Nasal and trans-nasal lung deposition of aerosols

Ronan MacLoughlin, PhD, MBS[a] and James B. Fink, PhD, RTT[b]
[a]Aerogen Limited
[b]Aerogen Pharma Corporation

Introduction

Therapeutic delivery via the nasal route is a well-established means of both topical and systemic targeting, and facilitates an easy-to-access, non-invasive means of drug administration. Broadly, presentation of therapeutics at the nose allows for targeting of specific areas within the respiratory tract; both the upper respiratory tract (via the nasal passages) and the lower respiratory tract (via trans-nasal delivery to the lungs). The requirements of both targets demand different approaches and delivery devices, but between them, allow for an exceptionally wide selection of topically and systemically targeted therapeutics to be administered, ranging from bronchodilators and vaccines to migraine and schizophrenia modulating formulations to small proteins such as insulin, and more.

Here we discuss these two targeting modalities as well as barriers to efficient targeted delivery and our perspectives on future prospects for nasal and trans-nasal targeted delivery.

Nasal deposition

The nasal anatomy, with its mucosal surface and dense vascularity, has been shown to facilitate topical deposition for both local action and rapid systemic absorption. There are several advantages associated with this delivery approach. It is a convenient and non-invasive method that also avoids losses of the active pharmaceutical ingredient (API) that typically occur at the liver, and absorption of the API and onset of drug activity are rapid. In addition, bioavailability for small molecules is reportedly high. Disadvantages include the potential histological toxicity of absorption enhancers used in formulations, the nasal cavity represents a smaller absorptive surface area compared with the gastrointestinal tract and the potential for irreversible damage to the nasal mucosal cilia from repeated exposure to formulation excipients.[1]

Therapeutic targets

The development of therapies for intranasal delivery focuses on three primary fields linked to pharmaceutical targeting: topical, systemic and central nervous system (CNS) action.

Topical administration is primarily used to treat inflammation of the nasal mucosa during both acute and chronic pathologies such as rhinosinusitis and allergic rhinitis. It is also used in the treatment of nasal congestion and/or obstruction.[2-6]

Topical administration is also used for immunization, by delivering vaccines to the mucosal surface. The majority of infectious diseases are mediated through the mucosal surfaces of the body. Many diseases, such as measles, pneumonia, meningitis and influenza are associated with the exposure of pathogenic microorganisms to the respiratory mucosal surfaces and are therefore considered logical candidates for targeted nasal vaccines. The advantage of intranasal vaccination includes the ability to elicit local and remote immune responses, increasing the strength of the response. Further, immunization strategies make use of relatively simple devices that allow for vaccination of large populations both non-invasively and quickly, e.g., the FluMist® quadrivalent influenza vaccine (Seqirus, Summit, NY, US).

Systemic access is also possible via the nose. Blood is supplied to the nasal vasculature and enables the basic functions of the nasal cavity such as heating and humidification, olfaction, mucociliary clearance and various immunological functions. The cavity itself has a relatively large surface area of approximately 155 cm^2. Permeation is dependent on the lipophilicity of the drug, and can occur either passively via the paracellular pathway or both passively and actively via the transcellular pathway. Several formulation strategies are employed to increase retention or permeability and are described in more detail below.

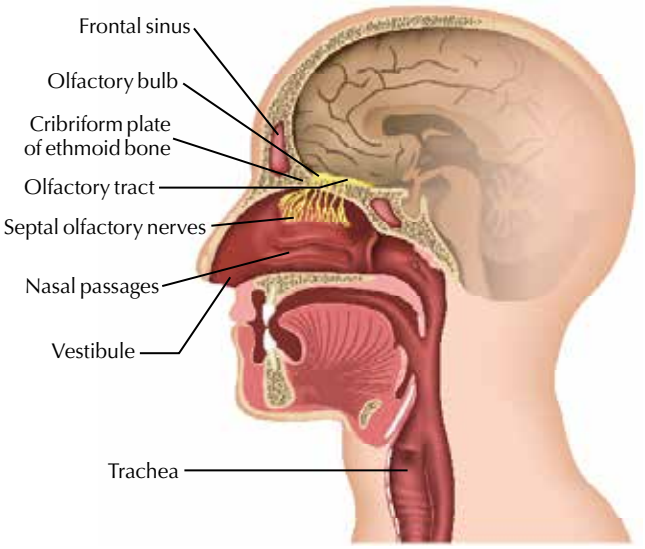
Using the nasal route to deliver medications to the CNS and the brain has also been reported. The connection between the nasal cavity and the CNS through the olfactory region has been investigated extensively to establish its feasibility in acting as a direct drug transport route to the CNS and the brain.[7,8] This drug transport route has garnered much interest as it may circumvent the blood-brain barrier, which is, in general, highly effective in preventing most drugs from entering the brain.

Anatomy

The complex internal nasal geometries, including the narrow anterior valve, poses a significant challenge to effective nasal targeted drug delivery. As comprehensively described by Le Guellac, et al,[9] successful therapy requires delivery of a therapeutic to a specific anatomical site (local, systemic, CNS/brain) and the intended therapeutic action and consequent success depends on delivering sufficient drug to those sites. For example, the middle meatus, the maxillary sinuses and the ethmoid regions have been identified as important drug delivery sites for local treatment of inflammation and infection in rhinological pathologies. Systemic delivery is enhanced by delivering drug to the middle and inferior turbinates, the septum and nasal floor around the turbinates. The anatomic connections between the nose and the brain are the olfactory bulb and the peripheral circulation. Figure 1 illustrates the nasal anatomy.

Figure 1

A diagram of the nasal anatomy



Formulations

Solutions and suspensions, the most common liquid formulations, are delivered as drops, sprays (pump- or propellant-driven) or aerosols (nebulizers). Powder formulations are also available and are administered by devices capable of aerosolizing powders.[10]

Factors influencing therapeutic absorption in the nose are varied and widely considered to be a function of the combination of device and formulation.[11] Primary factors include drug concentration wherein absorption follows first-order kinetics and wherein rates will depend on the initial concentration and the pH at the site of absorption. Nasal absorption is pH-dependent, and the local pH may be quite variable. Nasal pH ranges from 5.5 to 6.5 in adults and between 5.0 and 6.7 in infants and children. Complicating the matter further, pH varies with disease state and may become alkaline, for example, in acute cases of rhinitis and sinusitis. Additionally, mucociliary clearance has an effect. Materials deposited in the nasal passages are generally cleared in less than 15 minutes but may take more than 30 minutes if the mucociliary function is impaired.[12]

In an effort to develop optimal formulation strategies for nasal targets, a variety of excipient classes are typically used in nasal formulations.[13, 14] Examples are shown in Table 1.

Droplet/Particle size considerations

The ideal droplet or particle size distribution for a nasal spray is considered to be one wherein the vast majority of droplets or particles are larger than 10 microns.[15, 16] The intent of this seemingly large size is to promote inertial impaction within the nasal passages

Table 1

Formulation strategies for nasal preparations

Excipient class	Rationale for use	Examples
Solubilizers	Increase the concentration of drug in the liquid	Glycol, alcohol
Surfactants	Modify nasal mucosa permeability for altered absorption profile	Sodium laurylsulfate (SLS), Polyacrylic acid
Bioadhesive polymers	Increase residence time on the surface	Methylcellulose, Carboxymethylcellulose
Viscosity-modulating agents	Increase the viscosity of the solution in order to prolong retention time and the therapeutic activity	Hydroxypropyl cellulose
Preservatives	Prevent growth of microorganisms	Parabens, ethylenediamine tetra-acetic acid (EDTA), benzalkonium chloride, phenyl ethyl alcohol
Antioxidants	Prevent drug degradation by oxidation	Sodium meta bisulphite, sodium bisulfite, tocopherol

and also to avoid exposure of the lower respiratory tract. Of note, there are no guidelines or international consensus regarding the relationship between aerosol characteristics and the precise deposition site within the nasal cavities. However, international regulatory guidance and requirements state that droplet or particle size does need to be tightly controlled and validated through appropriate means, typically laser diffraction methods. Ultimately, the resultant efficacy of the product is very much reliant on clinical outcome studies, which in turn somewhat validate the appropriateness of the droplet or particles being generated. Much research is underway in this area; and indeed some of it is funded by agencies such as the United States Food and Drug Administration (FDA). Therefore, we can expect further guidance and insight as the relevant bodies become more informed.

Devices

Depending on the type of formulation, a variety of devices have been used to deliver drugs intranasally. Devices for liquid formulations include instillation catheters, droppers, unit-dose containers, squeeze bottles, pump sprays, airless and preservative-free sprays, compressed air nebulizers and metered dose inhalers (MDIs).

Devices for powder dosage forms include insufflators, single-dose and multi-dose powder inhalers and pressurized MDIs. A comprehensive review of nasal drug delivery devices is provided by Djupesland.[2]

Future possibilities

Considering the massive potential for nasal administration as a route for drug administration, there is a real need for improvements in the state of the art. We foresee that those improvements will center around formulations and devices and, most importantly, combinations of them. To facilitate this, Forbes, et al have recently published an expert consensus setting out the roadmap for future focus and developments in this field.[10] The relatively nascent field of targeting the CNS/brain is likely to see biggest strides. Non-obvious drivers such as healthcare economics and social drivers will probably provide the impetus. For example, in migraine treatment. Migraines are neurological disorders, often inherited, and affect patients ranging in age from adolescence to adulthood. This debilitating condition can have a direct impact on school performance, professional or work performance, social interactions and family life, and therefore is considered a high-value target. Treatment modalities today include oral, injection and, just recently, nasal. As described here, the ability to deliver a therapeutic API locally for fast action is a key advantage to be exploited.

Trans-nasal lung deposition

Trans-nasal lung deposition is typically achieved during concurrent high-flow nasal therapy (HFNT). HFNT is an increasingly common method of oxygenation of the lungs and delivers administered gas flow rates of typically between 5 and 60 liters per minute of heated, humidified air. Gas flows are set to match or exceed peak inspiratory flow rates in an effort to purge the upper airways of CO_2, at the same time as delivering oxygen to the airways. HFNT is commonly administered via nasal cannula but it can also be administered by tracheostomy or a nose mask. In the current climate of the worldwide spread of COVID-19, patients are becoming hypoxic, and the World Health Organization estimates that as many as 85% of patients will require some form of oxygen therapy. Many of those patients will likely be prescribed HFNT.[17]

The clinical HFNT literature has focused on examining patient outcomes when compared to the traditional and more invasive means of ventilatory support, such as invasive mechanical ventilation. HFNT finds application across emergency ward and critical care settings, and consequently is used in the treatment of a wide variety of disease states, and patient types, infant through adult.

Thus far, the number of reported therapeutics delivered concurrently during HFNT is quite low, with the most common being bronchodilators in the treatment of acute asthma exacerbations, saline for hydration of the airways, prostacylins for treatment of pulmonary arterial hypertension and maintenance of normal mucociliary function during extended treatment.[18-23]

High flow nasal therapy devices

HFNT devices are generally classified as systems relying on compressed oxygen and air supplied through the hospital wall or cylinders, systems generating their own flow by means of an integrated turbine, or systems whose primary function is mechanical ventilation, which includes HFNT functionality. Importantly, only some of these systems have approved accessories for nebulizer attachment and few were designed to optimize aerosol delivery efficiency. This remains a significant opportunity for future improvement in HFNT system design. For example, those systems with integrated turbines may benefit from integrated nebulizer control, where such controls act to mitigate drug losses resulting from the various influencing factors discussed in the following sections.

Aerosol delivery

Concurrent aerosol delivery during HFNT is commonplace. As previously mentioned, a relatively narrow range of therapeutics are delivered. A review of the literature would suggest that these therapeutics are mainly aerosolized using nebulizers and predominately vibrating mesh nebulizers (VMNs). This is likely due to the VMN mode of action, and the fact that they do not add flow or pressure to the HFNT circuit, a particularly important consideration in pediatric patients who have flows less than 20 liters per minute. A single bench model report on the use of pressurized metered dose inhalers (pMDIs) during HFNT indicated that

aerosol is delivered, however, it is likely that the low dose delivered, even after several pMDI actuations, is not a practical clinical solution.[24]

A randomized, crossover, single-photon emission computed tomography study in adults indicated that VMN devices deliver more to the lung than compressor-driven jet nebulizers (JN) at the clinically relevant 30 liters per minute applied gas flow rate.[25] Nevertheless, there are currently no clinical outcome studies comparing compressor-driven jet nebulizers to vibrating mesh nebulizers. However, the performance of both has been shown to deliver levels of aerosolized drug that provide comparable benefit to that seen in patients using a hand-held nebulizer during spontaneous breathing.[18, 22]

In the clinical setting, depending on physician preference, devices available locally, institutional protocols and patient requirements, aerosol may be presented to the patient, but by means of a nebulizer not included in the HFNT system itself. In these instances, JN and VMN in combination with both mouthpiece and facemask are often put to use. A recent bench study evaluated aerosol delivery across combinations of these drug delivery interfaces with and without concurrent HFNT.[26] Across the test combinations, the VMN plus mouthpiece was seen to deliver the highest amount of aerosol, with combinations of concurrent HFNT facilitating delivery of some aerosol, but generally low amounts compared to nebulizer alone.

Aerosol deposition in the lungs

Several studies have explored the principal factors determining the efficacy of aerosol delivery to the lungs. As early as 2008, Bhashyam, et al[27] described, in a bench study, the effect of infant, pediatric and adult gas flow rates and set-ups on the droplet size and location of deposition within the circuit as well as the delivered dose. The general trend was seen to be that increasing gas flow rate reduced the dose available for inhalation. Additionally, smaller internal diameter nasal cannula select for smaller droplets exiting the system. Both of these effects were most likely due to inertial impaction losses throughout the circuit. Subsequent studies in animal and human models verified these results and validated the utility of bench models in predicting the dose delivered *in vivo*.[28, 29]

Additional bench studies have assessed the effect of other variables such as position in the circuit and input droplet size,[30] as well as breathing pattern[23, 31] on HFNT aerosol delivery. Interestingly, distressed breathing was seen to increase the delivered dose. This suggests more efficient entrainment of aerosol in the breath, or the potential for efficient delivery at applied gas flow rates that closely match the peak inspiratory flow or the ratio of administered gas flow to peak inspiratory flow rate.[32] Findings from these studies have found application in the delivery of perhaps non-obvious therapeutics such as lidocaine as an airway analgesic during awake fiber optic intubation.[33]

Fugitive aerosols

One often-overlooked aspect of aerosol delivery, whether it be by nebulizer, pressurized metered dose inhaler, soft mist inhaler or dry powder inhaler, is the risk of aerosols being released to the environment on exhalation or simply because they bypass the patient. HFNT is a candidate for large fugitive drug aerosol emissions (as opposed to patient-derived bioaerosol emissions) considering that the gas flow carrying the aerosol is unidirectional and continuous throughout the breath maneuver. One study in the literature has quantified these emissions. In the study, emissions across combinations of nasal cannula, tracheostomy and gas flow rate were assessed. The main findings suggest fugitive aerosol are emitted to the local environment however, at the higher gas flow rates, they are lower than those recorded at the lower gas flow rates. Again, this is likely due to higher levels of inertial impaction losses within the nasal passages, and thus, less is available to escape.[34] Evidence suggests that covering the nasal cannula with a simple surgical mask can greatly reduce the dispersion of fugitive emissions.[35]

Future possibilities

With the use of HFNT increasing across the critical care and home care settings, the importance of optimized concurrent aerosol delivery will be critical. In order to facilitate that, custom-designed adapters or integrated nebulizer controls will be required and need to be designed through collaboration between partners, i.e., nebulizer and HFNT equipment manufacturers. We already see jet nebulizers being contraindicated by some systems, but often HFNT companies pay scant regard to the potential pitfalls of mismatched systems. It is proposed that more HFNT companies look to include provisions for nebulizer usage or, ideally, design specific adapters that facilitate optimal aerosol delivery.

Concluding remarks: Where do we go next?

Administration of aerosol to the nose is common and well accepted for a variety of local as well as systemic targets. Most therapeutic nasal sprays use relatively large particles to minimize pulmonary delivery, with seemingly little change in technology or approach over the last 40 years. However, with recent advances in the state of the art in both device and formulation, many more conditions are expected to be treatable with nasal delivery. Additionally, we can expect to see further innovations in the delivery device arena, with devices capable of greater control over reliability and reproducibility of dosing, as well as increased accuracy in targeting.

Now, more than ever, healthcare economics are providing the impetus for innovation in this space and consequently we will see some non-obvious disease states being treated using the nasal route, for example

autism and narcolepsy. Brain, central nervous system and systemic system therapies will all benefit from this increased focus and push for innovation from what has classically been a "me-too" space.

Trans-nasal pulmonary administration remains in its infancy but is poised to grow as evidenced by its rapid adoption to routine use in many intensive care units worldwide. As we better understand the relationships of particle size, delivered gas, patient anatomy, and inspiratory patterns across patient populations, we expect more optimized pulmonary delivery efficiency, expanding trans-nasal methods in treatment of neonates, infants, toddlers and older adults with a variety of agents. This could replace use of poorly tolerated ill-fitting masks and again enable new therapies. For toddlers who fight use of a mask for aerosol delivery at home, trans-nasal pulmonary delivery could greatly reduce drama while increasing efficacy and prescription compliance.

With nasal and trans-nasal pulmonary delivery, we are at the cusp of an inflection point in two intrinsically connected, but very different fields of research and product development. We believe the next decade should see significant advances in both, further increasing the quality of life for patients, as well as offering significant value and opportunity for those groups willing to focus on them now.

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Ronan MacLoughlin, PhD, MBS is Senior Science Manager, Aerogen Limited, Galway Business Park, Dangan, Galway, H91 HE94, Ireland; Senior Honorary Lecturer, School of Pharmacy and Biomolecular Sciences, Royal College of Surgeons, Dublin, Ireland; Adjunct Associate Professor, School of Pharmacy and Pharmaceutical Sciences, Trinity College, Dublin, Ireland; rmacloughlin@aerogen.com.

James B. Fink, PhD, RRT, FAARC, FCCP is Chief Scientific Officer, Aerogen Pharma Corporation, 1660 S. Amphlett Blvd., Suite 360, San Mateo, CA 94402, United States; Adjunct Professor, Division of Respiratory Care, Texas State University, Round Rock, Texas, United States; Adjunct Faculty, Division of Respiratory Therapy, Rush Medical School, Chicago, IL, United States; Visiting Professor, Department of Physical Therapy, Universidade Federal de Pernambuco, Recife, Pernambuco, Brazil; jfink@aerogenpharma.com.