm, an Aptar Pharma company, examine possible responses to the environmental impact of pressurised metered dose inhalers use and consider alternative inhaler types, with a focus on the strategies and support that can accelerate the development of the next generation of pMDIs.

In 2019, it was estimated that asthma affected over 250 million people worldwide, causing 455,000 deaths.¹ Such statistics put into context the criticality of pressurised metered dose inhalers (pMDIs), our costeffective, frontline defence for common respiratory disease. Estimates for 2020 indicate that close to ~70% of portable inhaler sales (by volume) were pMDIs, and that pMDIs accounted for >95% of rescue medications.² Even as we recognise our responsibility to minimise the environmental impact of pMDI use, we must acknowledge their value in preserving life and quality of life. Ensuring continuity of treatment and patient safety is critical as we work towards more sustainable pMDIs.

Concerns over the environmental impact of pMDIs are not new. The signing of the Montreal Protocol in 1987 triggered industry-wide reformulation to phase out chlorofluorocarbons (CFCs), ushering in the use of more environmentally benign hydrofluorocarbon (HFC) propellants. Now, we have aggressive and challenging targets to phase down the use of high global warming potential (GWP) products and the reformulation cycle is underway once more. Key players such as Chiesi, AstraZeneca and GSK have announced ambitious plans to reduce the carbon footprint of their pMDI products by upwards of 90% in the next few years by switching to alternative low-GWP propellants, which have a much lower carbon footprint.

This article examines possible responses to the environmental impact of pMDI use and considers the pros and cons of alternative "Ensuring continuity of treatment and patient safety is critical as we work towards more sustainable pMDIs."

inhaler types and lessons to be drawn from earlier reformulation activities. A key focus is on the strategies and support that can accelerate the development of the next generation of pMDIs, including the end-toend services available from Aptar Pharma.

ARE pMDIS THE ONLY ANSWER?

Given the availability of alternative inhaler platforms, it is reasonable to ask whether simply reducing our reliance on pMDIs would be the best way forward.

A switch to dry powder inhalers (DPIs) is an obvious potential solution since this is well-established propellant-free technology with a correspondingly lower CO_2 footprint, however, the net CO_2 footprint will be dependent on the design/type of DPI and the complicities of the respective manufacturing processes. DPIs undoubtedly have some compelling attractions. They enable the delivery of larger drug loadings and capsule devices, in particular, are relatively inexpensive.

For pharmaceutical companies, both multidose and reservoir DPIs provide considerable opportunity for establishing high-value intellectual property (IP) but the corollary for healthcare providers



Chris Baron Director Business Development T: +33 2 3209 1437 E: chris.baron@aptar.com

Aptar Pharma Avenue des Falaises 27100 Le Vaudreuil France

www.aptar.com/pharmaceutical



Dr William Ganley Head of Computational Pharmaceutics T: +44 1633 372 000 E: w.ganley@nanopharm.co.uk

Nanopharm UK Ltd Franklin House Grange Rd Cwmbran NP44 3WY United Kingdom

www.nanopharm.co.uk

is high cost and a multiplicity of device designs. Consequently, interchangeability and patient experience can be a major concern with respect to patient adherence and compliance. Switching a patient from a pMDI to any DPI requires care, training and monitoring to ensure ongoing, effective health management and, crucially, DPIs are not suitable for all patients or for rescue medication. Patients with compromised or reduced inspiratory effort may not have sufficient inspiratory flow rate to trigger the DPI, compromising dose delivery.

Soft mist inhalers are an alternative. These use propellant-free technology to generate a mist of fine droplets of consistent size and have a low CO_2 footprint relative to pMDIs. Patient experience is more akin to a pMDI, but cost is an issue and the technology is restricted to solution formulations, limiting application to drugs with appropriate solubility.

In summary, while we may be able to increase our use of alternative devices, notably for health maintenance, reformulating pMDIs with more sustainable propellants is vital, particularly for low- to middle-income countries and for the trusted delivery of rescue medications. Success will deliver safe therapeutics with an acceptable $\rm CO_2$ footprint in a design familiar to patients, at accessible cost.

MEET THE NEW PROPELLANTS

HFA 152a and HFO 1234ze are currently the leading low-GWP propellant candidates for pMDI reformulation. Table 1 summarises their key properties.

Turning first to HFA 152a (1,1 difluoroethane), this has a GWP >90% less than current propellants and has come up clean in a two-year toxicology programme (Lovelace Biomedical, NM,

US, sponsored by Koura, MA, US). A US FDA Drug Master File (DMF) was scheduled to be in place by the end of 2022, facilitating its use for reformulation activities. Flammability is a safety concern, primarily for manufacturing, but issues are manageable, albeit at additional cost.

HFO 1234ze (1,3,3,3 tetrafluoroprop-1-ene), the alternative candidate, has an even lower GWP and an associated potential to reduce the CO_2 footprint by ~99%. A DMF has already been submitted to the FDA, allowing companies to file IND applications, and GMP-grade HFO 1234ze is now available for testing and in commercial quantities. Toxicology data has been reviewed by the FDA, and Phase III studies are planned (Honeywell).

These two propellants are promising candidates for substitution. So, are there lessons to be drawn from the transition from CFCs to HFCs to accelerate progress towards their commercial use?

WHAT CAN HISTORY TEACH US?

There is a balance to be struck when reformulating between a "copy and paste", minimally disruptive approach, and taking the opportunity for significant product improvement. If we can establish a clear definition of the target product profile, then there is potential to simultaneously enhance other aspects of device and formulation performance. For example, in the last transition we learned that the inclusion of ethanol enabled smaller metering volumes. Duplicating this effect in the current phase down could magnify the CO₂ footprint reduction associated with propellant substitution. Switching to, for example, primeless valves would similarly augment environmental gains and, at the same time, ease patient use. Patient

Propellant	Formula	B. Pt °C	Density @20°C g/mL	Ozone depleting potential	Global warming potential $(CO_2 = 1)$
CFC 11	CFCI ₃	23.7	1.49	1	4,660
CFC 12	CF_2CI_2	-29.8	1.33	1	10,800
HFA 134a	CF ₃ -CFH ₂	-26.2	1.23	0	1,300
HFA 227a	CF ₃ -CFH-CF ₃	-16.5	1.41	0	3,350
HFA 152a	CF ₂ H-CH ₃	-24.7	0.91	0	138N
HFO1234ze	CF ₃ CH=CHF ₃	-18.9	1.29	0	<1

Table 1: Key properties of original CFC pMDI propellants, HFC replacements and next-generation low-GWP candidates.

"Patient adherence and compliance could be further improved through the increased adoption of, for example, dose counters, breath-actuated inhalers and connectivity."

adherence and compliance could be further improved through the increased adoption of, for example, dose counters, breathactuated inhalers and connectivity.

The shift to HFCs brought considerable challenges with respect to formulation stability and IP linked to the use of specific surfactants. In this respect, HFA 152a and HFO 1234ze appear to present a lesser challenge with behaviour somewhat similar to the currently used HFCs. Key formulation decisions to take this time centre on:

- Whether to develop a suspension or solution
- The extent of ethanol inclusion
- The impact of any inactive ingredients included.

Addressing the flammability of HFA 152a is also a focus as attention moves to filling/manufacturing, but propellant suppliers are more involved in the reformulation process this time around, which may be particularly helpful when it comes to tackling this issue.

TRACKING THE IMPACT OF REFORMULATION FROM ACTUATION TO EFFICACY

Against this background of clear motivation and targets, and armed with learnings from the past, we can look in more detail at the reformulation process. Despite considerable advances in our understanding of pMDIs over the last 20 years, the challenge remains significant.

Figure 1 shows the network of interrelated issues associated with development, use and commercialisation of a pMDI. The metering valve is rightly a primary focus, necessarily optimised in combination with the evolving formulation, taking into account all associated componentry and the intended manufacturing process. For instance, will the metering chamber volume need to be fine-tuned to deliver an equivalent



Figure 1: Reformulation involves rigorous and systematic consideration of a network of interacting factors centred on the formulation, the device and the manufacturing process.

dose to the existing pMDI product? Are there interactions between the proposed formulation and the closure containment system and actuator that necessitate a change of material or alternative approach? Is the valve compatible with a filling and crimping process that is appropriate for the new formulation? Wrapped around the central optimisation challenge is the need to develop a robust regulatory package and to recognise the influence of patient practice and technique.

Optimally leveraging in vitro and in silico methods to access the information required to progress is essential and can be difficult. This is where SmartTrack[™] can help. SmartTrack is a toolkit that draws together Aptar's collective expertise to accelerate pMDI reformulation projects. In vitro tests are packaged in Smart Track, which generates clinically relevant data, with in silico models that simulate lung deposition and pharmacokinetics (PK). Using the results, key activities can be accelerated, such as dose-ranging studies and excipient selection and, ultimately, minimise the number and size of clinical trials required to support commercialisation.

Tools and techniques earn their place in a pMDI reformulation toolkit by providing information that promotes faster, more secure progression. The following are used with SmartTrack:

 Particle image velocimetry and phase Doppler anemometry (PDA) to quantify plume dynamics and elucidate interactions between the device, inhalation profile, co-ordination and oropharynx that define behaviour in the initial stages of drug delivery

- Aerosol testing with anatomically realistic mouth-throat models and representative breathing profiles to study the deposition of drug particles
- Algebraic and computational fluid dynamic models to model the deposition of drug particle transport and deposition in the airways
- Microstructural characterisation and combined dissolution/permeability studies to investigate release of the active drug substance, post-deposition
- Validated physiologically-based PK (PBPK) models to predict clinical outcomes for specific patient populations from *in vitro* inputs
- Accelerated stability testing and extractable/leachable profiles to detect and mitigate stability and device component compatibility issues as early as possible.



Figure 2: Beclomethasone is markedly more soluble in HFA 152a than in alternative propellants.



Figure 3: Propellant choice directly influences plume dynamics notably with respect to changes in droplet size as a function of distance from the mouthpiece (left).

"Solubility of the active drug substance directs towards formulation as either a solution or suspension."

Let's take a closer look at some of the data already generated using these, and other complementary tools, to gain insight into the physicochemical properties of lower GWP propellants and support reformulation activities.

Study 1: Exploring Drug Solubility

Figure 2 shows solubility data for beclomethasone in current and nextgeneration propellants measured using high-pressure nuclear magnetic resonance.

Solubility of the active drug substance directs towards formulation as either a solution or suspension. For solution formulation, solubility influences the need for co-solvent while, in a suspension formulation, it controls particle size stability. Here, beclomethasone was found to have substantially higher solubility in HFA 152a (400 µg/mL) than in the other three propellants – signposting an opportunity for solution-based formulation with relatively low levels of co-solvent.

Study 2: Investigating Droplet Dynamics

Figure 3 shows droplet size and velocity data for four placebo propellant-only formulations measured as a function of distance from the mouthpiece, using PDA, at a test flow rate of 30 L/min. Data were also measured under no-flow conditions (not shown). Droplet size and velocity impact aerosol evaporation rate in the earliest stages of drug delivery, thereby affecting drug deposition in the airways. Under no-flow conditions (0 L/min) plume dynamics were closely comparable with all propellants but at 30 L/min (the rate specified for compendial testing for pMDIs) there are clear differences. Lower-GWP propellants result in larger droplets close to the mouthpiece, although this trend does not persist; larger droplet sizes are recorded at greater distances with HFA 227 and HFO 1234ze. In summary, a somewhat complex and differentiated pattern in droplet size evolution emerges, which may be helpful in elucidating deposition in the mouth and throat and determining what reaches the lung.

Plume velocity trends are simpler with velocity decaying with all propellants as a function of distance from the mouthpiece; HFA 152a exhibits the slowest decay, HFA 227 the fastest.



Figure 4: All propellants produce droplets carrying a net positive charge, but low-GWP propellants are highly differentiated; HFA 152a is associated with a high net charge while HFO 1234ze results in particles with minimal charge.

"During propellant evaporation, droplets may acquire charge, which can influence deposition behaviour, notably in the deep lung."

Study 3: Investigating Net Charge

Figure 4 shows charge data for droplets produced with each of the propellants, as a function of droplet size, measured in collaboration with the University of Sydney (Australia) using a bipolar charge analyser.

During propellant evaporation, droplets may acquire charge, which can influence deposition behaviour, notably in the deep lung. In this experiment, all propellants were found to produce a net positive charge on finer particles, but the magnitude of that charge varied significantly. HFA 152a resulted in the highest net charge with HFO 1234ze, in contrast, resulting in a net charge close to zero.

Further measurements identified a direct correlation between the water content of the propellant and net charge. A corresponding hypothesis is that the rapid temperature drop associated with propellant evaporation causes the formation of ice crystals that carry a charge, potentially the charge measured by the test.



Figure 5: Sedimentation rates for albuterol sulfate are relatively high in low-GWP propellants.

It is worth noting that water content is a function of the as-supplied propellants, so while these results may not indicate that the propellant droplets themselves are charged, they undoubtedly have implications for formulation.

Study 4: Exploring Sedimentation Rate

Figure 5 shows sedimentation data for HFA 134a and the two lower-GWP propellants measured for albuterol sulfate formulations, analogues of a commercial albuterol sulfate formulation (Ventolin, GSK) made with alternative propellants. These formulations were not optimised – the propellants were simply switched out to assess their differences.



Figure 6/Table 2: Regional Deposition Modelling using 1-D Lung Models.

Study 5: Assessing Drug Deposition

Figure 6/Table 2 shows drug deposition data for the commercial and analogue albuterol sulfate formulations. Cascade impaction was carried out using a realistic mouth-throat interface to determine aerodynamic particle size distribution (APSD) metrics, which were then used in an algebraic lung deposition model to compare likely drug deposition profiles.

These tests provide insight into how the observed physicochemical differences manifest in drug delivery performance. Relative to Ventolin, the HFA 152a formulation delivers a lower emitted dose (ED), potentially because of its lower density, but a comparable fine particle fraction (FPF). With HFO 1234ze, ED is closer to that of the reference product, but FPF is substantially lower. Plume dynamics and flocculation both provide a possible rationale (Table 3).

The modelling results illustrate the implications of these metrics for drug deposition. Both low-GWP propellants result in markedly reduced drug delivery to the deep lung, the outer, darker coloured region in each image, with the HFO 1234ze formulation substantially increasing the extra-thoracic dose, the dose depositing in the mouth and throat (see Figure 6).

THE WAY FORWARD

Our reliance on pMDIs, particularly for emergency treatment, makes them essential. Reformulation to deliver a lighter CO_2 footprint is therefore critical within the constraint of safeguarding patient health. Collectively we have tackled extensive pMDI reformulation before but, this time around, we have more knowledge to guide us and better

Formulation	ED/µg	ISM/µg	MMAD/µg	GSD	FPM/μg <5μm	FPF/%
Ventolin	111.12	72.04	2.22	2.26	54.27	58.68
Albuterol HFA-152a	105.32	65.79	2.13	2.50	50.18	58.70
Albuterol HFO-1234ze	108.91	51.00	2.29	2.60	38.32	34.89

Table 3: APSD metrics and deposition modelling highlight the poor performance of the unoptimised HFO 1234ze formulation relative to the commercial analogue; HFA 152a produces drug delivery performance intermediate between the two.

tools to use. Aptar Pharma is already using its skills to characterise the most promising low-GWP propellants for reformulation and develop technology to deliver their potential. By providing customers with cutting-edge expertise and tools to accelerate and improve every step of the reformulation journey, the company is reducing the work and risk involved in commercialising the next generation of pMDIs.

For more information about sustainable pMDIs, visit: https://www.aptar.com/ resources/investigating-the-propellantpathways-leading-to-a-sustainable-futureof-mdis

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, 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 leading provider of tailored analytical and drug development services, with a focus on orally inhaled and nasal drug products. The company's unique processing technologies and formulation development tools enable seamless translation of preclinical development through to clinical manufacturing. Nanopharm's integrated development services in materials characterisation, formulation development and inhaled biopharmaceutics aids successful product development by understanding how material properties and processing conditions influence product functionality.

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ABOUT THE AUTHORS

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

William Ganley, PhD, is Head of Computational Pharmaceutics at Nanopharm, an Aptar Pharma company, where he is responsible for developing *in silico* methodologies and data analytics services to support OINDP companies through clinical development to regulatory approval. Holding an MChem from the University of Southampton and a PhD from the University of Bristol, Dr Ganley has presented work on physical chemistry and pharmaceutics at multiple international conferences and published several peer-reviewed articles. He was awarded the Faculty of Science Prize for Physical Sciences and the Best Doctoral Research Thesis Prize by the Faculty of Science for his PhD.

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DUE DILIGENCE – THE KEY TO SUCCESS IN DRUG DELIVERY DEVICE SELECTION

In this article, Matt Jones, Senior Sector Manager – Medical and Scientific, and Rob Veasey, Senior Sector Manager – Medical and Scientific, both at DCA Design International, consider the process of matching the drug with the right delivery device and look at the importance of due diligence when "licensing in" technology.

One of the first questions a pharmaceutical or biotech company should ask when bringing a new pulmonary or intranasal drug to market is whether they should "make" their own custom delivery device for it or "buy" a technology from a specialist delivery device developer.

Developing new drug delivery devices, or improving existing ones, is important to continue to improve the efficacy and reliability of treatments, as well as to increase the compliance of patients with their treatments. The regulatory pathways are set up to reflect this ethos of continual improvement - what was acceptable in the past may not be anymore. However, if devices are already available that are suitable for a new drug, "licensing in" device technology can be a preferable option. This is because, depending on the quality, maturity and suitability of the device and vendor, it can be quicker, lower risk and require less up-front investment, but this is a route that requires careful consideration to help ensure success.

While buying a device technology might theoretically offer a lower up-front investment and quicker route to market than developing one in-house, there are typically still significant sums of money involved, and choosing the wrong device can risk encountering major problems. There have been several instances where pharmaceutical companies have made a bad device choice and subsequently needed help to resolve fundamental design issues. In

"It is essential to go much further than simply comparing potential feature sets or reviewing key performance aspects on paper."

> these cases, there have often been significant programme delays and serious financial implications arising from the need to make late-stage changes.

> There is a clear lesson to take from this: when selecting a delivery device, it is essential to go much further than simply comparing potential feature sets or reviewing key performance aspects on paper. It is important to have a thorough and effective process and to consider engaging an independent specialist with the right expertise in device development, who can review and understand potential risks at a deep technical level and provide suitable advice.

THE RIGHT APPROACH TO DUE DILIGENCE

Because the reviewer needs to be able to evaluate complex technical issues, an effective approach to due diligence for device selection relies on the same skillset and experience as delivery device design and development. The key difference is that at least some of the device design data has already been generated.





Matt Jones Senior Sector Manager – Medical and Scientific T: +44 1926 499461 E: matthew.jones@dca-design.com



Rob Veasey Senior Sector Manager – Medical and Scientific T: +44 1926 499461 E: rob.veasey@dca-design.com

DCA Design International Limited 19 Church Street

Warwick CV34 4AB United Kingdom

www.dca-design.com

"It is important for the device customer to determine the outline of a best practice development process, helping to establish the right expectations."

At the outset, it is important for the device customer to determine the outline of a best practice development process, helping to establish the right expectations. This outline can then be populated with the product information, documentation and evidence available from the supplier, after which key gaps can be identified.

Alongside this development process framework, a robust, evidence-based set of requirements for the device is required. As far as possible, these should be determined independently of the capabilities of any candidate devices and be free from "outside influences", such as marketing materials or industry hype. They should be based on a suitable understanding of factors, such as the intended dosing regimen(s), the specific needs of the target user population (dexterity issues in geriatric populations, for example), the potential future drug portfolio and pipeline (when evaluating a device platform) and issues with similar devices on market.

Next, a systematic risk assessment of candidate device performance and manufacturability should be undertaken. As an example, this assessment may ask questions such as those shown in Figure 1. The full list of questions for a given project will be much longer and should be tailored to the established requirements. Answering such questions will help generate an understanding of potential issues associated with a candidate device and allow for clearer judgements on the likelihood of potential delays or risks to the drug launch programme.

The key to success here is to have the support of a team with expertise and experience in drug delivery device development who can set out the process framework, establish the requirements and ask the right questions in a risk assessment to establish the suitability of a given

"Choosing a delivery device is an expensive and long-term commitment, so it is important to invest in the expertise that will ensure due diligence is properly performed."



candidate device. This expertise will need to encompass a range of disciplines, including usability, design, engineering, evaluation and, increasingly, software and electronics, all with specialist knowledge of the medical sector.

IS THIS REALLY NECESSARY?

It can be argued that, once a pharmaceutical company has chosen a device, the responsibility for ensuring its successful journey to market lies with the device developer. However, the reality is that no matter who bears responsibility on paper, once a pharmaceutical company has "bought in", it is they who will primarily suffer the consequences of any failures or issues. These can be extremely serious – from lost investment and fines, through to reputational damage and launch delays (which, in themselves, could potentially lead to significant revenue loss or even losing the opportunity to participate in the market).

While it might seem appealing to rely on the expertise of the designers of the candidate devices, it is critical to delve deeper than the marketing pitch for each potential device and draw unbiased conclusions on its suitability for the intended application and any potential development risks it might pose. Choosing a delivery device is an expensive and longterm commitment, so it is important to invest in the expertise that will ensure due diligence is properly performed.

KEY FOCUS AREAS FOR EVALUATING DEVICES

During the device selection process, the specific areas of focus will depend on the requirements of the project. However, there are some common issues that regularly arise when licensing or purchasing "off-the-shelf" technology, which can be worth considering during initial evaluations.

Focus on Small-Scale Manufacturing Process

Often, devices are designed with an exclusive focus on prototype manufacturing processes, the priority being to produce functional demonstrators and gain investment, with not enough consideration given to the process of manufacturing in larger volumes (Figure 2). This can manifest in a number of ways.

The first is that the component variation introduced when scaling-up to multicavity tooling can result in impaired device



functionality or assembly issues. These issues can often be traced back to an incomplete or incorrect tolerance analyses. For example, some years ago, a pharmaceutical company requested a review of the design of a nasal spray device that was urgently needed for a clinical trial. The device was in multicavity production-ready tooling, but was found to perform erratically, with significant variation and degradation in spray performance over the intended operating life. The root cause was identified as a tolerance problem with the actuating mechanism. This had not been evident in earlier singlecavity prototypes because the combination of component geometries had been favourable and had, therefore, been This overlooked. demonstrates the importance of scrutinising tolerance calculations for accuracy and completeness as part of the due diligence process.

The second is that the device components have not been designed with considerations for automated assembly. Component geometry may not incorporate the necessary features to enable efficient and effective feeding, gripping and manipulation with automated equipment. The interaction features may not have been designed with the speed and forces involved in automated assembly in mind, resulting in high scrap rates or unexpected damage during manufacture. For semi-manual lines, inadequate consideration may have been given to incorporating in-line checks and mitigating the possibility of human error.

The third is that a developer may not have given due consideration to control of the manufacturing process and supply

Figure 3: Work done to explore usability and design risks should be examined.

chain. There should be an appropriate level of traceability for the raw materials (including pigments, paints and adhesives, for example) and the component manufacturing and assembly process parameters should be controlled and optimised. While an understanding of the level of scrutiny placed on these issues can be gleaned from the available documentation, manufacturing site visits can be one of several additional "tools" that can be highly beneficial for gaining further insight.

Usability and Design

It is important to establish whether the risks associated with user error, misuse and malfunction have been thoroughly considered, tested and transparently reported (Figure 3). To assess this, it is essential to start by determining

whether the device developer has conducted a sufficiently detailed user risk assessment and component-level failure mode and effects (FMEA) analysis. These documents can also be a useful starting point for exploring the design history documentation of the device. For example, as part of a due diligence exercise for a major pharmaceutical company, they requested a review of the design and documentation for a dry powder inhaler that they were considering licensing. It was found that only a cursory risk analysis had been performed and a detailed FMEA was recommended. In undertaking this detailed analysis, the potential risk that a patient could receive a significant excess dose if the device were primed several times before inhaling was identified. This risk was

> confirmed by testing. This illustrates the value of early and detailed risk analysis, which considers not only correct use but also foreseeable misuse of the device.

Many modern drug delivery devices are designed as platforms that are intended to be adapted for use with a variety of medications and indications. This means that a version of the device may already have been launched, for example, by a competitor for a similar, or completely different, product. In these circumstances, it will very likely be important to consider

the potential cost and time involved in customising the platform device to provide adequate differentiation, both from a risk (avoiding mix-up of medications) and brand (standing out against competitors) perspective. One not always obvious issue to consider here is whether or not you will get the level of service and timeliness you need to get your version of the product to the market as you need.



Intellectual Property

The drug delivery device intellectual property (IP) landscape is crowded. Therefore, it is important to understand this landscape for the device type being considered, the IP held by the device developer and their arguments as to why their device does not present a significant risk of infringement (Figure 4).

As one of a number of assessment "tools", it can be useful to challenge the device IP and its design by adopting a potential competitor's mindset to consider how a candidate device could be argued to infringe, or why the developer's IP might not be valid. These

hypothetical

counterarguments can then be considered against those of the candidate device developer for a more balanced assessment of potential risk.

One thing to be particularly aware of is that a track record of a device being on-market is not a guarantee of "freedom to operate". It may only be when a device is combined with a particular drug that a competitor decides it is worth the effort and expense to launch an infringement challenge against it. There have been a number of recent high profile cases in the diabetes field in which exactly this scenario has occurred.

Regulatory Requirements

The level and quality of the documentation produced by the device developer may fall far short of what is necessary for successful regulatory submission in intended markets. It is therefore important to clarify exactly what documentation is required for submission and what will be provided by the device developer before committing to a candidate device (Figure 5). Having this understanding will be key to assessing what additional work will be needed for a successful submission. Particular attention should be paid to how any specific requirements of the drug in question may affect the submission file and what support the device developer is able to provide to fill any gaps.

It is often the case that important information is unavailable from the device developer, either because they simply do not have it or because they are restricting it to protect their IP – another situation that highlights the importance of independent expertise. To compensate for missing information, it is critical for the due diligence team to have a high level of technical understanding so that they can examine the situation and conduct assessments and tests of candidate devices.

CONCLUSION

Selecting a drug delivery device is not a simple process of browsing the available marketing materials for the device that appears to "fit the bill". It requires a thorough and structured process to ensure that due diligence is undertaken to match a drug with the right delivery device and avoid costly mistakes. An effective due diligence process is fundamentally similar to developing a device from scratch, requiring many of the same skills, experience and expertise, which are highly specific and may not be readily available within a pharmaceutical company.

Figure 5: The quality and quantity of regulatory documentation available may not match expectations. Ensuring that there is an effective approach to due diligence for device selection is easily overlooked but critical to the overall success of a drug development project. The benefits of getting it right can be enormous, and the consequences of getting it wrong can be dire. Partnering with independent experts with a proven record of drug delivery device design expertise can be the key to success, providing insight, de-risking a project and helping to pave the way to a smoother drug product launch and success on market.

ABOUT THE COMPANY

Founded in 1960, DCA is a leading product design and development consultancy. Its multidisciplinary service offering includes systems engineering, mechanical engineering, industrial design, insight and strategy, UX/UI, human factors, electronics, software and prototyping. With a range of global pharmaceutical, biotech and device companies amongst its long-standing clients, DCA has deep experience in the field of drug delivery devices. Work undertaken in this

area includes design, development, analysis and industrialisation support for injection devices, inhalers, wearables and intranasal devices and applicators, including smart and connected devices. DCA has won multiple major industry awards and contributed to over 1,700 granted patents in the last 10 years. The company's development service is certified to ISO 9001 and ISO 13485 standards.

ABOUT THE AUTHORS

Matt Jones is a Senior Sector Manager, leading key projects within DCA's Medical and Scientific Sector and working at a strategic level to ensure that the sector continues to develop and deliver success for DCA's clients. A mechanical engineer by training, he has over 20 years' experience in consultancy and is a specialist in the development of drug delivery devices. Mr Jones has device development experience that covers a wide range of technologies and routes of administration and, as part of the talented team at DCA, has worked to deliver several multi-award winning and successfully marketed devices.

Rob Veasey is a Senior Sector Manager, Medical and Scientific, leading drug device development projects within DCA's medical device sector. He has 30 years' experience in engineering, design and management roles for leading manufacturing and consultancy businesses, and has worked exclusively on development of drug delivery devices for 20 years. Mr Veasey's experience encompasses mechanical and electromechanical drug delivery devices, including work in the fields of injection, body-worn devices, metered dose inhalers, dry powder inhalers, intranasal sprays and topical applicators for global pharmaceutical and medical device companies.

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ISOTHERMAL DRY PARTICLE COATING – BACK TO THE FUTURE?

Here, Jasdip Koner, PhD, Development Director, Abdul Ershad, PhD, Business Development Manager, and David Wyatt, PhD, Chief Executive, all of Aston Particle Technologies, introduce the company's novel dry powder processing technology – isothermal dry particle coating (iDPC[™]) – explaining how it has the capacity to enhance and broaden the scope of what dry powder formulations can achieve in respiratory medicine. iDPC is a completely new way of processing powders at ambient temperature to create highly uniform mixtures without adulterating physical, chemical and biological properties. It is applicable to a wide range of particle types and can be used to coat smaller particles onto larger particles, utilising well established and controllable scientific principles.

FORMULATION FOR DPIs

Unit-dose dry powder inhalers (DPIs) have been in common use since the 1970s, key examples being Spinhaler (Fisons, acquired in 1995), Rotahaler (GSK), Breezhaler (Novartis) and HandiHaler (Boehringer Ingelheim). In the most basic form of a DPI, a drug capsule is manually loaded into the device, the device is primed, and the drug is drawn into the patient's lungs by inhalation. The formulated dose contains minute quantities of micronised API combined with larger "carrier" particles, which are used as both a bulking agent and a dispersing aid.

DPIs have evolved into more sophisticated multidose delivery devices over time, such as Turbohaler and Genuair (both AstraZeneca), Diskus and Ellipta (both GSK), Inhub (Mylan, now Viatris), NEXThaler (Chiesi, Parma, Italy) and RespiClick (Teva, Tel Aviv-Yafo, Israel). These evolutions have enhanced compliance, particularly in chronic therapy, improved drug delivery and become more patient friendly. Over this period, device design has changed dramatically but the critical part of the inhaler – the formulation – has not. This is because the technologies employed to produce homogeneous mixtures of micronised API with carrier particles have remained largely unchanged.

The current gold standards for formulation are high-shear blenders, originally designed for mixing liquids or slurries, and low-shear blenders, which, although designed ostensibly to mix powders, are highly inefficient when it comes to mixing cohesive materials. It could be argued that these blending standards have proved to be "good enough", however, the truth is that the

"Device design has changed dramatically but the critical part of the inhaler – the formulation – has not."

Dr Jasdip Koner

Development Director T: +44 7725 071 192 E: jasdipkoner@

astonparticletechnologies.com

Dr Abdul Ershad

Business Development Manager T: +44 7341 916 585

- E: abdulershad@
- astonparticletechnologies.com

Dr David Wyatt

Chief Executive Officer

- T: +44 7810 181 137
- E: davidwyatt@ astonparticletechnologies.com

Aston Particle Technologies Ltd Aston University Aston Triangle Birmingham B4 7ET

United Kingdom

www.astonparticletechnologies.com



industry has learned to work within their limitations, including:

- 1. The critical parameters of powdermixing processes that depend upon shear are not well defined, so control strategies work with indirect measures rather than applied scientific principles. Such processes do not scale easily and the rule of thumb is that process development must be carried out at the largest scale available. This means that such work is typically highly inefficient.
- 2. Fine powders are highly cohesive and at concentrations of greater than 5% w/w micronised API are extremely difficult to deagglomerate by mechanical shear of any kind.
- 3. In high-shear blending, the formulation is exposed to excessive mechanical stress due to the impact of high-speed blades, impellers, choppers and baffles, resulting in local frictional heating and particle attrition.
- 4. In low-shear mixing, tumbling energy is applied to mix powders and break down agglomerates; good content uniformity often requires multiple inefficient and wasteful sieving steps. In other cases, the powder is deliberately gently agglomerated by tumbling and the DPI device itself applies the energy to disperse the drug during the inhalation manoeuvre.
- 5. Solid-solid interactions in the shearblending process result in charge generation (triboelectrification) of the powder, which inhibits handling and requires the blends to be quarantined or conditioned before further processing. This extends the manufacturing time, and energy decay post-manufacture diminishes the performance of the product and limits shelf life.

The list could go on, so it is surprising that the industry has not made efforts to pursue better dispersion methods for dry powder formulation more vigorously. Good dispersability is particularly important for high-dose, low-potency compounds, as demonstrated by a small number of medicines such as Exubera (inhaled insulin, Pfizer), Tobi[®] Podhaler[®] (inhaled tobramycin, Novartis/Viatris) and Bronchitol[®] Orbital[™] (mannitol, Pharmaxis, Sydney, Australia) that have come to market using smart engineered particles deliverable without a carrier.



Figure 1: A schematic of the three steps within thin layer fluidisation.

While these are trailblazers for new formulations containing new components and novel physical forms, they introduce significantly more complexity into the drug development process and supply chains. There is a danger that such complexity will become the new standard. Undoubtedly, it is true that device innovation coupled with innovation in the manufacturing process is key to developing DPIs that are able to deliver better formulation performance. Aston Particle Technologies (APT) has an innovative new technology, isothermal dry particle coating (iDPCTM), that may yet put traditional carrier-based formulations back on the map.

INTRODUCTION TO iDPC

iDPC was developed from research in the Department of Pharmaceutics at Aston University (Birmingham, UK). The aim of the project was to find a means of increasing the concentration of API in paediatric formulations by the direct coating of excipients onto the surface of the API particles. An extensive investigation of the existing dry powder coating technologies failed to identify any that could achieve the required degree of content uniformity, let alone the necessary surface coating.

By looking at the problem from scratch, an apparatus¹ was constructed in which the particles to be coated, the "carrier", are mixed with the coating particles, the "guest", in a rotating chamber and dispersed together in such a way as to achieve both requirements. The process works through three simultaneous stages (Figure 1):

- De-agglomeration The fast rotation speed/centrifugal force holds the powder at the wall of the vessel and distributes it in a thin layer. The centrifugal force also acts to pull apart any agglomerates of fine and/or coarse material into single particles.
- Dispersion A nitrogen gas blade is injected and acts to disrupt the thin layer whilst also forming micro-pockets of fluidised powder in which the smaller, more mobile particles are readily dispersed throughout the coarse particles.
- 3. Coating within the micro-pockets of dispersed/fluidised powder the fine particles adhere to/coat the coarse particles.



Figure 2: SEM images of an iDPC-processed formulation (A1, A2) and a commercial formulation with the same composition (B1, B2).

These steps are distinctly different from the stochastic processes involved in conventional shear-blending techniques. There are no blades or baffles involved in the iDPC process, so highly energetic solid-solid interactions are avoided. In addition, there is minimal mechanical interaction with the particles, there are no dead spots, no frictional heating and reduced charge separation. The process runs at ambient temperature in an inert gas atmosphere and requires no temperature control or solvent use.

iDPC is a benign, exceptionally lowshear process because the bulk of the powder is held stationary during most of the processing, disrupted only by a gentle stream of dry nitrogen. iDPC is

"iDPC is applicable to a broad range of large and small molecules – including biologics, which are not denatured by the process – and can be used to coat smaller particles onto larger particles, provided there is a size difference of 2–3 times." applicable to a broad range of large and small molecules – including biologics, which are not denatured by the process – and can be used to coat smaller particles onto larger particles, provided there is a size difference of 2–3 times.

iDPC FOR DPI FORMULATIONS

In iDPC, adjustment of the formulation composition can be used to create fractional coverage, monolayer coverage or multilayer structures on the surface of the carrier particles. This gives iDPC technology unique capability across the range of carrier-based formulation concentrations, from low doses with a single API to fixeddose combinations (FDCs) such as those used in the treatment of asthma and COPD, and unprecedented high-efficiency delivery at high concentration, which could enable formulators to develop inhaled therapies for the direct treatment of lung infections, idiopathic pulmonary fibrosis and lung cancer, or even facilitate systemic treatment via the lungs. The following are examples that illustrate the capability of iDPC in the development of DPI formulations.

Exceptional Dispersion

Scanning electron micrographs (Figure 2) compare the structure of a formulation (A) and a sample from a commercial marketleading product of the same composition (B). In the iDPC formulation, the fine active is fully dispersed and coated evenly across the lactose carrier surface as single particles. The market leader, by comparison, contains agglomerates of fine particles deposited in a highly disordered manner across the lactose surface. This suggests that formulations manufactured by iDPC have undergone a more controlled coating process than that employed to manufacture the innovator product.



Figure 3: A 2D response surface model for a triple FDC formulation.

Exceptional Control

In iDPC, the blending of formulations is defined and controlled by the adjustment of just three critical process parameters – process speed, gas flow and process time – a science that is completely scalable. In contrast with conventional blending processes, which are notoriously difficult to optimise and scale, a quality-by-design approach is readily applicable to iDPC.

Figure 3 is a 2D response surface model from an experiment in which 30 formulations, including replicates, were prepared to explore the optimum operating conditions for the manufacture of a triple FDC formulation (salmeterol xinafoate/ fluticasone propionate/glycopyrronium bromide). The extensive green areas show that the formulations deliver controlled and high fine particle fraction (FPF) performance for each active in the blend under a broad range of iDPC process parameters. This demonstrates that the manipulation of the iDPC process can deliver targeted, consistent and predictable DPI formulation performance. In manufacturing, a well-specified control space is a critical component of the chemistry manufacturing and control (CMC) section of any regulatory dossier, be it in the hands of an innovator company maximising performance or a generic developer targeting specific critical quality attributes to match innovator performance.

Exceptional Flexibility

The creation of high-performance, carrier-based DPI formulations with efficient aerosolisation, even at high concentrations, become possible with iDPC. Under traditional shear processing at high concentrations, cohesive binding of



Figure 4: SEM images of an iDPC-processed lactose-based fluticasone propionate (FP) formulation with a multilayer structure.

micronised particles drives agglomeration/ aggregation, causing the efficiency of aerosolisation to diminish with increasing concentration. With iDPC at high concentrations, no such trend is found the carrier particle surfaces are first saturated with fine particles and then further layers of API particles are cohesively bound. With iDPC, these multi-layered particles form a unique structure akin to a house of cards (Figure 4), a structure that is readily aerosolised to release individual particles. This is reflected in consistently high FPF across the concentration range from 5%-90% w/w API, a feat that cannot be replicated by existing high-dose DPI dispersion technologies (Table 1).

Concentration (% w/w)	% Emitted	% FPF Emitted	Content Uniformity (% relative standard deviation)
0.7 (control)	92.2	27.2	2
5	72.7	50.3	1.5
12	77.8	56.8	2.3
25	61.1	45.6	1.8
50	65.1	56.6	2.7
75	72.3	51.8	2.3
90	79.7	51.2	1.2

Table 1: Aerosolisation performance of FP formulations produced using iDPC (evaluated using RS01, Qualicaps V-I capsules, next-generation impactor, 60 L/min).

THE POTENTIAL OF iDPC

The three attributes of iDPC described here are just scratching the surface of possibilities for its application. By taking a fundamental look at the principles of powder dispersion, the process of mixing cohesive, interacting particulate systems from "disorder to order" (ordered mixing²) can be exploited to a level that challenges the conceived wisdom in DPI formulation. Several advanced dispersion techniques, such as Mechanofusion (Hosokawa Micron, Doetinchem, the Netherlands) and resonance acoustic mixing (Resodyne, MT, US), are currently in use across the industry, however, APT believes that few have the promise of iDPC.

In an industry that is increasingly shifting towards lower potency molecules (small and large) for the treatments of respiratory diseases, and infection more broadly, iDPC has the potential to become a true one-stop shop for DPI formulation development. APT has a number of exciting programmes underway, one of which is to construct a plug-and-play system for high-dose, carrier-based DPI formulations. The object of this is to develop base formulations, suited to API types, properties and potencies, for rapid development into DPI formulations with highly efficient delivery - watch this space for updates.

"iDPC has the potential to be the go-to platform for carrier-based DPI formulations, from controlled and predictable manufacture of traditional FDC formulations to the efficient delivery of high doses and anything in between."

FINAL REMARKS

This article has highlighted that iDPC has the potential to be the go-to platform for carrier-based DPI formulations, from controlled and predictable manufacture of traditional FDC formulations to the efficient delivery of high doses and anything in between. Not only does iDPC make formulation of DPIs more controllable, predictable and simpler; it makes DPI manufacture greener, leaner and more cost effective. APT is engaging and partnering with companies ambitious to develop the DPI formulations of the future.

Meet Aston Particle Technologies at RDD Europe (Antibes, France, May 2–5, 2023), where the company will be presenting scientific posters.

ABOUT THE COMPANY

Aston Particle Technologies is an Aston University spin-out company formed in 2016. The company has a proprietary powder coating/formulation platform – isothermal dry particle coating ($iDPC^{TM}$) – that aims to revolutionise the manufacture

of powder-based respiratory, biologic and oral medicines. Distinct advantages of iDPC over other powder handling technologies lie in the simple, controllable and predictable manufacture of highperformance dry powder formulations across broad concentration ranges achieved at low shear. APT is led by a management team that contains innovative scientists and highly experienced pharma-industry executives, which, through partnership with pharma, aims to embed iDPC into the manufacturing supply chains of the future.

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ABOUT THE AUTHORS





Jasdip Koner, PhD, is Development Director at APT. He augments and maintains his professional development in patient-facing duties as a GPhC registered Pharmacist. He was one of the first employees of APT with an initial focus on developing the range of application areas for iDPC. He has made key contributions to the scale-up of

(UK). He has worked in the R&D sector for over eight years, holding a number of senior positions across various institutions, including the UK NHS and Public Health England, where he served as Lead Research Scientist, overseeing clinical development programmes, strategic planning and evaluation of related public health investments. His industry experience includes Janssen Pharmaceuticals and Pfizer, as well as academic experience in various research-based roles, including at Aston University and De Montfort University (Leicester, UK). Dr Ershad is passionate about advancing innovative technologies to provide forward-thinking solutions and shape global pharma conversations.



David Wyatt, PhD, is the Chief Executive Officer of APT and a pharmaceutical scientist with extensive medicine development experience. Dr Wyatt spent 32 years with GSK, holding a range of senior scientific and management positions spanning the development of five major new chemical entities from molecule selection to being amongst the gold standard respiratory medicines in today's marketplace. Immediately prior to joining APT, Dr Wyatt was the Vice-President and Head of the Respiratory Centre of Excellence for New Product Introduction within GSK Manufacturing and has a broad appreciation of what it takes to champion a good idea to bring it to industrial reality.

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CAPSULE FILLING FOR DPIS – LINKING PROCESS SCALES THROUGH ADVANCED CHARACTERISATION AND QUALITY BY DESIGN

In this article, Rui Churro, PhD, Senior Scientist, Carolina Lopes, Associate Scientist, and João Pires, PhD, R&D Manager, all of Hovione's Inhalation and Advanced Drug Delivery group, discuss the value of rheological characterisation of powders to expedite and de-risk the scale-up of DPI capsule-filling processes.

INTRODUCTION

Dry powder inhalers (DPIs) are becoming increasingly popular to treat both respiratory and systemic diseases as they are able to achieve better physical and chemical stability of the drug product. Conventional DPI formulations are traditionally composed of physical mixtures of coarse carriers with one or more micronised APIs, typically with an aerodynamic particle size below 5 µm.¹ While a well-established formulation strategy, carrier-based drug products come with several drawbacks, spanning from difficulties in uniformity of delivered dose to inefficient drug deposition.

Composite particles are, therefore, receiving increased attention as an alternative formulation strategy for DPIs. In these formulations, the API is embedded into an excipient matrix, in single engineered particles with low densities and small aerodynamic particle sizes that can be efficiently delivered to the lung. However, these unique properties can also cause operational challenges while processing these powders. Due to their large surface area and low densities, composite powders can be highly cohesive, resulting in poor flowability and intense aggregation during the downstream filling processes.

In DPIs, capsules are widely used as reservoirs for the formulation to be later inserted into a device that is then actuated "The wide adoption of capsules comes from them being a cost-effective solution with proven drug stability, as well as from being able to leverage well-established capsulefilling technologies and capacity."

by the patient for self-administration. The wide adoption of capsules comes from them being a cost-effective solution with proven drug stability, as well as from being able to leverage well-established capsulefilling technologies and capacity (Figure 1). To fill these capsules, several manufacturing technologies are commercially available, with dosator-based and vacuum-drum filling being two of the most popular types for low-dosage solutions.

On the one hand, dosator-based capsule filling is already a well-established technology for DPIs in the pharmaceutical industry. Several studies can be found addressing material property dependency and process parameters, especially for carrier-based formulations. However, the same does not apply to composite formulations, with little

Dr Rui Churro

Senior Scientist – Inhalation and Advanced Drug Delivery E: rmchurro@hovione.com

Carolina Lopes

Associate Scientist – Inhalation and Advanced Drug Delivery T: +351 915 223 430 E: cdlopes@hovione.com

Dr João Pires

R&D Manager – Inhalation and Advanced Drug Delivery T: +351 915 206 110 E: jmpires@hovione.com

Hovione PharmaCiência SA

Campus do Lumiar Edifício R Estrada do Paço do Lumiar 1649-038 Lisboa Portugal

www.hovione.com





Figure 1: Large-scale capsule filling process at one of Hovione's manufacturing lines.

information available on the performance of dosator-based technology using highly cohesive and poorly flowable powders.

On the other hand, vacuum-drum filling has also been identified as an accurate filling solution for capsule-based DPIs and is currently gaining traction in the industry. Few case studies are still available regarding its application for DPI formulations, although its working principles are thought to promote a more accurate filling process, especially for low-dosage composite formulations.²

The selection of the best filling technology and process conditions is critical, as DPI formulations may contain doses as low as a few milligrams. Indeed, for dosages as low as 5 mg, a single milligram difference can determine the acceptance or rejection of a filled capsule. Therefore, to achieve such a high level of accuracy and select the most suitable process parameters, it is essential to understand the filling powder's flowability at conditions representative of the manufacturing processes.²

Indeed, the characterisation of the rheological properties of inhalation-based

powders can provide valuable insights for both formulation and process optimisation, as one tries to achieve a specific capsule fill weight and aerodynamic performance. For capsule filling, especially for low dosages, powder compressibility, density, cohesiveness and, ultimately, flowability can be derived from analytical characterisation techniques. However, limited information is available regarding the relationship between rheological properties and the operational space of potential critical processs parameters, such as vacuum pressure in drum-filling processes, among others.

Due to the advantages of composite formulations for DPIs, but also due to their inherent challenges, Hovione has been deeply investing in developing formulation and process development strategies together with advanced characterisation tools to anticipate operational and performance risks from the very early stages of development. In this way, the company aims to minimise the development effort at both lab and manufacturing scales. In the following sections, a set of different case studies is presented, showing how such strategies can support capsule-filling process development with different technologies and at multiple scales.

DEFINING THE OPERATIONAL SPACE OF DIFFERENT FORMULATIONS

At Hovione, composite systems strategies are already an established platform for the formulation development of DPIs. As mentioned prior, formulations outside the carrier-based space typically exhibit poorer flowability because of their higher cohesiveness. Moreover, depending on the formulation – API alone versus spraydried composite (considering different excipients), for example – the rheologic behaviour can vary strongly and, therefore, impact the conditions that should be used in downstream processes, such as capsule filling.

Overlooking the flow properties of a given formulation can potentially prevent the identification of operational problems, such as inconsistent dosing, erratic flow and even complete blockages in the capsule filler equipment, which can affect manufacturing robustness and drug product quality. Therefore, understanding how these powder properties influence the filling process is essential to optimise the process parameters and achieve the desired outputs.

Shear cell testing is a widely used method for evaluating the flow properties and powder behaviour of different materials, providing valuable insights into the performance and quality of powders in several applications. For DPIs, such information can be used to guide both formulation and process development towards the optimisation of the filling process and the powder's aerodynamic performance.

For example, the comparison between the fundamental rheological properties of a micronised crystalline API alone and a composite formulation composed of 80%:20% w/w trehalose dihydrate and L-leucine was determined using the yield locus test (Table 1). Hydroxypropyl methylcellulose (HPMC) size 3 capsules were later filled with these formulations

Formulation	d(0.1) (µm)	d(0.5) (µm)	d(0.9) (µm)	FFC (-)	FFρ (-)	φE (°)	T,C (Pa)
Composite	0.6	2.9	6.8	1.3	0.5	62.3	838
Micronised	1.1	2.6	5.3	2.3	0.8	45.9	444

FFC – Flow function coefficient; FFp – Flow function coefficient normalised for bulk density; φE – Effective angle of internal friction; T,C – Cohesion Table 1: Particle size and shear cell powder characterisation at constant vertical normal stress at pre-shear.



Figure 2: Vacuum drum filling process performance (A) and operational space (B).

using a lab-scale drum filler (Drum Lab – Harro Höfliger, Allmersbach im Tal, Germany) to correlate the measured rheologic properties with the performance of the filling process.

Both formulations showed different flow properties, indicating that the composite formulation (flow function coefficient (FFC) of 1.3) was more cohesive than its API-alone counterpart (FFC of 2.3). As seen in Figure 2, this prediction was later confirmed during the capsule-filling process as, for the same target fill weight, higher vacuum pressure was required for the API-alone formulation. Furthermore, the API-alone formulation also had a tighter vacuum pressure range to achieve the same target 10 mg fill weight. Together, these outcomes indicate a clear dependence of the operational ranges on the type of formulation, supporting the potential value of rheological results in defining adequate process parameters, values or ranges, even before performing any experiments.

"Once the flowability properties of a formulation are known, the next step is to focus on developing the capsule-filling process at lab scale, with the goal of successfully transferring the process to manufacturing scale."

SCALING UP A COMPOSITE FORMULATION WITH DRUM FILLING

Once the flowability properties of a formulation are known, the next step is to focus on developing the capsule-filling process at lab scale, with the goal of successfully transferring the process to manufacturing scale. A possible example would be developing a capsule-filling process for the composite formulation used in the previous section at lab scale using a Drum Lab in order to de-risk a later scale-up to a pilot scale. In other words, this translates into scaling up a process from a throughput as low as six doses per minute up to 25,000 caps per hour, while assuring identical product quality.

In that regard, Hovione supports drug product development under quality-bydesign (QbD) methodologies, namely with the early identification of potential critical process parameters (pCPPs) and potential critical quality attributes (pCQAs). In the case of drum filling for capsule-based DPIs, powder fluidisation, vacuum pressure for plug formation and stirrer offset are factors often selected as pCPPs, while aerodynamic performance, uniformity of delivery dose and fine particle dose are some of the most common pCQAs. Additionally, other important indicators, such as relative weight variability and capsule rejection rate or yield, are also considered for optimising process performance and robustness.

For this specific case study,³ as seen in Figure 3, lab-scale trials indicated that higher vacuum pressures and sieving of the feed material are the most important contributors for process robustness. Conversely, the effect of the stirrer offset was found to be negligible for the chosen formulation.

Regarding vacuum pressures, process robustness improved with increasing vacuum pressure, which can be attributed to the formation of more compacted plugs, which can eventually result in lower fill-weight variability. However, care should be taken while pursuing higher vacuum pressures, as overly compacted material may prevent the redispersion of the plug and compromise the efficiency of powder aerosolisation in the DPI and subsequent delivery to the lung.

Regarding the sieving step, capsules with sieved material at lab scale presented an improved aerodynamic performance. However, this processing step might well have contributed to increased powder cohesiveness, resulting in a slightly lower emitted dose observed for these capsules.

Having these results in mind, a similar process analysis was later performed at the pilot scale.³ The results confirmed a similar response in filling performance to differences in vacuum pressure at both lab and pilot scale. However, it can be concluded that lab-scale trials always performed worse than the ones performed in the pilot unit – a higher variability was always obtained in the former for the same process conditions.

Both set of results indicate that lab-scale trials can be used as a process development and de-risking tool of the process at scale because:

- Impact of process parameters on process performance presents similar trends for both scales;
- 2. The process developed at lab scale represents a worst-case scenario in comparison with the pilot scale.


Figure 3: Capsule-filling process performance for the sieving and scale tests (A) and for the sieving and offset tests at the lab scale (B).

"Hovione equally supports dosator-based capsule-filling process development through a QbD approach, going from a manual dosator at lab scale to either pilot scale or to a fully commercial scale."

Using this strategy, Hovione's QbD approach to process development of inhalation drug products can significantly reduce risk during scale-up, while also adding robustness and predictability during routine supply.

SCALING UP A COMPOSITE FORMULATION WITH DOSATOR FILLING

Hovione equally supports dosator-based capsule-filling process development through a QbD approach, going from a manual dosator (MG2, Pianoro, Italy) at lab scale to either pilot scale (MG2 FlexaLab, up to 3,000 caps/h) or to a fully commercial scale (MG2 TEKNA, up to 55,000 caps/h). All this can be achieved by using the same dosators across scales through higher filling speed and multiple dosators, thereby facilitating progressive scaleups, reducing development effort and minimising potential risks in product quality and operations.

Similar to the drum-filling process, a riskassessment-based approach to the definition of an operational space is also employed from the early development stages. In dosator-based capsule filling, process parameters such as compaction ratio, filling speed and environmental conditions are typically considered pCPPs, alongside the same pCQAs and process indicators described for vacuum-drum processes.

As an example, a similar composite formulation from the previous sections was filled at a pilot scale (FlexaLab, MG2).⁴ Capsules were filled with three different fill weights (5, 10 and 20 mg), using different dosator diameters, powderbed heights and filling speeds (Table 2). For the 20 mg capsules, rejection rates were very low across the different levels of compaction tested, indicating a wide operational range at the pilot scale. However, as lower fill weights were attempted, higher rejection rates were obtained due to increased levels of compaction.

Consequently, the optimal chamber/layer compaction ratio values decreased with the target fill weight, although all were below a ratio of one, which would theoretically mean no pre-compression of the powder. Such trends come from the fact that the smaller dosators used for lower fill weight require a lower compaction ratio to transfer the formed plug from the powder bed into the capsule. Contrary to compaction ratio, capsule-filling speed had no significant impact on capsule-compaction level or rejection rate. Finally, similar aerodynamic

Average weight (mg)	Dosator diameter (mm)	Compaction ratio (-)	Rejection rate (%)	ED (%)	FPF (ED %)
20.9 ± 0.7	2.8	0.9	0	97.4	57.0
20.1 ± 0.6	3.4	0.7	0	103.1	58.5
20.0 ± 0.4	3.7	0.5	3	96.7	69.3
10.7 ± 0.0	2.8	0.6	20	-	
9.7 ± 0.3	2.8	0.5	0	88.7	72.7
4.9 ± 0.8	2.2	0.5	18	-	
5.1 ± 0.3	1.9	0.8	0	83.1	80.1
20	3.7	(Hand filled)	-	-	67.0

FPF – Fine particle fraction; ED – Emitted dose

Table 2: Dosator filling process parameters and performance characterisation.

performances were obtained at both lab and pilot scales.⁴ Once more, these results indicate a good match between early development studies, with small material needs, and the output from the process at later stages and higher throughputs.

CONCLUSION

Overall, although highly promising for DPIs, composite formulations bring multiple challenges to development, especially during the downstream capsulefilling process. However, the case studies presented here show that, through advanced characterisation tools and QbD-based process development, it is possible to anticipate challenges from the early stages and act upon them through formulation and process optimisation. This approach allows Hovione to accelerate the transfer of capsule-filling processes to larger scales, for both clinical and commercial supply, by minimising the required development effort and the level of risk associated with each scale-up.

ABOUT THE COMPANY

Hovione is an international company with over 60 years of experience in pharmaceutical development and manufacturing operations. As a contract and development manufacturing organisation (CDMO), Hovione has a fully integrated offering of services for drug substances, drug product intermediates and drug products. The company has four US FDA inspected sites in the US, Portugal, Ireland and China and development laboratories in Lisbon (Portugal) and New Jersey (US). Hovione provides pharmaceutical customers with services for the development and compliant manufacture of innovative drugs. In the inhalation area, Hovione offers a complete range of services, from API, formulation and manufacturing process development to proprietary devices.

ABOUT THE AUTHORS







Rui Churro is a Senior Scientist – Inhalation and Advanced Drug Delivery at Hovione and earned his PhD in the field of Refining, Petrochemical and Chemical Engineering at Faculdade de Engenharia, Universidade do Porto (Portugal) in 2020 with a thesis dedicated to heterogeneous catalysis. In 2020, he joined Hovione as a Drug Product Development Scientist, having been enrolled in drug product and drug product intermediate process development from early stage until commercial scale. Since 2022, he has been leading process development projects and internal R&D projects within the respiratory field, focusing on spray drying, capsule filling and formulation strategies for the Inhalation and Advanced Drug Delivery group.

Carolina Lopes is an Associate Scientist – Inhalation and Advanced Drug Delivery at Hovione and earned her master's degree in Chemical Engineering at Instituto Superior Técnico, Universidade de Lisboa (Portugal) in 2021, conducting a final dissertation focused on the use of microfluidics to produce RNA-loaded lipid nanoparticles. In 2022, she joined Hovione's Inhalation Advanced Drug Delivery group as an Associate Scientist and has been leading and supporting development of spray drying, high-pressure homogenisation and capsule-filling projects, as well as internal R&D innovation projects.

João Pires is R&D Manager – Inhalation and Advanced Drug Delivery at Hovione and earned his PhD in the field of Engineering Design and Advanced Manufacturing, under the MIT Portugal Program, at Instituto Superior Técnico (Lisbon, Portugal). In 2018, he joined Hovione as a Drug Product Development Scientist, leading process development for different administration routes, from early stage until commercial scale. Since 2021, he has been working as R&D Manager, leading the Process Development team in the Inhalation and Advanced Drug Delivery group.

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ARE YOU STRUGGLING TO PUT DIFFICULT POWDERS INTO CAPSULES?

In this article, Andy Cleall, Technical Director, and Ben Smith, Senior Project Engineer, both at 3P innovation, discuss process optimisation and cutting-edge technology for powder filling, including how 3P's R500 and R1000 robotic capsule fillers are pushing the boundaries of optimal filling and how its Fill2Weight technology enables increased filling accuracy and improved yields.

THE NEED FOR ADVANCED FILLING TECHNOLOGY

With the pharmaceutical industry under increasing pressure to develop novel drug products faster, it is important that manufacturers make use of the most advanced technologies. This is particularly true for capsule filling; drug developers often only have small-but-expensive amounts of test material to work with, so cost-efficiencies and time-to-market are critical.

3P innovation's R500 and R1000 are robotic capsule fillers (Figure 1). These machines were designed to provide a low-cost and flexible way to produce capsules. They can also be configured to fill certain delivery devices and containers, including vials, syringes and cartridges. One of the key issues concerning 3P's pharma customers is the difficulty associated with low-dose fill weights, particularly when they're looking at fill weights of 1.0 mg or less. By investigating this, 3P has generated quite a bit of data in terms of filling 0.5–1.0 mg of pure API into capsules.

The challenges manufacturers face when dealing with low fill weights include weighing accuracy, controlling static and regulating air movement, all while operating an automated process with an



Andy Cleall Technical Director T: +44 1926 408933 E: andy.cleall@3pinnovation.com



Ben Smith Senior Project Engineer T: +44 1926 408933 E: ben.smith@3pinnovation.com

3P innovation Ltd Tournament Fields Business Park Bosworth Avenue Warwick Warwickshire CV34 6UQ United Kingdom

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"Lower fill weights are becoming increasingly important as the pharmaceutical industry continues to consider drivers such as modularity, agility and the development of personalised medicines."

expected output of more than 200–300 capsules an hour. Furthermore, this needs to be achieved within the context of a fill-to-weight environment of chronicling 100% weight records.

Lower fill weights are becoming increasingly important as the pharmaceutical industry continues to consider drivers such as modularity, agility and the development of personalised medicines. 3P manufactures machines that are part of the production of current advanced therapies, and the company is fielding an increasing number of enquiries about using this filling technology.

R1000 AND R500

The R1000 and R500 are versatile and powerful production machines (Figure 2), capable of handling the most challenging and specialist powders – from pure API to blends, delicate spray-dried powders and micropellets. Featuring the groundbreaking Fill2Weight (F2W) powder-filling technology, these systems can handle a wide range of powders and deliver precise microdosing under adverse conditions, such as low relative humidity and containment. As such, they are able to handle pure and highly potent APIs. One of the benefits of the R500/R1000 range and F2W solutions is that they can use the same set of change parts. Without having to make any physical replacements or swap-outs, a user can change its target dose weight with the machine's software. This is a considerable advantage, as users can switch from a 2 mg to a 5 mg fill, or from a 10 mg to a 100 mg fill, with no part changeovers required at all.

The technology is also compatible with both free-flowing and highly cohesive powder types, and can handle either with the same reusable change parts. For example, with clinical trial batch dose sizing, this flexibility offers significant benefits in terms of reducing the complexity of the trial set-up. By compressing clinical development timescales and reducing costs, this highly flexible system can fill challenging powders without having to change the physical hardware. Even better, there is no minimum batch size.

Adding to that, 3P's customers are more frequently dealing with very difficult-tohandle powders, such as those with bulk densities down in the 0.2 g/cm³ range. These powders tend to be highly cohesive and difficult to fill using conventional technologies. By applying low amplitude,



Figure 2: Ben Smith in front of an R1000.

high frequency vibration at the nozzle, the cohesive bonds are overcome and van der Waals forces are disrupted enough to fluidise the powder to enable filling. Simply put, if the right parameters are not applied, the powder will not come out, but, with the right amount of Hertz and a certain amplitude, 3P has been able to mobilise some unbelievably difficult powders that would most likely choke a micro- or vertical auger.

3P'S IN-HOUSE TESTING

3P can run in-house trials for its customers with its F2W system, including for difficult powders, to optimise their recipe settings. This is important – if a drug developer is preparing to make a clinical batch, they do not always know the physical properties of the powder; therefore, they may not know what technologies to invest in. By the time the developer gets the powder, they need to have the appropriate technology ready; when companies put that powder through the machine for the first time, they cannot afford to spend time reformulating the recipe to make it work.

Test batches generally comprise 5–10 g of expensive micronised or spray-dried material and, not only do drug developers want results quickly, they want to know that their powder flows well enough to fill capsules with anything up to 200 mg. 3P provides the confidence that the customer can return to their machine, apply the same settings and achieve that goal. What 3P is doing is enabling and de-risking their customers' clinical trial programmes by reducing the number of formulation steps involved and getting to the first-in-human stage quicker.

F2W TECHNOLOGY IN PRACTICE

One material 3P has been working with is a spray-dried particle that is being used as an immunotherapy. Part of the spraydried formulation is a polymer, which gives the mix a certain plasticity, similar to polystyrene balls at a macroscopic scale. The inherent issue with these highly charged, static-sensitive powders is that they are difficult to dose. In fact, it is often more of a problem getting the powders into the equipment than it is getting them out; they tend to be cohesive and need gentle handling, which the R500 can accommodate (Figure 3).



Figure 3: Dosing 1.0 mg \pm 0.05 mg of a cohesive, spray-dried particle using 3P's F2W technology.

Getting difficult powders into a container with a long and/or narrow opening, such as a syringe, is something 3P has quite a lot of experience with. Typically, 3P will pass the nozzle tube into the device to place the dose at the base of the container and minimise particle adhesion to the container walls. The aim is to avoid any further need for reformulation and enable the customer to use the powder that they have already produced. From the starting point of a good working recipe, all that is required is to decide on the new dose weight and adjust the settings for a larger or smaller clinical trial accordingly, based on the initial settings, without having to reformulate to achieve a specific bulk density or needing access to a particular piece of equipment.

When attempting a deep fill under unidirectional airflow conditions, particularly when working with plastic containers, electrostatic effects can be problematic. At the same time, it is critical not to contaminate the side walls. This is something 3P does routinely – when filling syringes, 3P places the powder into the syringe barrel via an extended nozzle tube, which is vibrated at a high frequency to fluidise the powder, stop it sticking and complete the fill as quickly as possible.

"To improve yield, 3P developed a 'top-up' algorithm to correct slightly underweight doses." Real-time F2W works very well here; as the powder lands, its weight accumulates and the system plots the increase in weight, calculates the mass flow rate and then works out when to stop. The technology does this repeatedly throughout the dose at more than 50 times per second. For a larger

dose, it is typical to bulk dose up to two-thirds of the powder in very quickly and taper the flow rate until the target weight is achieved; a low dose weight, such as 1–10 mg, would be done in a single operation.

When working with very fine powders and very low doses, a few particles might clump together as they leave the nozzle. And, because the technology is weighing in divisions of hundredths of a milligram, the weight changes in a stepwise manner. So, as the machine approaches the target, it might interpret one of those increases in flow rate and make an adjustment to ensure an accurate fill, with the margin of error always erring on the side of underfilling rather than overfilling.

In the past, to make 1.0 mg work for a customer, 3P sought to achieve a a balance between yield and rejection rates. As long as a certain percentage of the capsules, say 60%–70%, had the required fill, customers were happy to accept that ratio – it is one of the compromises required when working with very low dose weights. So, to improve yield, 3P developed a "top-up" algorithm to correct slightly underweight doses. This top-up feature provides an excellent way to improve yields; when the fill volume is just underneath the target, the system now recognises what has happened and, instead of abandoning the dose, it goes back, has another go and adds a small amount of powder to reach the prescribed target. 3P's data show that this achieves very high yields (95%–100%) for more than 1,000 capsules.

Another area of application in which F2W shows great promise is that of inhaled and nasally delivered therapies. These dosage forms are often quite friable and, given the need to be aerosolised, the particles cannot clump together. Likewise, they cannot be compacted or compressed for delivery to the lungs. As such, it is often necessary to work with low-volume, concentrated doses of pure APIs, which makes dosing accuracy even more important.1 F2W technology is a non-compacting, lowshear process that overcomes many of these issues. Furthermore, an ioniser can be placed in the head to ionise the powder during feeding to minimise the static attraction between particles.



Figure 4: R1000 robotic capsule filler.

CONCLUSION

In summary, the upgraded weighcell in 3P's R1000 and R500 features a display resolution of 0.01 mg, retaining high-speed feedback for gravimetric filling precision control (Figure 4). It will weigh powder aliquots of less than 1 mg with a 1% tolerance during production to comply with USP <41> guidelines. In addition, the enhanced robot-controlled operation ensures a smooth filling process for weight stability at low dose weights. Finally, the upgraded F2W software provides additional controls with automated "top-up" functionality for higher yields and accuracy. These cutting-edge machines enable users to develop and launch new drugs to market quicker, reducing clinical development timescales and achieving first-in-human milestones faster and at lower costs.

ABOUT THE COMPANY

3P innovation is an employee-owned and UK-based engineering and custom automation company. It works with pharma and medical device businesses to help develop new products, devices and production processes. 3P specialises in aseptic automation and powder/liquid filling technologies. The company designs and builds scalable production solutions, supporting customers from lab-scale and bench-top equipment up to pilot plant and full production systems. The company has two divisions – 3P Pharma Equipment and 3P Custom Automation, which specialise in standard equipment and fully customised solutions, respectively.

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ABOUT THE AUTHORS

Andy Cleall is Technical Director at 3P with almost 40 years of automation experience, with 20 of them in pharmaceutical and medical device applications. Having delivered numerous projects across a range of industries and applications, from high-speed commercial production to low-speed clinical applications, he now applies his broad knowledge and experience to providing support for customer trials and the early stages of new projects to help build a solid technical foundation. Mr Cleall joined 3P in 2009, has expertise in powder filling and solving difficult problems, and is open to discuss any technical challenge.

Ben Smith is a Senior Project Engineer at 3P innovation. Since joining in 2017, Mr Smith has worked across a range of 3P's customer sectors, including medical devices, pharmaceutical manufacturing, fast-moving consumer goods and confectionary. Mr Smith has extensive powder-filling expertise, working with the full range of 3P's powder-filling technologies and delivering multiple projects that incorporate 3P's platform products. These include F2W-equipped R500 and R1000's, vibratory feeders and developing 3P's new vacuum-drum dosator.



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H&T PRESSPART

DEVELOPMENT APPROACH FOR A HIGH-PERFORMANCE CAPSULE-BASED DPI

In this article, Mirjam Kobler, PhD, Global Business Development Manager, Ameet Sule, Director Inhalation Product Technology Centre, and Sunita Sule, Inhalation Product Consultant, all at H&T Presspart, look at the factors affecting the performance of dry powder inhalers and discuss the company's development of high-performance prototypes.

NEW APPLICATIONS – THE NEED FOR HIGH PERFORMANCE

The pulmonary route for drug delivery is becoming increasingly attractive to drug developers, not only for low-dose locally acting therapies, such as asthma and chronic obstructive pulmonary disease (COPD), but also for systemic applications that often require higher doses or novel formulation technologies.

High-performance devices must be developed to accommodate the requirements for delivering these new formulations efficiently. To ensure the best performance, the development of the formulation and the device should go hand in hand.

Dry powder inhalers (DPIs) are used to deliver medications to the lungs in powder form via oral inhalation. Medication in powder form can be filled in either a capsule, blister, reservoir or cartridge, depending on the drug product configuration. The device can be either an active or a passive device. In many cases, capsule-based inhalers are the preferred solution for new applications because they offer several interesting features, such as the possibility to use a wide range of different APIs and doses, generally ranging from 5 to 50 mg. Further advantages include ease of use and a good feedback mechanism for the patient.

Due to the complexity and cost of manufacturing multidose DPIs, pharma companies try to minimise costs and risks in new applications by using simpler and more affordable devices.

For some new applications, such as pain relievers or antibiotics, a reusable device is beneficial; for others, such as vaccines, a disposable single-use device is preferable. In both cases, capsule-based inhalers can be a good solution.

The covid-19 pandemic has made it imperative that an easy-to-use vaccine is available worldwide and remains stable under ambient conditions. Research continues to focus on delivering the vaccine via the inhalation route.¹

However, there are some drawbacks associated with current capsule-based DPIs, such as low performance, which is an inherent feature of many capsule-based DPIs on the market. Even newly developed integrated

"In many cases, capsule-based inhalers are the preferred solution for new applications because they offer several interesting features."



Dr Mirjam Kobler Global Business Development Manager T: +49 15122425215 E: mirjam.kobler@presspart.com



Ameet Sule Director Inhalation Product Technology Centre T: +44 1254 586296 E: ameet.sule@presspart.com



Sunita Sule Inhalation Product Consultant T: +44 1254 582233 E: sunita.sule@presspart.com

H&T Presspart

Whitebirk Industrial Estate Blackburn Lancashire BB1 5RF United Kingdom

www.presspart.com





Figure 1: Schematics of DPI prototypes: (A) Prototype 1 without flow straightener and (B) Prototype 2 with flow straightener configuration. CFD simulations for (C) Prototype 1 and (D) Prototype 2 configuration.

solutions for antibiotics, such as tobramycin, do not reach a fine particle fraction (FPF) higher than 35%. To achieve the required therapeutic dose of the antibiotic, the patient must inhale four capsules a day.²

Many strategies for overcoming the inherent challenges of most existing devices are achieved by focusing on improving the dispersion properties of the formulations. Not much attention has been paid to improving the devices, either by technological advancements in device performance (higher de-agglomeration and less retention of powder in the device/ capsule) or on increasing patient adherence for better handling, and thus higher deposition in the deep lungs.³

The novel H&T Presspart DPI addresses the above problems and challenges of capsule-based inhalers. The most important features of an ideal capsule-based DPI are ease of use with a good feedback mechanism for the patient coupled with a costeffective design. In addition, dose delivery with high reliability and consistency, and high-performance efficiencies for a wide range of applications are desirable.

DEVICE ENGINE AND DEVELOPMENT APPROACH

While developing a novel capsule-based inhaler, the main focus was to create a high-efficiency engine to de-aggregate and aerosolise the powder formulation in a medium resistance and relatively flow-rateindependent device. Several prototypes were tested and studied throughout the development journey. The airflow through the capsule chamber was designed so that the capsule oscillates. This causes impaction of the capsule within the capsule chamber, leading to the breakdown of big powder aggregates inside the capsule and, consequently, an efficient release of the powder from the capsule.

After the initial de-aggregation of the powder in the capsule, the powder evacuates from the capsule and reaches the swirl chamber. Here, further de-aggregation takes place due to the shear forces caused by the turbulent airflow and the impaction of the powder on the walls of the swirl chamber. The combination of the capsule movement and powder flow in the swirl chamber leads to a highly dispersed powder. This powder exits into the tubular mouthpiece through the mesh.

The powder de-aggregation and dispersion potential of a device are critical parameters for achieving high efficiency. Various techniques can be used to study airflow and powder de-aggregation behaviour within a device. Here, a combination of simulation with computational fluid dynamics (CFD) modelling in a steady state and an experimental approach were used to develop the new device.

In one experimental design, CFD models were used to study the airflow structures within the device. Two prototypes were tested, Prototype 1 (Figure 1A), without a flow straightener, and Prototype 2 (Figure 1B), with an integrated flow straightener in the mouthpiece. A fine particle assessment using a next-generation impactor (NGI) was conducted on the prototypes. As seen in Figure 1C, the CFD data of Prototype 1 exhibits a swirling flow that proceeds out of the mouthpiece, reflecting a higher deposition and a swirl pattern observed in the induction port of the NGI. However, with the introduction of the flow straightener in Prototype 2, the CFD data shows a high reduction in the swirl exiting the mouthpiece (Figure 1D).

A comparison of the CFD data also shows a correlation with the NGI data (Figure 2). There was a higher deposition in the induction port at both the flow rates for Prototype 1, which was significantly



Figure 2: Comparison of NGI deposition of Prototype 1 and Prototype 2 at 30 L/min.

higher at 30 L/min (P < 0.05). The statistical analysis performed using an independent student t-test gave probability values of < 0.05, which was considered to be a significant difference. The flow straightener reduced the swirl of the airflow exiting the device, thereby reducing the deposition in the induction port. There was no significant difference in FPF between the two devices indicating that major de-aggregation occurs within the device. CFD proved to be a valuable tool for studying the air flow dynamics of the DPI. NGI testing provided the supporting data and visual observation of the drug deposition in the induction port, which indicated probable oropharyngeal deposition.

A modular engine set-up during development allowed for easily making small changes in the prototypes. Significant improvements could be achieved by changing different engine parameters. Figure 3 demonstrates the improvement in "The inspiratory resistance of the new H&T Presspart device was designed as a medium resistance device."

performance of the test data from Prototype 1 to 4. The NGI testing demonstrated a reduction in the deposition in the induction port and pre-separator stage, as well as an increase in the lower stages of the impactor, which resulted in an increase in FPF as design development progressed.

RESISTANCE

The intrinsic resistance of a device is often discussed controversially in the literature. For asthma and COPD applications, lowresistance devices often seem to be more beneficial for the patient struggling to achieve high flow rates. However, low device resistances often come with a lower deposition of fine particles of the API in



Figure 3: NGI deposition profile of a salbutamol sulfate carrier-based formulation with different prototypes of the Presspart capsule-based device.



Figure 4: Fine particle delivery of budesonide 200 μ g powder for inhalation at 2, 4 and 6 kPa.

the deep lung. Medium resistances have the big advantage of increasing deep lung deposition.⁴ The inspiratory resistance of the new H&T Presspart device was designed as a medium resistance device.

Another development target was to achieve a relatively flow-rate-independent device. The airflow path was designed and optimised such that there was no significant difference in the FPF for flow rates ranging from 30 L/min to 90 L/min (Figure 4).

EVALUATION OF DIFFERENT FORMULATION TYPES

Two types of formulations were studied: a binary mixture and spray-dried engineered particles.

Budesonide, a glucocorticoid, is known for its sticky nature – its difficulty to de-aggregate was the reason for its selection as the candidate formulation. A binary mixture of a marketed formulation of lactose and budesonide 200 µg per dose with a capsule fill weight of 25 mg was selected to test the prototype. In addition, the performance was compared with a marketed Plastiape (Osnago, Italy) RS01 equivalent device. The novel H&T Presspart device exhibited a high FPF compared with the marketed Plastiape RS01 device, confirming the engine's efficiency (Figure 5).

In a study in co-operation with the University of Bonn (Germany), the performance of the novel DPI was assessed by testing a spray-dried rifampicin formulation. More detailed information on that can be found in a recently published article.⁵ The formulation was used to benchmark the performance of

"The FPFs generated were highest for the H&T Presspart device when compared with the commercially available standard devices HandiHaler and RS01 equivalent."





Figure 5: Comparison of NGI deposition profile of the H&T Presspart DPI and RS01 equivalent with Budesonide 200 μ g powder for inhalation.

Flowrate	PP-DPI	RS01	Handihaler
50 L/min	73.4 ± 3.2	66.3 ± 5.5	47.8 ± 4.2
100 L/min	63.5 ± 4.2	53.7 ± 4.2	46.6 ± 4.1

Table 1: Comparison of FPFs at different flow rates for the H&T Presspart device, RS01 equivalent and HandiHaler for the rifampicin particle-engineered formulation.

the H&T Presspart device against devices already on the market. As shown in Table 1, the FPFs generated were highest for the H&T Presspart device when compared with the commercially available standard devices HandiHaler (Boehringer Ingelheim, Ingelheim, Germany) and RS01 equivalent.

CONCLUSION

Several key factors influence the performance of the DPI. The most important ones are the patient's inhalation technique, device handling and the device engine, in particular, the efficiency of the de-aggregation

ABOUT THE AUTHORS

Mirjam Kobler, PhD, is currently Global Business Development Manager for H&T Presspart. Dr Kobler oversees the management and business development activities for H&T Presspart's DPI device portfolio. Before joining H&T Presspart Dr Kobler worked at Meggle, where she headed the R&D Department of Meggle's Excipients and Technology business group. Dr Kobler's background includes seven years of experience in various areas of lactose excipients, especially for DPIs.

Ameet Sule, Director, Inhalation Product Technology Centre, H&T Presspart, is a pharmaceutical professional having worked in the industry for more than 20 years, specialising in the development of inhalation products and devices. Mr Sule works closely with H&T Presspart's customers around the globe, understanding and mitigating the frontend development challenges of new and generic products for inhalation drug delivery.

Sunita Sule, Inhalation Product Consultant, is a pharmaceutical professional who has over 25 years of experience in the pharmaceutical industry, with core expertise in formulation and device development of inhalation products.

mechanism of the device. Targeting a medium resistance and a relatively flow rate independence were critical factors within the device development approach.

Various complementary techniques were used to study airflow and powder de-aggregation behaviour within a device. Combining different development approaches of fast-paced prototyping, CFD technique and laboratory data for verification can effectively develop costeffective high-performance DPIs for the inhalation market. These techniques enabled H&T Presspart to develop a highperformance prototype independent of the formulation type tested (carrier-based as well as an engineered formulation).

ABOUT THE COMPANY

H&T Presspart is a market-leading manufacturer of drug delivery devices and components with more than 50 years' experience and enjoys a worldwide reputation for competence, quality and innovation in the pharmaceutical market. H&T Presspart's Technology Center supports its customers' new product developments and strategic initiatives. H&T Presspart has four European manufacturing sites in Germany, Spain, Switzerland and the UK and also has sales representation in China, India, the US and Uruguay.

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NOVEL INDUSTRIAL-SCALE ELECTROSTATIC CHARGE ELIMINATION METHOD FOR INHALATION PRODUCTS

In this article, Orest Lastow, PhD, Chief Technical Officer at Iconovo, describes a novel technique for removing the built-up charge from dry powder inhaler components, offering a potential solution to the issues caused by static charges in these devices, including decreased performance, altered powder properties and increased variability in delivered dose.

INTRODUCTION

According to US FDA guidance,¹ "interparticulate interactions between the drug substance and excipients and with the container closure/device constituent part at a microscopic level (e.g. cohesive and adhesive properties, surface activity, specific surface area, static charge properties of the formulation) can also be important. These properties and interactions can affect, for example, blend uniformity, powder flow and delivered dose." This is one of many indications as to how important a role electrostatics play in the field of dry DPIs.

The manufacturing of a DPI includes processes that generate surface charges on the plastic parts of the device and on the dry powder formulation. Injection moulding exposes the material to very high temperatures and shear forces. This leads to parts experiencing a high level of triboelectric charging.² Freshly injection moulded parts can become charged to such an extent that they can jump up from a collection bin simply due to electrostatic repelling forces. Plastic parts have very low conductivity, which makes them retain the charges for a very long time.

Any handling of a dry powder will generate surface charges due to high triboelectric charging. The high surface area of a powder makes it very susceptible to this charging. Formulations for inhalation can have some degree of conductivity, leading to a low rate of dissipation of the charge. Lactose, which is a primary constituent of many inhaled formulations, can slowly dissipate charges.

When observing the electrostatic properties of a DPI, a great variability can be seen. A study by Byron *et al* measured the charge of the powder aerosol exiting a Bricanyl[®] (terbutaline, AstraZeneca) Turbuhaler.³ The charge on the aerosol was measured from five different inhalers and showed a variability from 51 pC to -44 pC. Most surprising was that the charge showed two polarities. When measuring the aerosol charge of Pulmicort (budesonide, AstraZeneca), the variability was lower but still considerable – 55 pC to 89 pC.

Another study, by Kwok *et al*, investigated the charge level of different particle sizes.⁴ Bricanyl and Pulmicort Turbuhalers were compared and tested at different relative humidities (RHs). Both groups showed a bipolar charge distribution with respirable particles having positive polarity and larger particles being negative. The charge on Pulmicort was more or less independent of RH but Bricanyl showed a strong RH dependence. A low RH generated a much higher charge for all particle sizes, whereas a high RH showed a lower charge level.

A study by Hoe *et al* investigated the impact of inhalation flow rate on the electrostatic properties.⁵ Again, Bricanyl and



Dr Orest Lastow Chief Technical Officer E: orest.lastow@iconovo.se

Iconovo AB Ideongatan 3A-B SE-223 70 Lund Sweden

www.iconovo.se

"The electrostatic effects on the performance of a DPI are many and are predominantly caused by either adhesion of the powder to the plastic surfaces of the device or altered formulation properties in terms of cohesivity, density and flowability."

Pulmicort Turbuhalers were investigated. When the flow rate was varied from 30 L/min to 90 L/min, the net charge of Pulmicort increased by about a factor of four. For the same flow rate range, Bricanyl varied by a factor of eight to ten. A futher study by Telko *et al* also showed that the actuation of the DPI generates significant triboelectric charging of the powder.⁶ Lastly, a study by Melandri *et al* demonstrated that electrostatic charge greatly enhances the deposition of the inhaled powder in the patient's airways.⁷

These studies indicate that electrostatic properties depend on different inhalers, on the RH at which the dose is taken and on the inhalation flow rate. They also show that the formulation and API play a key role. In many studies, Bricanyl showed higher variability than Pulmicort. Together with the variability of the device charge, this can have a strong negative impact on the dose uniformity of the DPI and on the dose delivered to the lung.

The electrostatic effects on the performance of a DPI are many and are predominantly caused by either adhesion of the powder to the plastic surfaces of the device or altered formulation properties in terms of cohesivity, density and flowability. The adhesion of powder to the charged plastic components increases the retention of powder during the de-aggregation process and during transport of the aerosolised powder through the inhaler. This retention affects the dose delivery uniformity and particle size distribution of the delivered dose. A charged powder, together with charged plastic components, can also severely impair accurate and reproducible dose metering in a reservoir dry powder inhaler (Figure 1).



Figure 1: Dose metering feature in ICOres[®] before charge removal (left) and after charge removal (right).

Electrostatic effects are also present during the manufacturing process, presenting many challenges and quality issues. Electrostatic problems can come and go and are dependent on climate and season. Electrostatic effects cannot be avoided but can be controlled and their effect minimised by effective charge removal. When dealing with electrostatic issues, a good approach is to ascertain that it is actually an electrostatic problem and then prove that the remedy works in a robust and consistent way.

CHARGE REMOVAL BY PRESSURE REDUCTION

This section describes a novel charge removal process suitable for highthroughput industrial applications. The removal is permanent, and charges are removed from all surfaces that are exposed to air. The process works equally well for assembled devices and blisters. The scientific basis of the charge removal is a Townsend-like discharge around a charged dielectric surface.^{2,8-13}. The discharge is induced by reduction of air pressure.

"The method to remove surface charges by facilitating ionisation of the surrounding air by reducing the pressure was first described by the author in 2000."

The method to remove surface charges by facilitating ionisation of the surrounding air by reducing the pressure was first described by the author in 2000.13 Free electrons are always present in air, moving in the presence of an electric field and by diffusion. When electrons are accelerated in an electric field, they gain energy. Eventually, the electrons collide with molecules in the air and, if they have sufficient energy, one or more electrons are ejected from the molecule. The ejected electrons can then be accelerated and eject new electrons, forming an electron avalanche. A large number of avalanches combined result in an electrical breakdown of air. When the air breaks down, a large number of ions move towards the oppositely charged surface and neutralise the surface's charge.13

This process takes place spontaneously and continuously until an equilibrium is reached. Equilibrium is reached when the acceleration of the electrons provides insufficient energy to ionise the molecules. The process is very quick, and it can thus be assumed that an equilibrium has been reached in the surrounding air.

The parameter governing the ionisation is dependent on the mean free path of air and the present electric field. In air, the mean free path is directly proportional to the pressure, with the parameter able to be expressed as the electric field strength (*E*) to pressure (*p*) ratio, *E/p*. For a set gas and a set electric field, *p* and *E* will determine whether the breakdown criteria is fulfilled or not. Breakdown takes place when *E/p* exceeds a critical value, $[E/p]_{critical}$. When $E/p \leq [E/p]_{critical}$, the system is in equilibrium.

When p is reduced, the mean free path increases, giving the electrons a longer distance over which to accelerate, meaning that the energy threshold for breakdown can be reached. The value of E/p increases with decreased p until $E/p > [E/p]_{critical}$ and a discharge takes place. The ejected electrons then travel in the electric field and eventually reach the charged surface and discharge the surface's charge. As long as $E/p > [E/p]_{critical}$, the discharge will continue and the charged surface will be discharged. E will decrease and, consequently, E/p will decrease. The process will continue until the equilibrium level is reached. To induce further discharging, the pressure must be reduced further. If the pressure is increased, nothing happens - the system stays in equilibrium.

The value of $[E/p]_{critical}$ cannot be generally given, as it depends on from which point in space E(r) is defined. Since E increases closer to the surface, it can be argued that, when a breakdown has been initiated, its intensity should increase as the ions move towards the surface.

An experiment was performed to support this theory.¹³ A charged dielectric object, a polytetrafluoroethylene (PTFE) disc, was placed on a conductive base (Figure 2 A–B). The charges in the conductor were disassociated, leaving excess charges of the same polarity as the charged dielectric object. The base was connected to an electrometer (Figure 2C) and the excess charges were earthed.

When an ion impacted on the surface, it neutralised some of the charges on the surface of the charged dielectric object (Figure 2D). The image charges in the conductor then become excess charges that could be measured. The measured charge was of the same polarity as the neutralising ions. Using this method, the time of ion impaction and the magnitude of neutralising ions could be measured. However, this method only measures the net charge neutralisation – it does not discriminate between an equal number of positive and negative charges and no charges at all.

A further experiment was performed to measure the ion impaction on a dielectric disc as a function of pressure in real time. A PTFE disc was rubbed against a polyvinylchloride (PVC) disc and a surface charge of approximately $-1 \ \mu$ C/m² was obtained. The whole set-up was put into a vacuum chamber and the pressure signal was logged, together with the charge signal (Figure 3).



Figure 2: Experimental set-up.13







Figure 4. Diagram of the number of electrons versus pressure over time.¹³

Initially, as the pressure was reduced, no discharging could be observed. When a threshold level was reached, a clear discharging could be seen. When the pressure reduction stopped, the discharging stopped. At one point, the pressure was increased to verify that mere pressure change did not trigger any discharging; only when the pressure was reduced again – below the original pressure – did the discharging start again (Figure 4). A number of strong, clear discharges could be seen early in the pressure reduction sequence. After that, only minor discharging could be seen. These experiments support the concept of pressure-induced discharging and suggest the possibility of using this phenomenon in a large-scale industrial charge removal.

The method is to place injection moulded parts, or fully assembled devices, in a vessel and reduce the pressure. The process duration is dependent on the capacity of the vacuum pump and the volume of the vessel. The plastic parts or devices can be placed in an open bag or container inside the vessel. After the treatment, the bag or container is removed. All surfaces that are exposed to air during the pressure reduction will become permanently discharged.

The low-pressure charge-removal process is part of an approved US patent¹⁴ and a PTC patent application by AstraZeneca.¹⁵ In the application, it is shown that the use of lowpressure treatment can increase the delivered dose, reduce the amount of drug retained in the DPI and lower the variability of the dose (Figure 5). The degree of improvement is highly dependent on the device, formulation and API. Published data show that, in the case of a Bricanyl Turbuhaler, the dose increased by 15% and the variability decreased by 5%.

CONCLUSION

The electrostatic charging of a DPI during manufacturing and handling can have a strong influence on the performance and the dosing uniformity. An effective removal



Figure 5: Performance improvement after low-pressure treatment.14,15

of the triboelectric charge improves the dose size and decreases drug retention in the device, as well as reducing the dose variability. Using the pressure reduction method is suitable for efficient large-scale industrial charge elimination.

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.

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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 is the inventor behind more than 40 patents and 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 2014.

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THE APPLICATION DIVERSITY OF METERED PUMP-BASED SOFT MIST DEVICES

In this article, Marie-Christine Klein, PhD, Head of Development & Regulatory Affairs, Andreas Bilstein, PhD, General Manager, and Caroline Hoffmann, PhD, Project Manager, Development & Regulatory Affairs, all at URSATEC, discuss the underlying techniques involved in the use of metered pump-based soft mist devices and their application diversity.

The respiratory tract fulfils the physiological functions of vocalisation, protection against contaminants and active gas exchange between the blood and the atmosphere. Being exposed and the first line of defence, it is also a common site for infections and is subject to inflammatory events that can lead to chronic inflammatory diseases. As such, drug targeting to the distinctive parts of the respiratory tract is crucial in managing the treatment options.

The nose and the nasal cavities, with their angled architecture and the filter function of the epithelium, are a perfect chaperone for aerosols on their way to the lower respiratory tract. Together with the pharynx (throat), the nose and the nasal cavities create the upper airway, which in terms of inhalation is followed by the lower respiratory tract containing the larynx, the trachea, the bronchi and the lungs. The histological characteristic of each section is adapted to the respective function, which is for the so-called conducting zone (nose to

> "Drug targeting to the distinctive parts of the respiratory tract is crucial in managing the treatment options."

terminal bronchioles) to filter and warm the air as a prerequisite for the gas exchange that takes place in the respiratory zone, with the lungs as the main respiratory organs.

The upper respiratory tract, with its nasal cavities, constitutes an interesting entry of drugs for systemic uptake and even provides a way to bypass the blood-brain barrier by using the olfactory pathway for direct targeting of brain tissue. The intranasal route can overcome the hepatic first-pass effect, which results in higher bioavailability of the drug in a lower dosing – and consequently less side effects.

The limitations of the nose-to-brain target route are mainly the small volumes $(25-200 \ \mu$ l) that can be applied to the nasal cavity, which may limit the use to potent drugs. Furthermore, the olfactory region represents only a small surface fraction of the total cavity (5.2%), to be reached with a well-balanced droplet size. Also, the mucociliar clearance is an obstacle for drug delivery, since it generates a potent driving force from the respiratory cavity towards the larynx, limiting drug interaction time with the epithelium.

Drug targeting to the lower respiratory tract and the pulmonary tissue – the site of action for gas exchange – has the big advantage of having good pharmacokinetics for systemic-acting drugs to bypass the gastrointestinal (GI) tract with less effective absorbance. This is also the site of action



Dr Marie-Christine Klein Head of Development & Regulatory Affairs T: +49 0 6853 96199 0 E: klein@ursatec.com



Dr Andreas Bilstein General Manager T: +49 0 6853 96199 0 E: bilstein@ursatec.com



Dr Caroline Hoffmann Project Manager, Development & Regulatory Affairs T: +49 6853 96199 0 E: hoffmann@ursatec.com

URSATEC GmbH Marpinger Weg 4 66636 Tholey Germany

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for topically acting drugs specifically acting on the lung tissue. To successfully target a drug to the alveolates, the lower respiratory tract for metabolisation, many barriers built to prevent pathogen containing aerosols intruding into the lower airways need to be overcome and taken into consideration when creating a drug and choosing an application system. The mechanical barriers created by the architecture of the respiratory tract, and chemical and immunological barriers posed by the respective inhabitant cells and their secretion products, each lower the probability of successful drug bioavailability. Moreover, some clinical conditions lead to extensive mucous production or bronchoconstriction, which can increase the barriers for drug delivery.1

LARYNX AS AN INTERESTING TARGET SITE

Whereas the deep lung and the anterior nasal cavity are well-known drug targets, with many different devices on the market, the deep nasal cavity and the connection between the nasal cavity and the deep lung (trachea, larynx, voice cord) are not targeted specifically by many devices so far. The deep nasal cavity as an interesting area to be targeted for local application was described in issue 131 of ONdrugDelivery.²

The larynx, as part of the conducting zone that is inevitably passed during inhalation, is also worth looking at with regard to a potential drug target for some indications. Using the larynx route for rehydration therapy and airway hygiene is a simple and potentially highly effective idea. There are studies that show that poor hydration has a negative effect on infection protection, which made affected individuals more susceptible to covid-19.^{3,4}

The underlying mechanism for why airway dehydration has this impact is that inhaled contaminants are not filtered in an ideal way. Dehydration leads to thinning of the upper airway lining fluid, decreases the beat frequency of cilia and impairs epithelial cells. Of course, this not only holds true for SARS-COV2 - it applies to other airborne infections as well as allergies, asthma and chronic obstructive pulmonary disease,3 as well as general air dryness exposure, as in air-conditioned rooms. Furthermore, the larvnx also poses an interesting drug target for topical cancer treatment or local anaesthesia, the latter already being targeted by a spray nozzle unit (SNU)-based product, the Trachospray.5,6

"The ability of inhalers to target medication to a body part that is accessible from the outside has increased the treatment options for different highly prevalent diseases."

DIFFERENT INHALING DEVICES FOR TARGETING THE LOWER AIRWAYS

The ability of inhalers to target medication to a body part that is accessible from the outside has increased the treatment options for different highly prevalent diseases.

Metered dose inhalers (MDIs) store the medication in pressurised form. Using propellants for aerosol production, a high velocity of 8 m/sec during a time interval of 0.1-0.4 s is achieved.7 The lung deposition overall is 10%-20%, differing with formulations and the application by the patient, which is the main drawback because of the difficulty of timing inhaler use correctly.8 The cold sensation at the back of the throat as the propellant evaporates may be destructive since the patient may stop inhaling intuitively. Nevertheless, MDIs are widespread, relatively cost effective and contain many doses. The disadvantages are being partially overcome by developments such as breath-actuated MDIs, which help to co-ordinate firing and inhaling, and MDIs with spacers that leave the dose of medication in the spacer without being blown away.8 These further developments come at the cost of a less handy design and portability.

Dry powder inhalers are breath actuated and do not need any propellants to generate the aerosol. The need for a forceful inhalation to disperse the powder is crucial for the application and, at the same time, the major drawback as it requires good understanding of the device and training of the user.

Nebulisers use either jet, ultrasound or vibrating mesh to nebulise a liquid formulation. Each aerosol generation technique comes with its own advantages and disadvantages, but the overall idea is to allow the patient to inhale during normal tidal breathing, without the need for timing the firing or breathing forcefully. This may be attractive for patients with co-ordination problems – or in emergency cases. Nebulisers have a static design, are more expensive and sometimes struggle with correct dosing and lung deposition.⁹

Soft mist inhalers allow a handy design and make the use of propellants unnecessary. Multidoses of a liquid formulation are stored and a slow-moving aerosol is created by a precisely engineered nozzle system. The slow velocity is the main difference compared with pressurised MDIs (pMDIs) and the idea is to give the patient enough time to co-ordinate the firing and inhaling of the aerosol through the upper and lower respiratory tract.

HUMAN FACTORS IN DRUG DEPOSITION TO THE RESPIRATORY TRACT

The above walkthrough of the different inhalers makes it clear that the operating principle differs a lot from device to device – and the patient or physician has to choose the device that best fits the abilities of the operator and the underlying disease and its treatment regimen. Training and successful handling of the device have a significant influence on the success of drug targeting.¹⁰

REQUIREMENTS FOR THE DROPLET/PARTICLE SIZES OF THE INHALING DEVICE

Besides dealing with the anatomically and cellular circumstances and the exogenous factors by handling that influence the drug deposition, the drug needs to be transformed in droplet/particle sizes that are ideal to reach their distinctive site of action.

If the aerosol is entering the upper respiratory tract through the nose, small droplets < 5 μ m will not usually stay in the nasal cavity but will find their way to the lower respiratory tract. The higher the droplet size, the more the anterior parts of the nasal cavity will be targeted. Smaller droplets/particles have a higher chance of reaching the posterior parts of the nasal cavity, including, for example, the olfactory region, an ideal target for nose-to-brain delivery. It is not yet clear what is the best droplet size to reach the olfactory region, but there are suggestions that a diameter of ~10 μ m may be favourable.

In oral inhalation, particles > 5 μ m mainly deposit in the oral cavity, the larynx and the trachea – i.e. the upper and conductive airways. A deep-lung deposition is reached with a particle size of 0.5–4 μ m,

"A device technology that allows targeting of the different areas using the same base technology has been missing so far."

whereas 4-5 μ m sized particles deposit in the bronchi. Particles smaller than 0.5 μ m are being exhaled and are not therapeutically active.¹¹ As discussed, the different regions are targeted currently by different devices using diverse technologies to generate the particles. A device technology that allows targeting of the different areas using the same base technology has been missing so far.

SOFT MIST APPLICATOR WITH SNUS

The production of aerosol by the principle of Rayleigh break-up (the generated jet breaks up automatically in droplets) inside the platform of an MDI or a nasal spray is a



Figure 1: Median droplet sizes (μm) of inhalers or nasal spray containing different pore sizes of the SNU.

straightforward development that has a broad application spectrum and adaption possibilities that allow flexible therapeutic options for different target sites of the upper and lower respiratory pathways. The liquid is dispersed into droplets by mechanically pressing the liquid through a microchip with pores (SNU) and succeeds in



producing a very constant particle size distribution and delivery rate. All droplets are twice the size of the hole in the chip. By changing the diameter of the hole in the spray nozzle, the droplet size can be engineered for optimal performance.12,13 For generation of the necessary force to generate the droplets, either air pressure or liquid pump technology can be used. Metered pump technology, especially when combined with the possibility of delivering preservative-free solutions, should be the ideal liquid pressure generator for a device family that profits from both the portability of a standard MDI and the generation of soft mist.

On the basis of adapting the pore sizes, different targets of the respiratory tract can be tackled in an optimised manner. Figure 1 shows droplet sizes of different devices that are adjusted in terms of pore sizes and number of pores per chip. The data reflect the medium droplet sizes in micrometres and show that the adaption succeeds in producing devices with different application scenarios.



Figure 2: Deposition study of 0.5% fluorescein in 0.9% saline formulation using a next-generation impactor was performed with an airflow rate of 20 L/min. (A) Deposition based on emitted mass; (B) Deposition in an Alberta Idealized Throat (left: lung inhaler; right: larynx inhaler).



Figure 3: A: The SoftBreezer and the SoftBreezer Larynx are designed in line with a standard portable-inhaler design. They are propellant free and preservative free and generate a fine nebulisation. Exact dosages are generated and the actuation time dependent on the pore size is 1-3 s. B: The nasal spray for the soft mist generation embeds the spray nozzle unit inside the spray nozzle of a standard metered-dose nasal spray.

To test the different pore sizes in their real distribution of droplets among the impact sites, deposition tests in an Alberta Idealized Throat have been performed and quantified. An example measurement is given in Figure 2. The deposition in the model reflects the different distribution patterns in the oral cavity and throat dependent on the pore size of the SNU. The smaller pore size of the lung inhaler constructed to reach the deep lung achieved only 58% deposition in the oral cavity, compared with 95% deposition produced by the larynx inhaler.

Another winning fact is that the novelty of the device is completely embedded in the classical device aesthetics of an inhaler and a nasal spray with approved usability profiles and forms familiar to patients (Figure 3).

ONE DEVICE CLASS – DIVERSE TARGETS

Combining spray nozzle technology with pump-based actuation and the option of preservative-free solutions enables the development of similar devices targeting "Combining spray nozzle technology with pumpbased actuation and the option of preservativefree solutions enables the development of similar devices targeting specific regions of the lower and upper airways."

specific regions of the lower and upper airways. As a consequence, synergies in the development of drug products arise as one formulation can potentially be used for local application in different target sites, which allows efficiency in terms of galenic development, manufacturing and stability studies. The targeted local application also generates the potential of optimising drug dose towards a reduced total drug uptake. Moreover, the similar product concepts may allow the patient to use just one user-friendly application technology for drugs in the entire airway, potentially minimising use errors.

ABOUT THE COMPANIES

URSATEC was founded in 1993 to accomplish one mission: the establishment of preservative-free applications based on its proprietary packaging systems in different application areas, primarily the nasal, dermal, buccal and otological fields. Having sold almost 2 billion units within the last 30 years, URSATEC systems are widely established. URSATEC is consistently expanding its business and offers a full development service, dosage systems, primary packaging materials, filling services for OTC and Rx applications to the healthcare industry, and also stands for sophisticated cosmetic products and food supplements that completely lack preserving ingredients.

URSATEC's three principal shareholders are Aero Pump (Hochheim, Germany), Gaplast (Peiting, Germany) and URSAPHARM (Saarbrücken, Germany).

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

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ABOUT THE AUTHORS

Marie-Christine Klein, PhD, is a biochemist by training and joined URSATEC in 2019. She is head of the development team, which is focusing on innovative developments in combination with URSATEC application technology, for example, in preservative-free cosmetics.

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

Caroline Hoffmann, PhD, is a chemist who joined the development team of URSATEC in 2021. She is focusing on projects revolving around inhalation applications in the context of URSATEC technology.

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NAVIGATING THE CHALLENGES OF BRINGING INTRANASAL DRUG FORMULATIONS AND DEVICES TO PATIENTS

In this article, Joe Neale, Head of Innovation, Development and Programme Management, and Ross Errington, Head of Drug Product Development, both of Recipharm, explore the obstacles and opportunities facing the intranasal drug delivery market and how manufacturers can overcome them by harnessing innovative platforms like Unidose[®] Xtra.

The inhalation drug delivery market for both oral and nasal applications is expanding rapidly, offering a promising alternative to traditional routes of drug administration, such as solid-dose oral or injectable methods.

Key to this expansion is the diversification of administration routes for biologic drugs. Traditionally, these types of drugs were limited to parenteral administration – to preserve the API before reaching its target location. These APIs also pose bioavailability challenges to the oral route, as the large molecules within them may have difficulty passing through the membrane of the intestines into the bloodstream, whereas small-molecule APIs can do so with ease.

Advancements in formulation technology now allow for greater exploration of alternative delivery methods, such as inhalation.

A key segment of the inhalation market, intranasal drug delivery, offers additional treatment benefits to patients. Nasal inhalation therapies provide a larger surface area for absorption, as well as direct access to the central nervous system for faster action. These treatments can be administered in various forms, including solutions, suspensions, gels and powders. The selection of the appropriate form depends on the characteristics of the drug, the targeted tissue and the desired rate of absorption.

Drug developers must overcome a range of formulation challenges to ensure efficacy, safe dosage and ease of administration for patients. Manufacturers must also contend with device customisation to optimise spray performance and ensure that they meet the requirements of each treatment.

THE THERAPEUTIC NEED FOR INTRANASAL DRUG PRODUCTS

The global intranasal drug delivery market is projected to reach US\$71.3 billion (£59 billion) by 2026.¹ A number of drivers are behind this rapid growth.

The rapid onset of action of intranasal drug delivery products is highly attractive to drug developers. This is possible due to the

"Intranasal therapies offer more innovative treatment options for a wide variety of conditions."



Joe Neale Head of Innovation, Development and Programme Management



Ross Errington Head of Drug Product Development

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high surface area of accessible blood vessels within the nasal cavity, allowing for fast absorption into the patient's bloodstream. This also results in improved bioavailability for the drug product compared with oral administration, as nasal delivery allows the formulation to bypass the gastrointestinal system and hepatic metabolism.

As a result, intranasal therapies offer more innovative treatment options for a wide variety of conditions. They are particularly attractive for the treatment of chronic and neurological disorders,² such as chronic pain, inflammation and headaches. As a non-invasive treatment, this targeted delivery also means that there are typically fewer side effects for patients and a user-friendly, convenient and needlefree experience. This subsequently leads to a higher level of patient acceptance and compliance, as well as easier administration for healthcare professionals (HCPs).

Research has also shown that intranasal delivery of vaccines can result in a more robust immune response compared with delivery of the same vaccine via a traditional injection.³ Furthermore, this administration method enables user-independent delivery of nasal sprays – an essential, even life-saving, treatment in acute settings, emergencies and critical care situations, such as opioid overdoses or seizures. As a result, the need for intranasal drug delivery is increasing in the medical field as it offers a safe and efficient way to deliver medication to patients.

THE COMMERCIAL NEED FOR INTRANASAL DRUG PRODUCTS

From a commercial perspective, intranasal drug products offer a promising opportunity for drug developers to extend the lifecycle of their biologic products. For example, the patents for many biologics that have been on the market for a long time are set to expire soon, meaning that drug developers are facing

> "Intranasal drug products offer a promising opportunity for drug developers to extend the lifecycle of their biologic products."

"Research has shown that intranasal delivery of vaccines can result in a more robust immune response compared with delivery of the same vaccine via a traditional injection."

the challenge of finding new ways to extend their ownership of their discoveries amid competition from biosimilars.

By reformulating their biologics as an intranasal product, developers can extend their patent protection and maintain market exclusivity. This is because intranasal drug delivery is considered a novel administration route and can be considered as a new formulation, which can make an existing biologic eligible for new patents.

Other commercial opportunities include:

- Faster vaccine delivery the postcovid-19 drive to deliver vaccines on a mass scale at speed has led to more research into the mucosal delivery of vaccines to shorten administration time.
- Streamlined regulatory requirements as intranasal drugs are considered noninvasive and pose a lower risk of adverse reactions, the regulatory pathway for intranasal drugs is often less rigorous than for parenterally delivered biologics.
- Demand for self-administration – the demand for patients to be able to administer their own treatment is increasing, and intranasal drug delivery provides added convenience by enabling patients to take their own medication without visiting an HCP.
- Greater patient-centricity a focus on patient-centricity makes intranasal treatments a more convenient option for individuals who may need to take a vaccine for specific reasons, such as tropical disease vaccinations prior to going abroad.

THE CHALLENGES OF MANUFACTURING INTRANASAL DRUG PRODUCTS

In order to bring the benefits of intranasal drug products to patients, manufacturers must overcome several barriers across both the drug formulation and the design of drugdelivery devices. These barriers include:

• Compatible delivery device design – ensuring that the delivery device works well with complex formulations, such as small molecules, peptides, vaccines and biologic formulations, can be difficult when administering intranasally.

- Optimising spray design optimising the effectiveness of nasal sprays requires a high level of understanding of how the formulation and its delivery device interact with one another. The design of the spray nozzle, for example, has an impact on the droplet size and distribution of the formulation, which in turn affects the drug's bioavailability and speed of action.
- Tailoring to overcome excipient challenges – the addition of excipients can alter the viscosity and sprayability of the product, further influencing its effectiveness.
- Engineering the force of actuation the force of actuation when administered must also be carefully engineered in accordance with the characteristics of a specific drug formulation. This is because shear forces during administration can damage the API in some large-molecule formulations, risking rendering the treatment ineffective.
- Ensuring dosage uniformity biologic treatments require optimal spray techniques to ensure the correct dosage, with improper techniques resulting in most of the formulation being deposited on the walls of the nose, rather than penetrating further into the nasal cavity, impacting dose uniformity.
- Aseptic/sterile formulation development – maintaining sterility during filling in the drug device's primary container is key to launching a successful intranasal drug product.

Manufacturers must ensure compatibility for the drug and its delivery device and consider patient usability for self-administration. Formulators must also find ways to overcome the restricted bioavailability due to the low solubility of some of these drugs. Furthermore, the nasal cavity is a sensitive area, and the use of certain medications can cause irritation or discomfort for some patients, particularly in paediatrics. This can be particularly problematic for medications that need to be administered on a regular basis.

OVERCOMING THE CHALLENGES OF INTRANASAL DRUG DELIVERY

Recent technological advances in the market for both oral and nasal inhalation devices have meant that pharmaceutical companies now have more options available to overcome these issues than ever before. One such example is the proprietary Unidose[®] Xtra device by Recipharm.

This device was created in collaboration with a pharmaceutical development specialist to establish a "formulation-to device interface specification" for several potential single-dose nasal therapies. This specification informed the device design process, which adopted a platform approach, enabling it to be easily customised to meet the specific formulation and performance needs of the customer with minimal redesign required.

As demand for more convenient and comfortable drug delivery routes increases, devices such as Unidose[®] Xtra have been developed to accommodate peptides and vaccines, and have the potential to accommodate sensitive biologic molecules – with alternative nozzle technologies available, enabling delivery in a single dose for a variety of formulations. This makes Unidose[®] Xtra ideal for a wide range of treatments, such as vaccines, opioid overdose, pain relief, seizures and anxiety.

The device can be adjusted to suit formulations with a range of viscosities, and the speed and force of actuation required can be adjusted to ensure that the drug is delivered at the optimal rate for maximum efficacy. This level of customisation is particularly beneficial for users who may have limited strength or dexterity – such as geriatric, disabled or paediatric patients.

ABOUT THE AUTHORS

Joe Neale is a biochemist by training, with a master's degree in Translational Medicine. He has more than 25 years of experience developing products within the diagnostic, medical device and combination product fields.

Ross Errington is a chemist by training. He has 30 years' experience in pharmaceutical product development and manufacture, specialising in inhaled delivery systems. Unidose[®] Xtra is designed to allow patients to easily and safely administer their own medication, without the need for assistance from a healthcare professional, or for rapid use in emergency situations by a caregiver or the patient themselves.

GETTING INTRANASAL INNOVATIONS INTO THE HANDS OF PATIENTS

While intranasal drug delivery and devices offer promising innovations, drug developers looking to harness their potential have several considerations to take into account. Given the complexities of formulating and adapting a drug product to an intranasal drug delivery device, developers must ensure that they have not only the expertise but also the capacity, equipment and regulatory support to successfully bring it to market.

But by collaborating with specialist partners in this area, drug developers can overcome these challenges. The right partner will be equipped with the knowledge, capabilities and state-of-the-art facilities to support the development and manufacture of such innovations, no matter how complex the requirements. For example, by partnering with a company like Recipharm, which has expertise in innovative platforms like Unidose® Xtra alongside formulation development, pharmaceutical and biotech companies can benefit from its experience and resources to develop and manufacture intranasal drug products more efficiently and effectively.

These partnerships can be instrumental in getting intranasal innovations to patients, as they provide the necessary support for the development and manufacture of these products, which can be complex and difficult to produce. This collaboration is key to enabling the expansion and diversification of biopharmaceutical drugs and treatments, resulting in more cost-effective and patient-centric products.

HARNESSING INTRANASAL DRUG DELIVERY TO EXTEND THE DRUG PRODUCT LIFECYCLE

The potential of intranasal drug delivery extends much further than patient and HCP benefits – it also offers the opportunity for developers to extend the lifecycle of their existing products. As patents for injectable and oral biologics expire, drug product owners are looking for innovative solutions to prolong the lifecycle of their products. With the generics and biologics markets growing increasingly competitive, it is important for drug developers to explore all options for product lifecycle management. Intranasal drug delivery offers a promising solution, enabling companies to streamline the redevelopment process and enhance dosing precision, as well as improve the cost efficiency of the devices themselves. Patient and HCP benefits will also play a role in lifecycle management, with intranasal delivery offering multiple benefits.

Working closely with device experts like Recipharm will give intranasal drug developers access to the tools they require to take advantage of advancements in intranasal delivery technology. Additionally, these partnerships can help to extend the lifecycle of a wide range of drug products well into the future, whilst also offering significant patient convenience and costefficiency benefits.

ABOUT THE COMPANY

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

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THE POTENTIAL AND THE CHALLENGES OF NASAL VACCINATION

In this article Julie Suman, PhD, Vice-President, Scientific Affairs, and Nektaria Karavas, Director Business Development, Prescription Division, both at Aptar Pharma, discuss the challenges and opportunities of intranasal vaccination – showcasing current understanding for both liquid and powder products. Experimental studies highlight critical issues, the performance of commercially available devices and developments in formulation practice.

Nasal vaccines are intuitively logical for pathogens that enter via the nose, so it is unsurprising that the SARS-CoV-2 pandemic has reinvigorated interest in intranasal vaccine development. Globally there is growing recognition that such products could support efficient long-term management of the SARS-CoV-2 virus, as evidenced by remarks from the White House Summit in the US on next-generation vaccines.¹

Four intranasal vaccines have already been approved for use,² most recently iNCOVACC (Bharat Biotech, Hyderabad, India) and Convidecia Air[™] (CanSino Biologics, Tianjin, China) – and many more are in development.¹ More generally, the attractions of intranasal vaccination point to potential for other indications, such as respiratory syncytial virus.

Developing nasal vaccines is complex but the associated knowledge base is advancing rapidly, led by companies such as Aptar Pharma, which offers cutting-

> "Mucosal immunisation has the potential to alter disease trajectory by tackling the virus earlier, slowing any advance from the nasal cavity."

edge solutions and services to support commercialisation – incorporating an expanded skillset in nasal formulation by Nanopharm, an Aptar Pharma company.

WHY VACCINATE INTRANASALLY?

Intranasal vaccination offers the potential of mucosal immunity. The SARS-CoV-2 virus enters the body via the nasal and oral passages, subsequently replicating, shedding and translocating to other areas, notably the lungs. Mucosal immunisation has the potential to alter this disease trajectory by tackling the virus earlier, slowing any advance from the nasal cavity. In addition, mucosal immunity may prevent disease spread by limiting viral shedding. By enabling mucosal plus systemic immunity, alone or in combination with established intramuscular vaccines, intranasal vaccination offers better protection against SARS-CoV-2, along with improved patient outcomes.

Clearly, this clinical advantage is critical, not just for SARS-CoV-2 but also for other respiratory viruses that share its method of attack. But intranasal vaccination also comes with additional practical advantages, including:

- Elimination of needles, improving safety for healthcare practitioners and encouraging uptake by needle-phobic patients
- Easy delivery, including potential for self-administration



Dr Julie Suman Vice-President, Scientific Affairs T: +1 443 538 8373 E: julie.suman@aptar.com



Nektaria Karavas Director Business Development, Prescription Division T: +1 845 639 3660 E: nektaria.karavas@aptar.com

Aptar Pharma

250 North Route 303 Congers New York 10920 United States

www.aptar.com/pharmaceutical

- Reduced waste by eliminating use of syringes, bandages and alcohol swabs
- Opportunities to minimise cold-chain requirements with powder-based formulations.

DEFINING REQUIREMENTS FOR THE DELIVERY OF NASAL VACCINES

Figure 1 highlights the nasal-pharyngealassociated lymphoid tissue (NALT) that constitutes the nasal immune system and is consequently the primary target for intranasal vaccination. Dendritic cells in the nasal epithelia provide a secondary route for vaccine entry. Current research also indicates the importance of targeting the nasopharynx and throat.

To make an effective nasal vaccine, the device and formulation parameters need to be manipulated to transport the antigen efficiently to these target sites. The need for effective targeting is exacerbated by the risk of nose-to-brain drug delivery, which is reduced by minimising deposition in the olfactory region/superior turbinate. Particle size is a defining parameter with respect to *in vivo* deposition, with a delivered droplet or particle size in the region of 20–40 μ m typically optimal. Particles in the sub-10 μ m size range are prone to pulmonary delivery – triggering additional safety/toxicity concerns.

Other aspects of the physiology of the nasal cavity also require careful consideration. Firstly, it is a mildly acidic environment. Formulations that mirror this acidity and are also isotonic are therefore better tolerated. Positively charged particles interact more effectively with cell membranes and are associated with a better immune response. Enzymatic activity is limited compared with the gastrointestinal tract, but mucociliary clearance is a defining concern.

Mucociliary clearance is highly effective in sweeping contaminants towards the back of the nasal cavity, typically renewing the mucus layer every 15–20 minutes in a healthy adult. To navigate it, antigens must diffuse rapidly from the formulation into target cells. This is a major challenge, a clear differentiator relative to formulation for intramuscular delivery and a complicating factor for a direct switching of delivery routes.

Developing intranasal vaccines to meet these outlined requirements involves the twin-track optimisation of device and formulation – the tuning of a formulation for optimal performance in a specific



Figure 1: Side view of the nasal cavity highlighting the NALT, the primary target for intranasal vaccination.

commercially viable device, taking into account patient technique. Aptar Pharma supports customers through this complex optimisation process with an established portfolio of device platforms and exemplary formulation skills, thanks to the knowledge base at Nanopharm.

FORMULATING FOR INTRANASAL VACCINATION, LIQUID OR POWDER

Aqueous formulations for intranasal vaccination are often relatively simple. Formulators have comparatively few approved ingredients to work with, creating a need for skilful optimisation with the tools available. Some or all of the following ingredients are commonplace:

- Adjuvants
- Buffers
- Amino acids
- Sugars
- Viscosity modifiers
- Osmolality modifiers.

"Formulators must safeguard the stability of the antigen, preventing aggregation and physical and/or chemical degradation, and maximise immunogenicity."

nasal-pharyngealassociated lymphoid tissue

Using these components, formulators must safeguard the stability of the antigen, preventing aggregation and physical and/ or chemical degradation, and maximise immunogenicity. Adjuvants promote a stronger immune response although choice is limited to, for example, certain bacteria, cytokines, nucleic acids and viruslike particles. Within stability constraints, pH and osmolality can be optimised for comfort/tolerance. Viscosity modification is an important lever for efficient dispersion with the device of choice. Increasing viscosity may also improve retention in the nasal cavity and slow mucociliary clearance.

Dose volume is an important consideration for aqueous nasal vaccines, with considerable variation observed in commercial products. For example, influenza vaccine FluMist (MedImmune, MD, US) involves the delivery of a single 200 μ L spray shot, while the total dose volume for iNCOVACC is 500 μ L delivered as a series of nasal drops. Optimising dose volumes for specific delivery platforms remains a work in progress.

Formulation as a powder is appealing as it addresses certain challenges associated with aqueous nasal vaccines. Vaccine powders negate any requirement for coldchain storage, enable the delivery of higher payloads and offer inherently enhanced stability for biologics. Just like their aqueous counterparts, powder formulations include the antigen and adjuvant (if used), but often other uniquely essential components too, such as mucoadhesive agents, bulking agents and matrix stabilisers (Figure 2).



Figure 2: Powder formulation calls for the engineering of particles larger than 10 μ m in which the required constituents are uniformly distributed in a form that promotes rapid and effective activity upon deposition.

Preparation method is an important consideration for powder formulations since sophisticated particle engineering is required to ensure the uniform distribution of all the required components in a form that promotes rapid release and activity, postdeposition. As with aqueous formulations, the target delivered size range is >10 μ m, although the optimal size for antigen uptake by dendritic cells is in the region of just 200– 300 nm;³ nanostructured vaccine vehicles are an important area of development. Lyophilisation or freeze drying is the conventional preparation technique but "The availability of appropriate platforms for clinical and commercial use is a vital enabler for intranasal vaccine development."

alternatives such as thin film freeze drying, spray drying and/or vacuum drying are all promising with respect to producing stable dispersible particles with desirable properties for product manufacture.

DEVICE DESIGN: SURVEYING THE OPTIONS

When it comes to devices, the availability of appropriate platforms for clinical and commercial use is a vital enabler for intranasal vaccine development, for both aqueous and powder formulations. Key considerations include:

- Dispersion/deposition characteristics
 is the device effective in dispersing particles or liquid to the required size?
- Ease of use will healthcare professionals be able to deliver the vaccine efficiently with minimal training?
- Patient independent performance will every patient receive the required dose, regardless of technique? Even with self-administration?



Figure 3: Aptar Pharma offers a comprehensive range of devices for intranasal vaccination, antivirals and immunostimulants that facilitate efficient development through to commercialisation.

- Availability is the device suitable for clinical trials? Can it be scaled rapidly for commercial delivery?
- Compatibility with existing vaccine platforms can the device be used with existing vaccine bottles and vials in formulation manufacture, storage and delivery?
- Price will the overall vaccine solution be commercially viable?

These considerations guide the ongoing evolution of Aptar Pharma's portfolio of vaccine delivery platforms (Figure 3). The company's range includes options for both aqueous and powder formulation, prefilled/ready to use or transfer, single or multidose. BiVax and LuerVax are suitable for use from clinical trials to commercial use, while CPS, Unidose and Bidose already fulfil market requirements for off-the-shelf solutions for commercial use.

BiVaX is supplied as a complete assembled transfer device for aqueous or reconstituted formulations. Suitable for use with established vaccine containers – standard vials – it comes in two variants, 200 or 500 μL. An integrated dose divider simplifies dosing to each nostril.

LuerVax is a nozzle-based device for use with any Luer lock syringe. It can be used to develop either a prefilled-syringebased solution or for vaccine transfer at the point of need. A dose divider enables the sequential delivery of two equal doses.

CPS is a multidose spray delivery platform for dose volumes from 50 to 140 μ L. Interfacing directly with multidose vials, for easy product manufacturability, it is suitable for preservative-free formulation and can be irradiated, if necessary.

Unidose Powder and Bidose Liquid are convenient, prefilled, primeless single-use devices for the delivery of a single powder dose (10–80 mg) or two aqueous doses (200 μ L in total), respectively. Offering easy, one-handed actuation and patient independent performance, they are manufactured at commercial scale for marketed products.

The following case studies highlight aspects of performance of some of these devices and exemplify the work Aptar Pharma does to help customers use them to successfully develop intranasal vaccines.





Figure 4: A shallower holding angle and shorter insertion depth favour deposition in the turbinates, suggesting better performance for vaccine delivery.

Developing Nasal Vaccines:

Exploring the Impact of Delivery Technique Figure 4 shows data from an investigation of the impact of the holding angle, the angle of the device relative to the horizontal, and insertion depth on the deposition performance of BiVax. The graphs show data for holding angles of 30°, 45° and 50° at an insertion depth of 18 mm. Deposition data were measured using a nasal cast (Aeronose) for the nose, turbinate and nasopharynx regions.

The results show minimal deposition in the nasopharynx, where the NALT would be expected to lie, but relatively high levels of deposition in the turbinates. The potential for mucociliary clearance to sweep formulation from the turbinates to





Formulation	Polydispersity Index	Hydrodynamic Diameter (nm)	Zeta potential (mV)
Empty liposomes	0.24 ± 0.02	404.80 ± 11.59	+ 37.40 ± 1.13
Empty liposomes after spraying	0.22 ± 0.01	432.33 ± 3.59	+ 34.23 ± 0.98
DNA-loaded liposomes	0.20 ± 0.03	661.33 ± 27.14	+ 36.43 ± 0.97
DNA-loaded liposomes after spraying	0.13 ± 0.03	586.93 ± 11.05	+ 34.40 ± 1.07

Table 1: DLS measurements for empty liposomes formulation and DNA-loaded liposomes formulation before and after spraying show that structure is successfully preserved through the spraying process (average \pm standard deviation, n = 3).

the NALT make these data significant for vaccine delivery. Both holding angle and insertion depth affect deposition profiles, with a shallower holding angle and shorter insertion depth favouring higher deposition in the preferred area.

Developing Nasal Vaccines: Considerations for Nucleic-Acid-Based Formulations

While nasal vaccines may use different platforms, including nucleic acids such as mRNA and DNA, such nucleic acids are prone to degradation - necessitating the use of novel formulation strategies for successful product development. In this example, Nanopharm collaboration with the University of Bradford (UK), successfully developed and characterised a liposomal suspension loaded with a model small nucleic acid - herring sperm DNA - for nasal delivery.4 A nasal formulation matrix was made using trimethyl chitosan (TMC) as a mucoadhesive agent with adjuvant properties. The resulting formulations, with empty and DNA loaded liposomes, were put into an Aptar preservative-free CPS pump, 100 µl for *in vitro* performance evaluation.

Both empty and DNA-loaded liposomes were successfully manufactured and formulated for nasal delivery, with the pH and osmolality of the resulting formulations compatible with the nose. The droplet size distribution (DSD) of the emitted sprays (Figure 5) was in the range for nasal deposition, although towards the upper limit. Reducing the amount of TMC could help in producing smaller droplets, thereby potentially increasing deposition at the target region (NALT and turbinates).

Table 1 shows DLS data measured for the formulations before and after spraying. These confirm that liposomal structure and size is successfully preserved through the spraying process.



Figure 6: Aptar Pharma service offerings.

"Intranasal vaccination has broad potential for both prophylactic and therapeutic applications."

CONCLUSION

Drawn into the spotlight by the SARS-CoV-2 pandemic, intranasal vaccination has broad potential for both prophylactic and therapeutic applications. Realising this potential is high on the priority list for many pharmaceutical companies and Aptar Pharma has built a service offering to help. From cutting-edge formulation expertise from Nanopharm and an unrivalled portfolio of ready-to-go device platforms, through regulatory filing to patient training and onboarding tools, the company's integrated family of solutions can help clients progress faster to a better intranasal vaccine solution (Figure 6).

For more information about nasal vaccination, visit: https://www.aptar.com/ products/pharmaceutical/nasal-vaccines

ABOUT THE COMPANY

For pharma customers worldwide, Aptar Pharma provides drug delivery expertise, from formulation to patient, providing innovative drug delivery systems, components and active material solutions across a wide range of delivery routes, including nasal, pulmonary, ophthalmic, dermal and injectables. Aptar Pharma provides early-stage Services to commercialisation support to accelerate and derisk the development journey. With a strong focus on innovation, 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.

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ABOUT THE AUTHORS

Julie Suman, PhD, is the Vice-President of Scientific Affairs for Aptar Pharma. She manages strategic scientific planning and Aptar's Scientific Advisory Board. Dr Suman is also the co-founder of Next Breath. She holds a BSc in Pharmacy from Duquesne University (Pittsburgh, PA, US)) and a PhD in Pharmaceutical Sciences from the University of Maryland (Baltimore, MD, US). She is a co-editor for Respiratory Drug Delivery Proceedings, an international symposium, and an Affiliate Assistant Professor in the Department of Pharmaceutics, School of Pharmacy, Virginia Commonwealth University (VA, US).

Nektaria Karavas is the Global Director of Business Development for Nasal Vaccines, Antivirals and Immunostimulants at Aptar Pharma. Ms Karavas joined the company in 2004 and has held various commercial roles executing long-term strategy within key customer and global accounts in North America, focusing on nasal drug delivery. She has contributed to multiple nasal development programmes, and supported commercial scale-up and product launches for new drug applications using an Aptar delivery device for key pharmaceutical clients across different therapeutic indications. Ms Karavas holds a BSc from McGill University (Montreal, Canada).

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ACCELERATING THE GO-TO-MARKET OF NASAL COMBINATION PRODUCTS WITH INTEGRATED SOLUTIONS

In this article, Séverine Duband, Category Director, Drug Delivery Devices, and Audrey Chandra, Category Manager, both at Nemera, discuss emerging trends in the ear, nose and throat market and how Nemera can assist in bringing new devices to market.

The overall ear, nose and throat (ENT) market was heavily impacted by the covid-19 pandemic as a result of mask-wearing, lockdowns and reduced social interaction. These factors led to reduced exposure of individuals to respiratory viruses and allergens. People also avoided going to pharmacies for non-vital medicines during the pandemic, leading to a significant 9.5% drop in over-the-counter (OTC) demand in 2020. With the return to normal life post-pandemic, there was a clear rebound in the market during 2021, with an increase of 5.7%, which required a fast, agile turnaround from the pharmaceutical industry to secure supply for patients needing medication. The ENT market is estimated at 1.9 billion devices, with the majority of drug products being for nasal applications.1

ENT MARKET TRENDS OUTLOOK

Topical therapies still dominate the nasal market for the treatment of allergic rhinitis, sinusitis and nasal congestion. Allergic rhinitis is mostly seasonal and is usually relieved by a nasal spray containing topical-acting medication. Corticosteroids are currently the first-line treatment for allergic rhinitis as they reduce swelling, inflammation and mucus secretion in the nasal cavity. This long-standing market is still very dynamic following new pipelines from the generic players, representing opportunities for growth. In fact, currently, 65% of topical treatments are generics.² "With extensive experience in intranasal delivery and injectables, Nemera is developing a reliable, easy-to-use and safe nasal vaccine solution. The concept device is compatible with existing prefilled Luer lock syringes and comprises a nozzle and a dose divider."

Most of these topical treatments are available OTC. In many developed countries, OTC regulations have become increasingly stringent, approaching Rx drugs dossier requirements and strengthening barriers to entry to ensure patient safety. For instance, the recent medical device regulations for the European market provide an opportunity to upgrade the required standards for raw material compliance, control strategies and product documentation, as well as for the registration of OTC drug products. This implies a similar level of stringency as that of prescription-bound solutions.

The nasal route is non-invasive and does not require intervention from healthcare professionals. Unlike injectables, patients can self-administer their medication with rapid onset. Nasal administration offers better bioavailability as it avoids the hepatic



Séverine Duband Category Director, Devices E: severine.duband@nemera.net



Audrey Chandra Category Manager E: audrey.chandra@nemera.net

Nemera

Immeuble Eklaa 63-65, avenue Tony Garnier 69007 Lyon France

www.nemera.net
first-pass effect, which could be encountered when taking medications orally. Nasal devices are needle-free, which increases the patient acceptance level, leading to positive therapy outcomes following improved patient adherence and compliance.

More recently, there has been growing interest and further research in delivering drugs through the nose for systemically acting therapies by targeting nasal turbinates. Turbinates occupy a large surface area of the nasal mucosa and are highly vascularised, offering a convenient pathway for systemic delivery.

A rising number of prescribed systemic drugs originally administered in injectable forms have been successfully repurposed and made available as unit-dose nasal sprays. Patients and caregivers are now able to administer a one-shot spray easily and rapidly to manage emergency and crisis situations, such as overdoses, seizures and migraines. This allows therapies to target a broader patient population, increasing access to different end-user groups. To ensure patient safety, regulatory bodies impose strict regulations on this alternative route to optimise drug efficacy, requiring equivalence to their injectable counterparts, especially for life-saving drugs. The reliability of the device plays a key role in ensuring success in saving patients' lives.

A FULL RANGE OF PUMP SOLUTIONS FOR TOPICAL, MULTIDOSE ADMINISTRATION



Figure 1: Nemera provides a comprehensive range of multidose pumps and offers novel technologies to tap into new market needs.

Nemera's expertise in spray characterisation and bioequivalence has made it possible to commercialise a wide variety of combination products (Figure 1). Today, millions of patients rely on Nemera's devices to relieve the symptoms of chronic conditions, such as allergic rhinitis, sinusitis or nasal congestion.

SINGLE-METERED DOSE FOR SYSTEMIC DRUG ADMINISTRATION

Multidose nasal spray pumps have their place in chronic therapies, but not in acute applications. When use of the device is required to be punctual, meaning that repriming might waste valuable seconds; also, a large volume of a drug content could be wasted as it is a one-off usage. Consequently, novel therapies are starting to emerge with a precise, ready-to-use unit-dose nasal spray for emergency and crisis treatments.

Nemera's UniSpray delivers a single, metered 100 μ L dose spray and is suitable for new, repurposed or generic drugs (Figure 2). To ensure device reliability and robustness, as well as compliance with regulatory requirements, UniSpray has undergone different human factors studies, design verification and rigorous processes, assuring both patient safety and ease of use.

Excellent spray plume and characteristics



Figure 2: UniSpray, a safe and reliable single, metered spray for systemic drug administration.

This single-dose nasal spray is a ready-to-use, primeless device with 360° functionality, enabling one-handed activation. The device has an ergonomic and intuitive design to ensure its correct use. Once the device is activated, the plunger is locked in its position, preventing premature activation, which is extremely critical in emergency use, visually providing a clear message that the dose has been administered. The final locking also prevents device disassembly after activation.

UniSpray is a customisable platform, offering flexibility for spray adjustment for new formulations and generics. To accelerate time to market, UniSpray is compatible with existing marketed primary drug containers and has been adapted to fit conventional filling lines. In line with this objective, for generic drugs, the preliminary bioequivalence of selected molecules is performed by Nemera, which generates initial documentation, assuring spray characteristic equivalence and consistent performance; this foundation can then be built on by customers based on their formulation (Figure 3). For new or repurposed drugs, spray performance adjustment can also be made to ensure drug administration efficacy.

INNOVATIVE SOLUTIONS TO EXPLORE NOVEL THERAPIES

Nasal Delivery of Vaccines

Vaccine research and delivery have been accelerated amid the covid-19 pandemic. The nasal route is seen as an alternative to conventional injectable forms for vaccine delivery, benefitting from nasal-associated lymphoid tissue, a region associated with the lymphatic network, which can induce a mucosal and systemic immune response. By obtaining mucosal immunity in the nasal cavity, the immune response can combat respiratory pathogens as soon as they enter the upper respiratory tract, preventing further infection. It is also more accessible for patients with needle phobia, which is especially prevalent in younger age groups.

With extensive experience in intranasal delivery and injectables, Nemera is developing a reliable, easy-to-use and safe nasal vaccine solution. The concept device is compatible with existing prefilled Luer lock syringes and comprises a nozzle and a dose divider. It contains two doses, allowing vaccine delivery for each nostril.

Bypassing the Blood-Brain Barrier Via the Nasal Route

Another promising route under investigation is the nose-to-brain pathway, presenting opportunities to offer efficient drug delivery for therapies targeting the central nervous system (CNS). Direct-tobrain delivery would mean lower doses are required, resulting in less toxicity and fewer off-target effects, as the medications mitigate the first-pass metabolism. However, anatomically, our brain is protected by the blood-brain barrier, which prevents >95% of molecules from entering the CNS from the bloodstream. Additionally, nose-to-brain delivery poses the challenge of targeting the olfactory region of the nose, which has a small surface area and is difficult to reach.

Smart Solutions For Drug Security

Electronic components are also being explored to enhance patient safety, such as by securing potent drug administrations. Opioid treatments, such as fentanyl, are used to relieve pain with rapid onset of action through unit-dose or multidose nasal drug delivery.

Fentanyl is a potent drug, used to treat severe pain, that has become the main driver of recent increases in synthetic opioid deaths. Fentanyl is used on a regular basis by patients with cancer. For multidose "Nemera has developed a smart electronic concept device with child-resistant, dose-counting and locking features – Safe'n'Spray, which offers solutions to prevent overdosing of potent drugs."

nasal spray presentations, this may lead to opioid overdose when it is not used according to the treatment posology. It is therefore crucial to consider the mode and route of administration to ensure patient safety.

With this in mind, Nemera has investigated how to manage the issue of drug overdosing using a smart nasal spray device. Nemera has developed a smart electronic concept device with child-resistant, dose-counting and locking features – Safe'n'Spray – which offers solutions to prevent overdosing of potent drugs. It is an integrated device with a reusable electronic locking unit and fingerprint identification that monitors drug dose delivery in a defined period to ensure patient safety.





Figure 4: Full turn-key solutions to support nasal combination product development.

A HOLISTIC END-TO-END PARTNER FOR THE COMBINATION PRODUCT JOURNEY

"We put patients first" is Nemera's bottom line principle. Its development team works actively to understand patients' needs through discussions and tests with patients individually or in groups, as well as with round tables with key opinion leaders. Nemera's early-stage development concepts are evaluated through user test studies to ensure a profound understanding of patients' unmet needs. The purpose of this is, ultimately, to optimise the intuitiveness, ease-of-use and usability of the device, with the aim of reducing the occurrence of misuse and optimising the device performance when handled by patients.

Delivering drug products to the target site is challenging in the case of nasal delivery. Nemera continues to work on nasal delivery system concepts, aiming to achieve delivery to specific areas of the nasal cavity for optimum drug efficacy. To illustrate this, the company uses *in vitro* testing on nasal casts that replicate human anatomy to predict *in vivo* deposition. To support its internal projects, Nemera has developed its own nasal cast, which can also support joint development efforts with customers.

Nemera's expertise with spray technology is also key to nasal drug delivery. Understanding the physics of atomisation and achieving good control of the spray characteristics are two of the R&D pillars for developing a nasal delivery device. Nemera actively works on design processes and tools to support its spray development and reduce the number of design iterations required. "Not only does Nemera offer its expertise for robust device design and state-of-the-art manufacturing capacity, but it also accompanies its customers throughout the development phases with its integrated front-end solutions."

Nemera offers design services and customised development starting from a design brief, an idea and a concept. This design phase is finalised through a validated design that can be followed by stability and clinical samples all the way down the line to industrial volumes.

Furthermore, Nemera has observed a clear growing trend in pharmaceutical companies of seeking partners who foster a holistic approach to support and help them navigate through combination product development. To this end, not only does Nemera offer its expertise for robust device design and stateof-the-art manufacturing capacity, but it also accompanies its customers throughout the development phases with its integrated front-end solutions. Nemera's high-end laboratory facilities allow the company to offer device-plus-formulation test services, as well as the development of test methods for its customers' needs. Finally, to navigate through a dynamic regulatory landscape, Nemera's regulatory experts are ready to help guide projects (Figure 4).

Following regulatory guidance is extremely crucial in establishing bioequivalence. Nemera's *in vitro* testing capabilities enable it to provide comprehensive support for specific generic projects, including a complete set of tests that meet the regulatory requirements of the relevant authorities. This data generation will be statistically analysed regarding US and EU guidelines for eventual customers' *in vitro* bioequivalence dossier registration filings.

In line with the fundamental idea of integrating patients within combination product development, Nemera also provides a full understanding of the patient journey and recommends user-related activities to further optimise the patient's experience for a specific drug-device combination product. Due to Nemera's extensive human factors capabilities, the customer could ensure that their selected device, in combination with their drug, is appropriate, safe and effective for the target population. For instance, Nemera's support encompasses making specific instructions for use adapted to certain target populations, as well as supporting human factors activities in alignment with the customer's chosen regulatory path, such as ANDA versus NDA.

Integrating patient insights early on in the process is critical to driving Nemera's platform advancement. By leveraging the patient journey through its internal drug delivery device R&D, Nemera ensures that its devices meet the unmet needs of end-users and provide optimal usability and user experience.

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

CONCLUSION

In line with the growing interest across local-acting and systemic treatments within the nasal route, Nemera's device platforms coupled with an integrated end-to-end approach enable the company to support and bring drug-device combination solutions to the patient. Nemera is the optimal holistic partner and helps its customers succeed in the sprint to market.

ABOUT THE COMPANY

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

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ABOUT THE AUTHORS

Séverine Duband is Category Director for Drug Delivery devices at Nemera, steering overall category strategy, product portfolio and innovation development for key delivery routes such as ophthalmics, inhalation, ear-nose-throat, dermal and parenteral. She leads the parenteral segment, focusing on proprietary products such as safety systems, pen injectors and on-body injectors. Ms Duband graduated from Emlyon Business School (France) in 2004. Ms Duband worked in fast moving consumer goods in the chemical industry for 10 years as International Category Manager, supervising strategic planning, NPD launches, project management and brand communication. She joined Nemera's Global Marketing team in 2018 as a Global Category Manager, focusing on the parenteral segment.

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





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CONNECT IN PHARMA REPORT: FUTURE TRENDS IN DRUG DELIVERY DEVICES

"The Future of Pharma Production, Manufacturing and Packaging Trend Report", a new report from the organisers of Connect in Pharma, has highlighted a range of forces shaping the future of the pharmaceutical manufacturing and drug-delivery industry in Europe, from machine learning and connected devices to eco-friendly strategies. The report identifies a surge in advances within drug-delivery devices as one of several important trends for the industry.

This report, produced in partnership with Sciad Communications (London, UK), drew on a survey and exclusive interviews with industry insiders, including *ONdrugDelivery's* publisher Guy Furness. In addition to naming the top trends in pharmaceutical manufacturing for 2023, it also provides advice on how professionals in the pharma manufacturing and drug delivery sector can continue to survive and thrive. What follows is an expert from the report.

THE RISE OF DRUG DELIVERY TECHNOLOGIES AND BIOLOGICS

According to survey insights and industry insiders, pharma companies are seeing an explosion of advances within the drug delivery field. Three areas seeing marked innovation and market expansion include the inhalable biologics market, long-acting injectable formulations and connected devices that aim to improve the effectiveness and adherence of medications.

The rise in injectable and inhalable formulations is partially driven by an increase in genomic capabilities and biological and biosimilar medicines, whose large, fragile molecules need alternative delivery mechanisms that avoid



the harsh environment of the digestive tract. These complex and sensitive therapies require new techniques and advanced materials for administration to ensure their stability and safety.

INHALATION TECHNOLOGIES

Exactly half of the survey respondents confirmed that their company is or will be involved in developing, manufacturing or packaging drugs that are inhaled, with dry powder inhalers (DPIs) and nasal delivery devices revealed as the most popular formulations.

New breeds of inhalation device aim to treat a range of diseases, such as cancers, cystic fibrosis, diabetes and multiple sclerosis, among others. Devices that deliver drugs through the nasal passage show particular promise for drugs that need to cross the blood-brain barrier quickly, whether to counteract a migraine, an allergic reaction or an opioid overdose.

Several survey respondents noted the huge growth potential in inhalable drug

delivery devices, citing the potential for fast absorption and the high bioavailability of biologics delivered via the nasal passage or lungs. One respondent said that the development of designs for reusable inhalers to reduce their carbon footprint was an area of particular interest. Inhalation devices that can deliver vaccines was also cited as an area with many opportunities.

Industry insiders have high hopes – but not for the first time. Pharma has long pursued the development of inhalers for systemic drug delivery via the lungs. Yet, despite huge investment and many meaningful advances, the industry didn't reap the rewards expected in the 2000s, said *ONdrugDelivery's* publisher Guy Furness.

"There's been quite a renaissance of late though, spurred in large part by the biologics revolution. The current period of development around these new inhalation drug delivery devices seems more clear-eyed than the previous period," Furness said. "As such we're seeing real progress, there's every reason to believe that this sector will realise its huge potential."

While the field of systemic delivery via the lungs is now more mature, and technology has advanced apace, challenges still remain. The most significant hurdles are the need to demonstrate patient safety and satisfactory bioavailability via a patientfriendly device, according to Furness.

"New breeds of inhalation device aim to treat a range of diseases, such as cancers, cystic fibrosis, diabetes and multiple sclerosis, among others." "According to survey insights and industry insiders, pharma companies are seeing an explosion of advances within the drug delivery field."

"Connecting these delivery devices to the internet of medical things and ensuring their sustainability are also uppermost in the minds of companies working in this space," he added.

Developers of these drug delivery devices also need to navigate an evolving regulatory environment, a factor noted by several survey respondents. The new EU Medical Device Regulation, for example, creates significant regulatory challenges for drug device combination product manufacturers, which will delay the approval and launch process for many products.

Another survey respondent cited the increased demands placed on manufacturers to document their manufacturing flow. Other major challenges include the shorter-acting effects of inhalable drugs and the need to find carbon-neutral manufacturing solutions.

INJECTABLE TECHNOLOGIES

The other area singled out for major growth in the industry is the development of new drug delivery systems for injectable treatments. Half of survey respondents confirmed that their company is or will be involved in developing, manufacturing or packaging injectable formulations. "The increase in injectables is an important trend for manufacturers," commented one respondent, who noted that it's also a factor driving the focus on aseptic manufacturing.

The injectable drug delivery market is expected to introduce new devices aimed at a range of pathologies, including ocular conditions (through intravitreal injection) and new treatments for autoimmune diseases, oncology, respiratory therapies and pain management. The most established area where new devices have already made significant headway is for the treatment of diabetes.

Both survey and interview responses highlighted the positive influence these drug delivery innovations are having on the treatment of diabetes, a condition affecting about 422 million people worldwide, according to the WHO. Indeed, 79% of survey respondents whose companies are involved in injectables noted uses in diabetes treatment, with progress enabled by the possibilities derived from connected technology that uses embedded electronics and sensors to relay information back to the healthcare provider – including time, volume and site of injection.

ABOUT CONNECT IN PHARMA

After a successful launch in 2022, Connect in Pharma returns to Geneva, Switzerland on June 14–15, 2023, to bring together the community of professionals shaping the future of drug delivery, manufacturing, outsourcing and packaging. Connect in Pharma aims to drive innovation, business and new partnerships in four key areas – innovative packaging, drug delivery systems, sub-contracting and manufacturing. Taking place in Geneva, the centre of a major pharmaceutical and biopharma cluster, Connect in Pharma is the perfect place to meet key influencers from leading pharmaceutical groups, biopharma, industry clusters and suppliers.

Access the complete version of "The Future of Pharma Production, Manufacturing and Packaging Trend Report" by Connect in Pharma at: connectinpharma.com/ connect-365/trend-report-2023



Contact:

James Montero MacColl Senior Marketing Manager T: +44 20 3196 4428 E: james.montero@easyfairs.com

Connect in Pharma

Easyfairs UK Ltd 2nd Floor, Regal House, 70 London Road Twickenham TW1 3QS United Kingdom

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