ADDRESSING THE CHALLENGES OF NASAL BIOTHERAPEUTIC DRUG DELIVERY

In this article, Robert Lee, PhD, President of the CDMO Division at Lubrizol Life Science Health, discusses the benefits of administering drugs to the nasal cavity, as well as the main challenges in formulation for this route and the strategies that can be applied to overcome them.

Over the last decade, biotherapeutics have rapidly proliferated. Highly potent, patient-centric and offering a desirable safety profile, these drug products have fast become a staple of the development pipeline.

Most biological drugs are peptide- or protein-based therapeutics and have poor oral bioavailability, making parenteral injection the default route of administration. But, as with any innovation in pharma and biotech, there are unmet clinical needs that require novel delivery mechanisms. In meeting these needs, liquid-based and dry powder nasal drugs have emerged as a class of medications with significant benefits.

Nasal delivery is an attractive alternative for local and systemic delivery of biologics, being a non-invasive route of administration with the potential to treat various diseases, including cystic fibrosis, respiratory viral infections and asthma. Driven by this potential, the market was valued at US$7.8 billion (£5.7 billion) in 2018 and is predicted to reach close to $12 billion by the end of 2025.[1] Nasal products, however, are complex and require significant formulation expertise for successful development.

BENEFITS OF NASAL DELIVERY

The diversity of nasal delivery formulations is central to their appeal – they can be water based, hydroalcoholic, nonaqueous, suspensions or emulsions. Moreover, they can include diverse excipients, including solvents, mucoadhesive agents, buffers, antioxidants, preservatives and penetration enhancers, all of which address some of the fundamental challenges to drug development – solubility, bioavailability and patient acceptance being the big-ticket items.

Formulations for systemic delivery are absorbed directly into the bloodstream, bypassing the liver and first-pass metabolism, which can be an important consideration for drugs that are degraded in the gastrointestinal tract. Rapid absorption also leads to fast-acting systemic effects, even when a patient is unconscious, which can be important for emergencies. Delivery to the olfactory region of the nasal cavity also allows direct access to the central nervous system for some neurological therapies. Nasal delivery is also non-invasive and easy to use compared with injectables, leading to improved patient acceptance and compliance. In addition, it offers a method to administer diverse APIs for both local and systemic applications.

Where solution and suspension dosage forms cannot be developed, dry powders may offer an alternative method and offer additional benefits, including enhanced chemical stability, the absence of preservatives, lower risk of microbial spoilage (which means fewer or no preservatives) and the ability to administer larger amounts of API in each dose. The suitability of a powder formulation is dependent on the solubility, particle size, aerodynamic properties and nasal irritancy of the active drug and/or excipients.

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CHALLENGES TO FORMULATION DEVELOPMENT FOR NASAL DELIVERY

Biological Barriers

Despite relatively easy access, the complex geometry of the nose makes reliable and efficient delivery to the mucosal surfaces deep in the nose a challenge. The narrowest segment of the respiratory tract is the nasal valve, which accounts for around 80% of nasal resistance and a significant portion of total respiratory resistance. If the area is irritated or the patient has symptoms that lead to sniffing, this causes additional narrowing of the valve.

Bioavailability

The bioavailability of nasally administered drugs can be restricted by low drug solubility, enzymatic degradation in the nasal cavity, poor membrane penetration and rapid clearance. Particularly large molecular weight peptides and proteins also exhibit notably limited permeability in nasal mucosa.

While formulations can address these problems using a variety of strategies, they must be fully understood to ensure a tailored approach.

Clearance

The epithelium of the nasal passage is covered by a mucus layer that entraps particles. The mucus layer is cleared from the nasal cavity by cilia and is renewed every 10–15 minutes, with mucus moving through the nose at an approximate rate of 5–6 mm/min, resulting in particle clearance every 15-20 minutes. Drugs with poor solubility would be particularly challenging in this scenario, as they must guarantee sufficient bioavailability to achieve the desired therapeutic effect.

Mucoadhesives and bioadhesives are often used to reduce nasal clearance and may be formulated with permeation enhancers, certain co-solvents and, in order to avoid or minimise degradation, enzymatic inhibitors. In all instances, the potential for irritation has to be considered as it could lead to sniffing, which would counteract any reduction in clearance rate.

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COMPATIBILITY WITH THE DELIVERY DEVICE

There is a relatively small selection of dry powder nasal devices, considering the attractiveness of this route of administration. Nasal devices use numerous methods to deliver the drug, including actuation by pressure (manual actuation), patients blowing into the device, pressurised systems or propellants. When it comes to powders, there can be variability of efficacy when using devices where patients have to blow into the device to eject the powder to the nose. Pressurised systems or the use of propellants can result in more reproducible results, dependent upon the device, but they can create discomfort for patients during application.

Patient acceptance

Ergonomic aspects of the delivery device systems are also a factor as orientation, patient handling (dexterity) and actuation forces can affect use and patient compliance. The use of preservatives can also have an impact. Preservative-free systems are gaining popularity with patients who have experienced discomfort with preserved formulations and the local side effects attributed to them.

FORMULATION STRATEGIES

API solubility

The API needs to be formulated with excipients that enhance adhesion and, therefore, absorption in the nasal mucosa. The excipients selected depend on

the solubility of the API as well as the concentration needed to provide the necessary dose in each spray. The formulation needs to be made so it maximises contact with the nasal mucosa, holds off clearance for as long as possible and is rapidly absorbed.

Minimising clearance with mucoadhesives

With nasal delivery, versatile polymers can be leveraged as mucoadhesive and bioadhesive excipients in complex topical mucosal formulations to slow down clearance in the nasal cavity, increasing residence time to up to 30 minutes. The key benefit is in maximising drug absorption by prolonging contact time, which can increase bioavailability, reduce dosing frequency and subsequently improve patient compliance.

ADDRESSING BIOAVAILABILITY CHALLENGES

Bioavailability is always an essential consideration during the development of a new nasal drug. Absorption via the nasal mucosa directly into the bloodstream bypasses the liver and first-pass metabolism – a key consideration for drugs that have poor oral bioavailability. The bioavailability of large-molecule drugs delivered nasally can be improved with permeation enhancers.

> "By aligning development with the selection of the device, factors such as the method of powder ejection and deposition mechanism in the nasal cavity can be factored into the formulation."

Nanomilling and lipidic-based systems have proven to be a highly effective means of addressing bioavailability challenges in the case of small molecules.

The smaller API particles generated by nanomilling can dissolve more readily, with the rate of dissolution being inversely proportional to the diameter of the particle. This creates a high concentration gradient that facilitates the transfer of the API across biological barriers, including membranes.

Lipid-based systems, including nanoemulsions, liposomes and cubosomes, as well as mixed systems, such as lipid nanoparticles with a solid matrix or nanostructured lipid carriers (NLCs), have also been successfully employed in nasal formulations. While there are numerous articles describing these dosage forms and *in vitro* data, there is a scarcity of marketed products using these technologies. For example, in the case of solid lipid nanoparticles and NLCs, Montoto[2] counted 12 out of 211 reviewed publications (with pharmacodynamic and/or pharmacokinetic data) concerned a nasally administered formulation. They go on to state that, in general, very few nasal dosage forms reach the clinical trial stage.

CO-DEVELOPING FORMULATION AND DEVICE

Co-operation between teams that are involved in formulation and device development is often essential to successful commercialisation. Effective, targeted nasal drug delivery requires reaching the high and deep part of the nasal passages. This means the drug must be delivered beyond the nasal valve and above the inferior turbinate bone to reach the broad surfaces that are lined by the respiratory epithelium that surround sinus openings and where the nerves from the brain can be accessed. Selecting the nasal powder device in the early stages of formulation development is critical, due to the impact it can potentially have on the final product performance.

By aligning development with the selection of the device, factors such as the method of powder ejection and deposition mechanism in the nasal cavity can be factored into the formulation. The intended deposition location in the nasal cavity is important for efficacy and will depend on both the formulation and the device. The delivery device, whether a spray pump or a metered dose inhaler, must be effective for delivering a precise dose to this target area. The device should also be easy to use by the intended patient population.

CONCLUSION

Driven by the inherent benefits of nasal delivery, the number of new drug applications for nasal drugs will continue to increase in the coming years as pharmaceutical companies continue to explore more patient-friendly routes of administering biologics. Bioavailability, solubility and compliance remain the core challenges for formulations. However, a variety of strategies can be adopted and tailored to each drug. To successfully bring such products to market, extensive experience with a full range of formulation, analytic and manufacturing services in complex nasal drug products is required.

ABOUT THE COMPANY

The Lubrizol Corporation, a Berkshire Hathaway Company, leverages its unmatched science to unlock immense possibilities at the molecular level, driving sustainable and measurable results to help the world Move Cleaner, Create Smarter and Live Better. Founded in 1928, Lubrizol owns and operates more than 100 manufacturing facilities, sales and technical offices around the world and has approximately 8,800 employees.

ABOUT THE AUTHOR

Robert Lee, PhD, President, Lubrizol Life Science Health, CDMO Division, is responsible for product and business development, along with providing strategic direction. He holds BSc degrees in Biology and Chemistry from the University of Washington (Seattle, WA, US) and a PhD in Physical Bioorganic Chemistry from the University of California (Santa Barbara, CA, US). Dr Lee has published more than three dozen articles and five book chapters, as well as holding 11 issued patents and 15 provisional or PCT patent applications. He has over 30 years of experience in pharmaceutical research and development of both therapeutic drugs and diagnostic imaging agents.

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