



BREATH-ACTUATED BI-DIRECTIONAL DELIVERY SETS THE NASAL MARKET ON A NEW COURSE

Nasal drug delivery is already a thriving market but there is still a wide gap between what has been achieved in the past and what could be achieved were the full potential of this highly attractive administration route released. This article describes a technological breakthrough by OptiNose that has allowed the company to make that hitherto elusive step of achieving truly optimal nasal drug delivery.

Compiled by ONdrugDelivery on behalf of OptiNose.

The advantages of delivery via the nasal route are numerous. It is clearly a convenient, non-invasive administration route but this is not what sets it apart. Where other routes often offer such benefits at the expense of desirable pharmacokinetics, nasally administered formulations have true potential for rapid onset of action, high bioavailability and direct “nose-to-brain” delivery.

This potential arises predominantly because of the complicated structure of the nasal cavity, which has evolved to carry out multiple functions. They include physical protection of the lower airways (by filtering out large particles), immune protection, and optimisation of the temperature and humidity of air before it enters the lungs. What is more, the nose is an amazing and delicate sensory organ, able to detect minute traces of countless substances in the air via the olfactory nerves that enter the roof of the nose through the cribriform plate.

Despite the success of conventional nasal sprays there is still significant room for improved delivery

Of course previous systems have not been without their benefits – indeed, today several topical and systemic nasal products can be found on the market. However, the crux of the issue, and the point of this article, is that so much more can be accomplished. A simple yet remarkable technological leap offers to bridge the gap between previous nasal products with their limited efficacy and applications, and success in the pharmaceutical market for future nasal formulations on a scale that could exceed even the most optimistic expectations.

With an elegant adaptation to the mechanism of nasal delivery devices, OptiNose has suc-

cessfully taken this step. In-depth knowledge of the nasal anatomy and physiology, reinforced by detailed studies, have provided the information enabling OptiNose to understand how to optimise drug delivery while reducing or eliminating side effects. The result is nothing short of a medical breakthrough. The nose is now set to take its place as an ideal delivery route for any number of pharmaceutically active compounds for the treatment and prevention of diseases across the board.

WHY THE LONG WAIT?

To get to the core of why earlier nasal delivery systems only managed a degree of success within a narrow market, it is necessary to take a closer look at the complex structures and geometry that give the nose its exceptional functional properties.

Between the anterior third of the nose (roughly equivalent to the visible part of the nose on your face) and the posterior two thirds (deep inside your head above the roof of the mouth) the nasal valve disrupts the airflow to facilitate trapping and the filtering of particles. The posterior two thirds, beyond the nasal valve, is divided into slit-like passages by the nasal turbinates. Slowing of the airflow as it passes over the turbinates allows time for inhaled air to be heated and humidified before reaching the lungs and, crucially, causes particles to sediment out on the nasal mucosa.

The true nasal mucosa beyond the nasal valve is lined by a single cell-thick columnar epithelium, similar in structure to the respiratory epithelium that lines the lungs. As well as being rich in immunologically active cells, den-



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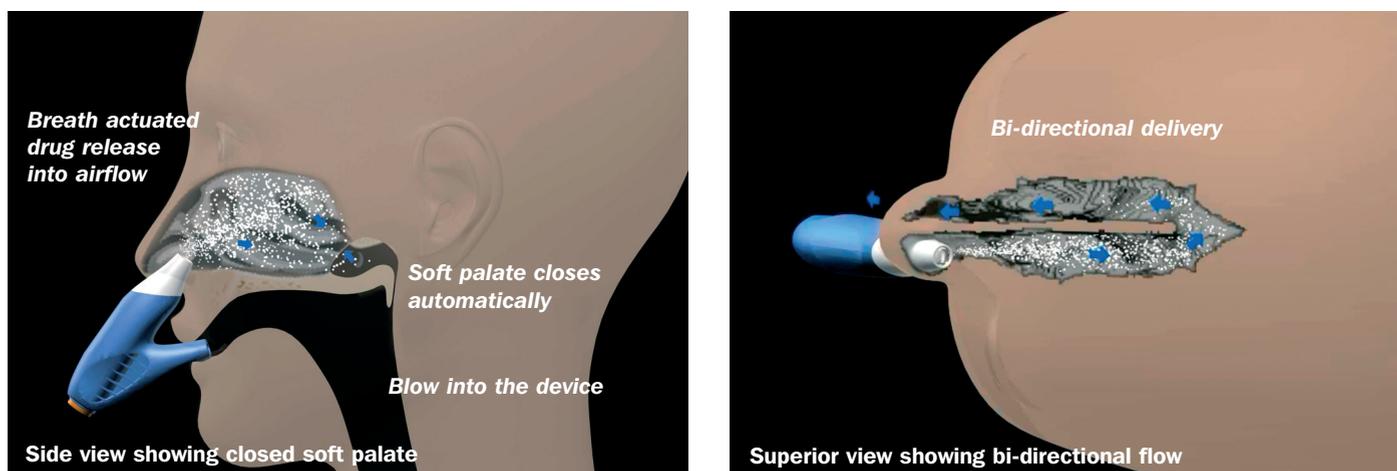


Figure 1: Two interlinked anatomical principles underlying bi-directional drug delivery

tritic cells and organised lymphatic tissues, the nasal mucosa is also highly vascularised making it an ideal target for optimal drug absorption.

The riddle that standard nasal delivery systems have been unable to solve is that if a dose consists of large particles, a significant proportion does not reach the true nasal mucosa beyond the valve but remains in the anterior region, which is not the target site. Absence of cilia in this region means that particles will largely remain stationary or will drip out or be wiped off, leaving large portions of the nasal surface unexposed to drug and thereby limiting their clinical effects. Pressurised metered-dose inhalers adapted for nasal use, nasal powder inhalers and mechanical spray pumps, have all been shown to suffer from this shortcoming.

Furthermore, sniffing too sharply during or after actuation causes the spaces between elastic tissues within the nasal valve to narrow, trapping more of the dose in the anterior segment. Particles that pass through the nasal valve during a strong sniff are sucked along the floor of the nose to the back of the mouth and swallowed.

The obvious solution to the problems encountered by large particles is to reduce particle size, but this is equally unsatisfactory since small particles (less than $5\text{--}10\ \mu\text{m}$) may travel beyond the nasal turbinates and be inhaled into the lungs. Clinical testing of nasal nebulisers delivering particles of $6\ \mu\text{m}$ resulted in better delivery to the mucosa but 33-56% of the dose was deposited in the lung.¹

It is tempting to reason that it might be satisfactory for most of the dose to be delivered to the target site with some reaching the lungs. However, for both systemic and topical nasal products there is a risk of adverse side effects in the lung, and the variability of the dosing increases. Lung deposition of nasal formulations is unacceptable, to the extent that the guidelines from regulatory authorities in major markets such as the US require nasal

spray pumps to limit the respirable fraction to 5%. For conventional technologies, this equates to a mean particle size of approximately $30\text{--}50\ \mu\text{m}$, which represents a true challenge for efficient and controlled delivery to the nasal mucosa.

One type of formulation – nasal drops – has been shown to achieve improved delivery beyond the nasal valve without lung deposition. However, correct administration requires the patient to carry out complex manoeuvres involving contorted head movements not acceptable to most patients. Any deviation from this process can preclude effective delivery, and thus nasal drop formulations result in poor compliance.

BI-DIRECTIONAL DELIVERY: AN ELEGANT SOLUTION

So, it seems that every approach to achieving efficient delivery via the nasal route that has been tried so far has one deficiency or another. Yet the particle-size riddle does have a solution. Once realised, the solution is strikingly simple and highly effective. The concept has been termed breath-actuated bi-directional delivery by OptiNose.

It is somehow appropriate that anatomical features of the nose have been the root of the tribulations of previous nasal delivery systems, and yet it is by harnessing two interlinked functional anatomical nasal features, that bi-directional delivery achieves its aim.

The first of these features is that during exhalation against a resistance the soft palate closes, separating the nasal and oral cavities (see figure 1a). Thus if nasal delivery can be achieved whilst exhaling against a resistance the previously insurmountable problem of lung deposition following nasal inhalation of smaller particles is immediately and completely avoided.

The second anatomical feature is that during closure of the soft palate there is a communication pathway that remains between the two nostrils, located behind the nasal septum. Under these circumstances, it is possible for air to enter via one nostril, turn through 180° passing through the communication pathway, and leave by the other (see figure 1b).

OptiNose's breath actuated bidirectional delivery couples together the act of blowing out and the use of a sealing nozzle to direct the airflow into the nose. The sealing nose piece allows control over pressure and flow conditions and, together with optimisation of particles size characteristics and the use of a breath-actuation mechanism, controlled and targeted nasal delivery of both liquid and powders can be achieved. At the same time lung deposition is avoided.

In a study of 16 healthy subjects using $^{99\text{m}}\text{Tc}$ -labelled nebulised particles with a mean particle size of $3.5\ \mu\text{m}$, bi-directional delivery prevented lung deposition, whereas significant fractions (12-39%) were deposited in the lungs in all 16 subjects following conventional nasal inhalation. The study concluded that bi-directional nasal delivery minimises the risks and problems related to lung deposition.²

FULLY FUNCTIONAL DEVICES

Bi-directional drug delivery has already made the transition from concept to reality. With the key to effective nasal delivery in its possession, OptiNose is proceeding rapidly with the development of several groundbreaking breath-actuated bi-directional nasal drug delivery devices for both liquid and powder.

All of these systems apply bi-directional drug delivery in the same way. A sealing nozzle is inserted into one nostril and the patient blows into the mouthpiece. The blowing action closes the soft palate and creates an airflow, which carries the formulation out of the device through

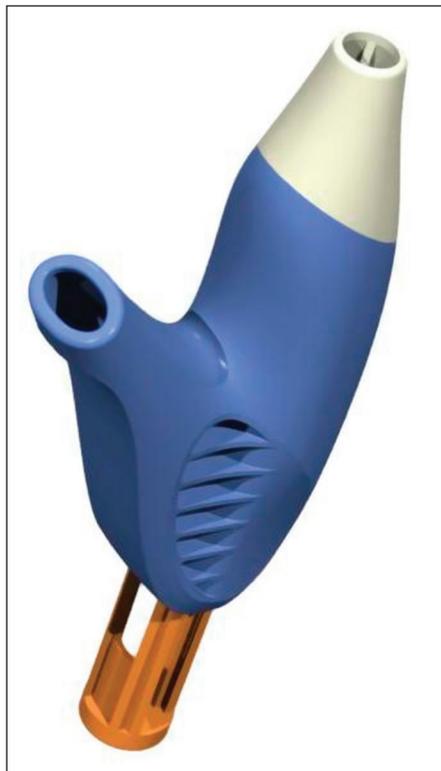


Figure 2: The single-use device

the sealing nozzle into one nostril to the target sites. The airflow passes through the communication pathway between the nostrils and back out through the other nostril.

An additional benefit of the positive pressure created as the patient blows into the sealing mouth-piece is the expansion of the narrow passages and opening of obstructed segments. This potentially improves distribution of delivered particles – the reverse of what happens during a sharp sniff.

The lead bi-directional device manufactured in collaboration with Ing Erich Pfeiffer GmbH, Germany, is a single-dose liquid spray technology, intended for the delivery of high-value drugs for systemic and “nose-to-brain” delivery, as well as vaccines. The value of bi-directional drug delivery in these applications is discussed in more detail below.

The device, which is shown in figure 2, is supplied pre-assembled with a single-dose vial and applicator from Pfeiffer located inside. The user primes the device by pushing the orange handle, positions the nose-piece and mouth-piece, and begins to exhale. The drug is released when the correct pressure-flow relationship is reached, and is carried to the desired site within the nose.

User studies have shown a clear preference for the bi-directional delivery format compared 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, compared with a traditional spray

pump, which tends to move during actuation. Second, the devices are breath actuated. Third, the airflow through the nose at actuation reduces the discomfort often experienced when the spray is released. Finally, there may be a reduction in the aftertaste at the back of the throat due to a different deposition and clearance pattern.

MULTI-DOSE AND POWDER DEVICES

Two other types of device under development by OptiNose are a multi-dose liquid reservoir device, shown in figure 3, and a powder delivery device.

The multi-dose liquid device has been designed to incorporate existing nasal spray pump technology and to incorporate proven breath actuation technology in order to reduce risk. Device design is currently being finalised and injection-moulded devices will be available in 2006.

Recent clinical studies comparing delivery from a traditional spray pump with delivery from an initial multi-use liquid bi-directional delivery device design (with the same spray pump incorporated inside), have shown significantly improved delivery beyond the nasal valve and in particular to the upper remote and clinically important nasal segments (see figure 4). Reproducibility of dosing was also improved with the bi-directional delivery device.

The powder device, which is at a slightly earlier stage of development, is designed for single- or multi-dose use and will allow the development of powder formulations with greater opportunity for stability to be delivered without the risk of pulmonary deposition.

THE NEW VISION FOR NASAL DRUG DELIVERY

Like all true breakthroughs, the implications of breath-actuated, bi-directional drug delivery reach far beyond simply addressing the predominant shortfall of existing systems – the particle size riddle. Indeed, bi-directional drug delivery is aptly named since the array of new opportunities it opens up for the nasal delivery market can be said to stretch in two directions.

In one direction, it allows a look back at standard nasal delivery devices and overcomes some of their other disadvantages, such as lack of consistency over dosing, local irritation, nosebleeds and uncomfortable taste from concentrated drugs reaching the mouth, as well as the failure to achieve optimal local and systemic absorption. Furthermore, breath actuation is likely to contribute strongly to improved patient compliance and acceptability as well as more consistent performance. When breath actuation

was introduced to pulmonary delivery two decades ago it transformed the pulmonary drug delivery market.

Looking in the other perhaps more interesting direction – forwards – bi-directional drug delivery expands the possible applications of nasal administration into new areas not previously considered as viable markets for conventional nasal technology.

For example, once the nasal circuit is isolated from the lungs during administration, nasal drug delivery is freed from other restrictions. Particle size – along with flow-rate and direction – can of course be optimised to target the nasal mucosa effectively. However, the ability of bi-directional delivery to deliver to structures not reached by traditional nasal sprays has been verified through gamma scintigraphy studies. As well as significantly reduced deposition in the anterior region and prevention of lung deposition, they have shown significantly improved and more targeted delivery to the parts of the nose where the olfactory nerves pass and, the entrances to the sinuses, middle ears and the adenoid are located.

In addition to delivery to specific structures within the nose for topical delivery, these findings present two further major opportunities.

The first of these is in the area of nasal vaccination. Bi-directional delivery of diphtheria and influenza antigens has shown a significant improvement in both the local and systemic immune response when compared with traditional spray pumps.

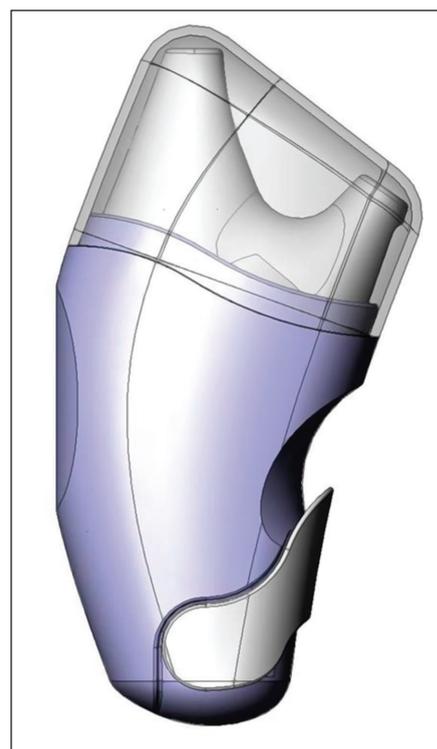


Figure 3: The multi-use liquid reservoir device

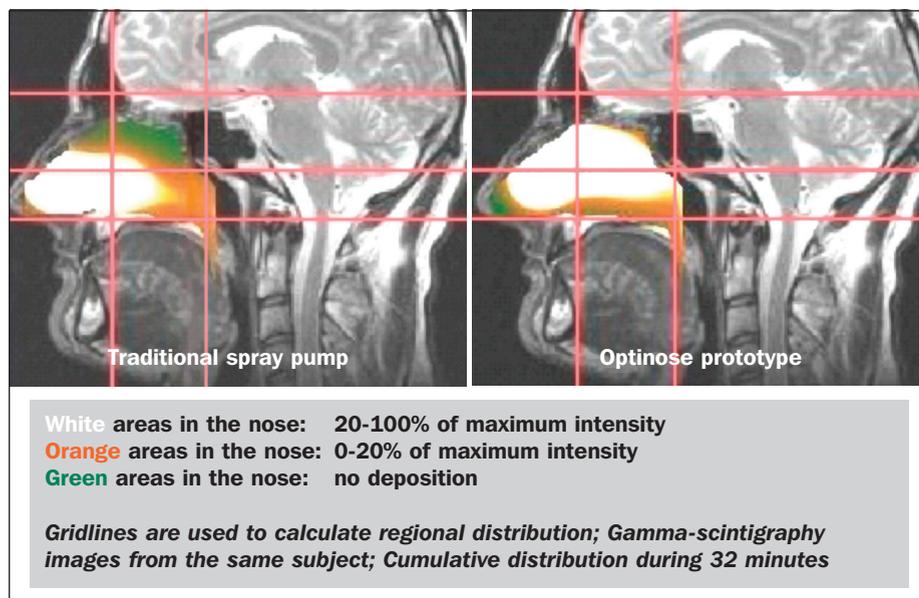


Figure 4: Gamma scintigraphy images comparing deposition following traditional and bi-directional delivery

The second opportunity is the real possibility of effective nose-to-brain drug delivery, an area in which OptiNose has taken a keen interest.

NOSE-TO-BRAIN DRUG DELIVERY

There is a growing body of evidence supporting the existence of a delivery route for pharmaceutically active compounds from the olfactory region of the nose directly into the central nervous system.

The olfactory epithelium is located just below the cribriform plate in the upper posterior quadrant of the nasal cavity. It contains olfactory receptor cells, which have a single dendrite that extends to the apical surface of the epithelium. At the basal end, the cell ends in an axon that joins into a bundle surrounded by glial cells and cerebrospinal fluid, and penetrates into the cranial cavity through the cribriform plate. To access this route of absorption, drug molecules must be delivered to the olfactory epithelium in meaningful quantities.

Nose-to-brain delivery offers two important benefits in the treatment of CNS disorders. First, it avoids the blood-brain barrier, which prevents the majority of compounds delivered via other routes – even injections – from gaining access to the cerebrospinal space.

Secondly, nose-to-brain drug delivery can achieve therapeutic levels in the cerebrospinal space while maintaining minimal systemic concentrations. Neuropeptides are one class of molecules whose usefulness could be greatly enhanced, as Born et al explained. “Biologically effective concentrations of neuropeptides can be achieved in the human brain without strong, systemic, hormone-like side effects. Such effects limit the systemic administration of pep-

tides to amounts too small to have substantial effects in the brain.”

Another interesting aspect of nose-to-brain drug delivery arises because the effects of some compounds differ in the brain compared with in the rest of the body. The potential that nose-to-brain delivery has for maintaining high drug concentrations in the CNS relative to the systemic circulation means that this route could take advantage of these diverse pharmaceutical activities.

Stockhurst et al give insulin as an illustration of this interesting phenomenon. “The intranasal route is a practicable way to reach the brain while maintaining euglycaemia. Additionally, the localization of insulin receptors in the olfactory bulb makes insulin interesting for the nose-to-brain pathway. Promising initial results have been reported with intranasal insulin corresponding to the diverse actions of insulin within the brain. Interestingly, initial data indicate that states of central insulin deficiencies (dopamine transporter [effects] and obesity) are accompanied by olfactory deviations. Thus, the nose-to-brain pathway deserves further attention.”⁴

A recent Phase I clinical trial compared pharmacokinetics and subjective sedation from the same dose (3.4 mg) of midazolam delivered intravenously, intranasally using a traditional pump spray, and intranasally using OptiNose’s bi-directional delivery device.

The speed of onset and level of sedation following iv administration were comparable with those achieved by OptiNose’s device, and the duration of sedation was longer from OptiNose’s device, compared with iv delivery. However, the bioavailability of the bi-directionally delivered formulation was only 68%, compared with 100% from iv.

The traditional intranasal device achieved significantly lower subjective sedation score compared with iv, despite achieving a bioavailability and C_{max} comparable with the formulation delivered by OptiNose’s device with the same dose.⁵

The discrepancy between the pharmacokinetic data and sedation results can be explained by a significant proportion of the dose having access to the CNS via a route that does not involve systemic absorption following administration via OptiNose’s device, rather than entering the systemic circulation.

CONCLUSION

Earlier on in the article, it was noted that OptiNose had successfully converted bi-directional drug delivery from a concept into a functioning technology. However, in delivery to the CNS as well as the other applications, the company is in fact going a stage further – applying its technology in a range of product development projects.

OptiNose is partnering its technology with pharmaceutical companies for indications where significant therapeutic benefits could arise from bi-directional delivery as well as progressing a number of in-house applications for indications such as rhinosinusitis, migraine and Parkinson’s disease.

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