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.

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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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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.

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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

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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 Convenient Non-invasive Rapid onset
Diazepam	Seizure clusters/ acute repetitive seizures	Rectal gel	Ease of administration and self-administration Convenient Rapid onset Rescue benefit Social acceptability in non-pediatric population
Metoclopramide	Diabetic gastroparesis	Oral tablet, intravenous injection	Ease of administration and self-administration Convenient Non-invasive (versus intravenous) 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 Administration to unconscious patient possible (versus buccal, oral) Convenient Non-invasive (versus intravenous) Rapid onset Rescue benefit

Table 1: Current commercial nasal delivery products.

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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.