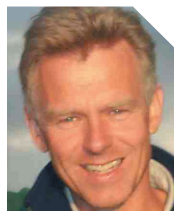


Who Nose How Far Nasal Delivery Can Go?



By Dr Per Gisle Djupesland, Head of R&D and Co-Founder of OptiNose AS

Dr Per Gisle Djupesland is Co-Founder, Head of R&D and Chairman of OptiNose AS, a Norwegian R&D company developing a novel concept for nasal delivery of drugs and vaccines. He is a specialist in Otorhinolaryngology with a PhD in Nasal Physiology from the University of Oslo and has been Research Fellow at the University of Toronto, Canada. He has a degree in International Health and Tropical Medicine from Paris, France, and has been Project Manager for a large-scale vaccination trial in the Norwegian Armed Forces.

Nasal delivery has traditionally been restricted to topically acting substances used to treat the common cold and nasal allergies. Recently, however, there has been increased interest in the nose as an alternative to oral delivery and injection for many systemic drugs and vaccines. The highly vascularised and immunogenic nasal mucosa offers potential advantages in terms of quick action, improved bio-availability and patient compliance as well as improved immune response for vaccines.

Faced with surging drug development costs and fierce generic competition, pharmaceutical companies are under increasing pressure to find ways to increase and prolong the profitability of both existing and new products. In addition, many of the advanced molecules being developed by biotechnology companies require more efficient delivery than that offered by conventional delivery routes and systems. The challenge of optimising the bio-availability and patient compliance of these expensive molecules are other significant drivers for the development of novel drug delivery systems.

If successful, reformulation allied with novel delivery systems provide powerful tools for improving efficiency and differentiating a product from those of competitors. In addition, more efficient and patient-friendly delivery systems and dosage forms can help extend patent life and increase competitiveness. Overall this provides companies with the opportunity to maintain and increase their market share for only a relatively limited investment.

It is against this background that interest and investment in novel delivery technologies have increased in recent years. According to a recent report, 13 per cent of the US\$337 billion global pharmaceutical market was related to sales of products incorporating a drug delivery system, a figure expected to grow to 20 per cent by 2005. Therefore, although oral delivery remains the preferred option of the patient and the pharmaceutical industry, alternatives such as transdermal, pulmonary and nasal delivery systems are gaining increased interest.

POTENTIAL OPPORTUNITIES FOR INTRODUCING NASAL DELIVERY

Nasal Delivery of Systemic Drugs

To exert its prime function as a filter and air-conditioner protecting the lower airways, the nose has a complex geometry lined by highly vascularised mucosa. The easy access to this large vascularised surface makes the nose particularly attractive for absorption of drugs which are difficult to deliver with conventional methods and normally require injection. Rapid absorption and the fast onset of action are essential in treating intense, acute pain and in management of severe events such as cardiovascular attacks, seizures, hypoglycemia, nausea and vomiting. Nasal administration limits the problems associated with degradation of drugs in the stomach and in the liver, which makes it particularly relevant for many of the new recombinant peptide and protein drugs. The nasal route provides an attractive needle-free alternative which may improve patient compliance and allow extended use of self-medication for many chronic diseases. This is why systemically-acting drugs such as calcitonin for the treatment of osteoporosis, cardiovascular drugs such as desmopressin and painkillers and anti-migraine drugs are already on the market in nasal formulations and more will follow.

Intranasal Vaccination

Nasal mucosa is also extremely rich in specialised cells and houses organised lymphatic tissues involved in the first line defence against airborne micro-organisms. Nasal vaccination avoids the discomfort and problems associated with injection, and stimulates local mucosal defence as well as a systemic immune

response. In addition, nasal vaccination induces protection in distant mucosal organs and appears to provide broader protection than injected vaccines. Several nasal vaccines are in the pipeline and expected to enter the market in the near future.

Nose to Brain

The olfactory region located in the upper remote parts of the nasal passages offers the potential for certain compounds to circumvent the blood-brain barrier and enter into the brain. Although the clinical potential of this delivery route still remains controversial, there is considerable interest in exploring this route for the treatment of common intra-cerebral diseases such as Parkinson's and Alzheimer's.

Topical Nasal Drugs

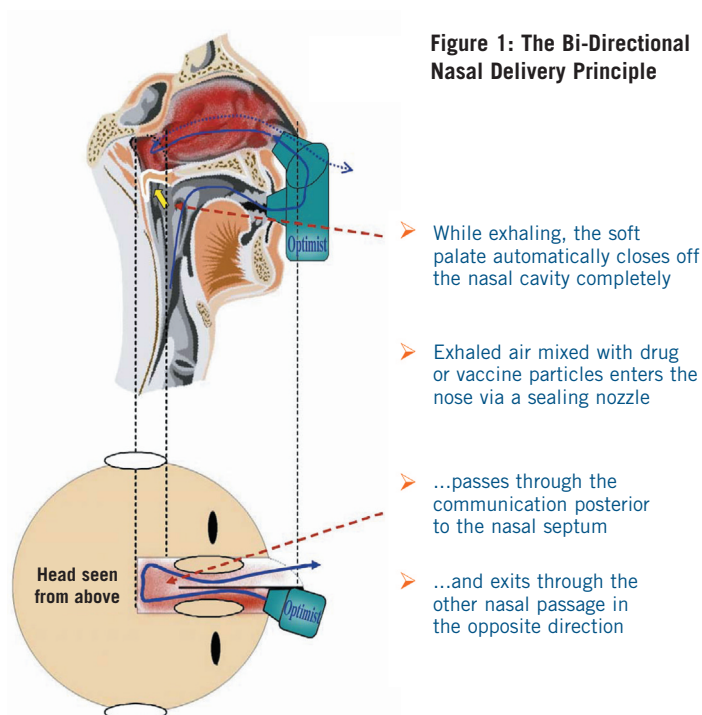
The current value of the nasal drug market is approximately US\$10 billion, with an expected growth of 10-15 per cent annually. Topical decongestants and topical steroids currently account for more than two thirds of the market value. Allergies are also on the rise worldwide and affect 5-10 per cent of the population. Topical steroids represent the drugs of choice for patients with chronic allergic and non-allergic mucosal inflammation. Furthermore, the topical steroids used to treat rhinitis are also used in patients with sinusitis. Chronic rhinosinusitis and nasal polyposis are often associated with asthma and require life-long treatment. However the clinical effect of topical steroids is often disappointing, largely due to the inadequate distribution to the nose and sinuses.

Thus, improved treatment modalities for chronic rhinitis and chronic sinusitis have the potential for considerable market growth in existing and new topical drugs, and open new avenues for novel delivery nasal systems able to improve patient compliance and the clinical effects.

CHALLENGES FOR NASAL DELIVERY

Existing nasal delivery devices such as spray pumps and pipettes cannot fully exploit the described potential advantages of nasal delivery. A large fraction of the dose is deposited on the anterior segment lined by skin, which is not the target for either topical drugs or systemic drugs. Irritation, bleeding and crusting in this region are common adverse effects of unwanted concentrated deposition of topical steroids in this anterior region. Drugs transported along the floor of the nose may cause bad taste and irritation and reduce patient acceptance. Finally, inadequate and variable deposition in the remote region housing the openings to the sinuses and middle ears, as well as the olfactory region, represents a real challenge for extended use of nasal administration of drugs and vaccines. This applies in particular to the new advanced and expensive drugs requiring a demanding combination of reliable dosing, high patient compliance and reproducible bio-availability to ensure their efficacy and safety.

A further major dilemma related to traditional spray pump technology is how to achieve improved deposition while limiting the fraction of small particles able to bypass the nose and enter into the lungs (FDA guidelines). This is because the nose is actually designed to trap and eliminate any foreign substances entering the body. Enzymes in the mucin blanket covering the mucosal membranes and the mucociliary clearance mechanisms may significantly limit absorption. Likewise properties such as polarity, lipophilicity, molecular size and pH will influence the absorption, bio-availability and ultimately the clinical effects. A further complicating factor is that nasal vaccines require mucosal adjuvants to boost the immune response. Indeed many new adjuvants and formulation technologies enhancing nasal absorption have been introduced.

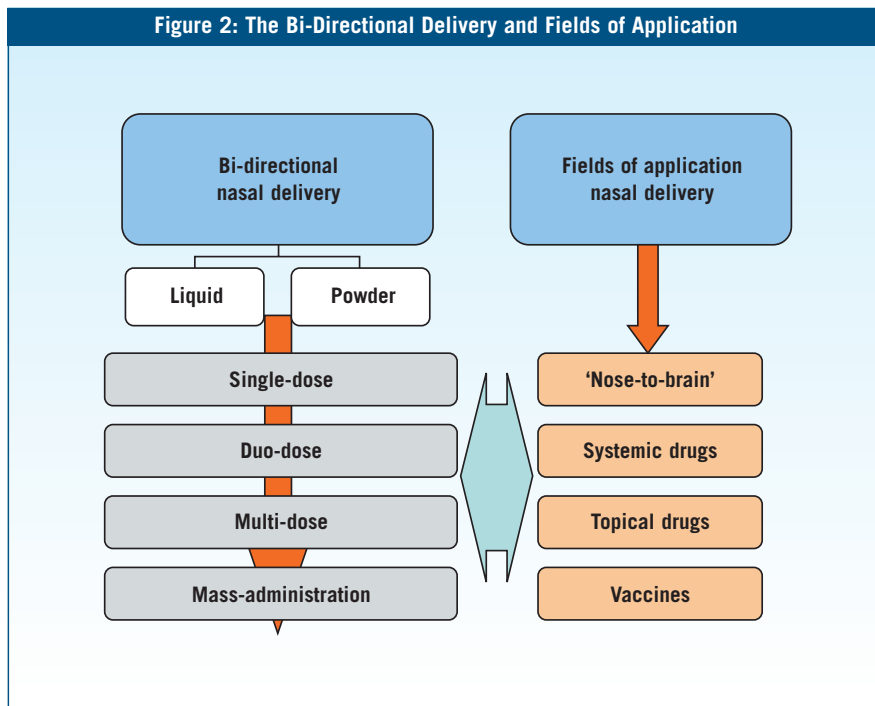


Regarding actual formulation, most nasal products are currently formulated as liquids and delivered by metered spray pumps. Liquid formulations can be limited by the solubility, stability and dose volume. Powders, on the other hand, are more stable and it is easier to customise the size and surface properties. Some studies indicate reduced local irritation and more rapid absorption of powders.

ADVANCES IN DELIVERY DEVICES

In the field of pulmonary delivery, several major pharmaceutical companies have developed their own breath-actuated delivery systems for powders and pressurised metered dose inhalers (pMDIs) to improve patient compliance and the clinical effects. The increased interest in nasally delivered drugs and vaccines has, however, spurred the demand for improved nasal delivery technologies. Disposable unit-dose devices reduce the problems associated with spray pump priming and hygiene but, to date, efficient and consistent distribution to the nasal mucosa has proven difficult to achieve in practice.

Figure 2: The Bi-Directional Delivery and Fields of Application



BI-DIRECTIONAL NASAL DELIVERY

Bi-directional nasal delivery devices seek to address the above problems and offer a unique solution for nasal delivery of drugs and vaccines. Bi-directional delivery devices improve distribution to the nasal mucosa in general and can target the sinus ostia and the organised nasal lymphatic tissues, while at the same time preventing lung deposition. Bi-directional delivery takes advantage of the posterior connection between the nasal passages persisting when the velum automatically closes during oral exhalation. Breath actuation and controlled particle release secure a reliable, efficient and safe delivery of vaccines to the target sites within the nasal passages with maximum patient comfort. By permitting delivery of nasal formulation to the target sites in the nose, benefits can be gained from increased absorption and lower dose. Any dispersion technology for liquid and powder particles can be combined with the bi-directional nasal delivery concept, adding to its versatility.

Deposition studies of bi-directional delivery using gamma-scintigraphy have shown significantly improved deposition patterns compared with traditional nasal spray pumps. Phase I nasal vaccination trials have shown a several fold increase in the immune response as compared with vaccine delivery by traditional spray devices. Patient acceptance and compliance

CHRONIC RHINOSINUSITIS is a very common disease worldwide. A recent epidemiological review (Vital Health Statistics, USA, 10:1999) ranks chronic rhinosinusitis as the most common chronic condition in the US, affecting more than 30 million people (15 per cent of the population). According to this official review, CRS is more common than hypertension and asthma. It has been estimated that the annual cost in the US is \$24 billion. Sinus surgery is among the most common surgical procedures performed in the US. Due to inadequate treatment, 45 per cent of patients with CRS seek alternative therapies, spending a total of \$15 billion annually on such therapies.

for the bi-directional device are excellent thanks to the two-point device fixation and breath actuation. Simple and safe self-administration is essential for more efficient treatment of many chronic diseases in the home setting, administration of vaccines and antidotes in epidemic situations and, most topically, for providing a rapid response in the case of bio-terrorism attacks. Bi-directional single-dose devices and mass-vaccination devices for both liquids and powders will soon be available for clinical testing.

CONCLUSION

Nasal delivery provides a cost-effective and user-friendly alternative to injection. Drugs delivered nasally act faster than tablets and mixtures, and the

onset of action is comparable to intravenous injection. Intranasal vaccination offers additional local immune protection for many vaccines. The nose is an attractive delivery route worth considering for many existing substances, as well as the complex protein drugs being developed by biotechnology companies. Progress in nasal formulation technologies and new delivery technologies such as bi-directional delivery may offer essential advantages and expand the market for nasal delivery of drugs and vaccines. ♦

The author can be contacted at pgd@optinose.no

Further Reading

Findlay G and Kermani F, *The Application of Drug Delivery Systems: Current Practices and Future Strategies*, *CMR International*, 2000

Vital Health Statistics, USA, 10:1999

Pontiroli E, *Peptide hormones: Review of current and emerging uses by nasal delivery*, *Advanced Drug Delivery Reviews*, Vol 29, pp81-87, 1998

Davis SS, *Nasal vaccines*, *Advanced Drug Delivery Reviews*, Vol 51, pp21-42, 2001

Jones N, *The nose and paranasal sinuses physiology and anatomy*, *Advanced Drug Delivery Reviews*, Volume 51, pp5-19, 2001

Guidance for Industry, *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products*, www.fda.gov/cder/guidance/index.htm