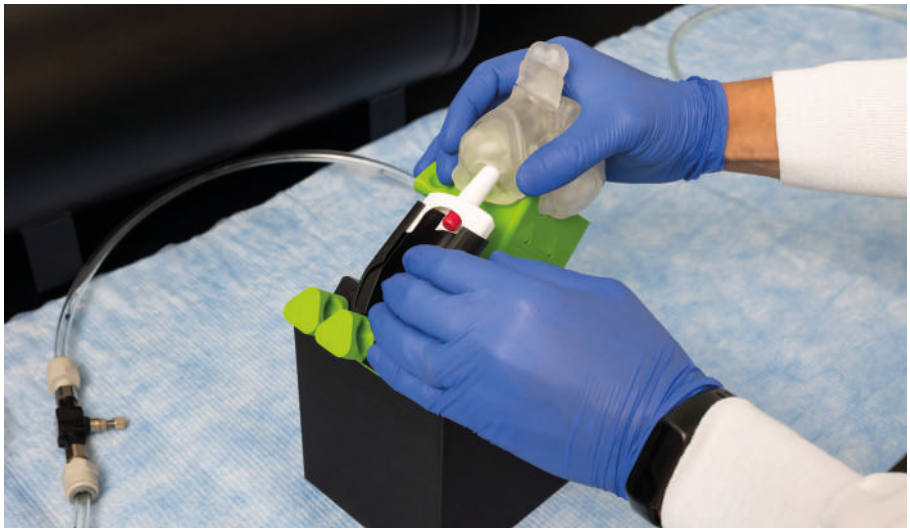
MedPharm

Alternative Drug Delivery Routes:
Opportunities, Challenges, and How to Overcome Them

Topical formulations are often preferable compared to oral and injectable options because they reduce systemic side effects, can efficiently target local delivery, eliminate the need for needles, and can improve patient adherence. These formulations, such as creams, gels, lotions, solutions, sprays, dissolvable patches, and foams, present a more complex medicine as the 'vehicle' is an integral part of the drug product. Topical therapies must be optimised to deliver the required clinical efficacy while providing the desired mix of physical properties that will make the product appealing to the patient, otherwise adherence will be hindered. At MedPharm, we define topical drug delivery as the application of a product directly to an epithelial surface – including the skin (intact or wounded), eye (corneal, intravitreal, and transscleral), respiratory tract (pharyngeal, pulmonary, and nasal), as well as oral, rectal, bladder, nail, and vaginal (including cervical) routes. Each of these delivery pathways presents unique biological and formulation challenges, requiring specialised expertise to navigate successfully and bring products to market with confidence.



Opportunities and Unmet Needs of Alternative Delivery Routes

The topical drug delivery market was estimated to be between $125 billion and $150 billion in 2024, depending on how 'topicals' are defined by route of administration. The dermal/skin route of delivery represents most of the market (approximately 40%–50%), primarily driven by the increasing prevalence of skin diseases such as acne, psoriasis, rosacea, atopic dermatitis, and fungal concerns. The ophthalmic route represents about 15% of the market, driven by the rising global prevalence of eye diseases such as macular degeneration, diabetic retinopathy, presbyopia, glaucoma, and eye infections. The nasal route of delivery is a growing area representing about 12% of the market driven by new therapies targeting allergic rhinitis, central nervous system (CNS) disorders, migraines, and vaccines. The oral topical market or delivery to the cheeks and gums represents about 8% of the market which provides opportunities for oral mucositis, ulcers, and gum diseases. Women's health is another growing area, where about 10% of the market accounts for vaginal drug delivery, focusing on applications such as infections, hormonal therapies, and contraception. The remaining 'other' topical delivery represents about 15% of the market such as rectal, urethral and bladder.

This series examines the advancements and emerging opportunities within the topical drug delivery market. The first article will focus on nasal delivery, examining how to design a robust formulation strategy that addresses the unique barriers and clearance mechanisms of this route. We will also discuss how MedPharm's preclinical models can be used strategically to de-risk your development program, accelerate timelines, and boost confidence in your product's success.

Understanding the Route of Delivery and its Unique Barrier

The nose has evolved to prevent foreign material in inhaled air from gaining access to the body. To this end, the nose has a multilayered system of defences. The innermost layer of this defence is comprised of specialised epithelial cells. These cells are tightly connected to each other to form a continuous, living, and responsive barrier between the air and the inside of the body. These cells are coated in a thin layer of constantly replenishing mucus, which serves to trap foreign particles such as dust, pollen, and microbes. Between the mucus and the cells are microscopic hairlike structures called cilia, which project from the surface of the cell layer. These cilia wave back and forth in a coordinated fashion to move mucus (along with trapped particulates) up and out of the nose for removal from the body, typically either by swallowing or coughing.

Together, this barrier poses some unique formulation challenges. As with any topical formulation, optimising the movement of the active pharmaceutical ingredient (API) from the formulation to the tissue is important. In the nose, however, the epithelium is expected to react to the presence of formulation and attempt to remove it. Unless checked or accounted for, the physical interaction with the epithelium will accelerate mucociliary transport through increased cilia beat frequency and the efflux of water into the nose through the epithelial layer, diluting the mucus and further increasing the speed of clearance.

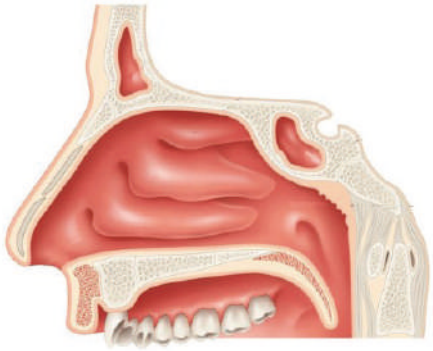
From a drug delivery perspective, the overall structure of the nose can be divided into five regions of interest. Going from the outside in, the first of these regions is the nasal vestibule or nostrils. This region has a different epithelium, transitioning from the mucosal layer of the interior of the nose to the dry, tough skin of the exterior. Behind that is the nasal cavity, which is characterised by three rigid, shell-shaped structures called turbinates. These serve to filter, warm,

and humidify inhaled air. The convoluted surface of the turbinates serves to slow the air and induce a turbulent flow, depositing any suspended particles or droplets to the mucus layer for removal before they can reach the lungs. Above the nasal cavity is the olfactory cleft. This small structure is densely packed with olfactory receptors and is connected to the olfactory nerve. The fourth region of interest is the nasopharynx, the region at the back of the nose where the respiratory tract temporarily merges with the oesophagus. Finally, the sinuses form a series of interconnected chambers throughout the nose. Although these are not directly air-conducting, they can serve as targets for certain formulation types.

Each of these regions acts as a unique target for delivery. Formulations intended for rapid absorption into the bloodstream should be delivered to the highly vascularised surface area of the turbinates. Formulations delivered to the olfactory bulb can be directly absorbed into the central nervous system, bypassing the blood-brain barrier. Vaccines are most commonly delivered to the nasopharynx. The combination of API, formulation, and delivery device determines where in the nose a formulation will be delivered. Understanding these interactions is a critically important component of any nasal drug delivery technology.

Formulation Strategies

MedPharm's formulation strategy is consistent across the different epithelium, where the formulation and excipients or ingredients are specifically designed around the drug, the site of action and the target product profile to optimise for drug stability and delivery to the site of action. The site of action may be local to the different epithelium (i.e. skin, nasal, eye, etc.) or systemic delivery to the bloodstream (i.e. transdermal/transepithelial). The excipients or ingredients included in the formulation are specific to the unique barrier properties for the different types of epithelia. For example, formulations interfacing with the skin's protective barrier, which has evolved to prevent harmful compounds from entering the body, require additional ingredients to aid in delivery.

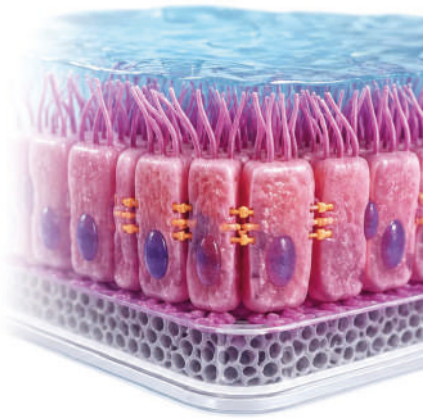


Topical skin formulations tend to be the most complex (e.g. creams) and often require the most development time. Other routes of delivery, such as nasal, may involve less ingredients but will require a device/drug combination adding a different set of complexities. In all dosage forms, it is preferable to select ingredients already approved for the intended delivery route (e.g those on the FDA inactive ingredient list) to minimise safety concerns, reduce regulatory hurdles and avoid the need for extensive and costly toxicological work.

Nasal formulation development at MedPharm initially involves preformulation work to determine drug solubility, stability (in excipients suitable for nasal use) and characterisation of the drug substance (e.g., particle size for drugs in suspension). This preformulation work provides vital information to understand degradation pathways/stabilisation strategies, drug loading and the most suitable excipients for use during development of prototype formulations.

Prototype formulations are then developed with close consideration of the target site. The drug solubility data versus required drug loading is used to determine whether a drug in solution or drug in suspension is required. Drug-in-solution systems are simpler, but drug loading may be limited. In contrast, drug-in-suspension formulations are more complex and require control of the drug particle size, both as a drug substance but also in the final product, to ensure effective delivery and to mitigate the risk of irritation in the nose/delivery to the lung, which may afford a higher drug loading. The higher drug loading can enhance drug delivery provided the formulation is designed to improve residence time on the cilia and/or mucous. For both drug-in-solution and suspension formulations it is vital that the device is considered at an early stage and throughout the development to ensure the formulations developed are suitable for use with the device.

The drug, formulation, and device can impact particle size and droplet size. For more targeted delivery to the back of the nose, with the intent to bypass the blood-brain barrier through the olfactory bulb, requires a device that orients the spray and may include carefully designed particles to enable

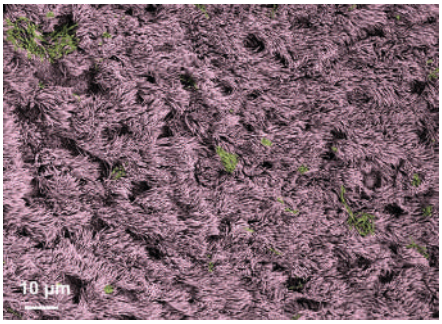


optimal site-specific delivery. Formulation characterisation throughout the development such as particle/droplet size distribution, physical stability, rheology, mucoadhesion assessment, osmolality, cascade impaction, suspension redispersibility and sedimentation, is important to enable selection of the most suitable formulations for short-term stability prior to assessment in preclinical models to enhance the chance of success later in the development pathway.

Use of Preclinical Models for Alternative Delivery Routes

Historically, nasal formulation performance has been assessed using frozen excised tissue from animal cadavers, byproducts of the agricultural industry. Formulation was applied to the apical side (facing the air) of the tissue, and samples were collected from the basolateral side (facing inward) at different timepoints to assess the performance of a given formulation. 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.

It has been said that all models are wrong, but some are useful. At MedPharm, we believe that all models are wrong, but some are more useful than others. And there's always room for improvement. This philosophy gave birth to our reconstructed nasal epithelial model (RNE). This model system uses primary human nasal epithelial cells regrown on permeable



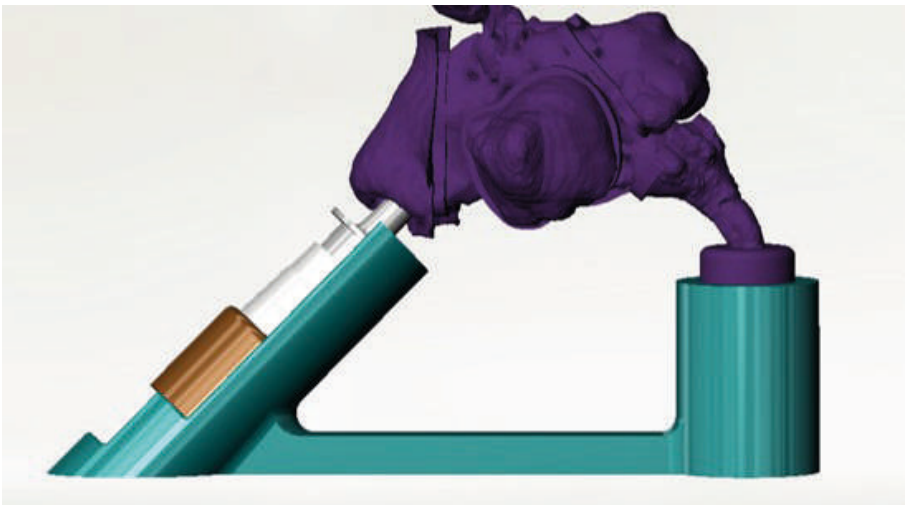


inserts and stimulated to develop into a well-differentiated nasal epithelium. A big part of this stimulation is the culture at an air-liquid interface (ALI). The top side of the tissue is exposed to air, with the bottom side exposed to media. This causes the reconstructed tissue to polarise, forming cilia, producing mucus, and forming tight junctions that make the respiratory barrier unique.

In the past few years, multiple methods of assessing formulation distribution into the nose have been developed in the form of nasal casts that simulate the internal structures of the nose, broken down into the more common regions of interest (e.g., nares, turbinates, olfactory region, and pharynx). Formulations are loaded into devices and sprayed into physical models of the interior of the nose. These models are then disassembled, and drug is extracted from each piece. This can help determine where the drug is being delivered by the device.

Again, these models have proven useful and have shown room for improvement. First, these are made from a single material (e.g., aluminium). Different formulations and APIs would be expected to adhere, and be extracted from, aluminium at different efficiencies. A low adherence efficiency could allow formulation to transfer from one region to another during disassembly. A low extraction efficiency could affect detection limits, missing places where drug had been delivered. Also, these models are limited to the regions that can be investigated. The pre-ordained regions are useful for development, but there is always room for improvement.

To address these limitations, MedPharm has developed the MedCastTM nasal cast model based on head CT scans. Because the MedCastTM is 3D printed, casts can be quickly made with regions of interest specific to a given delivery strategy. 3D printing also allows for the construction of the MedCastTM from a variety of materials. Part of our method development strategy is to test each of these materials with the formulation to evaluate how well the API adheres to the material, and how efficiently it can be extracted. We can then select the most compatible material for the construction of the MedCastTM. This model allows quantitation of the drug from specific regions within the nasal cavity dependent on your formulation and device combination, therefore giving a closer to 'real world' analysis of the drug product.



How We Can Help You Develop a Product for Alternative Routes of Delivery

MedPharm is an end-to-end CDMO that specialises in topical, transdermal and transepithelial drug product development and commercialisation.



Charles Evans

Charles Evans is Senior Vice President of Pharmaceutical Development at MedPharm, with more than 20 years of experience advancing complex drug products across topical, inhalation, transepithelial, and injectable delivery platforms. He leads global formulation development strategy and has played a key role in the development of MedPharm's proprietary MedSpray® technology.



Jon Lenn

Jon Lenn is Chief Scientific Officer at MedPharm, where he leads global research and development for complex topical and transepithelial drug products. With more than 20 years of pharmaceutical experience, Jon has helped advance innovative biological models, novel test systems, and formulation strategies supporting challenging routes of delivery and product development.



Jon Volmer

Jon Volmer is Senior Director of Research Biology at MedPharm, with more than 15 years of experience in biotechnology and preclinical drug development. He leads MedPharm's cross-functional Research Biology team, supporting the development of biological models, analytical approaches, and instrumentation for complex topical and transepithelial drug delivery applications.