Bi-directional nasal drug delivery

A new concept in nasal drug delivery looks set to transform the delivery efficiency of nasal spray products.

Per G Djupesland and Rod Hafner, OptiNose AS

"And the Lord God formed man of the dust and the ground, and breathed into his nostrils the breath of life; and man became a living soul." Genesis 2:7.

A revolutionary new technology is expected to have a dramatic impact on the delivery of drugs via the nasal route. Traditionally, the development of nasal spray products has been faced with a major dilemma: on the one hand, nasal delivery can be improved by using smaller particles, but on the other, this has to be balanced against the increased risk of drug being inhaled into the lungs. A new concept, bi-directional drug delivery, addresses this dilemma by isolating the nasal circuit from the lungs - enabling particle size, flow rate and direction to be optimised.

Effective drug delivery requires particles to be delivered beyond the nasal valve to the mucosal surfaces...

The nose – an advanced organ with many functions

The nasal passages are complex aerodynamic structures optimised during evolution to protect the lower airways. Specifically, large particles (>5-10µm) are efficiently filtered out, and infective agents are presented to the abundant nasal immune system. The inspired air has to be warmed and moistened, within fractions of a second, to transform cold winter air into conditions more reminiscent of a tropical summer. Last, but not least, the nose is a delicate sensory organ designed to provide us with the greatest pleasures, but also to warn and protect us against dangers (1).

The functionality of the nose is achieved by its structure and the complex, narrow nasal geometry. Amazingly, the relatively short air-path in the nose accounts for half of the total airway resistance during inhalation. In the nasal valve (the anterior triangular narrow segments in the nose) the flow rate can approach the speed of a hurricane. Beyond the nasal valve is a much larger space divided into slit-like passages by the nasal turbinates. Here the airflow is slowed down and disrupted, allowing close contact between the air and the mucosa. It is this close contact that enables effective filtering and conditioning of the inspired air.

Imagine leaves blowing in the wind through a narrow alleyway; the leaves will pile up behind edges and behind the corners at the exit of the alleyway. A similar process happens in the nose. Particles are deposited on the mucosa behind the valve from where the mucociliary transport mechanism carries them backwards to eventually be swallowed.

The challenge of nasal drug delivery

The anterior third of the nasal passage distal to the nasal valve is lined by a squamous epithelium that is not a true mucosal surface. Effective drug delivery requires particles to be delivered beyond the nasal valve to the mucosal surfaces which are lined by

a single cell-thick columnar epithelium (2). The question is how to achieve this?

Imagine a physics class investigating flow patterns by spraying particles into a bendy tube. For the most part, the particles will hit the sides and stop; however, when an airflow through the tube is introduced, the particles travel further into the tube. If the size of the particles is reduced sufficiently, some of them will be carried by the flow to the end of the tube.

In theory, therefore, it ought to be possible to improve delivery beyond the nasal valve by using smaller particles and asking people to inhale when the spray is actuated. Indeed, nebulisers producing very small particles are capable of improving deposition beyond the nasal valve. Unfortunately, the use of smaller particles results in up to 60% of the dose being delivered to the lungs (3, 4). Drug intended for nasal delivery is lost, and there may also be some undesired side-effects in the lung (5). Sniffing during actuation will cause additional narrowing of the elastic tissues of the valve and suck a large part of the dose through the nose to the mouth, to be lost to swallowing.

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Existing nasal sprays are trapped in the dilemma between producing smaller particles to improve deposition and the increasing risk of lung inhalation as the particles become smaller. A recent FDA Guidance addresses the potential safety concern of small droplets bypassing the nose with possible adverse pulmonary effects (6). Currently, nasal spray pumps must have a mean particle size large enough (≈50µm) to limit the fraction of respirable particles to 5%. This particle size is incompatible with efficient delivery to the nasal mucosa.

How to do it better

After years of experience treating patients with chronic rhinitis and sinusitis Dr Per Djupesland realised that, to improve therapeutic effects, a new delivery device was needed. Controlling the flow rate and reducing the particle size seemed sensible, but how to prevent smaller particles bypassing the nose and being inhaled into the lungs? Perhaps inspired by thinking about the aerodynamics of aviation, the concept of bi-directional nasal delivery was born just after lift-off from JFK airport.

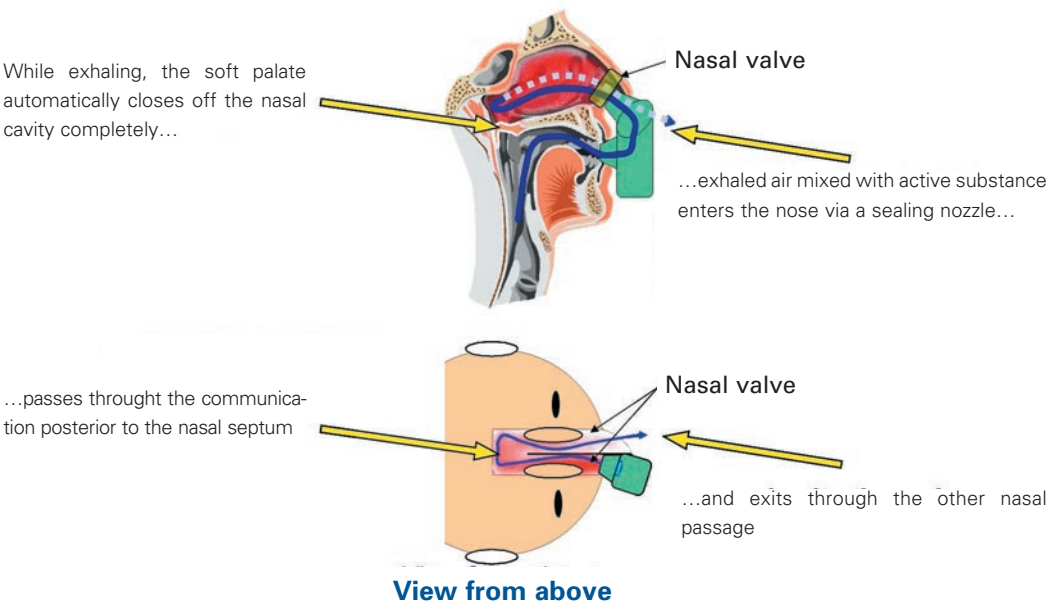
To understand bi-directional delivery requires an appreciation of two aspects of nasal anatomy (see Figure 1):

First, during exhalation against a resistance the soft palate closes due to positive pressure, separating the nasal and oral cavities. Consequently, it becomes possible to use smaller particles in a nasal spray and still avoid lung deposition by exhaling through the mouth during nasal administration.

Second, during closure of the soft palate there is a communication pathway between the two nostrils, located behind the walls separating the two passages. Under these circumstances, it is possible for an airflow to enter via one nostril and leave by the other.

The bi-directional delivery concept combines these two anatomical facts into one fully functional device. The device is inserted into one nostril by a sealing nozzle and the subject blows into the mouth-piece. The combination of closed soft palate and sealed nozzle creates an airflow which enters one nostril, turns 180° through the communication pathway and exits through the other nostril

Figure 1. Description of the bi-directional nasal delivery principle.



(bi-directional flow). Since delivery occurs during exhalation, small particles cannot enter the lungs.

There are additional benefits to isolating the nasal circuit from the lungs. Particle size, flow rate and direction can be optimised for efficient delivery to the nasal mucosa. By adding an exit resistor to give additional control of the driver pressure, it is possible to optimise distribution to the sinuses and the middle ear. Manipulation of the flow pattern enables delivery to the olfactory region, thereby achieving direct "nose-to-brain" delivery. The U-turn behind the septum will trap particles still airborne – like the U-bend of a sink – allowing targeted delivery of vaccines and drugs to the adenoid.

To sum up, the simplicity and flexibility of the bi-directional delivery concept offers a range of new and attractive nasal destinations not reached by traditional nasal spray pumps.

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Clinical studies

OptiNose has now completed a number of clinical studies evaluating the bi-directional delivery concept. Initial studies focused on demonstrating particle deposition. More recently, the benefits in terms of bioavailability and immune response that result from enhanced delivery have been investigated.

Deposition studies The ability of bi-directional delivery to reach structures not achieved by traditional nasal sprays has been verified through gamma scintigraphy studies (see Figures 2 and 3). These studies have shown:

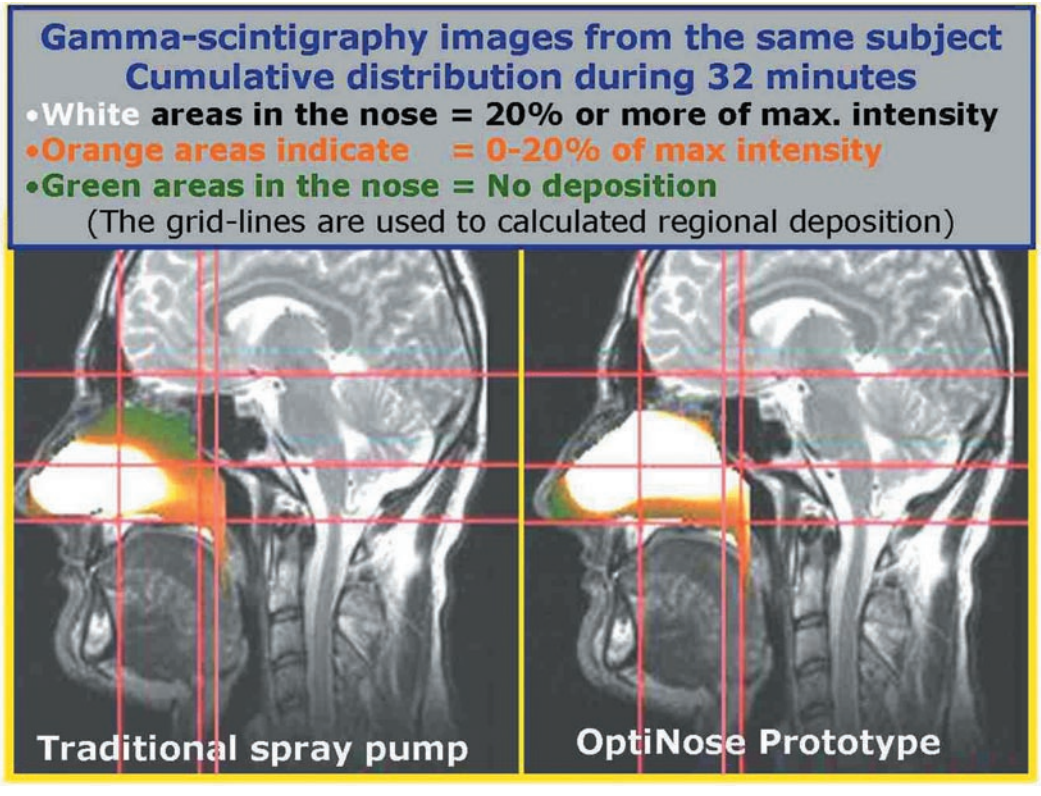
- Significantly improved deposition to the parts of the nose housing the olfactory region, the entrances to the sinuses, middle ears and the adenoid,
- Significantly reduced deposition in the anterior region,
- Prevention of lung deposition, and
- Targeted delivery to the olfactory region, openings to the sinuses and lymphatic tissues.

Nasal vaccination Bi-directional delivery of diptheria and influenza antigens has shown a several-fold increase in both the local and systemic immune response when compared with traditional spray pumps.

Systemic delivery Bio-availability studies comparing bi-directional delivery with conventional nasal delivery devices are underway.

User studies User studies have shown a clear preference for the bi-directional delivery format com-

Figure 2. Comparison of deposition patterns with traditional spray pump and bi-directional delivery device incorporating the same spray pump.



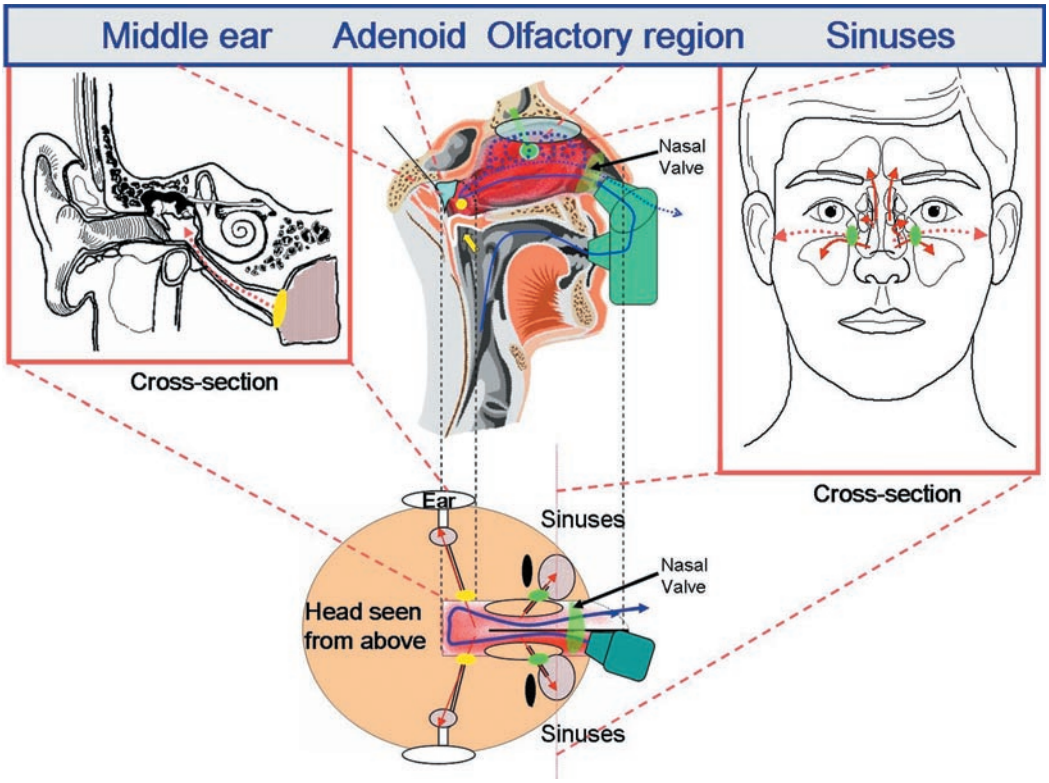


Figure 3. Target sites that are better served by bi-directional delivery.

pared with traditional nasal sprays, probably due to three separate effects. First, the bi-directional device is more comfortable because of its fixed position during use, whereas a traditional spray pump tends to move during actuation. Second, the airflow through the nose at actuation reduces the discomfort often experienced when the spray is released. Finally, there is a reduction in the after-taste at the back of the throat.

The flexibility of the bi-directional delivery concept allows optimisation of the performance of the device to particular clinical needs and cost profiles.

Designing the device

The lead bi-directional device is a breath-actuated single-dose nasal delivery device, intended for high-value drugs for systemic delivery, "nose-to-brain" delivery and commercial vaccines in the developed world (see Figure 4). It is on track to be ready for clinical testing within months. OptiNose decided to out-source development of the medical device to gain access to high-caliber expertise in an appropriate design control environment. The need to combine ergonomics and performance has been – and is – a priority. The UK product development consultancy, Team Consulting, were engaged to design the first device. To reduce the levels of risk, time and cost, components from existing device technologies were incorporated whenever possible, through alliances with the suppliers of these components. Pfeiffer, a world-leader in the development of pharmaceutical spray systems, is now an established partner, providing an internal spray pump system; the company is currently scaling up the design for pilot-scale production.

Several other devices are under development, including a single-dose powder device, a single-dose device for targeted delivery, and multi-use breath-actuated devices for both liquids and powders. The flexibility of the bi-directional delivery concept allows optimisation of the performance of the device to particular clinical needs and cost profiles.

Ensuring a strong intellectual property (IP) portfolio has been a priority from the start. Eighteen patent applications have been filed in a 'ring-fence' strategy. The first patent has been granted in a number of countries, including the UK and the US.

The OptiNose business model

OptiNose is partnering its technology with pharmaceutical companies for indications where significant therapeutic benefits could arise from bi-directional delivery. The device is also being progressed in-house for certain indications (see Table 1). Potential applications are envisaged as follows:

Nasal delivery of systemic drugs Mucosal delivery via the nose offers the potential for rapid absorption and fast onset of action, whilst avoiding hepatic first-pass metabolism. Possible applications include the treatment of acute pain, nausea and vomiting. Some

Figure 4. The OptiNose breath-actuated single-dose nasal delivery device.

- The device is supplied pre-assembled with a single dose vial located inside
- The device is primed by pushing in the orange slider
- The device is positioned in one nostril and in the mouth
- The user blows into the device and the drug is automatically released when the correct pressure/flow relationship is achieved
- The airflow carries the released particles deeper into the nasal passages

systemic drugs – such as calcitonin, desmopressin, painkillers and anti-migraine compounds – are already marketed in nasal formulations. The ability to improve bioavailability using bi-directional delivery should make future products more cost-effective and reliable.

Nose to brain (N2B) Delivery to the olfactory bulb region offers a potential approach to circumvent the blood-brain barrier and gain access to the cerebrospinal fluid. With traditional spray pumps, less than 5% of the dose reaches this region. Based on simulations and early tests with our targeted N2B nozzle this fraction can be increased considerably, possibly to more than 30-40% of the dose. There is considerable interest in exploring this route of administration for the treatment of diseases such as Parkinson's and Alzheimer's.

Intranasal vaccination Nasal vaccination stimulates both local mucosal and systemic immune responses, induces protection in distant mucosal organs, and appears to provide a broader level of protection than injected vaccines. Likely explanations for the improved immune response observed with the OptiNose device are, first, the larger area of mucosal surface that is reached, and second, the organised lymphatic tissue of the adenoid.

Rhinitis, polyposis and chronic rhinosinusitis Topical nasal steroids account for close to half of the total nasal drug market ($8-10 billion), which is growing at 10-15% annually. Topical steroids are the preferred treatment modality for rhinitis with mucosal swelling, and are regularly prescribed for nasal polyposis and chronic sinusitis. Allergic rhinitis currently affects 5-10% of the population, and is rapidly increasing in both developed and developing countries. Furthermore, mucosal inflammation and

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Table 1. OptiNose – current product portfolio.

	Planning	Preclinical	Phase I	Phase II-III
Feasibility studies				
Topical drugs				
Vasoconstrictor	In-house			
Systemic drugs				
Sedative	Collaboration			
"Nose-to brain"				
Undisclosed	Collaboration			
Nasal Vaccines				
Diptheria	Collaboration			
Influenza	Collaboration			
Product development				
Topical drugs				
Rhinitis/Sinusitis	In-house			
"Nose-to brain"				
Parkinson's	In-house			
Systemic drugs				
Undisclosed	Collaboration with Pharma			

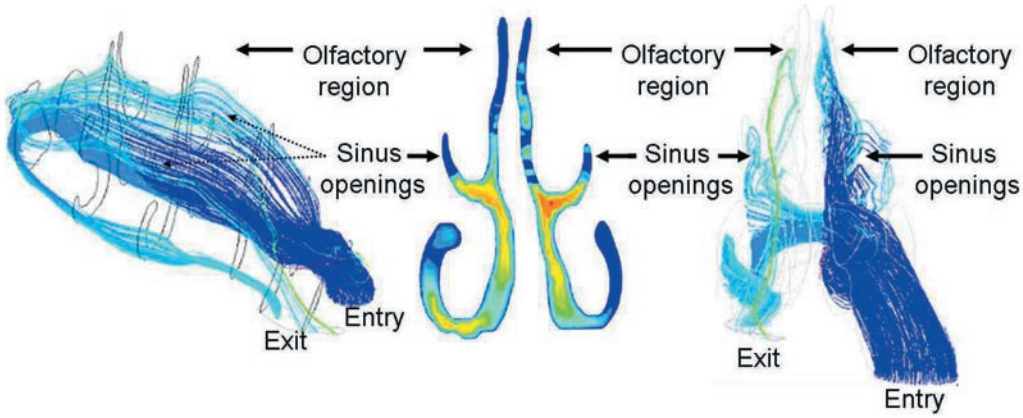

Figure 5. Computational Fluid Dynamic (CFD) model of nasal drug delivery. The model allows testing *in silico* of different delivery conditions. In the examples shown, modeling has established conditions where a large fraction of the dose is delivered to the middle meatus where the sinus openings are located. The CFD model allows rapid assessment of how altering flow rate and particle size affects delivery to different sites. CFD modeling has enabled OptiNose to efficiently develop variants of the core device technology to focus delivery on specific target sites.

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excess secretion can predispose patients to chronic sinusitis and middle-ear pathologies. A recent epidemiological review (7) ranks chronic rhinosinusitis as the most common chronic condition in the US, affecting more than 30 million people (15% of the population) – more common than hypertension and asthma. It has been estimated that the annual cost of this condition in the US is $24 billion. Indeed, sinus surgery is one of the most common surgical procedures performed in the US.

At OptiNose, we believe the ability to deliver steroids to the nasal mucosa and entrances to the sinuses will lead to a dramatic increase in the effectiveness of these drugs – resulting in a marked improvement in the condition, a reduced need for surgery and an improved quality of life. The company plans to initiate a number of in-house development projects in the rhinitis and rhinosinusitis marketplace, with the intent of progressing these into early clinical testing.

For further information, please contact: Per Djupesland, MD, PhD, CSO, OptiNose AS. Tel: +47 22 49 59 85 Fax: +47 22 49 53 50 E-mail: pgd@optinose.no Web: www.optinose.no

Dr Per Gisle Djupesland is Co-founder, CSO and Chairman of OptiNose AS, a Norwegian drug delivery company developing novel concepts for the nasal delivery of drugs and vaccines. Dr Djupesland is a specialist in otorhinolaryngology; he has a PhD in nasal physiology from the University of Oslo, Norway, 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.*

Dr Rod Hafner is Director of Operations at OptiNose. He has a PhD in biochemistry from Cambridge University, UK. Dr Hafner has led multiple R&D projects in the drug delivery and vaccines field for 13-plus years whilst employed at Procter & Gamble, Wyeth and Cortecs. Most recently at PowderJect Pharmaceuticals, he held a number of positions including Programme Manager, Vice-President Early Stage Development and Vice-President Portfolio Management.

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