# NASAL & PULMONARY DRUG DELIVERY

ON drugDELIVERY

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ONdrugDelivery Issue N° 119, May 17th, 2021

## NASAL & PULMONARY DRUG DELIVERY

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

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| May 2021 | Injectable Drug Delivery |
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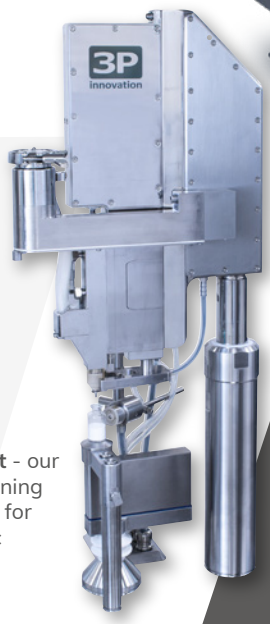

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# FORMULATION OPTIONS IN NASAL DRUG DELIVERY

Here, Richard Johnson, PhD, Founder and Chief Executive Officer of Upperton Pharma Solutions, discusses a number of advantages that the nasal delivery route offers and why there is growing interest in this sector of drug delivery, as well as considering some of the challenges that may arise during the development of nasal formulations for use in the clinic and the regulatory and testing requirements associated with them.

*This article was first published as a blog series on Upperton Pharma Solutions' website.*

The anatomy and physiology of the nasal cavity creates a number of unique opportunities for the successful delivery of drugs and vaccines. The target can be local, systemic or direct to the central nervous system (CNS). This utility has resulted in growing interest from scientists looking to administer both therapeutic agents and vaccines via the nasal route. This interest has been further fuelled by a number of factors, not least the surge in interest in delivering covid-19 prophylactic treatments and vaccines to the nasal cavity, the site of first infection.

Devices delivering drugs or vaccines into the nasal cavity can generally be divided into those delivering either a liquid or dry powder formulation. There has been a surge in interest in nasal delivery for both of these formulation approaches.

## EXPLOITING NASAL PHYSIOLOGY FOR DRUG DELIVERY

In order for the nose to both smell and breathe, the human nasal cavity has developed a number of unique physiological features (Figure 1). These features can in turn be exploited for drug delivery purposes.

The nostrils mark the entrance into the nasal cavities, which narrow to a point called the nasal ostium. The septum separates the two cavities, which extend, on average, 12–14 cm from the nostrils to the junction between the nose and pharynx. This junction is called the nasopharynx. The nasal-associated lymphoid tissue (NALT), an area that may be associated with inducing mucosal immunity, is located in the nasopharynx.

Within the nose itself, the main nasal passage is further divided by three projections from the septum called turbinates. These turbinates are designed to maximise contact between the air and mucosal surface. The inferior, middle, and superior turbinates are highly vascularised with relatively thin membranes. The result is an increase in the total surface area of the nasal cavity to 150 $cm^2$, making them an ideal target for systemic drug delivery. Other physiological targets for delivery are the olfactory and trigeminal nerves which innervate the nasal cavity. These neurones

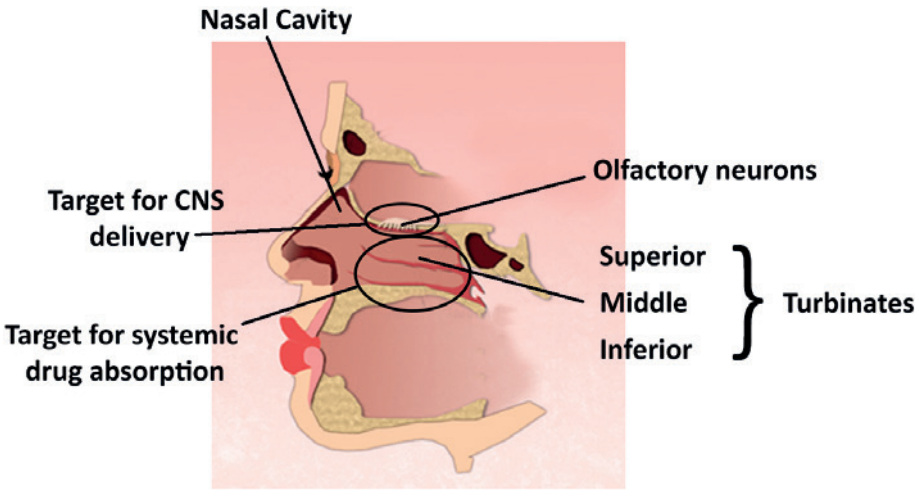


Figure 1: Regions of the nasal cavity.

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"One of the most obvious advantages of nasal delivery is the rapid absorption across the nasal membranes into the systemic circulation, resulting in fast onset of action. This means that systemically acting nasal products to be easily and rapidly administered for acute indications."

offer a potential target for nose-to-brain delivery and represent around 10% of the total nasal surface area.

## WHAT ADVANTAGES DOES NASAL DELIVERY OFFER?

Nasal delivery offers a number of advantages for certain classes of drug compounds and vaccines. These advantages include:

- Fast onset of action (rapid absorption)
- Potential for local, systemic and CNS delivery
- High levels of patient acceptance
- Improved bioavailability (avoids first-pass metabolism encountered with oral delivery)
- Needle-free (enabling easier self-administration)
- Delivery independent of inspiration (advantageous in some acute settings)
- Dry powder or liquid options available (stability advantages)
- Vaccines can elicit immune response in the area of initial infection (nasal cavity).

One of the most obvious advantages of nasal delivery is the rapid absorption across the nasal membranes into the systemic circulation, resulting in fast onset of action. This means that systemically acting nasal products to be easily and rapidly administered for acute indications. Examples include pain medications for migraines, such as GlaxoSmithKline's Imitrex® (sumatriptan), Bausch Health's Migranal® (dihydroergotamine) and Amneal Pharmaceuticals' Zomig® (zolmitriptan). Generally speaking, drug uptake across the nasal membrane is dictated by the hydrophobicity of the drug (improving transport) and residence time on the membrane.

In addition to rapid delivery, nasal administration is generally considered more user-friendly, with greater compliance among patients and easier administration for carers and healthcare professionals (HCPs). This route of administration also alleviates the need for the patient to be conscious, uncoupling the need for inspiration from successful delivery, which provides an advantage over pulmonary delivery. These factors have been exploited for the delivery of dry powder glucagon to treat very low blood sugar (hypoglycaemia). Baqsimi®, Eli Lilly's single-dose, dry powder spray formulation of this rescue treatment, received US FDA approval in 2019 in a portable, single-use, ready-to-use device (Figure 2).

Another major advantage of nasal delivery is that it removes the need for a drug to withstand the harsh environment in the gastrointestinal (GI) tract that arises during oral delivery. As a result, it is possible to avoid first-pass metabolism in the liver, without the need for injection, thereby increasing bioavailability.

A more specialised aspect of nasal delivery that has been under investigation for many years but has recently been enjoying growing interest, is the potential to deliver therapeutic agents directly to the brain. Both the olfactory and trigeminal nerves innervate the nasal cavity, making them a potential target for nose-to-brain delivery. This is a challenging prospect, but next generation devices currently in development may have particular utility in the area of brain disorders such as Parkinson's disease.

"A more specialised aspect of nasal delivery that has been under investigation for many years but has recently been enjoying growing interest, is the potential to deliver therapeutic agents directly to the brain. Both the olfactory and trigeminal nerves innervate the nasal cavity, making them a potential target for nose-to-brain delivery."


Figure 2: Eli Lilly's Baqsimi®, a dry powder glucagon nasal spray for the rapid treatment of hypoglycaemia. (Image courtesy Eli Lilly and Company. Reproduced with kind permission.)

The final factor currently driving growth in nasal delivery at present is the covid-19 pandemic. The primary route of viral infection is via the upper respiratory tract (i.e. the nose), before increased viral load results in further infection in the lungs. Delivering a range of prophylactics, such as antivirals, and vaccines through the nasal cavity is now considered the best route of delivery for prevention and treatment of this disease.

Nasal vaccination is not new, MedImmue's FluMist®, approved in 2003, delivers an annual influenza vaccine intranasally and other groups, such as Mymetics (Épalinges, Switzerland), have reported promising results with nasally administered HIV vaccines.

In conclusion, the benefits of nasal delivery have, and continue to be, utilised for a variety of purposes and the growing interest in this area is sure to lead to both new and improved possibilities for nasal administration

## LIQUID OR DRY POWDER DELIVERY?

When considering options for nasal delivery of a drug or vaccine, the first decision is usually choice of device type. The options are to deliver the active either in a liquid/

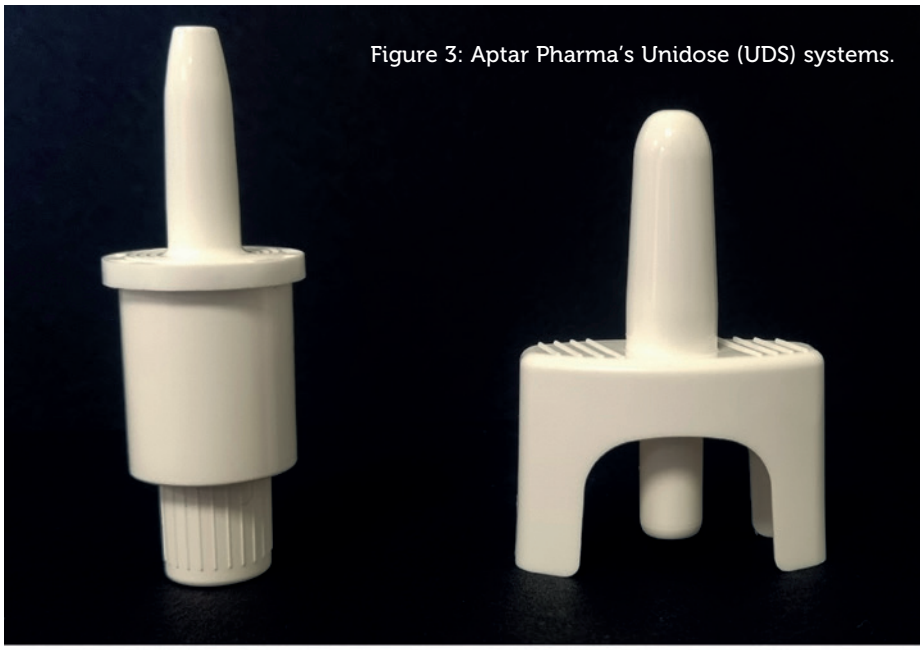

Figure 3: Aptar Pharma's Unidose (UDS) systems.

UDS Powder UDS Liquid

solution (as a multidose or single dose unit), or as a dry powder (generally single dose devices), as shown in Figure 3.

Liquid nasal dosage forms are the most prevalent and offer the simplest and most flexible formulation approach. There are a wide range of device options available, which can be purchased relatively inexpensively. The filling of API formulations into liquid devices is easier in comparison with their powder counterparts, and liquid devices also offer the option of either unit-dose or multi-dose delivery. With liquid devices, the droplet size emitted is dictated by the properties of the liquid formulation (viscosity) combined with the performance of the device itself.

In contrast, dry powder devices require specialised formulation techniques, such as spray drying, to engineer the correct particle size required for nasal delivery. This particle size is generally agreed to be in the region of 10–50 µm, with a requirement to minimise small respirable particles (below 10 µm) to avoid the potential of particles being inhaled into the lungs.

Dry powder delivery devices are of growing interest and differ from liquid delivery systems in a number of key areas (Table 1). For example, dry powder formulations are particularly useful in the formulation and delivery of molecules that are relatively unstable in solution but can be stabilised and delivered in the dry powder form, such as peptides and proteins. The delivered dry powder dissolves on the membrane surface of the turbinates, with release of the active ingredients for either local or systemic delivery. However, dry powder devices are generally only single-dose use, and tend to be more expensive than their liquid counterparts.

"Ideally, formulators will want to choose excipients that are listed in the FDA Inactive Ingredients Database for nasally delivered products. However, the list is relatively small and other excipients can be used, although additional toxicology information will be required as part of an IMP/IND/CTD submission."

| | Liquid Devices | Dry Powder Devices |
|---|---|---|
| **Advantages** | Simplest, most flexible approach | Improved stability for some formulations |
| | Large range of devices available | Fewer solubility constraints |
| | Lower unit cost | Longer nasal residence time |
| | Droplet size device controlled | Particle size engineered prior to device filing |
| **Disadvantages** | Challenge for poorly soluble API's | Complex manufacture (particle size) |
| | Less stable (aqueous instability of some molecules) | Irritation/discomfort |
| | Shorter nasal residence time | Limited device options |
| | | Higher cost |

Table 1: Advantages and disadvantages of dry powder and liquid nasal devices.

## FORMULATION DEVELOPMENT: CONSIDERATIONS AND OPTIONS

When developing either a liquid or dry powder formulation, there are challenges and opportunities that can be exploited to achieve the target product profile for the drug or vaccine being delivered. For example, ideally, formulators will want to choose excipients that are listed in the FDA Inactive Ingredients Database for nasally delivered products. However, the list is relatively small and other excipients can be used, although additional toxicology information will be required as part of an IMP/IND/CTD submission.

There are many factors to consider when developing therapeutics and vaccines for nasal delivery, both in regard to optimising the formulations themselves and the devices through which they are delivered. Once the choice between a liquid or dry powder approach has been made, there are a number of particle engineering and excipient options that can be utilised by formulators to achieve the desired product performance attributes needed for successful delivery, release and absorption in the nasal cavity. Some of the formulation considerations are summarised in Table 2, along with suggestions for overcoming the challenges presented.

| Delivery Challenge | Formulation options |
|---|---|
| **Achieving required dose delivery into the nose** | For liquid devices, formulate API solution (typically 0.1 mL dose will be delivered)<br>For dry powder devices, formulating API into correct dry powder mass is important (note there may be constraints on mass of powder that can be delivered from the device; typically 10–20 mg) |
| **Targeting the nasal membranes** | Liquid formulation and devices, properties adjusted to achieve target droplet size, in particular the use of viscosity enhancements (e.g. HPMC, PVP) to achieve correct droplet size<br>For dry powder devices, it is necessary to engineer correct particle size in powder formulation prior to filling device (typically 20–50 µm)<br>Spray drying is often used to produce particles of correct size |
| **Addressing solubility** | For liquid formulations, solubility can be achieved by pH adjustment, salt formation or use of non-aqueous solvents (e.g. ethanol, cyclodextrins)<br>For dry powder devices this is less of an issue, formulation of the API and production of particles is achieved prior to device filling |
| **Achieving pH control** | Average value for pH reported as 6.3–6.4<br>Many nasal products have lower pH e.g. Narcan® (naloxone) pH 3.5–5.5 |
| **Achieving osmolality** | Isotonic solution (~290 mOsmol/kg) will minimise irritancy/maximise tolerability<br>Achieved by adding NaCl or sugars for osmolality upwards adjustment |
| **Avoiding microbial growth in final dosage form** | Multidose products have preservatives (e.g. benzalkonium chloride) but single dose (liquid) devices are usually preservative-free<br>Not an issue with dry powder devices (no growth) |
| **Adsorption modulation** | Potential to slow down the rate of absorption<br>Add viscous polymers (e.g. cellulouses, pectin)<br>Applicable to liquid and dry powder devices |
| **Adsorption enhancement** | Chemical enhancement of drug uptake by adding enhancers such as dodecylphosphocholine, (zwitterionic detergent used in Baqsimi®) or chitosan (cationic polymer that binds to mucus)<br>Applicable to liquid and dry powder devices |

Table 2: Delivery considerations and formulation options.

## TESTING LIQUID AND DRY POWDER DEVICES

Similar to the choice of device and formulation type, the choice of analytical methods will be very different for the liquid and dry powder dosage forms, and depend greatly on the stage of development and regulatory territory. Broadly speaking, the required analysis will include:

- Liquid dosage form:
  - Comprehensive testing of the liquid in the device, including the API and key excipients
  - Droplet size
  - Plume geometry
  - Spray pattern
  - Quantity of liquid/drug delivered.
- Dry powder dosage form:
  - Comprehensive testing of the dry powder drug product within the device
  - Particle size
  - Plume geometry
  - Quantity of dry powder delivered from the device.

## DEVELOPMENT STUDIES

During development of nasal products, a wide range of performance attribute tests are recommended and/or stipulated by the regulatory authorities in addition to the more typical expected specified final product release testing. Both the EMA and FDA provide detail on a lot of these tests, which are often dependent on both the

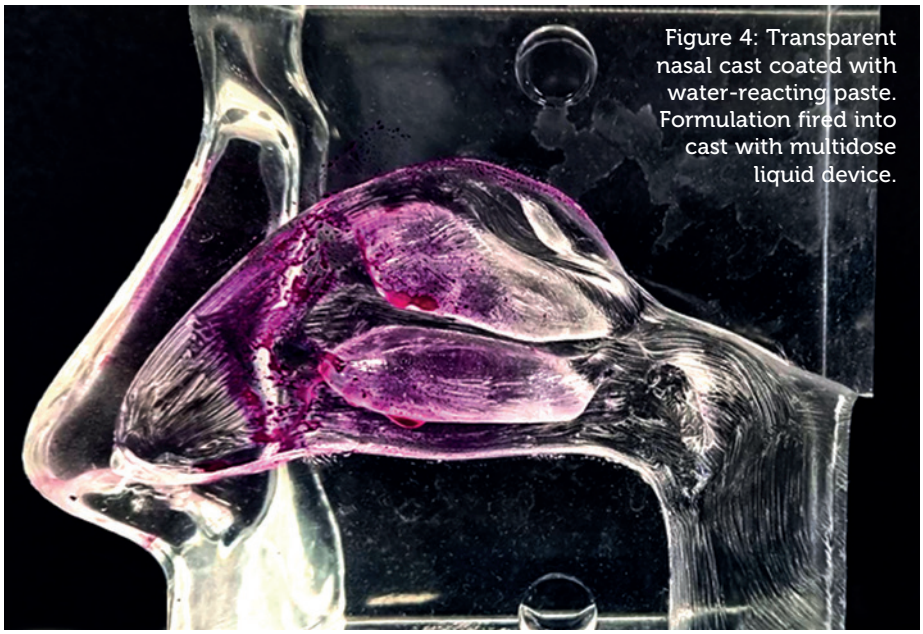

Figure 4: Transparent nasal cast coated with water-reacting paste. Formulation fired into cast with multidose liquid device.

formulation and the device and can be used to discriminate between formulation variants. These tests include:

- Delivered dose throughout the life of the product
- Priming requirements
- Effect of dosing orientation on emitted dose
- Plume geometry and spray pattern.

Another tool that has proven useful in comparing and selecting formulations during development is the transparent nasal cavity (Figure 4), which can visualise the effect of formulation changes, the delivery device and changes in orientation during use. The cavity is coated such that a colour change occurs when it comes into contact with the formulation delivered from the nasal device. By examination of the colour, the specific areas of deposition in the nasal cavity can be identified and key performance failure modes can be observed, such as excessive formulation run-off to the throat or excessive deposition in the nasal vestibule resulting in the formulation "dripping out".

| Assay type | Comment |
|---|---|
| **Spray Characteristics** | Solutions (droplets size, plume geometry) usually for information only |
| | For dry powders will include particle size determination (specify small/inhalable particles) |
| **Assay/Delivered Dose** | Should correlate/verify any weight method with drug capture |
| **Quantification (API and functional excipients)** | Assay (e.g. preservatives) |
| | Physical measurements (viscosity) |

Table 3: Testing nasally delivered drug products for use in Phase I studies.

| Test | FDA | EMA | Comments |
|---|---|---|---|
| **Description** | ✓ | | |
| **Identification** | ✓ | | |
| **Assay** | ✓ | ✓ | API content and stability |
| **Impurities/related substances** | ✓ | ✓ | API content and stability |
| **Preservatives** | ✓ | | Confirm levels and stability of preservative |
| **Pump delivery** | ✓ | | |
| **Spray content uniformity** | ✓ | ✓ | Solutions measured by weight difference. Powder devices; collect in container and assay for active |
| **Spray pattern** | ✓ | | Laser based system or TLC plate analysis |
| **Droplet/particle size distribution** | ✓ | | Laser diffraction (e.g. Malvern Panalytical's Spraytec) for liquids or Andersen type impactor/laser diffraction for dry powders |
| **Plume geometry** | ✓ | | Video/photographic imaging at specified distance |
| **Particulate matter** | ✓ | | Sub-visible particle analysis |
| **Microbial limits** | ✓ | ✓ | Confirm levels and stability of preservative (if present) |
| **Net content** | ✓ | | |
| **Weight loss** | ✓ | | |
| **Extractable/Leachables** | ✓ | ✓ | Required for plastic devices (FDA) Not required by EMA for compendial plastics |
| **pH** | ✓ | | Typical values would be in the pH 5.0–8.0 range |
| **Osmolality** | ✓ | | Isotonic solution (~290 mOsmol/kg) will minimise irritation |
| **Viscosity** | ✓ | | Impacts droplet size and plumegeometry |

Table 4: Product specifications for nasal drug products.

## TESTING CONSIDERATIONS FOR PHASE I STUDIES

The exhaustive list of tests needed for commercial products are generally not required for Phase I (first-in-human) studies. Instead, a more pragmatic approach can be taken. Table 3 shows typical assays that are suitable for supporting Phase I studies.

## TESTING NASAL FORMULATIONS: REGULATORY REQUIREMENTS

The degree of testing necessary will be dictated by the regulatory setting and the stage of development of the drug/device combination. Typical testing regimens for liquid and dry powder nasal products are shown in Table 4.

> "There is an extensive range of tests required when developing nasal dosage forms for human use. Some of these tests require sophisticated pieces of equipment, many of which might only be found in laboratories that have established nasal testing capabilities."

As can be seen, there is an extensive range of tests required when developing nasal dosage forms for human use. Some of these tests require sophisticated pieces of equipment, many of which might only be found in laboratories that have established nasal testing capabilities.

The range and extent of testing will primarily be dictated by the development stage of the formulation to be tested. In simple terms, products earmarked for use in Phase I clinical testing will require significantly less testing than products being tested for commercial use. In Phase I studies, the key tests will be those that impact product safety, such as particle size/droplet size (impact on pulmonary toxicity) and emitted dose. These tests will provide key safety and delivery information to support use in first in human studies.

As the drug product moves further through the development process, the extent of testing will be required to increase to allow the drug to be sold and used commercially and more stringent tests, such as device compatibility (extractables/leachables), will become necessary.

## CONCLUSION

This article has outlined the logistics and considerations associated with developing a drug or vaccine for nasal delivery. It has discussed the advantages the anatomy of the nasal cavity provides for drug delivery, the challenges of developing both liquid and dry powder formulations, analytical techniques and regulatory testing requirements.

## ABOUT THE COMPANY

Upperton Pharma Solutions is a specialist CDMO, offering clients a complete development package: early feasibility studies, process optimisation, scale-up and clinical trial (GMP) manufacturing. The company has experience working with a range of dosage forms and the expertise to develop challenging molecules. Upperton's formulation work is complemented by a comprehensive range of analytical services. The company's core expertise is in spray-drying technology, which has an ever-expanding list of applications.

Upperton has an extensive, multinational client-base, ranging from small start-ups to global pharma companies and the company prides itself on its client focus, flexible approach and scientific excellence.

## ABOUT THE AUTHOR

**Richard Johnson** founded Upperton Pharma Solutions in August 1999, and continues to play a key role in the management and strategic development of the company. With over 30 years of experience in the pharmaceutical, biotechnology and drug delivery fields, Dr Johnson previously held senior management positions at Andaris Group (Vectura) and Delta Biotechnology (now Albumedix, Nottingham, UK). Dr Johnson holds an honours degree in Biology from the University of York (UK), a PhD from the University of Warwick (UK), and has a proven track record in successfully developing innovative pharmaceutical products from early feasibility studies through to commercial products.

# NASAL DELIVERY: AN OPPORTUNITY FOR SIGNIFICANT IMPROVEMENTS IN PATIENT CARE

In this article, Stuart Madden, PhD, Chief Scientific Officer at Neurelis, discusses the advantages of the nasal route of administration for the systemic delivery of therapeutics.

Nasal sprays have a long history of use in medicine but, historically, this has been predominantly for their local effects on the mucosa. Nasal rhinitis (e.g. sinusitis, nasal congestion and /or a runny nose) brought about by infections, (such as colds and flu), allergens or irritants that inflame the mucosa is traditionally treated by the application of a locally acting nasal spray. These sprays can be prescribed but are more typically an over-the-counter (OTC) medication, such as a nasal decongestant, saline rinse and/or concomitant antihistamine.

> "Nasal administration has unique prerequisites relative to other routes of administration that necessitate significant expertise from both the formulation scientists and the engineers tasked with developing these products."

It is only recently that the nasal route of administration has come to prominence for the systemic delivery of therapeutics. At the end of the last century, there were relatively few approved nasal spray drug products commercially available in the US; nafarelin, nicotine and sumatriptan are some early examples. Since that time, there has been a growing interest in nasal delivery for several reasons that cover a wide range of factors, evidenced by the significant increase in approved nasal spray drug products for a wide range of therapeutic indications.

## PRODUCT DEVELOPMENT CHALLENGES

There are two key aspects for a safe and efficacious nasal spray:

1. Robust formulation that provides a therapeutic dose that is rapidly and highly absorbed
2. A pump that is capable of providing a consistent dose with respect to dose delivered and plume characteristics.

Combined, this ensures that the drug is delivered to the patient in a reproducible manner, ensuring consistent therapeutic drug levels. While these may appear to be modest requirements, nasal administration has unique prerequisites relative to other routes of administration that necessitate significant expertise from both the formulation scientists and the engineers tasked with developing these products. In addition, because these are classed as combination products, the regulatory landscape becomes more complex – compliance with the appropriate sections of the US FDA's 21CFR 210 and 211 (drug GMPs) and 21CFR 820 (medical device quality system regulation) depends on the approach the sponsor selects for its overarching quality system.

### Drug Product Characteristics

The formulation must meet several important criteria to be acceptable for nasal delivery. Firstly, it must have adequate solubility because of dose volume limitation in the nose. Typical doses do not exceed much more than 100 µL before potential leakage becomes a concern, via dripping back out the nostril or going past the upper reaches of the nostril to be swallowed via the oesophagus.

Dosing in each nostril is an option, as is a second dose in each nostril (15 minutes after the first dose has been absorbed) when solubility is limited, but this is suboptimal from a patient convenience and compliance standpoint. Overcoming this limitation using solubility enhancers or selecting cosolvents is preferable,

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"The rheological properties of a solution have a significant influence on the spray characteristics as they relate to droplet size and plume shape."

but potentially difficult due to possible nasal sensitivity that may induce irritation to the mucosal membrane, sneezing or epistaxis, resulting in poor patient compliance and suboptimal dosing.

In addition, the rheological properties of a solution have a significant influence on the spray characteristics as they relate to droplet size and plume shape. Including the need for a buffer system and preservative system further complicates the development. Thus, formulation development has numerous constraints that have to be taken into consideration to achieve a solution suitable for nasal delivery.

Secondly, the extent of absorption is dependent on the rate. The nose has a mucociliary clearance system that effectively replaces the mucosal film approximately every 15 to 20 minutes, so rapid absorption is critical for achieving high bioavailability. In its favour, the nasal cavity is highly vascularised and, because of its relatively small volume, is amenable to the application of various formulation technologies. One approach to increasing nasal residence time is the use of muco-adhesive systems that retain the drug solution longer in the nose. Another is the use of permeation-enhancing technologies that facilitate both the rate and extent of absorption. Small, neutral lipophilic drugs, non-ionised acidic and basic drugs tend to be more readily absorbed than hydrophilic, ionised, or high molecular weight drugs.

"Nasal sprays have numerous parameters that must meet predefined acceptance criteria to ensure consistent performance."

High molecular weight drugs can gain significant adsorption improvements with the addition of a permeation enhancer to the formulation. There are numerous examples of absorption enhancers in the literature, including chitosan and its derivatives, bile salts, fatty acids, phospholipids and non-ionic surfactants. The latter, in the form of N-dodecyl β-D-maltoside, has recently been approved in two US commercial nasal sprays. This permeation enhancer can also facilitate the absorption of molecules up to 40 kDa, enabling the nasal delivery of peptides and proteins, that traditionally have had to be delivered via parenteral administration due to enzymatic degradation in the gastrointestinal tract.

### Device Characteristics

Delivery of the formulation must be precise, robust and consistent. Nasal sprays have numerous parameters that must meet predefined acceptance criteria to ensure consistent performance. Dose delivered, droplet size distribution and spray pattern (plume geometry) are a combination of the pump characteristics and the formulation itself, and thus make a unique combination. The device can be single dose, bidose or multidose, depending on therapeutic requirements, and must be robust enough to withstand shipping, handling and other mechanical stresses that are typically encountered in the commercial environment.

## BENEFITS OF NASAL DELIVERY

Given the complexities of nasal drug development described thus far, it is pertinent to expound on the benefits that nasal delivery has over other routes of administration.

From a patient perspective, a nasal spray is a convenient, discreet, easy to use, easy to carry and reliable way to take medication or, as a caregiver, to administer the medication to someone in their care. The importance of this cannot be underestimated. Nasal sprays are also common in everyday use for allergy treatments so there is a significant level of general familiarity with the use of nasal sprays.

Drugs can be delivered to the systemic circulation via several routes. Parenteral (intravenous, intramuscular, subcutaneous) administration typically provides for full dose delivery but suffers the drawback

"The nasal route is an attractive alternative that provides access to highly vascularised mucosa, is easy to self-administer and can, with the appropriate formulation and delivery system, deliver the drug dose conveniently and reproducibly – and bypass the hepatic metabolism."

of the use of needles and associated patient concerns, as well as the need for a healthcare practitioner for intravenous administration. In contrast, non-parenteral administration (oral or rectal, for example) has the drawback of possible susceptibility to enzymatic degradation or first-pass (hepatic) metabolism. These alone, or in combination, may have a significant impact on the effective dose that eventually reaches the site of action.

The nasal route is thus an attractive alternative that provides access to highly vascularised mucosa, is easy to self-administer and can, with the appropriate formulation and delivery system, deliver the drug dose conveniently and reproducibly – and bypass the hepatic metabolism.

Another important benefit is the "rescue treatment" setting. Numerous medical conditions call for swift drug administration and rapid onset. A critical example of this would be an opioid overdose, where death can easily result if the drug effects are not quickly reversed. Intravenous administration is often impractical because of the need for a healthcare provider to administer. Using a nasal spray that provides a rapid onset is an ideal solution that can be used by anyone. Additionally, these types of products can be kept on hand by schools, emergency response teams, police and other first responders or caregivers. The rapid onset is also relevant to other situations, for example, treatment of seizures, anxiety attacks, migraines and similar neurological conditions.

An additional aspect of nasal delivery is the potential for direct nose-to-brain delivery. One of the limiting factors of

| Drug | Indication | Current Dosage Forms | Benefits of Nasal Spray over Current Dosage Forms |
|---|---|---|---|
| Sumatriptan | Migraine | SC injection | Ease of administration<br>Convenient<br>Non-invasive<br>Rapid onset |
| Diazepam | Seizure clusters/ acute repetitive seizures | Rectal gel | Ease of administration and self-administration<br>Convenient<br>Rapid onset<br>Rescue benefit<br>Social acceptability in non-pediatric population |
| Metoclopramide | Diabetic gastroparesis | Oral tablet, intravenous injection | Ease of administration and self-administration Convenient<br>Non-invasive (versus intravenous)<br>Avoids poor absorption due to GI motility, nausea and vomiting associated with gastroparesis (versus oral) |
| loxone | Drug overdose | Oral tablet, buccal film, intravenous injection | Ease of administration and self-administration<br>Administration to unconscious patient possible (versus buccal, oral)<br>Convenient<br>Non-invasive (versus intravenous)<br>Rapid onset<br>Rescue benefit |

Table 1: Current commercial nasal delivery products.

> "Nasal delivery has significant advantages over other routes of administration that make it an attractive option for clinicians, healthcare providers and patients alike."

certain drug molecules to treat neurological conditions is their inability to cross the blood-brain barrier. Blood capillary endothelial cells have tight junctions that act as a barrier to most drugs, especially large and/or hydrophilic drugs. Nasal delivery provides a direct route to the central nervous system via the trigeminal nerve and olfactory lobe. This direct route may also contribute to the rapid onset aspect of nasal delivery, although a full understanding of the potential of this has yet to be explored.

## CURRENT COMMERCIAL NASAL PRODUCTS

Table 1 lists some nasal sprays that have been approved recently and compares them with the innovator products. As can be seen, the benefits of nasal administration make it an attractive alternative to the innovator dosage forms.

## CONCLUSIONS

Nasal delivery has significant advantages over other routes of administration that make it an attractive option for clinicians, healthcare providers and patients alike. There are significant challenges associated with the development of nasal spray products due to constraints around the physicochemical properties of the molecule, limited excipient choices, the need for rapid absorption and ensuring reproducibility of the dose delivery for consistent product performance. These challenges are being overcome by innovative formulation design, incorporation of permeation enhancers and muco adhesives, and robust pumps delivering consistent performance. As knowledge in these areas increases, nasal delivery will be increasingly important in the clinician's armamentarium.

## ABOUT THE COMPANY

Neurelis is a privately held specialty pharmaceutical company focused on licensing, developing and commercialising product candidates for epilepsy and the broader central nervous system market.

## ABOUT THE AUTHOR

**Stuart Madden**, PhD, has over 30 years of experience in the pharmaceutical industry, working on drug development programmes from proof of concept through to commercialisation for new chemical entity (NCE) and 505(b)(2) products that have encompassed small molecules, biologics and combination products. Dr Madden received his BSc degree in Chemistry and his PhD in Physical Chemistry from the University of Wales (Swansea, UK). He is a Chartered Chemist and Fellow of the Royal Society of Chemistry and a past special government employee for the US FDA's Advisory Committee for Pharmaceutical Science and Clinical Pharmacology.

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NextBreath
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# HOW EVOLVING PATIENT NEEDS HAVE FUELLED THE DEVELOPMENT OF NASAL DRUG DELIVERY

**In this article, Julie Suman, PhD, President of Next Breath, considers how the needs of the patient have driven advances in nasal drug delivery and looks at the latest developments and benefits of this method of drug delivery.**

The development programme for every new drug or medical device is driven by one overarching objective: creating safe and effective medications that improve patient outcomes.

However, while this might be the clear aim that guides pharmaceutical partners on their path of continuous improvement and development, achieving it in practice is far from easy. The notion of patient outcomes is recognised as a complex construct that can be measured in various ways, and success is dependent on several interlinked elements being correctly aligned.[1]

Pharmaceutical companies are challenged to deliver this alignment by delicately balancing their primary goal – achieving a desired therapeutic effect – with several other factors, including patient adherence and compliance, which are heavily influenced by the method of drug delivery. Intravenous routes of administration, for example, may provide advantages in terms of rapid and accurate dosing, but less-invasive alternatives, such as oral or nasal drug delivery, are more readily accepted by patients and are also easier to administer by healthcare professionals (HCPs) and patients alike. Innovation by drug device development partners such as Aptar Pharma is therefore crucial to the continued success of pharmaceutical companies in delivering better outcomes via more patient-friendly techniques.

> "Innovation by drug device development partners such as Aptar Pharma is therefore crucial to the continued success of pharmaceutical companies in delivering better outcomes via more patient-friendly techniques."

## A BRIEF REVIEW OF THE BENEFITS OF NASAL DRUG DELIVERY

From the patient's perspective, research has demonstrated a preference for less-invasive drug delivery methods such as intranasal administration. In a study examining patients' responses between epinephrine delivered via a nasal spray or via an autoinjector, it was found that patients – all of whom suffered from severe allergies – reported a significant preference for nasal epinephrine, specifically citing factors including ease of learning and use, device portability, safety and comfort within their responses.[2]

As an accessible, non-invasive route to rival the pharmacokinetic profile of some intravenously administered drugs, nasal drug delivery is increasing in profile and potential. Advances in intranasal drug delivery technologies mean the benefits of this method are being brought to bear in an

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expanding range of therapeutic treatments, both local acting and systemic.

This is all made possible as a result of the biology of the nasal cavity, a highly vascularised area of approximately 160 $cm^2$ in size.[3] This large surface area provides the basis for relatively rapid drug absorption rates, leading to a fast onset of drug action. Unlike oral administration routes, nasal drug delivery also offers the advantage of bypassing the gastrointestinal tract, thus avoiding the risk of bioavailability being reduced as a result of first-pass metabolism.

Exploiting the benefits of nasal drug delivery is not new. In fact, the nose has long been recognised for its characteristics as a drug-administration pathway, as exemplified by the nasal insufflation of powders for local and systemic disorders in medieval Persia (Nofookh).[4] Modern, Western medicine accelerated its interest in the mid-20th century, when early nasal drug delivery products were dominated by local-acting treatments for conditions such as nasal congestion and allergic rhinitis. Product examples include fluticasone propionate (Flonase, GlaxoSmithKline) and oxymetazoline hydrochloride (Afrin, Bayer Healthcare).

## DEVELOPMENTS IN NASAL DEVICE TECHNOLOGY

As these products evolved into over-the-counter (OTC) remedies from their prescription origins, the convenience and ease of use of aerosolised delivery made them highly marketable to patients, particularly when contrasted with alternative methods for administering local-acting compounds. Nasal drops, for example, typically demand that the patient adopts a rather unorthodox head position, such as Mygind or Kaiteki, to achieve the gravitational conditions to support improved coverage in the nasal cavity. However, the discomfort and complexity associated with such manoeuvres can understandably lead to poor compliance among patients.

Such weaknesses have paved the way for metered-dose spray pumps to emerge as the dominant option for nasal drug delivery. Equally appropriate for drugs targeting local action as well as systemic absorption, and compatible with formulations in suspension as well as solution, these devices provide a platform for accurate, repeatable dosing and targeted delivery. A specified volume of liquid, between 50 and 140 µl, is contained within the device's metering chamber and then aerosolised via compression of the actuator – following initial priming of the device. Releasing the actuator causes a pressure imbalance that triggers the refilling of the metering chamber via the dip tube.

During the spraying manoeuvre, make-up air enters the bottle, which potentially exposes the formulation to bacterial contaminants. As aqueous formulations may support bacterial growth, antimicrobial preservatives may be included within the formulation to maintain stability and prevent contamination throughout the product's shelf life. The use of preservatives such as benzalkonium chloride (BAC), however, has led to concerns over their potential role in causing undesirable side effects such as damage to the ciliated tissue in the nasal cavity.[5] While discussions continue on this contested subject, there has undoubtedly been a growing momentum behind preservative-free formulations, encouraged by the EMA's advice that the threshold for BAC should be zero for all routes of administration, including nasal.[6]

In response, device manufacturers have developed innovative preservative-free intranasal spray systems. Aptar Pharma is no exception, with examples including its CPS technology platform and Advanced Preservative-Free (APF) system, which incorporate a filter membrane in the ventilation channel to prevent the ingress of any microbiological contamination with venting air. This ventilation channel is combined with a spring-loaded tip seal mechanism to eliminate the need for any preservatives or additives, such as silver ions or surface coatings. Rigorous integrity tests have proved that both the tip seal and ventilation channel protect against any ingress of bacteria from either air or liquid.

## ENHANCING PATIENT CARE

For a growing number of applications, multi-dose nasal sprays are being replaced by devices that can deliver a controlled single dose (Unidose (UDS), Figure 1A) or two doses (Bidose (BDS), Figure 1B). Through their intuitive design, ease of use and no need for priming, such products allow for needle-free administration (or self-administration) of potentially life-saving emergency medicines where there is urgent need. Examples include naloxone (NARCAN®, Opiant) for treatment of opioid overdose and midazolam (Nayzilam®, UCB) and diazepam (Valtoco®, Neurelis) for treatment of seizures.

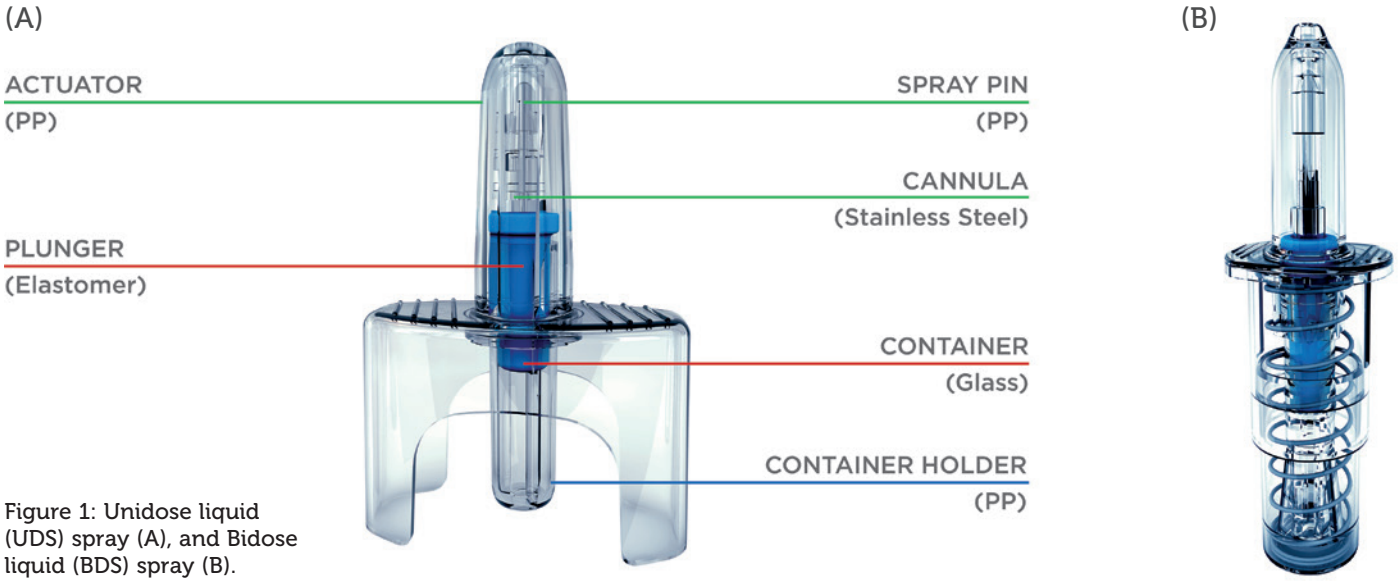



Figure 1: Unidose liquid (UDS) spray (A), and Bidose liquid (BDS) spray (B).

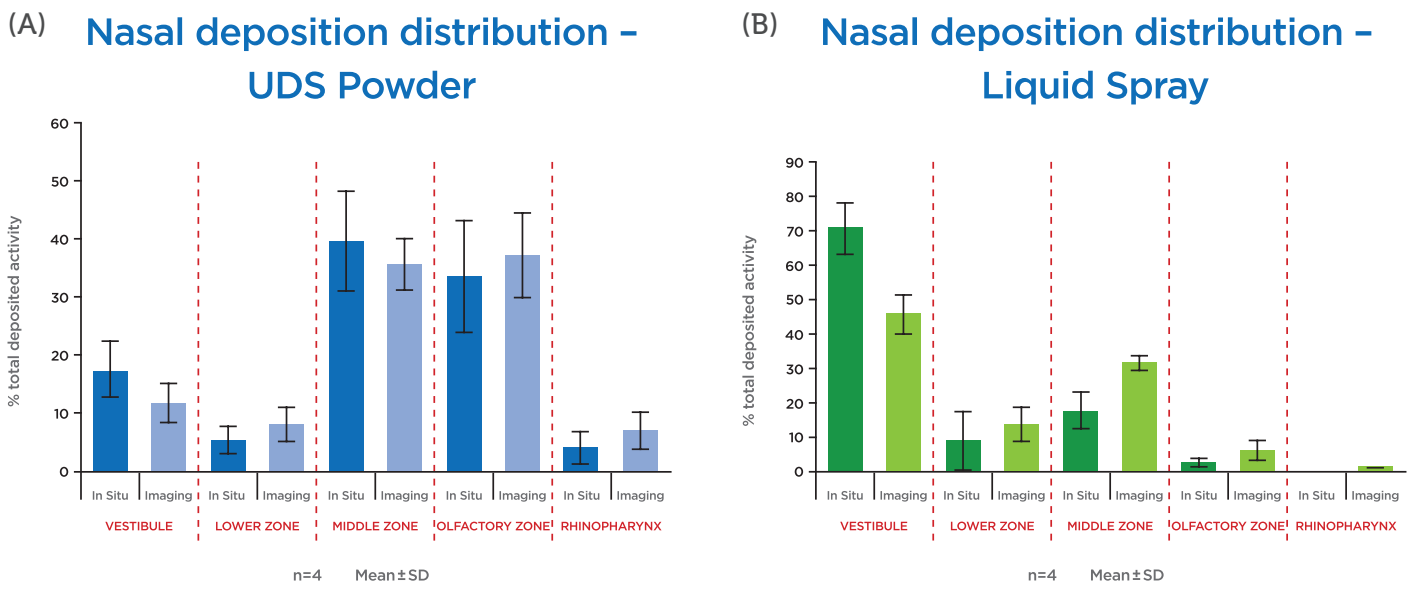



Figure 2: Nasal Powder Unidose device (UDSp) gives higher deposition than Liquid Unidose device.

Further breakthroughs in recent years include esketamine nasal spray (Spravato®, Janssen Pharmaceuticals) for treatment-resistant depression. In addition, diabetic patients have benefited from the introduction of glucagon nasal powder (Baqsimi®, Eli Lilly and Company), which can be used in the event of a severe hypoglycaemic episode. Portability, ease of use and reliability of dosing are critical qualities in an application such as this, and a single-use nasally administered powder device represents significant advantages over the alternative option of a glucagon injection, which also requires refrigeration. This is a clear example of nasal drug delivery's potential in the sphere of drug repurposing, where the reformulation of existing compounds can bring significant new advantages in terms of patient and caregiver accessibility.

In addition to the treatment of diabetes, nasal powder also provides a delivery platform for migraine sufferers in the form of sumatriptan (Onzetra®, Avanir Pharmaceuticals). Such products exploit the unique advantages of nasal powders, which include their suitability for accommodating larger doses and supporting compounds lacking aqueous stability. In addition, a study of *in vitro* deposition has also shown that, when compared with an aqueous spray, nasal powder may improve targeting to the olfactory region (Figures 2 A & B).

> "As well as their intuitive design, nasal inhalation devices are subject to continued innovation by pharmaceutical companies and device partners to enhance the care and support provided to patients."

## EMERGING OPPORTUNITIES FOR NASAL DEVICES

As well as their intuitive design, nasal inhalation devices are subject to continued innovation by pharmaceutical companies and device partners to enhance the care and support provided to patients. With emergency therapies, for example, training kits have been developed that closely mirror the real-life experience of using a nasal spray with a view to optimising compliance and decreasing the mortality risk. Patient safety is also being addressed through the inclusion of lock-out mechanisms on devices, while the development of laterally actuated nasal sprays provides greater levels of comfort and simplicity for certain patient populations.

Dose counters have long been recognised as benefiting adherence, and rapid advances in technology have built on this platform to create an ecosystem for connected devices that play a more "active" role in supporting greater adherence. By monitoring, recording and communicating data on usage via the internet, connected devices represent a potent opportunity for establishing an ecosystem where pharmaceutical company, patient and healthcare practitioner are more closely integrated (Figure 3). Apps can prompt patients to take their medication, healthcare professionals can accurately track progress and pharmaceutical companies can receive anonymised data on real-world medicines use. In this scenario,


Figure 3. Connected devices are the future for digital healthcare.

"At the other end of the spectrum, nasal drug delivery is demonstrating success at treating neurological conditions via the central nervous system (CNS). It has been shown that targeting drugs at the roof of the nasal cavity enables molecules to be transported to the CNS via the olfactory or trigeminal pathway."

avoiding medicines wastage is an obvious benefit, but it also represents a fundamental opportunity for delivering better long-term health outcomes.

Further high-value opportunities exist in the OTC space, where there is growing evidence of the benefits of nasal saline in promoting well-being and addressing the symptoms of air pollution, which causes the deaths of an estimated seven million people worldwide every year.[7]

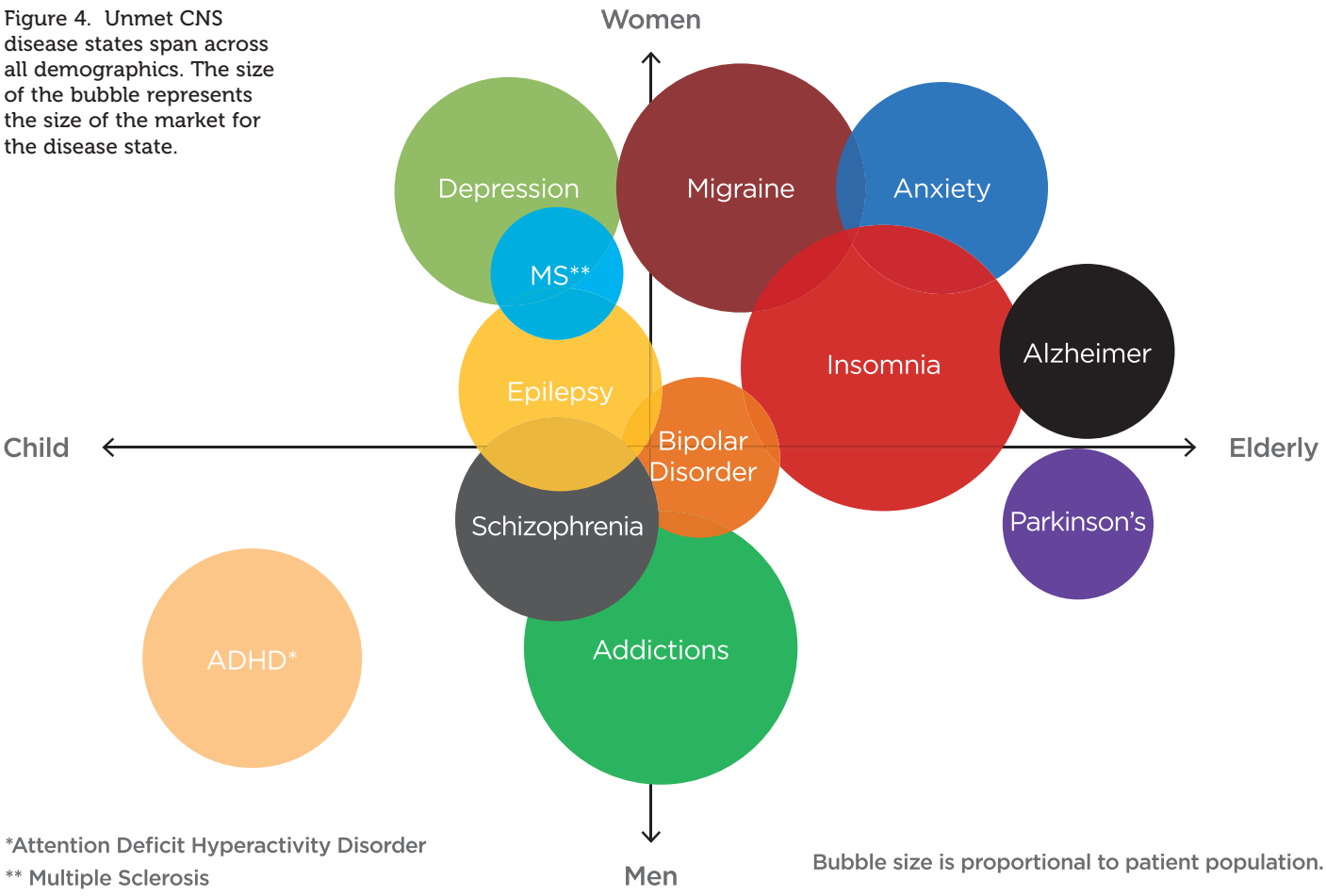
## OVERCOMING THE BLOOD-BRAIN BARRIER

At the other end of the spectrum, nasal drug delivery is demonstrating success at treating neurological conditions via the central nervous system (CNS) (Figure 4). It has been shown that targeting drugs at the roof of the nasal cavity enables molecules to be transported to the CNS via the olfactory or trigeminal pathway.[8] Many existing therapies targeting these conditions suffer from poor bioavailability due to the blocking effect of the blood-brain barrier (BBB). In bypassing the BBB, intranasal delivery methods can be used with targeting strategies to increase the level of drug reaching the intended site of action.

As research into this important area continues, nasal devices continue to be deployed in a prophylactic capacity through the delivery of vaccines. In the 2019–20 season, over three million children were vaccinated against flu across the UK with the live attenuated influenza vaccine (LAIV)[9] nasal spray. Immunity is achieved through interaction with immune modulators in the nasal cavity and dendritic cells in the nasal epithelium. With vaccines in development for conditions including anthrax, HIV and Hepatitis B, among others, further opportunities exist in this area, where sufficient activity can be achieved by overcoming challenges in drug absorption, mucociliary clearance, the mucus barrier and enzymatic degradation at the nasal mucosa.

Today, the more immediate potential for nasal drug delivery concerns treatments for covid-19, which has rapidly emerged as the most urgent healthcare challenge of modern times. Promising treatments are currently in development that eradicate the virus from the upper respiratory tract while blocking the ACE-2 receptor, essential for the virus to infect cells. Examples of nasally administered treatments include antibodies such as immunoglobulin G (IgG) and immunoglobulin Y (IgY). According to the WHO, at least five nasal spray vaccines are now in early clinical trials. In tandem with mass vaccination programmes, nasal devices may enable therapies such as these to play an important part in our protection against covid-19 in its various forms in the years to come.

Figure 4. Unmet CNS disease states span across all demographics. The size of the bubble represents the size of the market for the disease state.




*Attention Deficit Hyperactivity Disorder
** Multiple Sclerosis

Bubble size is proportional to patient population.

Nasal drug delivery has evolved into a highly versatile method of administration for locally acting and systemic drugs; for administering emergency doses and managing long-term conditions; and, in the case of preventative vaccines or breaking new ground, in challenging therapeutic areas. Central to all these diverse applications is the fact that patient outcomes have been enhanced by delivering medicines and therapies in a way that is more accessible and acceptable to the patient, smoothing their access to the care they need. With continued innovation, driven by pharmaceutical companies and their drug delivery partners, nasal administration is poised to play an ever-more important role in tackling unmet patient needs in the future.

*All images courtesy of Aptar Pharma.*

## ABOUT THE COMPANY

Next Breath is a speciality company of Aptar Pharma, and a full-service cGMP-compliant laboratory specialising in analytical testing of a range of drug delivery systems, from early stage to commercialisation. Next Breath provides comprehensive solutions for the product development process from formulation and CMC support, to finished batch release and post-approval stability, to regulatory agencies worldwide.

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## ABOUT THE AUTHOR

**Julie Suman** is the President of Next Breath, an Aptar Pharma company, and manager of Scientific Affairs for Aptar Pharma. Dr Suman holds a BSc in Pharmacy and a PhD in Pharmaceutical Sciences. Dr Suman is co-editor for Respiratory Drug Delivery Proceedings, and an Affiliate Assistant Professor in the Department of Pharmaceutics, Virginia Commonwealth University, VA, US. A Past-Chair of the AAPS Inhalation Technology Focus Group, Dr Suman has published in several peer-reviewed journals and presented at numerous international meetings.

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ON drugDELIVERY

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| June | Connecting Drug Delivery | May 27, 2021 |
| July | Novel Oral Delivery Systems | Jun 17, 2021 |
| August | Industrialising Drug Delivery | Jul 1, 2021 |
| September | Wearable Injectors | Aug 5, 2021 |
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| October | Prefilled Syringes & Injection Devices | Sep 9, 2021 |
| November | Pulmonary & Nasal Drug Delivery | Oct 7, 2021 |
| December | Connecting Drug Delivery | Nov 4, 2021 |
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| May | Delivering Injectables: Devices & Formulations | Apr 7, 2022 |

Nemera

# INTEGRATED TURNKEY SOLUTIONS: KEY TO SUCCESSFUL NASAL COMBINATION PRODUCT DEVELOPMENT

**In this article, Alain Regard, Technology Product Manager, Audrey Chandra, Category Project Manager, and Pascale Farjas, Global Category Manager – ENT, all of Nemera, discuss the use of the nasal route for locally and systemic-acting drug treatments.**

It's that time of the year – the pollen season – and some of us might be experiencing what is commonly known as "hay fever". One of the most common chronic conditions for which medical care – such as a nasal spray – is sought is rhinitis. Currently, approximately 10–30% of adults and 40% of children are affected.[1] In fact, rhinitis can be induced by allergic stimuli, non-allergic triggers or both (mixed rhinitis). Allergic rhinitis only occurs in patients with a genetic predisposition to developing allergies.

Whilst the underlying mechanisms behind non-allergic rhinitis are quite variable and less well understood, nasal symptoms can be triggered by environmental irritants, such as smells and particulate materials, as well as changes in weather and barometric pressure. Some patients respond to emotional stress, hormonal changes and other unidentified stimuli.[2]

Allergic rhinitis is thus mostly seasonal – a hypersensitivity reaction is triggered when allergens are present. The symptoms of such a condition can often be relieved and controlled; a nasal spray containing topical-acting medications is normally prescribed for patients to treat the affected nasal cavity regions.

## THE NASAL ROUTE USED FOR LOCAL AND SYSTEMIC-ACTING TREATMENT

Other than treating conditions locally, nasal delivery is also an attractive option to administer systemic therapies to target a range of conditions, from benign to serious. What's more, the nasal route is non-invasive and does not require a healthcare professional's intervention when patients can self-administer their remedy, to rapid effect. Additionally, it provides better bioavailability as drug administration via the nasal route avoids the hepatic first-pass effect which could be encountered when taking medications orally.

> "Drug administration via the nasal route avoids the hepatic first-pass effect which could be encountered when taking medications orally."

Taking into account these advantages, there is much to explore with the intranasal route. The anatomy of the nose allows for the administration of medications systemically or locally by targeting the optimal nasal region for drug deposition to eventually treat certain pathologies. To precisely address the exact part of the nasal cavity, the delivery device used within the drug combination product is a critical element and may vary depending on the therapeutic indications.

In Figure 1, for instance, allergic rhinitis and sinusitis are two of the pathologies which could be treated with topical medications. These are often relieved by nasal spray administration to reduce inflammation. More recently, there has been growing interest in delivering drugs via the nose for systemic conditions. This can be explained by the nasal turbinates

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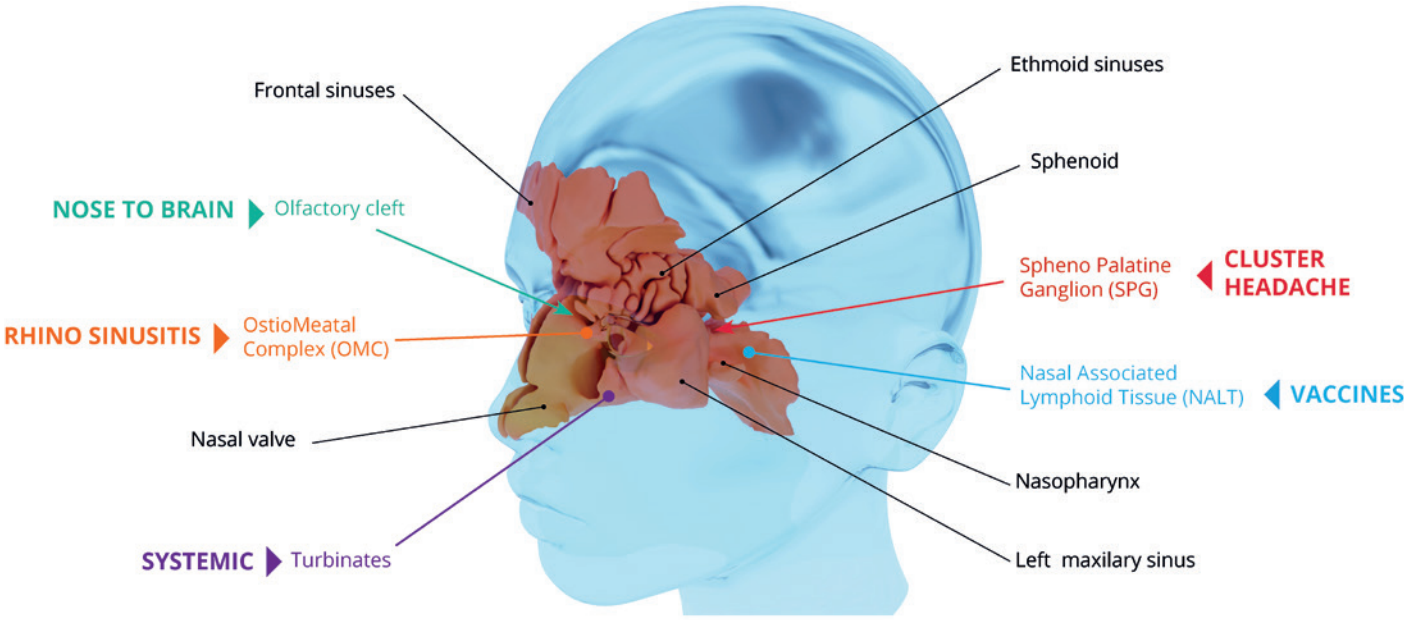


Figure 1: 3D rendering of nasal anatomy and its entry points for topical and systemic therapies to treat different conditions.

occupying a large surface area of the nasal mucosa and being highly vascularised, which therefore is convenient for systemic delivery. As an alternative to conventional injections, certain vaccines could also be delivered via the nasal route as nasal associated lymphoid tissue (NALT) is connected to the lymphatic network and can induce a mucosal and systemic immune response.

Another aspect of intranasal delivery being explored is a nose-to-brain pathway that can be targeted through the olfactory region to treat central nervous system (CNS) conditions such as Alzheimer's disease. In addition, cluster headache can be treated via the sphenopalatine ganglion (SPG). Cluster headache occurs in cyclical patterns, with cluster periods that may last from weeks to months (average 30-40 days) typically followed by remission periods. To block the pain, a numbing drug is applied to the SPG, an area which consists of a nerve bundle located deep inside the nose.

Therefore, specific expertise and a holistic approach are crucial when developing a combination product for administration via the nasal route to ensure optimal region targeting and drug deposition efficacy.

"Specific expertise and a holistic approach are crucial when developing a combination product for administration via the nasal route to ensure optimal region targeting and drug deposition efficacy."

## EXTENSIVE END-TO-END CAPABILITY OFFERINGS

Nemera has several decades of experience developing and manufacturing complex nasal devices – with a wide range of successful market references across the globe, both in regulated and low-regulated countries – to ultimately improve the quality of life of end users. The company has robust large-scale GMP manufacturing capabilities and produces millions of various nasal spray pumps every year. These devices are used to deliver drug formulations through the nose, optimised for drug efficacy and patient or care-giver use. Today, millions of patients rely on Nemera devices to treat their acute or chronic conditions, such as allergic rhinitis, sinusitis or nasal congestion.

"We put patients first" is Nemera's principle. Its development team works actively to understand patients' needs through discussions and tests with patients, individually or within groups, and round tables with key opinion leaders. Early-stage development concepts and insights go through user test studies to ensure a profound understanding of patients' unmet needs. This is to optimise the intuitiveness and usability of the device, with the aim of reducing occurrences of misuse and optimising the performance of the device when handled by patients.

"Delivering the drug product to the target site is challenging in the case of nasal delivery."

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

Expertise in spray technology is also key to nasal drug delivery. Understanding the physics of the atomisation and achieving good control of the spray characteristics are two of the R&D pillars for nasal drug delivery. Nemera actively works on design processes and tools to support its spray development and reduce the number of design iterations required.

The company 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 which can be followed by stability and clinical samples, all the way to industrial volumes.

Furthermore, Nemera fosters a holistic approach in its partnerships with pharma companies, helping them navigate through their combination product development. In this way, not only does Nemera offer its expertise in robust device design and state-of-the-art manufacturing capacity, it also accompanies its customers throughout their development with its integrated front-end solutions. Thanks to its high-end laboratory facilities, Nemera offers device-plus-formulation test services, as well as test method development for customers' needs. In addition, the company's regulatory experts are ready to help guide projects through a dynamic regulatory landscape.

In the case of establishing bioequivalence, following regulatory guidance is crucial. Thanks to its *in vitro* testing capabilities, Nemera can support specific generic projects with a complete set of tests that meet the regulatory requirements. The generated data is statistically analysed with respect to US and EU guidelines for customers' eventual *in vitro* bioequivalence (IVBE) dossier registration filing.

Nemera also provides full understanding of the patient journey and recommends user-related activities to further optimise patients' experience with a combination product. Thanks to Nemera's extensive human factors capabilities, pharma companies can ensure their selected device, in combination with their drug, is appropriate, safe and effective for the target population. For example, Nemera's support includes making instructions for use (IFU) adapted to specific target populations, as well as supporting human factors activities in alignment with a pharma company's chosen regulatory path, including ANDA versus NDA.

Incorporating patients' insights as early as possible to feed into product development is crucial. This is done by leveraging the patients' journey throughout the drug delivery device R&D process to ensure that the device addresses the unmet needs of the end users. 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 (Figure 2).

## HOW NEMERA SEES THE FUTURE OF THE NASAL ROUTE

Although nasal sprays are mainly used for local therapeutic purposes (e.g. allergic rhinitis, colds, etc.) with conventional pump devices, new indications with systemic mode of action and associated delivery systems are emerging. Indeed, several

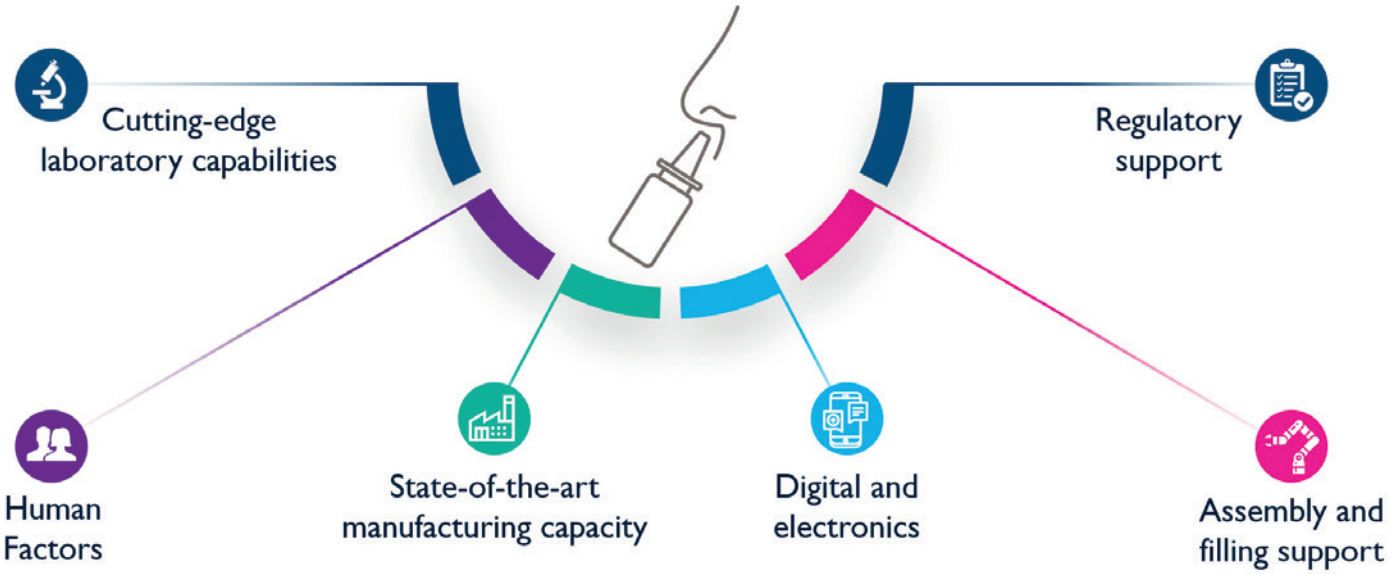


Figure 2: Nemera's full turnkey solutions to support nasal combination product development.

"Nasal vaccination is seen as an attractive and complementary option to traditional injectable vaccines, especially in the covid-19 pandemic situation. There are more than 100 pipelines of nasal vaccines under development today."

rescue drugs have been recently launched using the nasal route, addressing opioid overdose, hypoglycaemia and seizures. This development can be easily explained by the attractiveness of the nasal route over injectable administration.

This change in mindset is a huge opportunity from a market perspective. However, to make the most of it, nasal drug products need to be as reliable and efficient as injectable ones. This opens the door to drug repurposing and product life-cycle management for the pharmaceutical industry, presenting a new administration route for existing drug products, either for acute needs, such as life-saving rescue medications, or for chronic diseases.

The development of such nasal sprays needs to be accompanied by a reliable device, with an accurate dose delivery and a specific deposition area in the nasal cavity, in order to achieve maximum therapeutic efficacy for the combination product.

To illustrate, nasal vaccination is seen as an attractive and complementary option to traditional injectable vaccines, especially in the covid-19 pandemic situation. There are more than 100 pipelines of nasal vaccines under development today, according to analytics data from Pharmacircle.

In addition, the RetroNose concept, with the principle of delivering drug product to the entirety of the upper airways, could also be advantageous in the fight against pneumoviruses and other pathogens. Last but not least, nose-to-brain drug delivery is another promising and challenging area, requiring the development of both a specific drug formulation and delivery system to reach the olfactory region in the upper part of the nasal cavity.

## CONCLUSION

As a device developer and manufacturer, Nemera's mission is to ensure proper drug delivery by depositing a precise amount of drug product in the right place, while fostering patient adherence via easy-to-use and intuitive devices. Nemera understands how important it is to continue exploring customised solutions for nasal delivery treatments to address unmet medical needs and to propose alternatives to the pharmaceutical industry, for both life-saving drugs and lifelong treatments.

The practice of embedding electronics into medical devices should provide further advantages and attractiveness for nasal delivery in the years to come. As such, Nemera has invested in R&D to develop various e-device concepts (e.g. Safe'n'Spray) and showcased the added value and technical features provided by electronics, which can be developed and customised according to customer needs.

In line with the growing interest in the nasal route for both local and systemic treatments, Nemera's device platforms, coupled with its integrated end-to-end approach, enable it to support and bring drug/device combination solutions to patients.

## 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 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, the company works with its customers as colleagues. Together, they go the extra mile to fulfil Nemera's mission.

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# THE CRITICAL ROLE OF TRAINING IN THE USE OF NASAL RESCUE THERAPIES

**In this article, Tim McLeroy, Executive Director, Marketing and Patient Services, at Noble, discusses the role of nasally administered rescue treatments in preventing deaths from opioid overdose or misuse – highlighting the importance of training and treatment availability.**

Startling statistics have revealed the magnitude of the global opioid epidemic. According to the World Health Organization (WHO), in 2018 about 58 million people worldwide used opioids, and another 35.6 million suffered from drug use disorders.[1]

This uptick in opioid use worldwide is a leading factor in the escalation of the conversations around – and the use of – nasally administered rescue drugs such as naloxone, and the efforts to ensure healthcare providers (HCPs), first responders, care networks and the general public are properly trained in their use.

Echoing these findings from the WHO, the International Journal of Drug Policy reports that the use of illicit opioids and misuse of prescription opioids are the main causes of drug-related deaths across the world, calling the continuing rise in opioid-related mortality a public health challenge that is especially affecting North America, Australia and Europe. The journal estimates there were 1.3 million high-risk opioid users in the EU in 2017, with 77% of them in Germany, Spain, France, Italy and the UK. Additionally, there were 9,461 overdose deaths in the 28 EU member states plus Norway and Turkey. Of these, 78% involved opioids.[2]

In the US, an estimated 1.7 million people suffered from substance use disorders related to prescription opioid pain relievers in 2017, prompting the federal Department of Health and Human Services (HHS) to declare the nation's opioid crisis a public health emergency. The agency cited increasing rates of opioid-related deaths and use disorders as the primary factors for this declaration. In 2019, almost 50,000 Americans died from opioid-involved overdoses.[3]

In addition to the overwhelming human toll, there is also an economic toll, including the costs of healthcare, lost productivity and addiction treatment. The US Centers for Disease Control and Prevention (CDC) estimates that the total economic burden of prescription opioid misuse in the US alone is $78.5 billion (£56.2 billion) a year.[4]

> "In the US, an estimated 1.7 million people suffered from substance use disorders related to prescription opioid pain relievers in 2017."

## THE CHALLENGES OF NASAL RESCUE THERAPY DEVICES FOR OPIOID OVERDOSES

Naloxone is a life-saving medication that rapidly reverses the effects of opioids when administered via the nose and is considered a front-line defence in battling the opioid crisis.[5] Efforts are underway to make this

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rescue therapy more readily available to individuals, families, first responders and communities to help reduce the number of overdoses and deaths.[6] But the rescue therapy can only be effective if it is in the right hands, and those administering the rescue therapy know how to use the intranasal drug delivery device correctly.

According to the US FDA, an important element of continued efforts to increase the availability of this life-saving drug is to ensure that treatments are available first and foremost to two major groups: individuals at a higher risk of an overdose – which includes people with a history of substance use disorder – and those in communities who are most likely to witness an overdose.[6]

## BARRIERS TO ACCESSING LIFE-SAVING RESCUE TREATMENTS FOR OPIOID OVERDOSE

Essential to preventing opioid overdoses and deaths is increasing the availability of all forms of naloxone – including nasal sprays – to individuals most at risk, as well as to their care networks, first responders and others.

> "When prescribing opioids for the treatment of certain types of pain, co-prescribing naloxone alongside them has the potential to save lives."

All forms of naloxone currently require a prescription, which can be a barrier for people who are not under the care of an HCP or are reluctant to admit having an issue with substance abuse and thus do not seek help. Some US states – as well as some countries in Europe, the Middle East and Africa – have passed laws allowing pharmacists to dispense naloxone under a standing order, which takes the place of an individual prescription, while others have given pharmacists direct authority to prescribe naloxone to consumers.[6]

Additionally, when prescribing opioids for the treatment of certain types of pain, co-prescribing naloxone alongside them has the potential to save lives. However, US data on patients to whom clinicians should consider co-prescribing naloxone shows that less than 1% actually receive the prescription.[7]

## DRUG DELIVERY SOLUTIONS FOR NASALLY ADMINISTERED OPIOID OVERDOSE RESCUE TREATMENT

Aptar Pharma's Unidose systems are ready-to-use, one-step nasal drug delivery devices that deliver a precise single dose quickly, easily and reliably without the need for administration by an HCP.

Aptar Pharma's patented Unidose devices are approved by the FDA and European regulatory authorities for a wide range of treatments, from chronic conditions, such as migraine and vitamin B12 deficiency, to life-saving drugs that counter an opioid overdose, seizure clusters or epilepsy, such as naloxone, midazolam or diazepam.

Noble, an Aptar Pharma company, offers medical device training solutions and patient onboarding strategies that are leveraged by biopharmaceutical companies and original equipment manufacturers (OEMs) to support patients who self-administer their prescribed medications – or, in the case of naloxone, for people who are at a high risk of needing someone in their care network to administer the drug to them to counteract an opioid overdose.

Figure 1: Noble's training device replicates the form and function of Aptar Pharma's Unidose device while also featuring a novel twist reset function.

Noble has designed a training device that replicates the form and function of Aptar Pharma's Unidose device while also featuring a novel twist reset function that allows for repeated practice and makes it easier for users to become familiar and comfortable with actuating the device. Noble's nasal delivery device training kit also includes training device instructions for use (IFUs) to empower patients and engage care networks with the knowledge and confidence to administer the actual drug therapy in an emergency (Figure 1).

Recently, Aptar Pharma and Noble entered a collaboration with dne pharma, a leader in addiction medicine in Northern Europe. The companies are providing Aptar Pharma's Unidose drug delivery device and Noble's training solution for dne pharma's Ventizolve® nasal naloxone, which is currently approved in 12 countries across Europe. Noble's training kit will be used as part of dne pharma's broad patient onboarding and awareness programme for Ventizolve in outreach and drug treatment centres across the Nordics – the first of its kind for a naloxone nasal drug product launch (Figure 2).


Figure 2: Noble's training solution for dne pharma's Ventizolve nasal naloxone.

> "Nasally administered medications are widely recognised in the rescue therapy space, as they are quickly absorbed by the nasal mucosa, passing the blood-brain barrier more rapidly than other forms of administration."

According to dne pharma, the inclusion of Noble's training device with dne pharma's Ventizolve nasal naloxone will help broaden the impact of its life-saving treatment.

## BENEFITS OF NASALLY ADMINISTERED RESCUE TREATMENTS

A 2019 study solidified that intranasal administration in general – and thus naloxone as well – has several advantages over intramuscular administration of medicine. Intranasal administration removes the possibility of needlestick injury and, more importantly, administration through injection often requires more training and practice than is necessary with nasal drug delivery.[7]

Additionally, nasally administered medications are widely recognised in the rescue therapy space, as they are quickly absorbed by the nasal mucosa, passing the blood-brain barrier more rapidly than other forms of administration.

These reasons, among others, explain the benefits of nasally administered rescue therapies. Additionally, because overdoses can happen anywhere and at any time, the FDA sees nasally administered naloxone as a preferred treatment, due to the fact that it is designed so that anyone can use it. "With naloxone, anyone can help save the life of someone who's having an opioid overdose," said Douglas C Throckmorton, MD, Deputy Director for Regulatory Programs at the FDA's Center for Drug Evaluation and Research. "We want everyone who may witness an opioid overdose – family members, friends, neighbours and others close to people who use opioids – to have access to naloxone and to feel confident using it during an emergency. Without naloxone, the risk of an overdose being fatal is significant."[8]

## TRAINING PROGRAMMES INCREASE CONFIDENCE FOR CARE NETWORKS

The greatest benefit of nasal rescue therapies – the fact that they are created so that anyone (a person's care network or the public, for example) can administer them – is also one of their greatest challenges. When faced with an emergency, will users have the confidence and knowledge to administer the rescue treatment?

> "Training the public in the use of nasally administered rescue treatments, such as naloxone, is critical. But if that life-saving drug is not on hand in an emergency, that training cannot be acted upon."

Training helps to reduce use errors and can also aid in addressing user anxiety. In 2014, Noble conducted research with 55 participants in conjunction with Auburn University (AL, US). Data showed that practising with a training device prior to self-administering (or, in the case of naloxone, teaching a care network to administer) results in an 86% increase in user confidence.[9]

> "Training the public in the use of nasally administered rescue treatments, such as naloxone, is critical. But if that life-saving drug is not on hand in an emergency, that training cannot be acted upon."

Furthermore, when people are trained in the proper use of nasally administered rescue treatments and confident in training others, they – and those around them – are better prepared for a potential emergency.

## SUMMARY

Combatting the global opioid overdose epidemic remains an urgent public health priority worldwide. Making life-saving treatments more readily available is critical in addressing the crisis, as these treatments can play a crucial role in preventing deaths from opioid overdose or misuse.

Furthermore, training the public in the use of nasally administered rescue treatments, such as naloxone, is critical. But if that life-saving drug is not on hand in an emergency, that training cannot be acted upon. This lack of access to these drugs creates a secondary problem: ensuring naloxone is in the right hands and in the right communities.

As with all products that place the burden of administration in the hands of the user, proper training and onboarding helps to build user confidence, which in the rescue therapy setting can be a crucial factor. A training kit that includes a resettable demonstration device – precisely as is included in the Noble training kit for Aptar Pharma's Unidose device – can help to ensure a high level of user confidence in what will be unscheduled, stressful and potentially life-threatening circumstances.

Minimal access to naloxone is a barrier to mitigating the often-deadly impact of opioid overdoses as well. In most countries, access is limited to HCPs and, even then, that access can still be inadequate. Recently, the UK, Canada, Australia, Italy and others have made these drugs available over the counter. While this is a powerful first step, it means training becomes even more essential to ensure that users accessing these over-the-counter drugs are prepared to properly administer them.[1]

Nasally administered rescue treatments, such as those delivered using Aptar Pharma's Unidose system, are critical contributors to helping solve the global opioid crisis. When combined with Noble's Unidose training kit, people at high risk of an overdose can train and prepare their care network in the proper administration of the life-saving drug. In the best-case scenario, the rescue drug will never be used; however, should a situation arise where it must be, users should feel confident in administering it to save a life – which begins with simply understanding how to use the drug delivery device quickly and effectively.

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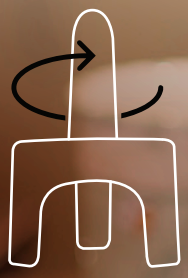

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## ABOUT THE COMPANY

Noble develops robust training devices and onboarding solutions for the world's top pharma and biotech companies and is focused on fostering healthy patient outcomes for those who self-administer drug therapies. Noble manufactures and commercialises training devices that mimic the exact feel, force and function of drug delivery devices, including autoinjectors, prefilled syringes, on-body injectors, nasal sprays and pulmonary inhalers, in order to increase patient adherence and confidence and decrease usage errors. Noble was founded in 1994 and is based in Orlando, Florida.

Noble is an Aptar Pharma company, which is part of AptarGroup, Inc, a global leader in the design and manufacturing of a broad range of drug delivery, consumer product dispensing and active material science solutions. Aptar's innovative solutions and services serve a variety of end markets including pharmaceutical, beauty, personal care, home, food and beverage.

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## ABOUT THE AUTHOR

**Tim McLeroy**, Executive Director of Marketing and Patient Services at Noble, an Aptar Pharma company, is responsible for the development and execution of product and service launch initiatives and directing Noble's communications strategies. McLeroy led the Nayzilam launch for UCB's US Neurology Patient Value Unit, developing global pre-launch and launch marketing strategies for the first major treatment development for patients with seizure clusters in more than two decades. He has over 25 years of medical and pharmaceutical experience and earned his Bachelor of Science degree from Howard Payne University (Texas, US).

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# ASSESSING THE NASAL DRUG DELIVERY LANDSCAPE

**In this article, Jon Volmer, PhD, Senior Director Research Biology and Innovations; Jon Lenn, PhD, Chief Scientific Officer; and Professor Marc Brown, PhD, Chair of Scientific Advisory Committee – all of MedPharm – discuss the role of reconstituted nasal epithelium in intranasal drug delivery.**

Intranasal delivery has always been a tantalising target for topical and systemic drug delivery due to readily available access, high levels of vascularisation, a large surface area and the ability to deliver directly to the central nervous system (CNS). As one of the primary sites of infection for respiratory diseases, it is also a logical target for vaccine delivery. Delivery is relatively painless, onset of drug action can be rapid and formulations can be easily administered in emergency situations – for example, the Narcan (naloxone) intranasal spray (Emergent BioSolutions, Gaithersburg, MD, US).

As with all methods of drug delivery, development of new intranasal formulations and treatments can only advance as fast as the existing models allow. Therefore, it is always important to reassess and improve upon the models that are currently available. MedPharm is always looking for ways to use its expertise to improve the formulations and the models used to develop these potential products. Reconstituted nasal epithelium (RNE) is one of the latest advancements MedPharm is using to help clients de-risk and expedite intranasal delivery, thereby giving a strategic competitive edge.

"RNE is one of the latest advancements MedPharm is using to help clients de-risk and expedite intranasal delivery, thereby giving a strategic competitive edge."

## NASAL DRUG DELIVERY

The epithelial surfaces of the nose can be divided into four general regions. The most distal of these is the nasal vestibule, characterised by a squamous mucosa that slowly transitions to keratinised skin towards the nares. Just proximal to the nares is the nasal cavity, the largest of the four regions. It is macroscopically characterised by three rigid shell-like protrusions known as turbinates. These structures serve to filter, warm and humidify incoming air. The convoluted surface of the nasal cavity slows incoming air, promoting the deposition of particulate matter on the nasal mucosa. A high level of vascularisation in these structures provides the moisture and warmth required to condition incoming air for optimal gas exchange. Combined, these four regions make an excellent target for drug delivery.

Droplets from sprays or particulate from powders will enter the nasal cavity, encounter the turbinates and adhere to the mucosal surface, where they gain access to the vasculature. Delivery is complicated, however, by the presence of tight junctions, active ciliated epithelial cells and a protective layer of mucus on the epithelium. Particulates are trapped in the mucus layer, which is swept along by the cilia to the oropharynx, where they can be cleared by swallowing, coughing or expectoration.

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This rapid clearance necessitates similarly rapid release and absorbance before the drug product is removed from the target epithelium.

Situated above the nasal cavity is the olfactory mucosa, a specialised region of the nose characterised by the presence of olfactory neurons and supporting sustentacular cells. The olfactory mucosa provides another dimension to nasal drug delivery by providing direct access to the CNS, bypassing the blood-brain barrier and making it possible to effectively deliver a drug to a CNS target within seconds. The mechanism by which this happens is still the subject of some discussion, but likely involves transport of the drug through the paracellular space between olfactory axons or via the conduit-like lamina propria in which olfactory axons are bundled.[1]

## RECONSTITUTED NASAL EPITHELIUM

Historically, one of the more common *in vitro* models used to screen various formulations for nasal delivery is excised animal nasal mucosa (e.g. sheep) mounted in a Franz cell. Formulations are applied to the apical side of the tissue, and receptor solution is sampled from the basolateral side to determine formulation performance. This model has proven quite successful in the development of nasal drug formulations for decades and MedPharm has used it with many clients in the development of several drug products.

However, like all models, this model of nasal drug performance has some limitations for a more complete picture of nasal drug delivery. Although passive barriers such as basement membrane and matrix binding remain intact, the active components such as tight junctions, mucus production, cilia and other cellular activities do not. To build on and improve this model, MedPharma has developed an RNE model. This model system uses primary human nasal epithelial cells, harvested from the mucosa at the turbinates, regrown on permeable inserts and stimulated to develop into a well-differentiated nasal epithelium.

Differentiation of airway epithelium in air-liquid interface (ALI) cultures has been described since the early 1980s.[2] These models have historically been highly complex and difficult to reproduce, and reliable sources of primary cells are hard to obtain. MedPharm has leveraged the recent technological advancements, years of tissue culture and organoculture expertise to build

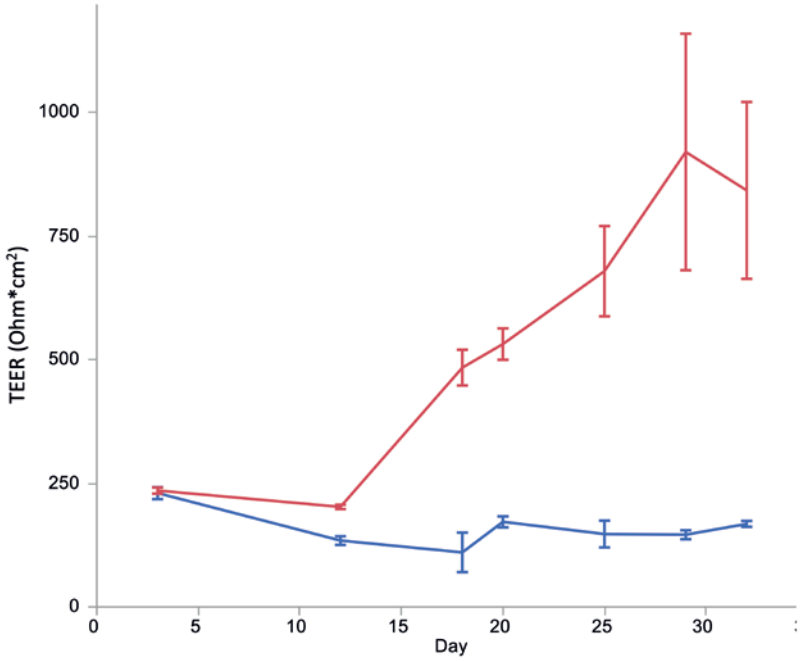


Figure 1: Primary human nasal epithelial cells were seeded on a permeable membrane which was suspended in media. The apical side of the membrane was also covered in media. Cells were allowed to grow until confluent (approximately 10 days), at which point they were switched to air-liquid interface and given differentiation media, or left in the growth conditions. TEER (Ohm*cm²) is plotted versus time (days) for cells treated with growth media (blue) or differentiation media (red). Error bars are SEM, n=5.

> "Nasal epithelial cells are harvested from a donor using a nasal swab and resuspended in a gentle proteolytic media bath."

on and develop new methods that allow for a reproducible RNE construct that can be used in a high throughput fashion to develop and optimise intranasal formulations.

Nasal epithelial cells are harvested from a donor using a nasal swab and resuspended in a gentle proteolytic media bath. Epithelial cells are isolated from resident immune cells and fibroblasts and then expanded in monolayer culture using specific epithelial growth media. Cells are then seeded onto porous membranes, supported over a bath of similar growth media. Over the course of about a week, cells expand and become fully confluent, beginning the differentiation process. At this point, MedPharm's proprietary media is changed and the apical surface is kept dry to promote full differentiation, which occurs over the span of 3–4 additional weeks. Over this time, the epithelial cells adopt a pseudostratified columnar compound epithelial layer. These cells exhibit mucus production, ciliary activity and tight junctions, and this architecture typically persists for approximately four weeks.

Development of barrier function in RNE cultures is confirmed by measuring trans-epithelial resistance (TEER). Tight junctions form an electrochemical barrier between the basolateral and apical chambers, and this can be measured by determining electrical resistance. This slowly builds over time to a stable state after about three weeks and is dependent on the presence of differentiation media (Figure 1). TEER can be measured immediately prior to administration of formulation, to ensure that only intact and well-differentiated constructs are used in analysis.

Oxycodone and buprenorphine have been the subject of clinical studies in which intranasal administration has been compared with intravenous administration.[3] In an effort to determine if the same qualitative trends would translate from those studies to the MedPharm model, buprenorphine and oxycodone formulations were prepared to closely mimic the formulations used in the clinical studies. In the trials, the oxycodone formulation was reported to have approximately seven-fold higher Cmax than the buprenorphine formulation. The overall ranking was similar, with some slight differences in the magnitude of differentiation (Figure 2).

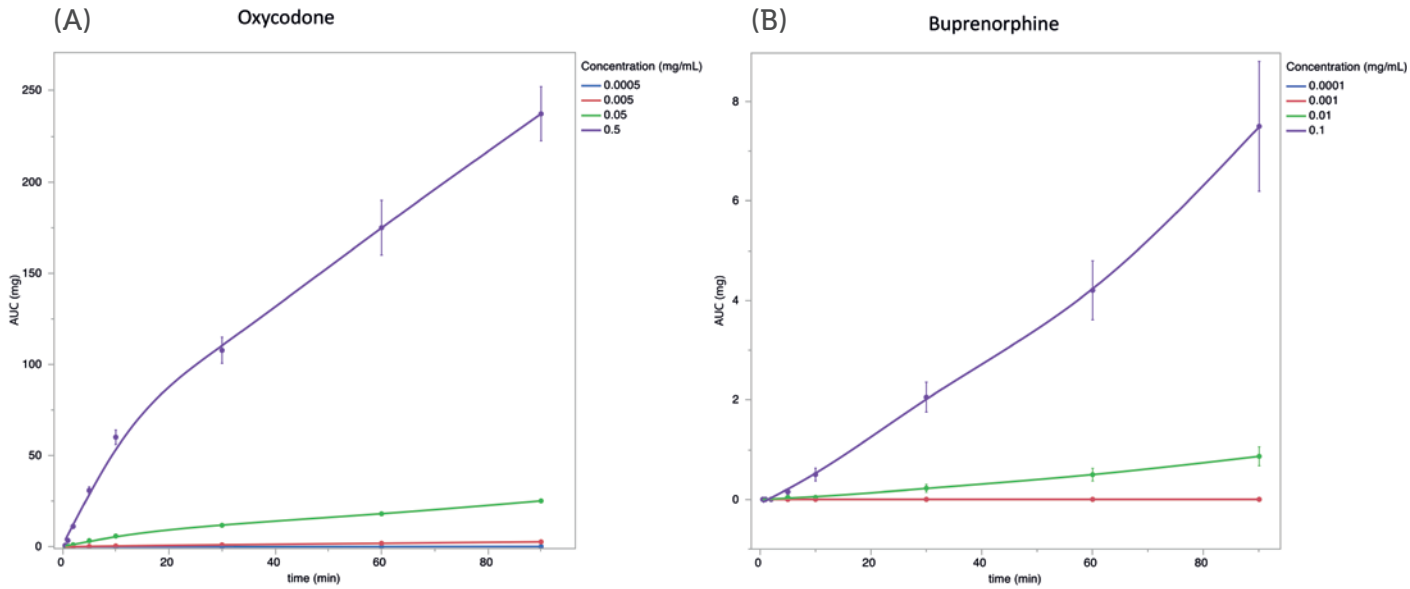


Figure 2: 10 µL of oxycodone (A) or buprenorphine (B) in saline solution at the indicated concentrations was applied to the apical side of well-differentiated RNE. At the indicated times, basolateral media was collected, and replaced with an equal volume of fresh, prewarmed media. Total permeated quantity at each timepoint (AUC) was calculated and plotted versus time. Error bars are SEM, n=5.

To further determine formulation discrimination in the RNE model, a dose-response series was conducted for the oxycodone formulation. Four concentrations of oxycodone formulation were prepared and administered apically to RNE constructs (n=5). At designated intervals, a sample of media from the basolateral side was collected, and the basolateral volume replenished. A total cumulative amount was calculated for each time point. The total cumulative amount at all time points past two minutes showed a linear response to formulation concentration ($R^2$ >0.9) showing a dose-response for the oxycodone formulations (see Table 1).

| Time (min) | $R^2$ |
|---|---|
| 0.5 | 0.85 |
| 1 | 0.87 |
| 2 | 0.92 |
| 5 | 0.95 |
| 10 | 0.95 |
| 20 | 0.95 |
| 30 | 0.95 |
| 60 | 0.94 |
| 90 | 0.96 |

Table 1: Formulations of oxycodone were prepared at four concentrations. Total cumulative amount was calculated for each formulation at each of nine time points. Total cumulative amount for each time point was plotted against formulation concentration to determine if there is a linear relationship between total cumulative amount and concentration of API in formulation. For each time point after two minutes post-administration, a strong relationship ($R^2$ >0.9) was observed.

## CONCLUSIONS AND FUTURE DIRECTIONS

RNE opens new avenues of investigation in drug delivery to or via the nasal route. In addition to being a closer approximation of the nasal mucosal barrier than traditional animal tissue models, RNE cultures allow for additional analyses that are not possible using *ex vivo* tissue. Mucosal epithelium contains influx/efflux pumps, which can transport drugs into or out of the cell layer. A host of constitutive and inducible metabolic enzymes can alter drugs as they pass through the cell layer. Active changes in the type and quantity of mucus in response to formulation delivery can impact permeation. Certain excipients can have active or indirect effects on tight junctions. This model can also be used to monitor direct effects of drugs targeting the nasal epithelium due to cellular responses and can be used to assess local toxicity or irritation.

This model has been extended to include nasal infection. The advent of the covid-19 pandemic has highlighted the significance of respiratory disease, the importance of good models of infection and pathology, and the role of the nasal epithelium in infection and viral propagation. MedPharm has begun the development of models of coronavirus infection in the nasal epithelium, using reconstituted nasal epithelium. Modelling infection in RNE instead of cell lines (such as HBE4 and A549) bypasses many of the well-known shortcomings associated with cell lines in general. Well-differentiated primary cells more closely mimic *in vitro* physiology, cell signalling and architecture. This has special importance in viral infection models, as the conditions in the host cell (such as protease and receptor expression) can generate artificial selection during propagation and infection. This selection can cast doubt on results from such work. Although the use of RNE does not eliminate this effect, it can reduce it.

> "Modelling infection in RNE instead of cell lines bypasses many of the well-known shortcomings associated with cell lines in general."

The RNE model can also be easily adapted for bronchial epithelium, allowing for the testing of a host of new formulation types, such as those for the treatment of asthma, COPD, bronchiectasis and cystic fibrosis. In the case of cystic fibrosis (and other genetic diseases), epithelial constructs can be grown from cells collected from the affected patient population during routine medical care.

RNE and other airway epithelial models can further expand their utility through the use of co-culture systems. Co-culture with inflammatory cells can allow for invasion assays, comparing the performance of anti-inflammatory and antibiotic drugs. Reconstructed airway tissue can be co-cultured with airway smooth muscle to compare efficacy of drugs treating airway hyperresponsiveness in asthma. Due to the long-term viability of these constructs, remodelling effects from irritants such as smoke, diesel exhaust particles and other environmental particulates can be monitored, and recovery from insult compared.

It is always the goal to develop the next more useful model, and thereby advance drug discovery. With this RNE model, MedPharm has increased the utility of available models for intranasal delivery.

## ABOUT THE AUTHORS

**Jon Volmer**, PhD, Senior Director of Research Biology and Innovations, joined MedPharm in 2016 to generate new technologies, systems and biological models, and expand MedPharm's capabilities into new areas, while serving the needs of current clients. He has more than 15 years' experience developing a variety of biological models and technological lab support equipment in fields including immunology, microbiology, pulmonary disease and mechanical remodelling. Dr Volmer received his PhD on the biochemical basis of inflammatory remodelling in the lung from the University of Texas Graduate School of Biomedical Sciences (TX, US).

**Jon Lenn** has direct responsibility for MedPharm's operations in the US, based out of Durham, North Carolina. Since joining in 2015, he has led MedPharm's development of cutting-edge performance models for assessing penetration and activity of clients' products targeted towards key biochemical pathways. He has over 15 years' experience in developing dermatological projects with Connetics, Stiefel and GSK and has been directly involved with the development and approval of eight products. He received his PhD on the topical delivery of macromolecules from the University of Reading.

**Marc Brown** co-founded MedPharm in August 1999 and has been the guiding force behind all the company's scientific developments and intellectual property. He has been Professor of Pharmaceutics at the School of Pharmacy, University of Hertfordshire, since 2006 and has visiting/honorary professorships at the Universities of Reading and King's College London. Dr Brown has over 200 publications and 26 patents describing his work. His research interests lie mainly in drug delivery to the skin, nail and airways. To date, he has been involved in the pharmaceutical development of over 55 products that are now on the market in Europe, America and Japan.

## ABOUT THE COMPANY

MedPharm is a leading contract provider of topical and transdermal product design and formulation development services. MedPharm are experts at reducing risk and accelerating development times for generic and proprietary pharmaceutical customers through their unique, cost-effective and industry-leading performance testing models. Well established as a global leader in dermatology, nail, mucosal membrane and transdermal product development, MedPharm can also offer innovative solutions for ophthalmic and airway preparations recognised for their scientific rigour by regulators and investors. MedPharm has fully established Centres of Excellence in the US and the UK.

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# BIOCOMPATIBILITY OF MEDICINAL PRODUCT MEDICAL DEVICE COMBINATIONS FOR AIRWAY DELIVERY

In this article, Mark Turner, Managing Director of Medical Engineering Technologies, discusses biocompatibility testing for inhaled medical products, with particular reference to ISO 18562, and what MET has learned from three years of breathing component biocompatibility testing.

## INTRODUCTION

Prefilled nebulisers, inhalers and nasal sprays are all drug delivery devices that may need to be assessed for biocompatibility as part of a combination product, under the specific standard developed for demonstrating toxicological safety of airway products – ISO 18562.[1] This ISO standard covers the biocompatibility evaluation of breathing gas pathways in healthcare applications.

The regulatory requirements for combination devices in Europe are given in Article 117[2] of the MDR. Regardless of which jurisdiction and filing approach is used, the US FDA will also be seeking evidence of biological safety.

Published in 2017, ISO 18562 has become the reference standard for breathing component biocompatibility testing. It precedes the current version of ISO 10993-1,[3] the general reference for medical device biocompatibility testing, published in 2018. ISO 10993 includes examples of breathing components and lists them as mucosal membrane contact. ISO 18562 very sensibly adds particulate and gas testing to ISO 10993.

ISO 18562 has four components: general principles, evaluation of particle emission, evaluation of volatile gas emission and evaluation of liquid-borne leachables in condensate.

## ISO 18562-1 – EVALUATION AND TESTING WITHIN A RISK MANAGEMENT PROCESS

This section of the standard discusses the applied principles of testing and toxicological risk assessment. In the scope, we are told that it applies to devices that deliver respired air or other materials into the respiratory tract. It also states that if there is contact between the outside of the device and the patient then ISO 10993 should be considered. In keeping with ISO 10993-18,[4] it emphasises that data may already be available and this should be included in the risk analysis. Here we are told that a representative device, which has been manufactured in the same way as the final product, can be tested, as long as there are no subsequent changes. If risk analysis shows that it has the same toxicological hazard, a biological evaluation plan should then be formulated to decide what testing (if any) is required. A re-evaluation is required if processing, materials, handling or purpose change.

### Toxicological Risk Assessment

Section six of ISO 18562-1 contains information on calculating the dosage of volatile organic compounds (VOCs) given to a patient during use. It has five categories:

1. **Short-term use:** use the actual gas flow in calculations
2. **Neonate:** default inspired volume is 0.23 $m^3$ per day
3. **Infant:** default inspired volume is 2.0 $m^3$ per day
4. **Paediatric:** default inspired volume is 5.0 $m^3$ per day
5. **Adult:** default inspired volume is 20 $m^3$ per day.

These volumes can be used to calculate the inspired dose delivered from the µg of VOC per litre of inspired air figure delivered by the test laboratory.

This section, along with section seven, looks into the toxicological risks posed by any VOCs and leachates found to be entering the patient. It is stated that materials should be assessed according to their individual toxicity data. If no inhalation toxicity data exists there is the possibility to use standard thresholds of toxicological concern[5] according to patient

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"It is relatively simple to test multiple samples of 'mass produced' components for short-term use. This is likely to be the case for combination devices. For long-term use ventilators, the availability of samples can be very limited and the testing procedure protracted, taking up to 30 days."

mass and duration of contact. If the volume of condensate entering a patient is unknown, there is an allowance for a volume of 1 mL per day to be used in the calculations.

### Sample Numbers

The standard does not specify the number of samples that should be tested. In traditional biocompatibility testing, ISO 10993-12[6] defines a sample requirement by surface area (or mass) and it is not concerned with the number of products used. This applies to section four of ISO 18562, which covers the leachables. However, there is no guidance for particles and gases.

It is relatively simple to test multiple samples of 'mass produced' components for short-term use. This is likely to be the case for combination devices. For long-term use ventilators, the availability of samples can be very limited and the testing procedure protracted, taking up to 30 days. To make matters worse, samples may be bulky, making testing multiple samples for VOCs expensive. For the full duration of sampling, each test unit must be housed in its own temperature-controlled test chamber to avoid cross contamination.

The use of representative samples is allowed. This can mean a pre-production sample for a complicated product, such as a ventilator. Smaller components are generally tested in their final format and from their distribution packaging.

To date, MET has tested single-use components at a sample size of three and a ventilator with a sample size of one. It is expected that there will be pressure for these numbers to rise.

## ISO 18562-2 – EVALUATION OF BREATHING GAS PATHWAYS, PARTICULATE EMISSION

The standard gives a choice of test methods for capturing particles. The first is gravimetric filtering through a 0.2 µm filter, with all particles that are emitted over 24 hours and caught in the filter being counted. The second method is a particle counter, which siphons off a small part of the airflow.

The test is normally carried out at the maximum recommended flow rate for the product, which is intended to dislodge particles, forming a worst-case test. There is allowance for the use of an expansion chamber to help with the syphoning process. Both methods have their strengths and weaknesses.

The filtration method lends itself well to longer-term and higher-flow monitoring, as multiple filters can be used in parallel to increase the airflow. The weakness is in obtaining accurate measurements for tiny masses of particles. This method also captures all particles greater than 0.2 µm in size. The standard states that it gives methods for quantifying particles between 0.2 µm and 10 µm, but also implies that other sizes should be included in a risk analysis. So, whilst one 20 µm particle could outweigh many 0.2 µm particles, registering its presence is helpful. Subsequent microscopic inspection can gather information on particle sizes.

Because the particle-counter method siphons off a fraction of the airflow, it cannot be certain that a representative sample has been taken. Additionally, many laboratories previously stocked counters with a minimum particle size of 0.25 µm, which do not conform to the standard. The counters are generally not designed for continuous use, and careful selection is required to ensure that the full reading over 24 hours is obtained. An expansion chamber can be added to the system if very high flow rates over a short time are required. This can be used to simulate a cough or sudden inspiration.

For both methods, measures must be taken to minimise and subtract the background particle count. The test should be conducted with an air supply filtered at 0.1 µm or less and should be very dry.

"There are several options for collecting the emitted VOCs. Primarily, the standard highlights thermal desorption (TD) systems, but includes alternatives such as activated carbon filters."

## ISO 18562-3 – EVALUATION OF BREATHING GAS PATHWAYS, VOC EMISSIONS

VOC emissions testing is normally carried out at the device's minimum flow rate to allow time for diffusion of emitted vapours into the airflow. Additionally, the test is often carried out at an elevated temperature to increase volatility. VOCs are materials that become gases below 260°C.

For short-term devices, measurements are made after 30 minutes, 60 minutes and 24 hours. The results for 30 and 60 minutes are included to allow an assessment of the rate of decay in emission production.

For long-term devices, measurements are also made after 30 minutes, 60 minutes and 24 hours. Subsequent readings are taken according to the results, usually at 48 hours and then approximately every three days (to a maximum of 30 days) until the emission level falls below 40 µg per day.

There are several options for collecting the emitted VOCs. Primarily, the standard highlights thermal desorption (TD) systems, but includes alternatives such as activated carbon filters. Furthermore, ISO 16000-6[7] is referenced.

Similar to a laser-counting particle test, the thermal desorption system has the disadvantage that it samples only a small portion of the airflow, which decreases sensitivity. Gas mixing is likely to be complete, so a lack of homogeneity should not be a problem in capture. Captured gases are subsequently released for analysis. In this phase of the test, a lack of homogeneity can be a problem and quite complicated release and recapture mechanisms can be required to ensure that low boiling point gases are accurately measured.

Apart from the method of adsorbing the released gas for later analysis, there is very little overlap between ISO 16000-6 and ISO 18562. Gases are sampled externally to the device in the environmental standard and internally in the biocompatibility standard. Additionally, the standard test temperatures are different. For the breathing component, the test device should be chambered at its maximum recommended temperature of use. This ensures that the worst-case VOC release is assessed. The absorbed gas is then desorbed and analysed by gas chromatography mass spectrometry (GC-MS). This technique is ultra-sensitive and can detect parts-per-billion levels or less. Once the chemical analysis data is available, it goes into a toxicological risk assessment.

The test system at MET includes negative and positive controls. The positive control consists of a mixture of 12 possible VOCs at known concentrations. The information from these controls is used to identify the system efficiencies, limit of detection (LOD) and limit of quantification (LOQ).

### Inorganic Gases

The environmental standards for respired air contain limits for the abundance of certain very low boiling point inorganic gases. Some of these gases can react with VOCs to produce irritants. Specifically, measurements of carbon dioxide, carbon monoxide and ozone concentrations are required in the US for electrical equipment.

## ISO 18562-4 – BIOCOMPATIBILITY EVALUATION OF BREATHING GAS PATHWAY, TESTS FOR LEACHABLES IN CONDENSATE

Section four of the standard only comes into play if there is a liquid path from the gas pathway to the patient. This can occur if device use involves two-way breathing and condensates from exhaled air can flow into the patient, or if water is introduced into the system through nebulisation or humidification. In these cases, chemical and biological testing is required (ISO 18562 does not allow chemical analysis to replace the biological testing, in contrast to ISO 10993-1: 2020). The sample requirement follows ISO 10993-12 with aqueous-only extract for the chemical analysis. It is possible that some nebulised drugs will be aliphatic. This circumstance is covered by the biological testing. Chemical testing includes analysis for metals and organic compounds.

> "A sampling strategy is required for many ventilators and diagnostic systems. Because it is the gas pathway that is under test, it is desirable to extract samples from the inner surfaces of the device without cutting or disassembling it."

Obtaining samples for test is relatively easy for a nebuliser or vaporiser. However, as with the other tests, VOCs and particles, it can become very complicated for large devices. A sampling strategy is required for many ventilators and diagnostic systems. Because it is the gas pathway that is under test, it is desirable to extract samples from the inner surfaces of the device without cutting or disassembling it. It is stated in the introduction to section four that devices with significant patient contact, such as tracheal tubes, should follow the normal requirements of ISO 10993.

Once the extracts are available, chemical analysis is usually conducted for organic and inorganic materials. The inorganic materials (metals) are detected by ionisation followed by spectral or mass measurements in an electric field. The organic materials (most carbon-based materials) are detected by chromatographic separation and mass spectroscopy analysis.

The chemical analysis is controlled and quantified with the use of negative controls, a sample where pure solvent has been through all the same processes with no product present, and positive controls, negative samples spiked with known amounts of suspected contaminants.

> "Section four of the standard only comes into play if there is a liquid path from the gas pathway to the patient. This can occur if device use involves two-way breathing and condensates from exhaled air can flow into the patient, or if water is introduced into the system through nebulisation or humidification."

The biological testing encompasses cytotoxicity and sensitisation studies. These are carried out according to the standard good laboratory practice protocols.

## CONCLUSION

There is a requirement for the biocompatibility assessment of a huge array of medical and drug delivery devices (both combination products and co-packaged devices) to go beyond ISO 10993 and include consideration of particles and volatile materials delivered to a patient. This assessment can be carried out by examining existing data, but frequently requires testing of each specific product.

Particle testing is relatively straightforward, but the VOC testing can be complicated in both execution and analysis. The devices range in question from inhalers to larger inspiratory systems. Chemical testing is then very likely to identify a number of unexpected materials from these items which need to be analysed by a toxicologist, and there is a variety of ways of expressing the gathered data and toxicity evaluation, which can lead to confusion.

The requirements for leachate testing for fluid that can enter the respiratory system are better established but can still pose challenges. However, there are currently no specific requirements for the interaction between the pharmaceuticals and their delivery device as far as ISO 18562 is concerned.

## ABOUT THE COMPANY

Medical Engineering Technologies (MET) has successfully delivered design validation testing to medical device and pharmaceutical companies in 20 countries across Africa, Asia, Australasia, Europe and North America. MET knowledgeably, reliably and effectively delivers medical device and

packaging testing. Services include protocol development, laboratory testing and data analysis. The laboratory is equipped for performance testing, chemical analyses and sterile barrier verification and – with accreditation to ISO 17025 – customers can have complete confidence in the quality and accuracy of results.

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## ABOUT THE AUTHOR

**Mark Turner** is Managing Director of Medical Engineering Technologies, which provides a wide range of services to engineers and project managers in the medical device industry. Mr Turner founded MET in 1997 after 12 years of project management and device design with Smiths Medical. He has also worked as a perfusionist in the cardiac unit of King's College Hospital (London, UK), providing experience of the application of medical devices first-hand. He received a BSc in Chemistry (with Biochemistry) from the University of Wales (UK) in 1983 and has also studied astronomy, business administration, cosmology and opto-electronics.

# CHARACTERISATION OF LACTOSE POWDERS FOR DPI APPLICATIONS

Here, Aurélien Neveu, PhD, Particle Scientist at GranuTools, and Michael Crowley, Process Technology Director, and Tony McGorisk, European Commercial Director Pharma, of Kerry, discuss the characterisation of lactose powders for use as excipients in DPI formulations. The authors go on to discuss an analysis of six Kerry lactose powders using GranuTools technology.

## INTRODUCTION

Lactose clearly meets the criteria for an ideal carrier for inhalation applications; it is chemically and physically inert to other excipients and APIs, widely available worldwide, well characterised, easy to store, cost-effective and typically has low lot-to-lot variability. Dry powder inhaler (DPI) products are designed to deliver a dry powder formulation to a patient's lungs, typically consisting of a homogenous blend of the API and an excipient (most often lactose) and contained within a reservoir, capsule or blister prior to inhalation. Such formulations are produced by physically mixing micronised drug particles with the larger excipient "carrier" particles.

Unlike in many conventional tableting formulations, the excipient is an important functional ingredient in a DPI formulation, playing at least two roles in the formulation. Since the API is used in very small quantities, blending with the excipient is necessary to enable its delivery to the desired location within the lung. Second, the excipient must separate from the drug during inhalation so that the drug can be inhaled into the patient's lungs.

The excipient's physical properties and interfacial forces affect the blend uniformity and drug release characteristics of the DPI formulation. Some of these properties include the particle size distribution, flowability, surface chemistry, morphology and electrostatic properties of the excipient. It is critical that these characteristics are controlled during manufacture and storage of the excipient. When considering excipients for DPI development, the key considerations are producing a uniform blend for accurate dosing and then proper drug separation

> "When considering excipients for DPI development, the key considerations are producing a uniform blend for accurate dosing and then proper drug separation during inhalation. Beyond that, reducing batch-to-batch variability is also extremely challenging in these types of formulations."

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"During the last decade, GranuTools has updated these techniques to meet the present requirements of R&D laboratories and production departments. In particular, measurement processes have been automated and rigorous initialisation methods have been developed to obtain reproducible and interpretable results."

during inhalation. Beyond that, reducing batch-to-batch variability is also extremely challenging in these types of formulations.

Development of a robust DPI product depends on understanding the aforementioned characteristics of the inhalation carrier and the effects that variations in these characteristics have on the performance of the DPI product. However, the analytical methods used to measure these characteristics vary between suppliers of inhalation lactose, users and academics interested in dry powder inhalation. Additionally, many simple, traditional excipient tests, such as sieve particle size testing, are not adequate for producing a robust DPI formulation. Formulation variability can be reduced if better methods are employed to reduce batch-to-batch variability of the excipient.

During the last decade, GranuTools has updated these techniques to meet the present requirements of R&D laboratories and production departments. In particular, measurement processes have been automated and rigorous initialisation methods have been developed to obtain reproducible and interpretable results. This article details an investigation into the packing dynamics, flowability and tribocharging properties of six lactose powders. The authors show how these methods can help to gather important information on powder behaviour, which in turn can help with the design of new products with improved performance.

## EXPERIMENTAL METHOD

### Dynamic Cohesive Index (GranuDrum)

GranuDrum is a tool for investigating the rheology of powders, using an automated powder flowability measurement method based on the rotating drum principle. A small amount of powder (50 mL in this study) is placed in a horizontal drum with transparent sidewalls. The drum rotates around its axis at an angular velocity of 2–60 rpm. Snapshots (40 images at one-second intervals) are taken by a charge-coupled device (CCD) camera for each angular velocity. The air/powder interface is detected on each picture using an edge detection algorithm.

Afterwards, the average interface position and the fluctuations around this average position are computed. For each angular velocity, the dynamic cohesive index is measured from the temporal interface fluctuations, which are caused solely by the cohesive forces acting between the grains.[1] Therefore, the dynamic cohesive index is close to zero for non-cohesive powders and increases as the cohesive forces intensify. Furthermore, by varying the rotation rate, complex rheological properties of powders (shear thinning, shear thickening and thixotropic behaviour) can be investigated.

### Tapped Density Analysis

The "tap-tap" test, which measures the bulk density, tapped density and Hausner ratio, is a popular method for powder characterisation because it is both simple and fast. The packing dynamics of a powder give useful information about its cohesive behaviour; a more cohesive powder is able to sustain a looser packing at rest, extending its packing range compared with a less cohesive one. The Hausner ratio, defined as the ratio of the tapped to the apparent (untapped) bulk density, is thus a measure of the cohesiveness of powders – the higher the Hausner ratio, the higher the cohesiveness.

In this study, the packing properties of powders were investigated with the GranuPack instrument (GranuTools), which uses an automated and improved tapped density measurement method.[2] The powder is placed in a metallic tube with a rigorous automated initialisation process. The height ($h$) of the powder bed is measured automatically after each tap using an inductive sensor. From $h$, the volume ($V$) of the pile is computed. As the powder sample mass ($m$) is known, the bulk density ($\rho$) is evaluated and plotted after each tap.

The bulk density is the ratio between $m$ and $V$. With the GranuPack method, the results are reproducible with a small quantity of powder (typically 35 mL). The Hausner ratio ($H_r$) is related to the compaction ratio and is calculated by the equation $H_r = \rho(500) / \rho(0)$, where $\rho(0)$ is the initial bulk density and $\rho(500)$ the tapped density obtained after 500 taps. In this study, three independent tests were performed on fresh powder.

### Tribocharging Sensitivity

Electrostatic charges of the excipient and API particles can affect the performance of DPI drug formulations. Electrostatic forces on the excipient could cause the API particle to adhere to the surface of the excipient and prevent release. Furthermore, electrostatic forces in the final blend could affect the release of the powder from the DPI device. Therefore, variability in charge profiles could cause variability in the final drug fine particle fraction (the API that is released to the patient).

| Powder | Type | D10 (µm) | D50 (µm) | D90 (µm) |
|---|---|---|---|---|
| Aero Flo® 25, NF Anhydrous | Milled | 1-6 | 18-26 | 60-85 |
| Aero Flo® 35, NF Monohydrate | Milled | 3-12 | 28-42 | 70-95 |
| Aero Flo® 55, NF Monohydrate | Milled | 6-16 | 48-62 | 115-135 |
| Aero Flo® 60S, NF Monohydrate | Milled/Sieved | 19-43 | 53-66 | 75-106 |
| Aero Flo® 65, NF Monohydrate | Milled | 9-18 | 55-70 | 135-160 |
| Aero Flo® 85S, NF Anhydrous | Milled/Sieved | 15-50 | 70-105 | 170-220 |

Table 1: Type and size distribution of the particles composing the five powders.

Characterisation of these charges can prove to be an important tool for achieving a higher percentage of the API being released from the excipient/device. Managing or controlling these charges could also be an important factor for reducing the variability of API release. Lastly, measurement of charge could be an important tool for the excipient manufacturer and drug formulator in determining if there is a build-up or variation of charge during manufacturing.

The tribocharging properties of the selected excipients were investigated with the GranuCharge (Granutools).[3] First, the initial charge density ($q_0$) is measured by pouring 55 mL of powder into a Faraday cup. The powder then flows through a V-shape stainless steel (SS316L) pipe and the final charge density ($q_f$) is measured. Finally, the charge density variation ($\Delta q$) is calculated as $\Delta q = (q_0 - q_f)$.

## MATERIALS

Kerry is a leading pharmaceutical-grade lactose supplier and offers a full line of lactose for inhalation under its Aero Flo® brand name. For this study, six of these grades of lactose powders specifically designed for DPI applications were selected.

Particle size distribution is summarised in Table 1. The Aero Flo® 25 has the smallest particle size and the most fines (smallest D10). Powders Aero Flo® 60S and Aero Flo® 85S are sieved and thus have the fewest fines. All samples are monohydrate powders, except Aero Flo® 25 and Aero Flo® 85S which are anhydrous. The milling production method of the powders produces particles with a "shard" shape as seen in the single electron microscope (SEM) images presented in Figure 1.

## RESULTS AND DISCUSSION

### Packing Dynamics

Packing curves obtained with the GranuPack are presented in Figure 2 and summarised in Table 2. From these results, the tested powders can be clearly differentiated by their packing behaviour. Indeed, Aero Flo® 60S and Aero Flo® 85S exhibit a Hausner ratio below 1.20, which is commonly associated with good flowability. Aero Flo® 25 and Aero Flo® 65 have an intermediate-to-high Hausner ratio. Finally, Aero Flo® 35 and Aero Flo® 55 demonstrate a higher Hausner ratio, and thus have the higher cohesiveness among the tested powders.

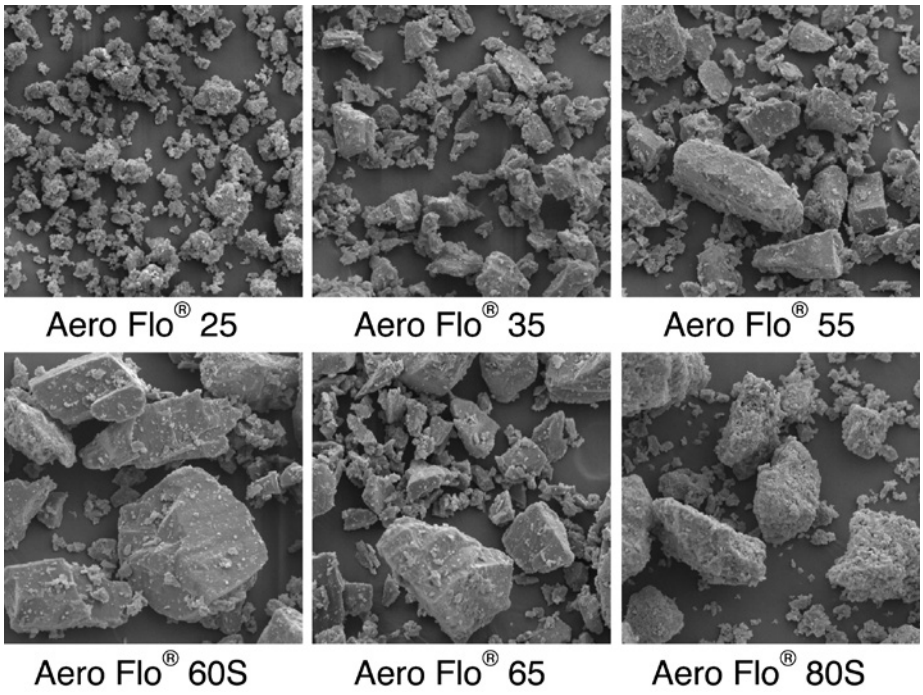


Figure 1: SEM images of the powders at a magnification x300.

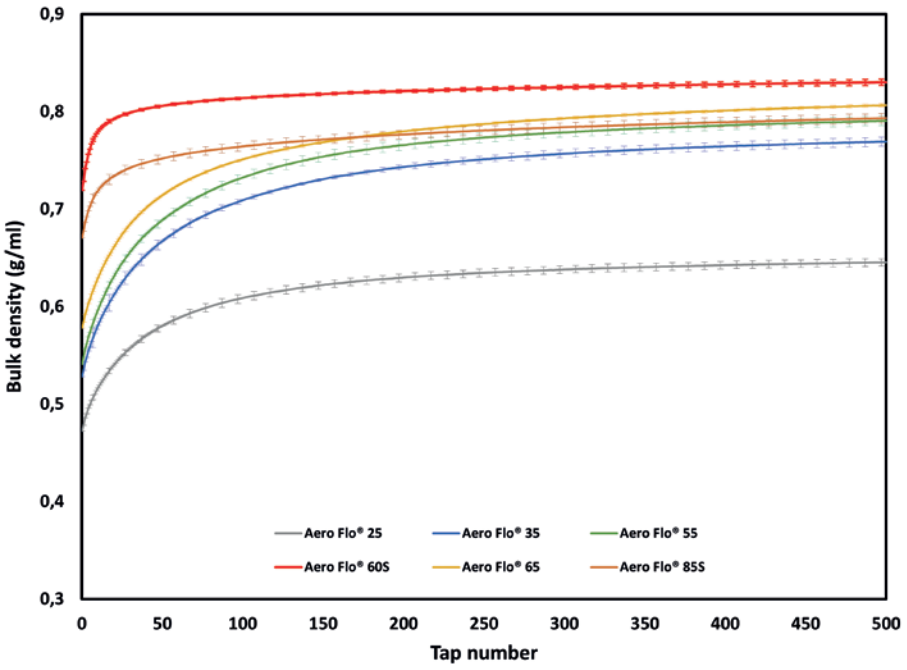


Figure 2: Bulk density versus the number of taps obtained with the GranuPack.

| Sample Name | ρ(0) (g/ml) | ρ(n) (g/ml) | n½ | Hr |
|---|---|---|---|---|
| Aero Flo® 60S | 0.719 | 0.830 | 8.1 | 1.15 |
| Aero Flo® 85S | 0.670 | 0.793 | 18.1 | 1.18 |
| Aero Flo® 25 | 0.472 | 0.645 | 31.1 | 1.37 |
| Aero Flo® 65 | 0.578 | 0.807 | 34.3 | 1.40 |
| Aero Flo® 35 | 0.528 | 0.769 | 37.2 | 1.46 |
| Aero Flo® 55 | 0.541 | 0.790 | 34.9 | 1.46 |

Table 2: Packing properties of the six lactose powders obtained with the GranuPack.

The global cohesiveness of a powder usually decreases with increasing particle size, and so the good flowability of Aero Flo® 85S can be attributed to its larger particle size (D50 = 70-105 µm). Aero Flo® 60S and Aero Flo® 65 have a similar D50 but the higher D10 of Aero Flo® 60S, indicating fewer fines, is probably why this powder exhibits the best flowability characteristic.

An exception is found for Aero Flo® 25. Judging by it having the lowest D50 and D10 compared with the other powders, we could expect it to demonstrate the lowest flowability. However, it exhibits a lower Hausner ratio than Aero Flo® 65, Aero Flo® 35 and Aero Flo® 55, which from the classical interpretation of the Hausner ratio should denote higher flowability. One explanation could be the anhydrous nature of Aero Flo® 25. Indeed, moisture inside powder leads to the setting of capillary bridges that contribute to the cohesiveness. The anhydrous properties of Aero Flo® 25, and thus its lower moisture content, seem to result in a lower cohesiveness despite the smaller particle sizes of this powder.

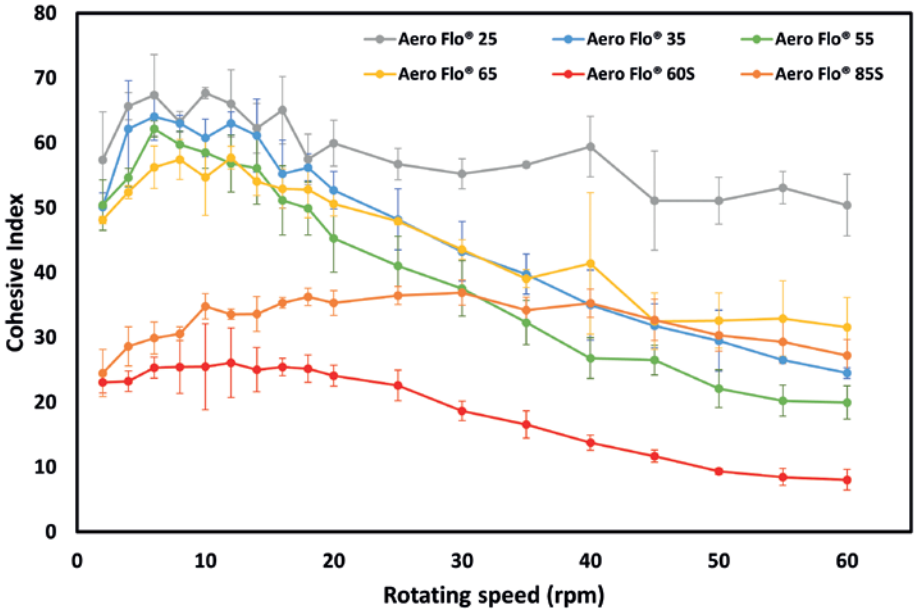


Figure 3: Dynamic cohesive index measured for angular velocities between 2rpm and 60rpm.

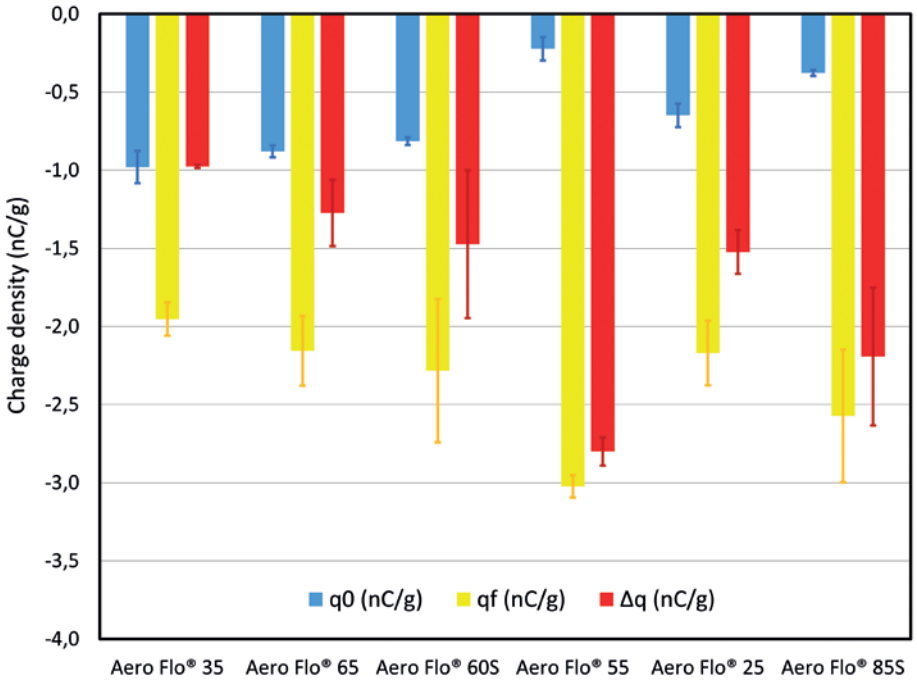


Figure 4: Charge density before and after flowing through SS316L pipes.

## Flowability Results

Figure 3 presents the cohesive index versus the drum angular velocity. At low angular velocities, the observations on powder cohesiveness made during the analysis of the packing dynamics hold true. Indeed, Aero Flo® 60S and Aero Flo® 85S clearly exhibit the lowest cohesive indices, corresponding to having the best flowability.

However, upon increasing the angular velocity, powders Aero Flo® 35, Aero Flo®55 and Aero Flo® 65 exhibit a strong shear-thinning effect, i.e. an increase of flowability with increasing applied stress. This behaviour is very interesting; it means that an increase in the processing speed will lead to an increase of flowability. In a high stress state, the flowability even becomes similar to that of Aero Flo® 85S, especially for Aero Flo® 55, which reaches a cohesive index of around 20, denoting a major drop in cohesiveness. However, Powder Aero Flo® 60S remains the least cohesive across the full range of angular velocities tested.

Contrary to the observation made with the GranuPack, powder Aero Flo® 25 exhibits higher cohesiveness and did not benefit from the shear-thinning observed with the other powders. The smaller particle sizes, especially the large number of fines, are probably the source of this cohesive behaviour.

## Triboelectric Behaviour

Figure 4 presents the charge density before ($q_0$) and after ($q_f$) flowing through the SS316L pipes, as measured with the GranuCharge. The flow through the pipes resulted in all the powders tested building up a charge due to triboelectric effect, increasing the powder charge density. The Aero Flo® 35 exhibits the lowest charge build-up, below 1 nC/g, and thus is the least sensitive to tribocharging. Powders Aero Flo® 65, Aero Flo® 60S and Aero Flo® 25 demonstrated a moderate charge build-up and cannot be clearly differentiated from each other by their electrostatic behaviour. Finally, the Aero Flo® 85S and Aero Flo® 55 are the most sensitive to tribocharging, with a charge build-up above 2nC/g.

These results suggest that the lower the d50, the lower the sensitivity to tribocharging. This is probably due to a lower contact surface area available for tribocharging for a powder with smaller particle sizes. Higher moisture content is also expected to influence electrostatics, with the setting of a high conductivity contact network allowing efficient dissipation of

charges in the material. Despite its small particle sizes, Aero Flo® 25 doesn't exhibit the lowest charge density, which might be due to its anhydrous nature.

Moreover, the Aero Flo® 55, which exhibited the highest charge build-up, showed the lowest initial charge density. This trend is seen for the other powders and may indicate that higher chargeability is associated with a more efficient dissipation inside the material.

## CONCLUSION

Six lactose powders designed for DPI applications were characterised according to their flowability, packing dynamics and tribocharging behaviour. It was observed that the powder flowability is directly linked to the particle size distribution, powders with larger particles and fewer fines exhibited a higher flowability. Moreover, a strong shear-thinning behaviour was observed, denoting a decrease of cohesiveness when the powders were in a high stress state.

> "Electrostatic investigation provides useful knowledge of the tribocharging ability of the different powders. These results are of particular interest for DPI applications, in particular with respect to drug release from the lactose carrier."

Furthermore, electrostatic investigation provides useful knowledge of the tribocharging ability of the different powders. These results are of particular interest for DPI applications, in particular with respect to drug release from the lactose carrier. Based on these results, further studies should give insights into improving post-manufacturing conditioning of the excipient and/or drug formulation to help reduce the charge build-up and variability.

## ABOUT THE COMPANIES

**Granutools** combines decades of experience in scientific instrumentation with fundamental research on powder characterisation to develop and manufacture instruments for measuring physical powder characteristics such as: flow, static cohesion, dynamic cohesion, tapped density and triboelectric charging.

**Kerry** is a successful pharmaceutical supplier that has demonstrated excellence in consistent, high-yield, customer-specific solutions for the biotech, pharma and nutrition markets for more than 80 years. The company brings together superior products with innovative solutions and market-driving alternatives, such as pharmaceutical-grade lactose excipients, film coatings, self-lubricating excipients, tableting systems and flavours to help its customers succeed in today's challenging global marketplace. Kerry has the worldwide resources and global technical platform to deliver consistent, high-quality products backed by unparalleled service, technical support and formulation customisation capabilities.

## ABOUT THE AUTHORS

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

**Michael Crowley** is the Process Technology Director of Excipients for Kerry. He received his Bachelor's Degree in Biology from St. Bonaventure University (NY, US). He has been with Kerry for 22 years, and has worked in quality assurance, validation, R&D for hydrolysed proteins, R&D for excipients, and now process technology for excipients (for the past 10 years).

**Tony McGorisk** is the European Commercial Director for Pharma at Kerry. He received his BPharm from King's College London (UK) and his MBA from Warwick Business School (UK). He has been with Kerry for 10 years and worked in many technical sales roles before assuming the commercial role he now holds.

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# SPRAY CHARACTERISATION TESTING FOR ORALLY INHALED AND NASAL DRUG PRODUCTS

In this article, Francois Billard, Associate Director of Analytical Services Sales, and Lei Mao, PhD, Director of Inhalation Science and Product Development, both of Recipharm, look at measurement systems for spray pattern and plume geometry dispensed by orally inhaled and nasal drug products.

## BACKGROUND

Inhalation products are extremely complex to develop and manufacture, and it is important to understand potential interactions between the formulation and the delivery device throughout the development stages. For the characterisation of orally inhaled and nasal drug products (OINDPs) including nasal sprays, oral sprays and metered-dose inhalers (MDIs), spray performance, such as droplet size distribution, spray pattern (SP) and plume geometry (PG) can be assessed using laser-based techniques. These techniques include the use of specific mechanical equipment for the actuation of the device, which generates the spray, combined with laser-based equipment for the characterisation of the spray.

SprayVIEW® measurement systems from Proveris Scientific Corporation (Hudson, MA, US) are the industry standard for the measurement of SP and PG dispensed by nasal sprays, oral sprays and MDIs. They are used by pharmaceutical companies, contract development and manufacturing organisations (CDMOs) and contract research organisations, as well as manufacturers of metered valves and pumps, and regulatory agencies worldwide.

For device actuation, the use of automated equipment such as Vereo® Actuator NSx (Proveris) (for nasal and oral sprays) or Vereo® Actuator MDx (Proveris) (for MDIs) is required to eliminate the variability associated with manual actuation. The automated actuation stations of SprayVIEW® measurement systems allow for consistent actuation of the device. Motion is controlled via an electromechanical motor that requires input parameters such as stroke length, velocity, acceleration and hold time. These systems allow for controlled and repeatable actuations and, as such, they are ideal for quality control release testing, and they also offer valuable support for product development to assess the overall performance of the product throughout its lifecycle.

> "SprayVIEW® measurement systems from Proveris Scientific Corporation (Hudson, MA, US) are the industry standard for the measurement of SP and PG dispensed by nasal sprays, oral sprays and MDIs."

For spray characterisation, real-time images of aerosols or sprays emitted from the device through a laser sheet are

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acquired using a high-speed camera. For SP measurements, the laser sheet is positioned in a direction perpendicular to the axis of the spray at a given distance from the device tip. For PG measurements, the laser sheet is orientated in the axis of the spray through the device tip, and the plume is imaged from the side. Subsequent data analysis of SP (via a cross section of the aerosol or spray perpendicular to the axis of the plume) and PG (via a side view of the aerosol or spray parallel to the axis of the plume) can be used to determine the shape and size of the aerosol or spray.

SP and PG tests are required for chemistry, manufacturing and controls (CMC) characterisation by the US FDA. SP analysis must be included in the release specification for the finished drug product and, for MDIs, must appear in stability studies of registration batches. PG, on the other hand, is complementary to SP. It does not have to be tested on a routine basis and so does not have to be included in the release specification for the finished drug product. However, as with SP, it must be included in the stability studies of registration batches for MDIs.

## DETERMINATION OF ACTUATION PARAMETERS

Actuation parameters are typically the first settings that should be established when developing SP and PG methods for OINDPs. The FDA recommends that actuation settings should reflect proper usage of the product by trained patients and be documented based on exploratory studies in which the relevant parameters are varied to simulate *in vitro* performance upon hand actuation.[1] Such actuation settings may be provided by the suppliers of metered valves and pumps to be used as a starting point for product development.

In the absence of recommendations from the pump supplier, human actuation studies can also be provided by Proveris Scientific®. Using the company's proprietary Ergo™ technology, hand actuation data are acquired from trained testers in the targeted population for the product, and through statistical analysis the information is translated into average values and ranges for the input parameters of the equipment, including stroke length, velocity, acceleration and hold time. These settings will enable the automated actuator to operate and produce actuations based on actual data from human actuations.

## METHOD DEVELOPMENT

SP testing is typically performed on a routine basis as a quality control method for release of the drug product, while PG testing is only performed during the characterisation of the product. SP testing is used to report qualitative metrics such as shape (e.g. circular, ellipsoid) and quantitative metrics such as size (e.g. longest diameter [$D_{max}$], shortest diameter [$D_{min}$] and ratio of $D_{max}$/$D_{min}$), which should lie in a specified range (for *in vitro* population bioequivalence [PBE] studies, area will also need to be assessed). PG testing is used to report metrics such as plume angle and width reported at a single delay time while the fully developed phase of the plume is still in contact with the actuator tip.

Once the actuation settings have been established, the parameters to be optimised during method development will typically include camera position, tip-to-laser distance, frame rate (125, 250 or 500 frames per second), as well as spray duration (start and stop time for analysis) in the case of SP, or time delay (single frame representative of the stable phase of the plume) in the case of PG.

The overall goal in method development is to identify the optimum operating parameters where test results will be most repeatable. Points that need to be considered during method development include:

- For SP, camera placement should be optimised so that SPs are consistently within the field of view. It is recommended that the SP percentage area be at least 5% of the total field of view. However, it is important to keep in mind that, although higher SP percentage area values will increase the size of the pattern and will improve overall measurement sensibility, it could also lead to patterns outside the field of view and unable to be measured if the patterns are too large.
- Similarly, for PG testing, it should be ensured that the edges of the plume are consistently within the field of view. The measurement of wide plumes may require the use of a wide-angle lens.
- There is a risk of the device being detected by the camera, which can result in the software of the SprayVIEW® measurement system processing the image of the device as a second pattern. This phenomenon is caused by light reflection from the laser on the device. Whenever this occurs, reflection light blockers should be used.
- All sources of variability should be thoroughly assessed during method development. It should not be assumed that measurement variability is inherent to the method or solely due to interactions between device and formulation. For instance, it should be ensured that the actuation of the device is robust. The device must be securely connected to the actuation station using the appropriate jig to avoid any movement during firing, as this could cause some measurement variability. The design of the jig should also ensure proper alignment of the device. The test environment could be another source of measurement variability. For instance, formulations containing ethanol may exhibit variability in spray performance depending on the relative humidity level in the laboratory.

SP and PG testing are typically performed at the same tip-to-laser distance. For *in vitro* PBE studies of nasal spray drug products, SP will have to be measured at two distances, while PG testing will only have to be performed at one distance equal

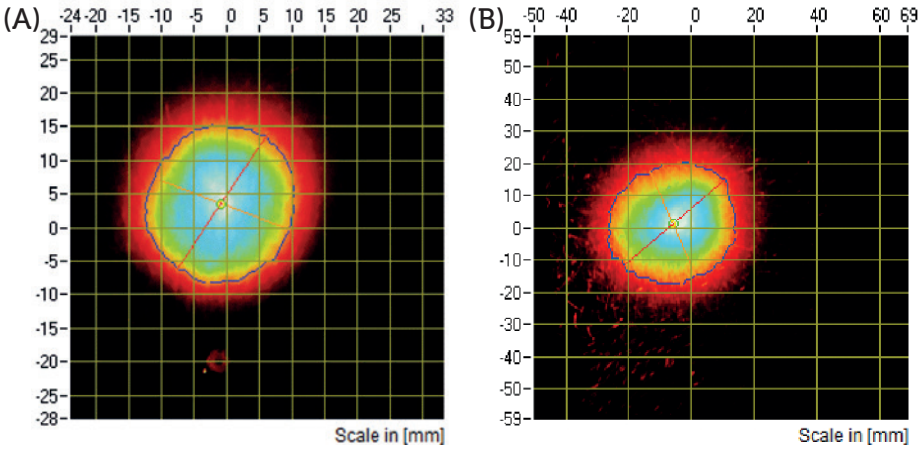


Figure 1: SP images from a nasal spray captured at 30 mm (A) and 60 mm (B) distances.

to the greater of the two distances selected for characterisation of the SP. The FDA recommends that these two distances be at least 3 cm apart within the range of 3–7 cm[2]. For these applications, SP measurement will either be performed at tip-to-laser distances of 3 and 6 cm or 4 and 7 cm (Figures 1 and 2).

For nasal spray applications other than PBE studies, SP determination at one distance is sufficient to meet regulatory requirements. However, collecting SP data at two distances is preferred in the case of MDIs, as the formation of aerosol plume may vary in shape (e.g. jet, mushroom), which will require plume characterisation at several distances in order to ensure full drug product understanding.

## METHOD VALIDATION

Validation of SP and PG methods should be completed before the start of the release and stability studies for the clinical/registration batches. SP and PG methods are typically validated for repeatability, intermediate precision and robustness as defined by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH).[2]

Repeatability expresses the precision under the same operating conditions over a short interval of time. Repeatability is typically assessed by one analyst performing replicate measurements on the same day using the same equipment.

Intermediate precision expresses variations within laboratories, such as different days, different analysts and different equipment. Intermediate precision is typically assessed by a second analyst performing the same number of replicate measurements on a different day using the same equipment.

The robustness of an analytical procedure is a measure of its capacity to remain unaffected by small but deliberate variations in method parameters and indicates its reliability during normal usage. Robustness for SP and PG methods

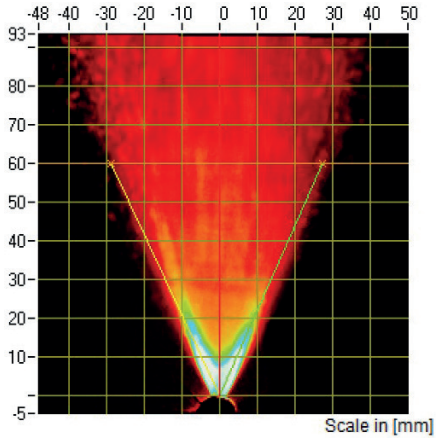


Figure 2: PG images from a nasal spray captured at 60 mm distance.

may include variation of test parameters from the actuation portion of the method (e.g. velocity, stroke length) or from the laser portion of the method such as tip-to-laser distance, as well as spray duration (SP) or time delay (PG).

Acceptance criteria are typically set on $D_{max}$, $D_{min}$, ratio of $D_{max}/D_{min}$, and area for SP or plume angle and width for PG.

## BEYOND SPRAY PATTERN AND PLUME GEOMETRY TESTING

Spray characterisation studies should be initiated early on during the drug product development process to support device selection and formulation optimisation. Once the formulation has been finalised and the device selected, spray characterisation studies should be performed to assess product performance ahead of clinical studies. SprayVIEW® measurement systems are valuable tools to guide drug product development. These systems can also support quality control for container closure components (e.g. valves, pumps) and finished drug products throughout the product's lifecycle.

Additionally, specifications for OINDPs should include performance attributes of the pump such as minimum actuation force to achieve desired spray characteristics.[3] Using the built-in actuation stations from the SprayVIEW® measurement system, actuation graphs can be collected as output parameters displaying the actuation profile, which, for instance, can be used to determine the force-to-actuate of the device (Figure 3, next page).

SprayVIEW® measurement systems can also be used to determinate the spray duration and spray velocity from an MDI. Time-synchronised image sequences of an aerosol plume are processed frame by frame starting when the plume first appears at the mouthpiece edge. The distance and associated time can be recorded for each image of the spray event until moving outside the camera's field of view to allow for the determination of the emitted aerosol spray velocity (Figure 4, next page). This methodology can be used to support comparison studies of spray duration and spray velocity between test samples.

Other applications, including studies on the effect of ethanol concentration on pressurised MDI (pMDI) evaporation fraction using SprayVIEW® measurement systems, have been published by Proveris Scientific® in recent years. Finally, beyond the scope of OINDPs, SprayVIEW® measurement systems can support the spray characterisation for the development of nasal vaccines or of any other applications where the drug product is sprayed.

## BENEFITING FROM SPECIALIST TESTING SUPPORT

In order to accurately gauge device performance, it is vital to have access to expert and specialist testing support. Working closely with CDMOs with

"SprayVIEW® measurement systems are valuable tools to guide drug product development. These systems can also support quality control for container closure components (e.g. valves, pumps) and finished drug products throughout the product's lifecycle."

"Working closely with CDMOs with dedicated experience in inhalation products can ensure that inhalation drug developers benefit from high precision testing capabilities to fully understand the performance of their chosen device and, in turn, gain a better idea of the therapeutic effect of their finished product."

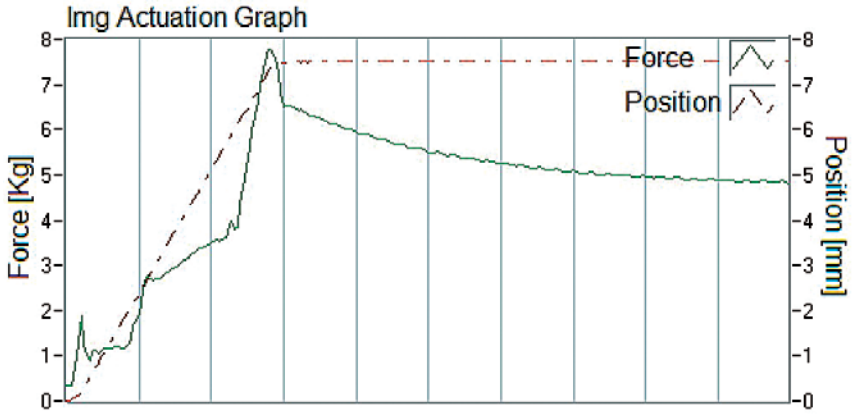


Figure 3: Actuation graph recorded during spray pattern measurement.

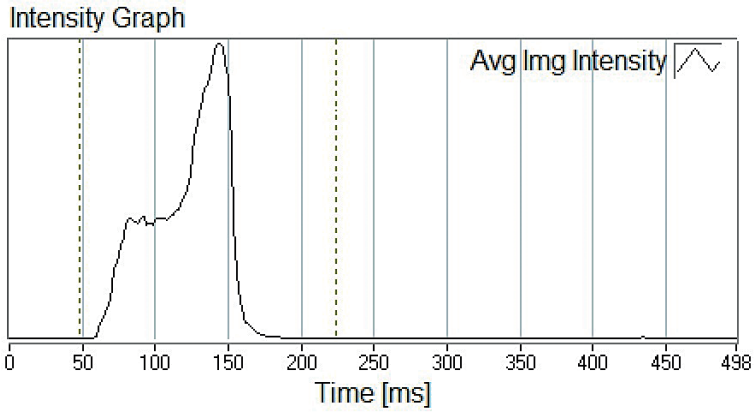


Figure 4: Intensity graph recorded during spray pattern measurement.

dedicated experience in inhalation products can ensure that inhalation drug developers benefit from high precision testing capabilities to fully understand the performance of their chosen device and, in turn, gain a better idea of the therapeutic effect of their finished product.

Recipharm Inhalation Solutions™, for example, provides SP and PG testing services, supporting inhalation and nasal spray product development from initial formulation/process development to registration, product characterisation, commercial batch release and stability. The company performs *in vitro* PBE studies in both generic inhalation and nasal spray product development, and has expertise in developing and validating SprayVIEW®-based methods for aerosol and nasal spray testing. The company's expert team also supports device formulation or process-related changes during product lifecycle management.

Working with a specialist inhalation CDMO offers considerable advantages for drug developers. Partnering with a company with an end-to-end service manages complexity and reduces risk. The company's expertise in the segment means that it understands the unique challenges of inhalation drug development, and has the ingenuity to address them quickly, eliminating hurdles and minimising time to market.

By seeking the support of such partners, drug developers will be well placed to develop high-quality, truly effective inhalation products that will thrive in the competitive global pharmaceutical market and will transform patients' lives for the better.

*SprayVIEW® is a registered trademark of Proveris Scientific Corporation.*

## ABOUT THE COMPANY

Recipharm is a leading CDMO headquartered in Stockholm, Sweden. The company operates development and manufacturing facilities in France, Germany, India, Israel, Italy, Portugal, Spain, Sweden, the UK and the US and is continuing to grow and expand its offering for its customers. Employing around 9,000 people, Recipharm is focused on supporting pharmaceutical companies with its full-service offering, taking products from early development through to commercial production. For over 25 years, Recipharm has been there for its clients throughout the entire product lifecycle, providing pharmaceutical expertise and managing complexity, time and time again. Despite its growing global footprint, Recipharm conducts its business as it always has and continues to deliver value for money with each customer's needs firmly at the heart of all that it does. That's the Recipharm way.

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## ABOUT THE AUTHORS

**Francois Billard** is Associate Director of Analytical Services Sales at Recipharm Laboratories. His previous industry roles include leadership positions in quality, laboratory operations and product development at Aptar Pharma and Catalent Pharma Solutions. Mr Billard has more than 20 years' experience in the pharmaceutical industry, including over 15 years supporting the development of OINDPs. He holds master's degrees in Chemistry/Chemical Engineering and Industrial Process Engineering.

**Lei Mao** is the Director of Inhalation Science and Product Development at Recipharm. With over 20 years of experience, Dr Mao has a wealth of knowledge in formulation and inhalation product development within the pharmaceutical industry. He started his career working as a senior scientist, where he developed particulate formulations for inhalation applications, and has since held managerial positions for big pharma companies. He also holds a PhD in Pharmaceutical Sciences and a degree in Pharmacy.

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- Design Validation Testing
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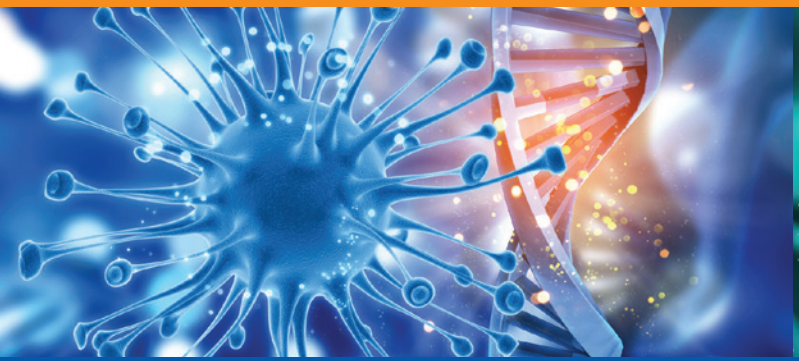
- Extractables and Leachables



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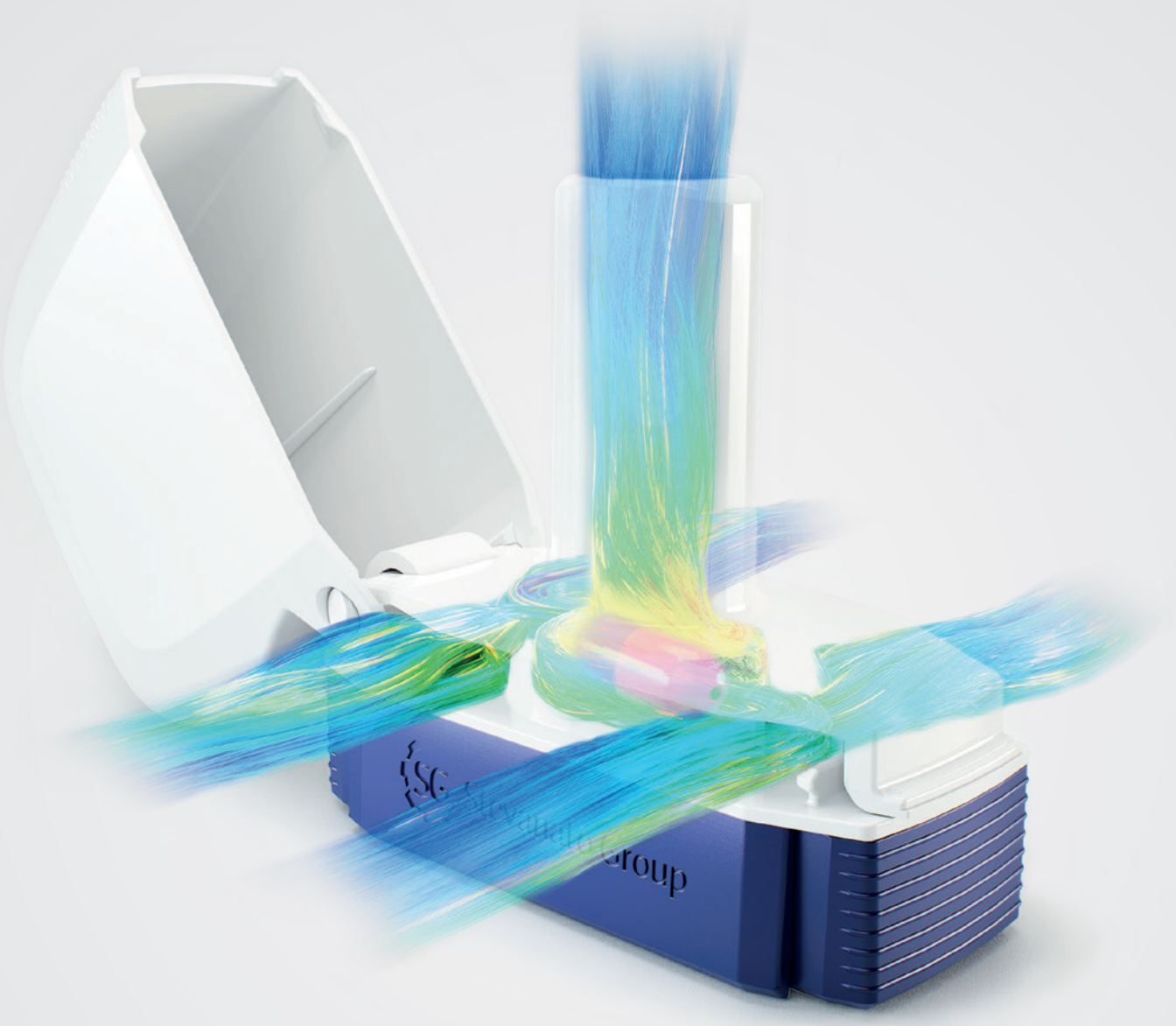

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