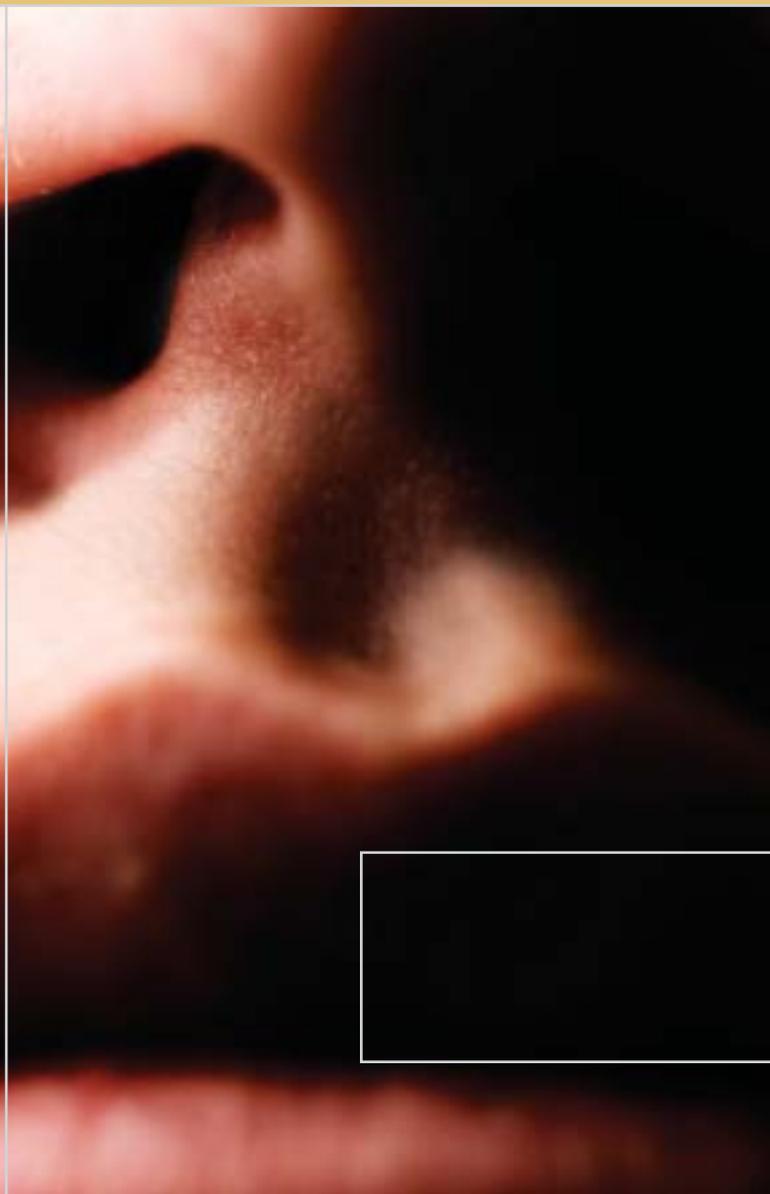


# NASAL DRUG DELIVERY

RAPID ONSET VIA A CONVENIENT ROUTE



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## “Nasal drug delivery: rapid onset via a convenient route”

This edition is one of a series of sponsored themed publications from ONdrugDelivery Ltd. Each issue will focus on a specific topic within the field of drug delivery, and contain up to eight articles contributed by industry experts.

Full contact information appears alongside each article. Contributing companies would be delighted to hear from interested readers directly. ONdrugDelivery would also be very pleased to pass on to authors, or answer as appropriate, any queries you might have in relation to this publication or others in the series.

Forthcoming editions cover: safer injections; advanced transdermal drug delivery; drug delivery in diabetes; pulmonary delivery; advanced oral drug delivery; needle-free injection; and pre-filled syringes. To find out more about receiving or participating with any of these issues, please contact ONdrugDelivery Ltd.

### Contact:

Guy Furness, Managing Director

T: +44 1273 831 370

E: [guy.furness@ondrugdelivery.com](mailto:guy.furness@ondrugdelivery.com)



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OptiNose

20-23

# INTRODUCTION



Welcome to this, the third edition in ONdrugDelivery's novel series of sponsored publications, each of which focuses exclusively on one specific area within the field of drug delivery.

Nasal drug delivery, the topic of this edition, is undoubtedly becoming an increasingly attractive consideration in many quarters. The scientific, technological and medical factors that are promoting current interest are discussed briefly below, and in closer detail in the articles that follow.

It is important first to highlight one quality of nasal delivery technologies that is capturing the interest of potential partners in both the pharmaceutical industry and the investment community. The word is on the lips of many delivery industry commentators these days – products!

There are a number non-invasive delivery routes – pulmonary, transdermal, needle-free, buccal and others – for which optimised technologies are under development to a) enhance the performance of products that have already been delivered with some success via that route and b) access larger markets by enabling the effective delivery of a broader range of compounds – particularly those compounds which have previously only been suitable for injection.

Among these routes, the proven track record of nasal drug delivery technologies to pass the concept stage in this quest, and go on to facilitate the development and launch of viable product candidates, stands out. Many nasal products for the topical treatment of conditions such as rhinitis and

sinusitis have of course been marketed for decades. More recently, several systemic nasal formulations of, for example, hormones, vaccines and compounds for the treatment of migraine, have also reached the market – and more still are progressing through clinical development. As Michael Sheckler of Javelin Pharmaceuticals (formerly IDDS) reports herein, Greystone Associates predicts that the nasal drug delivery market will enjoy annual growth of 24% between 2004 and 2007, increasing the market value from around US\$2 billion to US\$4.3 billion.

Nasal anatomy and physiology play a crucial role in making it such an appealing administration route. The details of structures within the nose are described in this issue but, in general terms, it is clear that no other portal so close to the exterior gives such ready access to a range of systems, without the need to cross barriers such as the stratum corneum, which hinders transdermal delivery.

Chief among the systems that intranasal administration can reach is the systemic circulation, which is made accessible by the rich vasculature of the nasal mucosa. But the lymphatic and immune systems, the sinuses, and the adenoids can also all be accessed through intranasal delivery. Furthermore, for direct “nose-to-brain delivery”, by-passing the blood-brain barrier, the olfactory region enables drugs to enter the cerebrospinal space, for effective treatment of the central nervous system.

“As aging-population demographics and managed-care initiatives drive growth in home health care and self-administration of drug therapies for chronic conditions

such as diabetes, arthritis, and hormone replacement therapy, drug developers are showing increased interest in routes of administration that are patient friendly and cost effective,” says Greystone Associates. “Intranasal administration is well positioned to take advantage of these trends.”

Of course, nasal drug delivery research faces significant challenges. They include: accurately targeting the correct sites within the nose; avoiding unwanted deposition in the stomach and lungs; microbial contamination of multi-use devices; successful development of preservative-free formulations; and the incorporation of dose-counting mechanisms.

There is a view that available nasal delivery technologies have not advanced in a meaningful way for perhaps more than a decade, meaning that a technology gap has opened up. The sector is waiting to take advantage of the opportunities the nasal route presents but cannot do so until a suitable nasal delivery technology becomes available. A read of the articles that follow would suggest that the wait is over.

The leading players in the nasal drug delivery field that have contributed to this publication are developing technologies that aim to meet these challenges and products that have the potential to prove it. Looking ahead, we hope to be able to update you with more news of progress and success from these companies and others when we cover nasal drug delivery again in May 2006.

*Guy Furness*  
*Managing Director, ONdrugDelivery Ltd*



# ADVANCED SIMPLIFICATION OF NASAL DELIVERY TECHNOLOGY:

## ANATOMY + INNOVATIVE DEVICE = ADDED VALUE OPPORTUNITY

**Direct-Haler A/S has invented and developed a novel nasal delivery device and nasal delivery principle. The innovation takes advantage of the patient's anatomy to improve nasal delivery effectiveness and convenience. The integrated nasal device and delivery method enables nasal delivery of very fine particles, without the risk of pulmonary deposition. Dr Troels Keldmann, Managing Director, Direct-Haler A/S, explains.**

The DirectHaler Nasal device has successfully been used in clinical trials, and has confirmed patient acceptability. The single-use, disposable device is for both mono and bi-dose delivery, in a pre-metered, prefilled dose format. The device offers effective, accurate, repeatable and hygienic dosing, and is intuitively easy-to-use. Furthermore, the straightforward device design possesses unequalled cost-effective manufacturability.

### DELIVERY METHOD INNOVATION AND DEVICE INNOVATION

When air is being blown out of the mouth against a resistance, the airway passage between the oral and nasal cavities automatically closes. The same reflex is activated when a person blows up a balloon; none of the air escapes through the nose. This anatomical feature is activated when the patient uses DirectHaler Nasal for blowing their nasal dry-powder dose into their nostril. Thus, the dose is captured in the nasal cavity, where it is intended to act or to be absorbed into the systemic circulation. After completion of the dose delivery blow, the nasal/oral connection returns to its normal open state (see figure 1).

This delivery method holds the potential to become the dominant delivery principle in nasal drug delivery. Direct-Haler is the first drug delivery company to take advantage of this device-dependent reflex for enhancing nasal drug delivery. Naturally, the increased interest in this princi-

ple for enhanced nasal delivery has recently led other companies to seek exploitation of the same delivery principle. However, Direct-Haler has broadly issued device and delivery method patents for this area. Patents are issued in more than 40 countries, with priority dates going back to 1997.

### REMOVING DISADVANTAGES OF CURRENTLY AVAILABLE SYSTEMS

A range of nasally delivered products has been on the market during recent decades. These products belong to therapeutic areas such as allergic rhinitis treatment, migraine relief, hormone replacement therapy (HRT) and common cold relief. The products have applied nasal delivery systems based primarily on four different formulation/device technology types: liquid nasal drops; liquid nasal sprays; pressurised metered-dose inhalers (HFA, CFC); and dry-powder inhalers and insufflators. Performance and characteristics of these nasal delivery systems have been studied widely (see figure 2), and various disadvantages have been identified. The DirectHaler Nasal device and delivery method can solve or significantly reduce these problems.

Liquid nasal sprays and drops are currently the most widely used nasal delivery systems. Among the drawbacks with which they have been associated are:

- Risk of liquid dose dripping out from nostril after dose delivery.<sup>1</sup>
- Risk of liquid dose being swallowed immedi-



Dr Troels Keldmann  
Managing Director

T: +45 3917 9696  
F: +45 3917 9690  
E: keldmann@directhaler.com

Direct-Haler A/S  
Symbion Science Park  
Fruebjergvej 3  
2100 Copenhagen  
Denmark

[www.directhaler.com](http://www.directhaler.com)

ately after delivery – giving limited absorption time and unpleasant taste.<sup>2</sup>

- Complicated device priming procedure before first use, and if many days pass between uses.<sup>3,4,5</sup>
- Risk of small delivered dose for the last actuations as container begins to empty; no dose counter, patient has to keep records to ensure the product is discarded before the dose size becomes insufficient.<sup>3,4,5</sup>
- Acceptability problems for liquid formulations with preservatives, for chronic use.<sup>6</sup>
- Multi-dose containers include risk of contamination, necessitating preservatives in formulation and frequent device cleaning.<sup>6,7</sup>

Dry-powder formulations can offer important advantages over liquid formulations such as: enabling higher drug payload per dose delivered; prolonging absorption time in nasal cavity; reducing temperature sensitivity during product distribution and storage. Further to these advantages, DirectHaler Nasal eliminates the risk of contamination and thereby eliminates the need for preservatives. It also removes the need for priming and cleaning.

The pressurised metered-dose inhaler (pMDI) technology, widely used in pulmonary administration, has also been applied for nasal delivery. However, patient acceptability has not been impressive with the unpleasant “cold-blow” and “hard-blow” of medication from pMDI being one of the commonly reported problems.<sup>8</sup>

In contrast, when using DirectHaler Nasal, the patient contributes the blow energy using their own breath. Therefore, the nasal dose blow is naturally at the correct temperature for high patient acceptability.

Dry-powder nasal formulations have historically been used mostly for locally acting drugs, in rhinitis treatment, for example. Several of these delivery devices comprise pulmonary dry-powder inhalers with a nostril piece instead of a mouthpiece.

Such devices are activated by the patient snorting in the medication. This means that the patient is effectively breathing in the formulation through the nose, by use of the lungs. Unfortunately, therefore, while some of the dose will be trapped in the nasal mucosa en route, the lungs will inevitably be the final delivery site for part of the dose.<sup>9</sup>

The DirectHaler Nasal device and method automatically activates the anatomical reflex that closes the airway passage between the nasal and oral cavities. This activated reflex removes the risk of pulmonary deposition of drug particles.

In summary, DirectHaler Nasal provides a novel opportunity for overcoming the recognised problems, described above, associated with currently marketed nasal delivery device concepts (see figure 2).

## NEW HORIZONS FOR NASAL DELIVERY

New opportunities in nasal drug delivery include the possibility for direct nose-to-brain delivery, requiring dose particle deposition in the olfactory region. However, researchers working in this area currently face a dilemma. Traditionally, nasal formulations ideally have particle sizes above 20-30  $\mu\text{m}$  to minimise the degree of deposition in the lower airways, which increases as particle size decreases. But at the same time, to reach the olfactory region requires dose particle sizes below 5  $\mu\text{m}$ .



Figure 1: DirectHaler Nasal: Device innovation and delivery method innovation.

tive results gathered during the development of Direct-Haler’s dry-powder pulmonary delivery technology. With DirectHaler Nasal the ambition was to develop a disposable dry powder delivery device offering effective, accurate and

Disadvantages reported on current nasal delivery systems	Solved by DirectHaler Nasal
Risk of liquid dose dripping out from nostril after dose delivery. [1]	Dry powder formulations adhere to the nasal mucosa.
Risk of liquid dose being swallowed immediately after delivery – giving limited absorption time and unpleasant taste. [2]	No risk of immediate swallowing. Reduction of taste sensation.
Complicated device priming procedure before first use, and if many days pass between uses [3,4,5]	Primeless.
Risk of small delivered dose for the last actuations as container begins to empty; no dose counter, patient has to keep records to ensure the product is discarded before the dose size becomes insufficient [3,4,5]	Pre-metered, pre-filled unit dose/di-dose device system. No risk of reduced dose.
Acceptability problems for liquid formulations with preservatives, for chronic use [6]	No preservatives.
Multi-dose containers include risk of contamination, necessitating preservatives in formulation and frequent device cleaning. [6,7]	Hygienic single-use, disposable. No contamination risk.
Unpleasant “cold-blow” and “hard-blow” of medication from pMDI. [8]	Tempered & pleasant blow.
Risk of pulmonary dose deposition for “snorting-in” DPI devices. [9]	No risk of pulmonary deposition.

Figure 2: DirectHaler Nasal overcomes disadvantages of currently marketed nasal delivery device systems.

A new nasal delivery method is therefore needed to prevent deposition of fine particle nasal dose in the lower airways. Working in concert with the patient’s anatomy, DirectHaler Nasal’s delivery method represents the type of breakthrough required to overcome this issue.

## BASED ON PROVEN TECHNOLOGY APPLIED IN PULMONARY DELIVERY

The R&D program for DirectHaler Nasal was initiated on the basis of the expertise and posi-

repeatable dosing and in addition being compact and easy-to-use. Our ambition also included making it possible for pharmaceutical companies to manage their own manufacture, filling and device packaging. The innovative result of

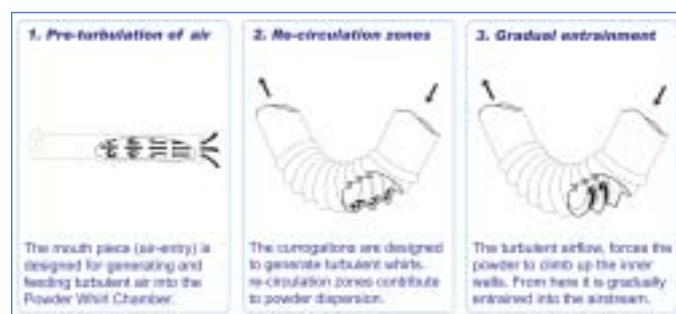


Figure 3: Three powder dispersion principles are applied simultaneously in DirectHaler Nasal.



Figure 4: Applying DirectHaler Nasal.

our nasal R&D is patent protected worldwide.

The nasal device comprises an engineered curved and bendable inhaler tube with a “mouth-to-nose” optimised corrugated flexible bend, and a double cap that seals each end of the device’s tube. As DirectHaler Nasal is intended for nasal delivery of dry-powder formulations, it takes advantage of the PowderWhirl chamber for dispersion, and powder entrainment. The PowderWhirl chamber was originally developed for pulmonary delivery applications, where powder dispersion and gradual entrainment into the airflow is important.

Three principles governing airflow and powder dispersion are applied in the design (see figure 3), so that DirectHaler Nasal delivers the complete dose gradually over one administration blow as a well-dispersed powder.

First, the mouthpiece is designed for generating and feeding in turbulent air to the PowderWhirl chamber. Secondly, the corrugations of the PowderWhirl chamber are designed to generate turbulent whirls. These recirculation zones contribute to powder dispersion. Finally, the turbulent airflow forces the powder up on the inner walls of the corrugations. From here, it is gradually entrained into the blown air stream until the device is completely empty.

### EASY-TO-USE MEANS EASY-TO-INSTRUCT AND CHECK

DirectHaler Nasal is intuitively easy to use, which minimises the instruction task – and makes it easy to check the patient’s technique. The pre-metered and pre-filled powder dose in the DirectHaler Nasal, is always visible due to device transparency. This allows the patient to have visual contact with the dose –

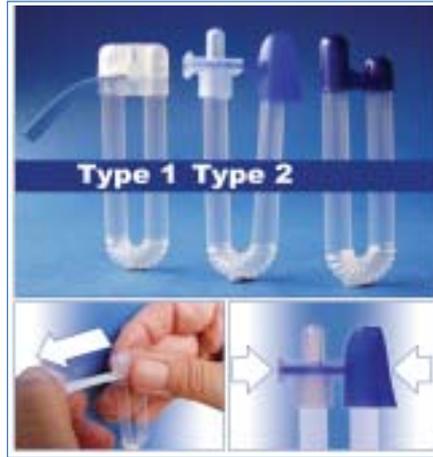


Figure 5: New device cap types for DirectHaler.

ensuring confirmed “dose ready” before delivery and “dose taken” after delivery. The compact device dimensions ensure portability and discretion in using the device.

To use DirectHaler Nasal, the cap is taken off leaving both ends of the tube open and the dose resting at the bottom of the “U”. Holding and pressing the mouthpiece between the thumb and forefinger, facilitated by the flexible bend, the patient inserts the nostril piece into a nostril and the mouthpiece into their mouth. They then blow into the mouthpiece and thereafter completely release the finger pressure on the tube (see figure 4). The blow of the patient will close the airway passage between the nasal and oral cavities, and then disperse the powder dose and transport it via the nostril piece to the nasal mucosa.

### ACCOMMODATING SENSITIVE POWDERS AND SPECIAL APPLICATIONS

Special therapeutic applications require delivery of two nasal doses – one to each nostril. Two

DirectHaler Nasal devices can be “clicked” together to constitute such a compact bi-dose. Further, we have developed additional types of device caps to accommodate bi-dose requests, and APIs/formulations which have variable sensitivities to moisture, light, temperature and mechanical impact.

Examples of such new cap types are shown in figure 5, along with the original cap. Such new caps enable bi-dose storage and dose encapsulation, along with customised device appearance – both designed for optimal ease of use.

Type 1 (left side): the powder dose is sealed inside the cap with a foil strip, which is easily torn off for dose loading to the PowderWhirl chamber, before removing the cap and delivering the dose.

Type 2 (centre): the isolated dose inside the cap is loaded by pressing the two cap parts together until a “click” is heard.

### HOW CAN THE DEVICE APPEAR SO STRAIGHTFORWARD?

The high degree of function-integration in only two device components (with a total weight of 0.6 g) has been achieved by an R&D philosophy focusing on identifying the essential device functionality requirements, and on sophisticated engineering.

The analysis of previous nasal delivery device concepts shows that these possess a range of mechanisms which make the devices complicated to use and/or expensive to manufacture. As a new and innovative device concept, the DirectHaler Nasal device eliminates the need for a number of the common device mechanisms. This has allowed us to focus on new principles for nasal delivery.

Figure 6 shows our identification of the most essential functional elements for a powder based

nasal device technology. Moving from left to right, the diagram progresses from overall aims to detailed functional elements.

### UNIQUE MANUFACTURABILITY

DirectHaler Nasal is extremely straightforward and cost effective to manufacture, fill and assemble using high-speed standard mass production technology. The device tube is manufactured using extrusion and roll forming and the device cap by injection moulding.

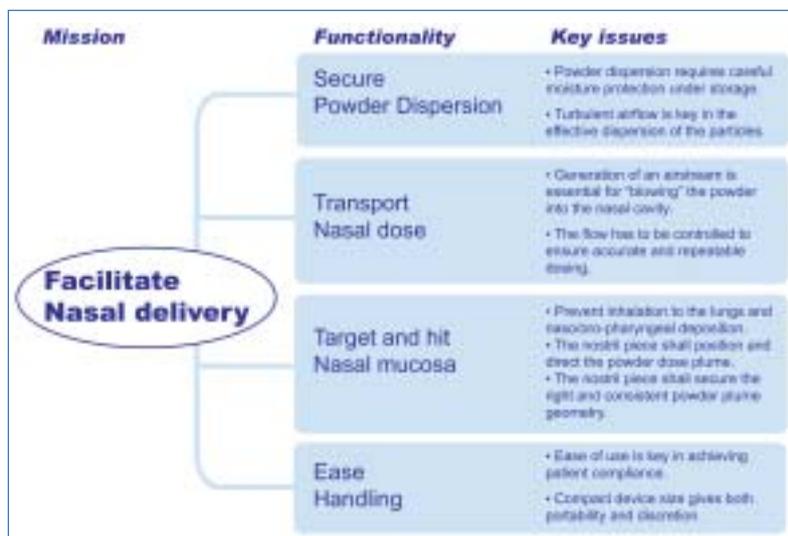


Figure 6: Defining the key device functionality for facilitating nasal delivery.



Figure 7: Equipment for integrated filling and assembly of DirectHaler Nasal.



Figure 8: Combining an oral dose with DirectHaler Nasal.

The device's initial design was partly inspired by the design of a standard drug capsule. Thus, powder-dose filling is carried out using modified high-speed capsule filling equipment supplied by MG2 (see figure 7), ensuring high-precision pre-metered doses.

The overall extremely straightforward DirectHaler manufacturing process – rare in the inhaler market – adds flexibility when it comes to choosing a device supply strategy.

One option for DirectHaler technology licensees is to select local suppliers for manufacturing the device components, and keep in-house complete filling and packing lines. Such lines could be placed locally for regional supply of the finished product. Another option is for pharmaceutical companies to take advantage of the straightforward and efficient production process, which allows them to manage device manufacture, filling and packing in house, without the usual contract manufacture and filling link in the supply chain.

### BUILDING FURTHER ON THE ADVANTAGES OF NASAL DELIVERY...

The manufacturing simplicity and compactness of the DirectHaler Nasal opens new opportunities to address future needs for combination therapy. The DirectHaler device can be considered as the basic building block in any combination therapy or dosing sequencing involving nasal delivery. This means that the DirectHaler device could be the nasal component in a com-

ination therapy consisting of, for instance: one nasal dose + one oral dose in the same blister pack (see figure 8).

Such innovative combination therapy options for the use of two delivery routes at the same time would enable design of delivery systems for achieving for example:

- Local action (nasal) + systemic action (oral)
- Rapid onset of action (nasal) + delayed and sustained release (oral)

### ... AND TARGETING THE COMPLETE RESPIRATORY SYSTEM

The building block characteristic of DirectHaler Nasal can be exploited further, as this characteristic is shared with our pulmonary device technology, DirectHaler Pulmonary.

Dosing to the complete respiratory system has previously only been possible by special nebulizers with facemasks, and limited portability. Such highly specialised equipment is expensive, complicated, and mainly suitable for stationary use.

The DirectHaler technologies do away with these limitations, and open a completely new option for drug delivery to the whole respiratory system with dry-powder formulations. DirectHaler Pulmonary and DirectHaler Nasal are the first unit-dose devices that can be clicked together as one device (see figure 9), enabling specific dosing to the nasal and pulmonary airways, and thereby targeting the complete airway system. Such targeting can be highly relevant in treatment of respiratory diseases, and in prevention/treatment of respiratory infections (also in relation to biodefence).

The two devices are packed together but applied separately, allowing separate formulation technologies for reaching the nasal airways and the pulmonary airways. This is important, as nasal delivery and pulmonary delivery each have specific optimal powder formulation characteristics.

## CONCLUSION

The DirectHaler Nasal technology offers advanced nasal delivery characteristics, in a straightforward, patent protected and cost-effective device embodiment. The DirectHaler Nasal device not only removes the disadvantages of currently available nasal delivery technologies, but it enables new therapeutic approaches exploiting the nasal route of administration to be pursued.

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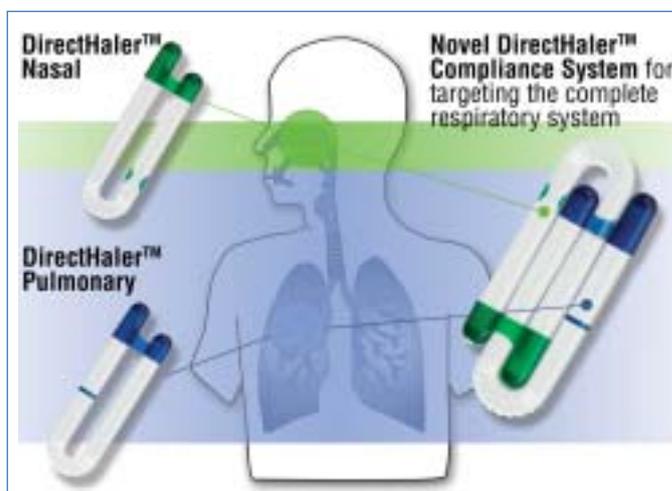


Figure 9: DirectHaler CombinationUnit for pulmonary and nasal delivery.



# N A S T E C H

PHARMACEUTICAL COMPANY INC.

## PHARMACOKINETIC ATTRIBUTES OF INTRANASAL DELIVERY: CASE STUDIES AND NEW OPPORTUNITIES

Intranasal drug delivery represents a non-invasive route with the potential (particularly for large molecule drugs) to improve convenience, patient comfort, compliance and hence the overall efficacy of pharmacological interventions. Here, Henry R Costantino, PhD, Director, Formulations; Paul H Johnson, PhD, Senior Vice President, Research & Development and Chief Scientific Officer; and Anthony P Sileno, MS, Senior Director, Clinical Affairs & Toxicology (all of Nastech Pharmaceutical Company) present a series of case studies illustrating these attributes. The technologies they describe demonstrate the versatility of IN drug administration, ranging from straightforward formulations of small molecules, to advanced formulations that leverage the ability to modulate epithelial tight junctions and enable delivery of peptides and proteins.

Intranasal (IN) delivery is suitable for the local and systemic delivery of diverse therapeutic compounds.<sup>1-2</sup> Attributes of this approach include a large surface area for introduction of drug to the bloodstream, rapid onset of therapeutic drug levels, potential for direct-to-central nervous system delivery, no first-pass metabolism, and non-invasiveness to maximise patient comfort and compliance. Although the nasal mucosa poses a permeation barrier to high-molecular-weight therapeutics such as peptides and proteins, the tight junctions that form this barrier to paracellular drug delivery can be reversibly and safely opened.<sup>3</sup> Owing to these and other factors, marketed IN formulations exist for a variety of low- and high-molecular-weight drugs (for example, peptides), and additional products are under development. Examples of intranasal formulations Nastech has developed are presented in figure 1.

The following series of case studies describe a range of IN formulations, from simple small molecules that are established, marketed products, to developmental tight junction-modulating formulations of peptides and proteins. Through this series of case studies, various attributes of intranasal administration are demonstrated.

### CASE STUDY: BUTORPHANOL

Butorphanol tartrate is an analgesic possessing mixed agonist-antagonist activity at opiate recep-

tors. Its therapeutic uses include management of pain when the use of an opioid analgesic is appropriate. Butorphanol is extensively metabolised upon first pass through the gastro-intestinal (GI) tract and as a result has very poor oral bioavailability (5-17%). The intravenous (IV) and intramuscular (IM) routes provide improved bioavailability and rapid drug onset but at the cost of invasiveness, pain and inconvenience. IN butorphanol offers a convenient alternative to IV and IM delivery and has been successfully developed commercially (marketed as STADOL NS®).<sup>4</sup>

Representative human pharmacokinetic data generated by Nastech comparing IM and IN butorphanol tartrate are depicted in figure 2. As can be seen, IN delivery can achieve similar or greater drug levels in the blood (at the same dose) and is as fast or faster compared with IM dosing. Rapid drug onset is a key attribute for many pain management applications. It is important to note that human clinical testing demonstrated that rhinitis conditions did not significantly impact intranasal pharmacokinetics.<sup>4</sup>

### CASE STUDY: GALANTAMINE

Dementia affects approximately 5% of people over 65 years of age, primarily due to Alzheimer's disease. Currently, the first-line treatments for Alzheimer's disease symptoms are acetylcholinesterase inhibitors such as galantamine.



Henry R Costantino, PhD  
Director, Formulations



Anthony P Sileno, MS  
Senior Director, Clinical Affairs  
& Toxicology



Paul H Johnson, PhD  
Senior Vice President, Research &  
Development and Chief Scientific Officer

Contact: Ms Crystal Whitehead,  
Marketing Associate  
T: +1 425 908 3600  
F: +1 425 908 3653  
E: cwhitehead@nastech.com

Nastech Pharmaceutical  
Company Inc  
3540, Monte Villa Parkway, Bothell  
WA 98021  
USA

[www.nastech.com](http://www.nastech.com)

Drug Form	MW (Da)	Comments
butorphanol tartrate	478	Marketed as STADOL NS <sup>®</sup>
cyanocobalamin gel	1355	Marketed as NASCOBAL <sup>®</sup>
cyanocobalamin spray		FDA Approved
scopolamine hydrobromide	384	For an example human clinical testing reference, see Admed <i>et al</i> <sup>6</sup>
galantamine	368	For an example human clinical testing reference, see Leonard <i>et al</i> <sup>9</sup>
apomorphine hydrochloride	304	For an example human clinical testing reference, see Brandt <i>et al</i> <sup>7</sup>
morphine gluconate	433	Phase II clinical trials
salmon calcitonin	3432	ANDA filing accepted
human parathyroid hormone 1-34	4118	Phase I clinical trials
human peptide YY 3-36	4050	Phase I clinical trials
human interferon-beta	22.5k	For an example human clinical testing reference, see Vitkun <i>et al</i> <sup>8</sup>
undisclosed macromolecules	~1-50k	Various feasibility stages, preclinical testing

**Figure 1. Examples of various Nastech IN formulations**

Similar to other orally delivered acetylcholinesterase inhibitors, galantamine has a clinically significant level of mechanism-based GI side effects including nausea and vomiting. Thus, it was of interest to explore IN galantamine and evaluate the potential for reducing such undesirable effects.

Nastech has previously reported on the feasibility of IN galantamine.<sup>9</sup> A key challenge was increasing drug solubility in order to deliver a therapeutically relevant dose given the limitations of IN dose volume. A more than 12-fold improvement in solubility was successfully achieved by exchanging drug salt form. Having established the feasibility of an IN formulation, the pharmacokinetics and emetic responses were evaluated in an animal model.<sup>10</sup>

A much more rapid drug onset was observed for IN administration ( $T_{max} = 5$  min) compared with oral dosing ( $T_{max} = 240$  min). The emetic response data depicted in figure 3 confirms that IN delivery can reduce the GI and related side effects associated with oral administration.

### CASE STUDY: SCOPOLAMINE

Scopolamine, an antimuscarinic agent used for the treatment of motion sickness, is another good candidate for IN delivery. This compound has very low oral bioavailability due to an extensive first-pass metabolism. Transdermal delivery provides an option, but this route results in a very slow drug onset, while rapid onset has obvious benefits for the treatment of motion sickness. Furthermore, unnecessarily prolonged drug levels

result in a significant side-effect profile including dry mouth, drowsiness and blurred vision.

In a previous publication, Nastech researchers reported on the clinical pharmacokinetic and side-effect profile of various IN scopolamine formulations.<sup>6</sup> IN scopolamine, compared with transdermal dosing, exhibited a more rapid onset. Although a variety of side effects have been reported for transdermal scopolamine, no significant adverse effects were observed for the various IN formulations tested.

### CASE STUDY: APOMORPHINE

Apomorphine is a dopamine receptor agonist with high affinity for D1 and D2 receptor subtypes in sites within the brain known to be involved in the mediation of erection. The compound is currently approved for several indications and uses including: as a diagnostic aid in predicting a patient's responsiveness to levodopa for treating early-morning motor dysfunction in late-stage Parkinson's disease and "off" episodes; and as an emetic in acute oral poisoning and drug overdoses.

Various *in vivo* studies have shown that the erection

tile effects of apomorphine are mediated at dopamine receptors in various nuclei of the hypothalamus and midbrain.

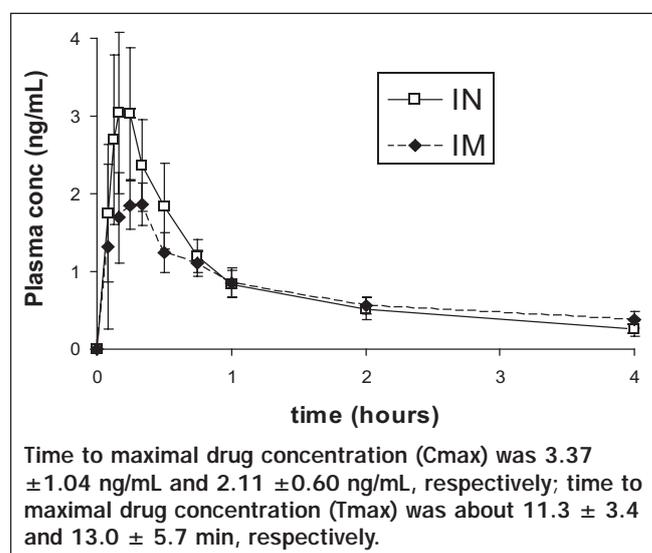
When administered intranasally, apomorphine hydrochloride is absorbed as rapidly as the subcutaneously injected preparation. Compared with sublingual preparation, IN delivery resulted in increased absorption. Indeed, the bioavailability of sublingual apomorphine was only 56% that of IN apomorphine.

Nastech has investigated the uptake of IN apomorphine into human cerebrospinal fluid (CSF) as compared with sublingual dosing. The data revealed an approximately five-fold increase in the ratio of apomorphine levels in the CSF to plasma (see figure 4).

Interestingly, we have observed that the rates of significant adverse events were reduced dramatically after changing the route of administration to IN even though the systemic drug exposure was similar. For sublingual apomorphine delivery, the rates of nausea and vomiting observed are about 18-22% and 1-4%, respectively. In contrast, following IN delivery of a dose corresponding to about the same AUC as the sublingual dose, the incidence of nausea (3%) was nearly an order of magnitude less compared with sublingual delivery and there were no incidences of vomiting.

### CASE STUDY: MORPHINE GLUCONATE

Nastech has developed an IN formulation of the opioid, morphine, as a gluconate salt.<sup>11</sup> Similarly to butorphanol and scopolamine discussed above, morphine has relatively low oral bioavailability due to extensive first-pass metabolism. For this reason, IN delivery is a highly attractive dosing route. The additional benefit of IN delivery described previously –



**Figure 2. PK for IN versus IM butorphanol tartrate (1.0mg dose) in humans**

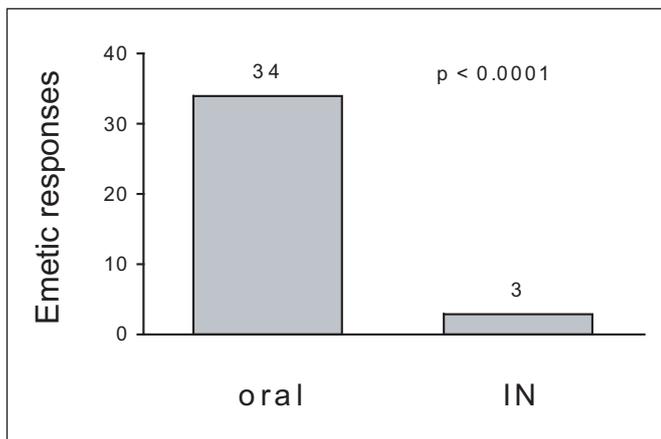


Figure 3. Emetic response for oral versus IN galantamine (Source: Leonard *et al*<sup>10</sup>)

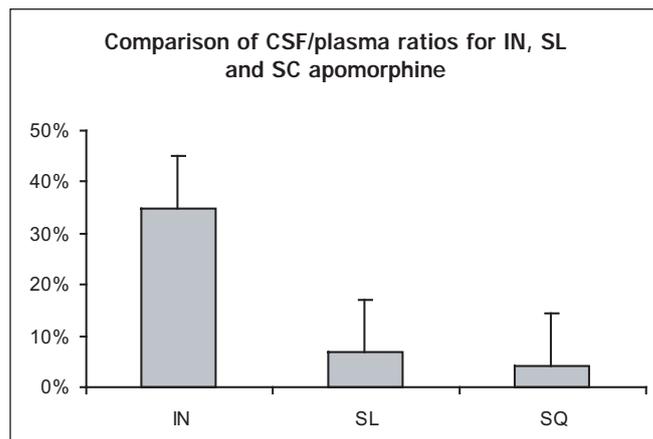


Figure 4. Human clinical testing of IN apomorphine. Sublingual and subcutaneous dosing in 12 subjects

relieving pain as rapidly as the injected product – serves only to add to its appeal.

The patented gluconate salt enables a therapeutic level of morphine to be delivered to opioid-tolerant patients in volumes associated with nasal delivery. Figure 5 illustrates the pharmacokinetics of the IN formulation compared with the traditional IM and oral routes. The data show that IN dosing achieves a similarly fast drug onset ( $T_{max}$  = 15 minutes) compared with IM dosing, and is much faster than oral dosing ( $T_{max}$  = 50 minutes).

As is the case with butorphanol, speed of onset for morphine is a highly desired attribute, particularly for the treatment of breakthrough pain in cancer where rapid onset of meaningful pain relief is critical. IN morphine has achieved such meaningful pain relief in 2.2 minutes (data not shown).

### PROTEIN/PEPTIDE DELIVERY VIA TIGHT JUNCTION-MODULATING EXCIPIENTS

Recent trends in drug discovery methods and the continuing emergence of biotechnology

products, have meant that IN delivery of peptides and proteins is becoming an ever more attractive therapeutic option, receiving increased attention from the industry.

Such macromolecules have extremely poor bioavailability due to enzymatic digestion in the GI tract. Therefore, delivery by injection is the predominant route for commercial applications. Even so, some peptide products have successfully reached the market as IN formulations, albeit as simple formulations with relatively low bioavailability due to the permeation barrier presented by the nasal mucosa.

In order to improve IN delivery of macromolecules and expand the possibilities for future development, Nastech has devised strategies to increase permeability of the nasal mucosa safely and reversibly.

Specifically, we have focused on transient modulation of the nasal (and other) epithelial tight junctions, allowing for their safe and reversible opening and to improve paracellular transport. A variety of compounds, from small-

molecule permeation enhancers to tight junction-modulator (TJM) peptides<sup>3</sup>, illustrate beneficial effects.

Figure 6 depicts a specific example of improved IN absorption of a peptide by comparing plasma levels when using small molecule versus peptide tight junction-modulating excipients. The data show a dramatic improvement in bioavailability (50- to 70-fold improvement in  $C_{max}$  and AUC) of the therapeutic peptide when dosed with 50  $\mu$ M of a TJM peptide. Notably, the effect was superior even when a much higher concentration (39.2 mM) of low-molecular-weight permeation enhancers was used. These data demonstrate the promise of developing such potent TJM peptides for enhancing IN delivery of macromolecules.

### CONCLUSIONS

For many drugs, intranasal administration offers an effective alternative both to oral delivery, with its associated problems with poor bioavail-

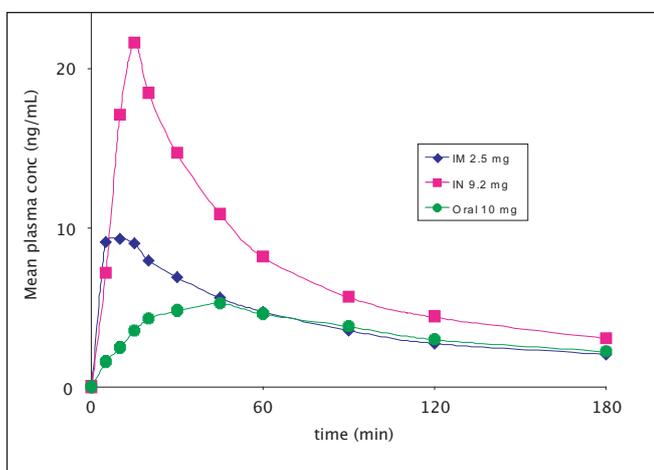


Figure 5. Clinical testing of IN morphine gluconate compared with traditional IM and oral products. AUClast ng/mL.min: IM = 765; IN = 1359; oral = 747

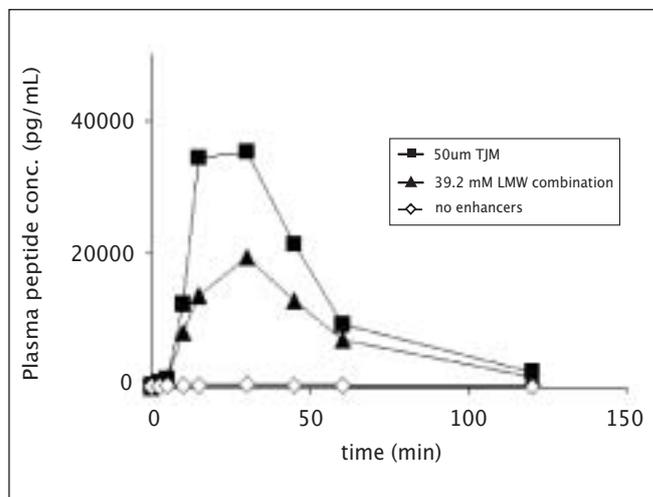


Figure 6. IN dosing of a therapeutic peptide (rabbit pharmacokinetic data) (Source: Chen *et al*<sup>12</sup>)

ability, and invasive injections. This article has illustrated how IN delivery may be preferred for various applications.

Currently, an active area of development at Nastech is to optimise IN delivery of peptides and proteins by modulation of epithelial tight junctions. Nastech employs a rational, molecular biology-based approach to this end, which includes the use of relevant and predictive *in vitro* models to identify optimal combinations of existing and/or novel excipients. Nastech uses its Tight Junction Modulator technology to isolate and develop mechanism-based compounds or excipients that can effect reversible responses in tight junctions.

These technologies are the foundation of Nastech's drug delivery platform. The results as demonstrated here, and in ongoing clinical and research projects, are safe and effective drug formulations. Nastech believes this work will significantly advance the development of non-invasive large-molecule products that do not require injection, and may further mitigate other undesirable consequences of traditional pharmaceutical modalities. Progress to date suggests that IN delivery can continue to expand and become an increasingly important delivery route.

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# CONTROLLED PARTICLE DISPERSION™:

## EFFECTIVE NASAL DELIVERY FROM A VERSATILE, FLEXIBLE TECHNOLOGY PLATFORM

Today's nasal delivery technology – the spray pump – has been the status quo for over 25 years. Despite the fact that up to 90% of the drug ends up in the stomach, somehow spray pumps became accepted as nasal drug delivery devices. Increasing demands for targeted deposition, less peripheral delivery, fewer side effects, compliance monitoring and dose counting, render spray bottle technology ever more inadequate. Clearly, says Marc Giroux, Chief Executive Officer of Kurve Technology, the pharmaceutical industry needs a comprehensive, versatile technology platform that addresses the inevitable paradigm shifts coming in nasal drug delivery.

### INTRODUCING CONTROLLED PARTICLE DISPERSION™

Controlled Particle Dispersion (CPD) is a technology platform that pharmaceutical companies can use to deliver most compounds regardless of characteristics or target conditions. Whether the applications are systemic or topical, solutions or suspensions, CPD meets the demands of today and tomorrow's full nasal delivery product line. CPD offers a vast improvement in efficacy and performance while presenting design flexibility for maximum compliance.

Building a more efficient nasal drug delivery device requires not only better device design but a far more versatile technology platform; one that delivers optimal nasal deposition, with formulation flexibility to work successfully with the many variables of the formulation itself.

Rather than build a single device, Kurve Technology developed CPD – a comprehensive nasal drug delivery technology platform. Using new principals such as vortical flow, CPD effectively disrupts inherent nasal cavity airflows to deliver compounds to the entire nasal cavity, the olfactory region and the paranasal sinuses. CPD optimises droplet size and trajectory to saturate the nasal cavity, lengthens compound residence time, and minimises deposition to the lungs and stomach. This leads to more effective and efficient treatments than delivery via traditional

nasal spray bottles that deliver compounds only as far as the anterior portion of the nasal cavity.

#### CPD's adjustable variables include:

- droplet size variability from 3 to 50  $\mu\text{m}$
- atomisation rate
- delivery of solutions, suspensions and dry powder
- small and large molecules
- proteins and peptides
- preservative-free, unit-dose ampoules
- targeted deposition including to the paranasal sinuses and the olfactory region
- variable medication volumes in the device and in the nasal cavity
- wide viscosity range
- vortex characteristic variability
- electronics and power (compliance monitoring, dose counters, etc)

CPD powers ViaNase™ – Kurve Technology's electronic atomiser (see figure 1). Understanding the flexibility of these parameters as it pertains to ViaNase is key to appreciating the versatility of CPD.

#### DROPLET SIZE VARIABILITY

As a nasal drug delivery company, Kurve's goal is to get close to 100% of the drug into the nasal cavity and onto the nasal mucosa. To accom-



Figure 1: The ViaNase™ electronic atomizer



Marc Giroux  
Chief Executive Officer

T: +1 425 640 9249  
E: info@kurvetech.com

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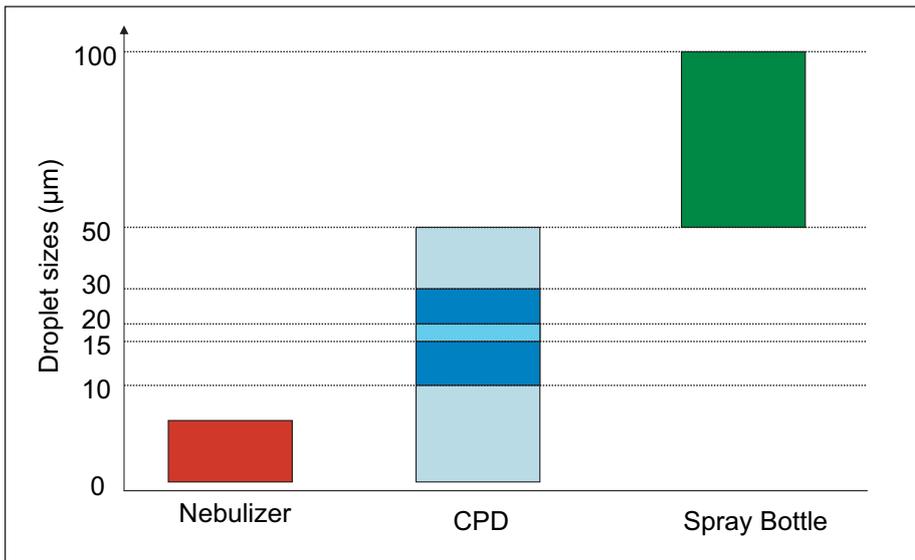


Figure 2: Droplet size comparison (CPD, nebulizers, and spray bottles)

plish this, ViaNase delivers droplets  $\geq 8 \mu\text{m}$  in order to avoid pulmonary deposition. In fact, ViaNase is capable of generating narrow droplet distributions from 3-50  $\mu\text{m}$ . However, for optimal nasal drug delivery device, Kurve uses a size range between 10 and 30  $\mu\text{m}$ .

The upper limit of 30  $\mu\text{m}$  was determined because larger droplets are more difficult to control in vortical flow and deposition is reduced. CPD's ability to generate a range of droplets in tight distribution curves allows for small incremental changes in the mass median aerodynamic diameter (MMAD), so slight adjustments can be made to optimise performance of a particular formulation.

In early tests, droplet sizes of 15-20  $\mu\text{m}$  consistently performed well across many com-

pounds. CPD produces a droplet distribution curve with droplets at a Dv10 of 9  $\mu\text{m}$ , a Dv50 of 19  $\mu\text{m}$  and a Dv90 of 29  $\mu\text{m}$ . This distribution not only leaves all of the droplets within a controllable range, but virtually eliminates peripheral deposition in the stomach and lungs.

Figure 2 compares droplet sizes from CPD, nebulizers, and spray bottles.

### ATOMISATION RATE

CPD can control the rate at which the droplets are created and how quickly they will exit the device. Kurve designed its unique droplet generator for short treatment times – a characteristic necessary to improve compliance in patients frequently using the device.

While a typical atomisation rate would be 1 ml/min, the droplet generator can achieve a volume rate of over 4 ml/min. This offers increased output capacity should a formulation warrant a larger volume to be delivered in a short treatment time. The rate at which the device generates droplets does not affect the droplet size to any measurable degree.

### SOLUTIONS, SUSPENSIONS AND DRY POWDER

CPD can effectively deliver solutions and suspensions, and conceptual designs and development are already underway for dry-powder delivery. Of the current technologies available, none are capable of delivering all three formulation types. All the principles of CPD will be applied to dry powder delivery.

### SMALL AND LARGE MOLECULES, PROTEINS AND PEPTIDES

CPD can deliver more than small molecules. A potential pharmaceutical partner independently tested ViaNase with one small molecule and two large peptides (>20 amino acids). In each instance the droplets exiting the machine were 98% pure. In addition, Kurve also tested salmon calcitonin exiting the device and found minimal degradation. It is well known that salmon calcitonin is fairly durable, but one of the peptides tested was more fragile and it fared as well as the others. While ViaNase's droplet generator is fast, it is not overly harsh on compounds.

### VISCOSITY

Viscosity of a formulation is not a limiting factor with CPD. Viscosities ranging from 1 to 30 centipoise were tested with no significant change in droplet size (see figure 3). The atomisation rate changed slightly, but droplet sizes remained consistent.

### PRESERVATIVE-FREE PACKAGING

The pharmaceutical industry is shifting away from preservatives given the inherent difficulties with side effects and production. Kurve designed ViaNase to use form, fill and seal unit-dose ampoules. Filled sterile and used within minutes of opening, unit-dose ampoules are the least expensive packaging for formulations. Ampoules eliminate the need for costly preservatives and minimise preservative-induced side effects.

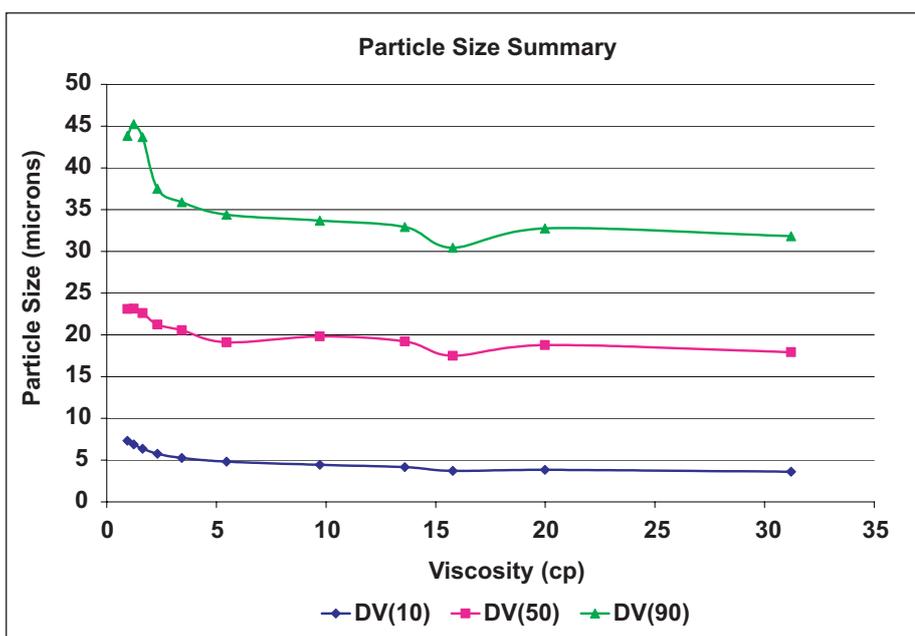


Figure 3. Droplet size versus formulation viscosity at three points along the volume diameter distribution curve

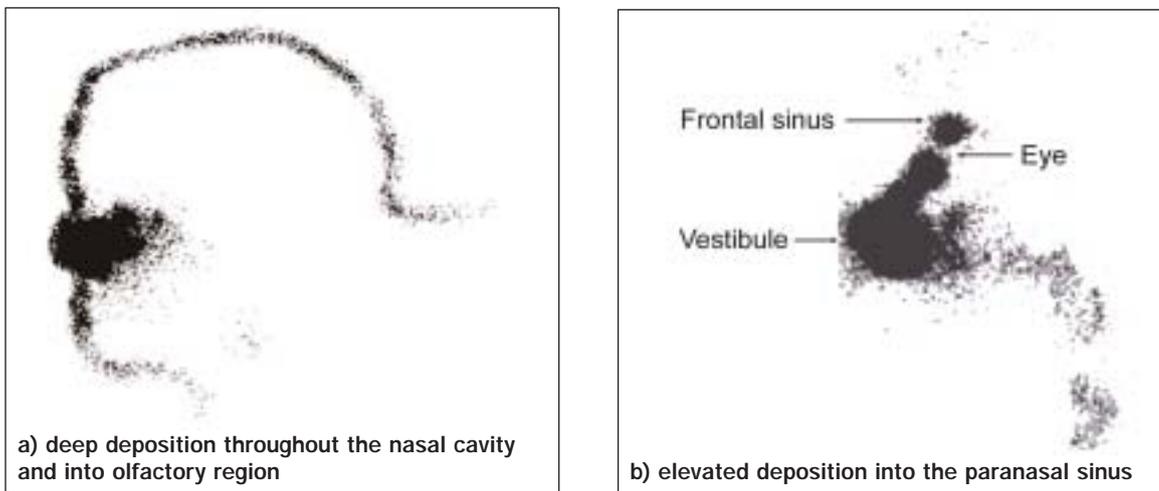


Figure 4: Scintigraphy studies showing CPD's ability to target deposition in different areas of the nasal cavity

## TARGETED DEPOSITION

Published scintigraphy studies show CPD's capability to reach the paranasal sinuses<sup>1</sup> and the olfactory region<sup>2</sup>. Kurve found that manipulating CPD's many available parameters resulted in significantly different deposition patterns (see figures 4a & 4b). While testing continues in vivo, a large test result database allows adjustment of parameters to optimise deposition regions for any compound.

## VOLUME

Delivering greater medication volumes to the nasal cavity often provides an added therapeutic effect. Unlike current methods, CPD allows the formulator to deliver these larger volumes. This is particularly important for relatively insoluble compounds

ViaNase's droplet generator requires only minimal space in the device housing. This allows a large volume in the chamber itself. As much as 5-6 ml is possible in the existing device while even more volume is possible with a slight retrofit.

## VORTEX CHARACTERISTICS

CPD induces a vortical flow on the droplets as they exit the device. The induced vortical flow characteristics can be altered in circular velocity and direction to achieve different droplet trajectories. Variations can be added to the vortical flow characteristics involving rate of spin, series of vortices and combinations of vortices. Deposition differences are noticeable with vortex variation and testing is ongoing.

## THE FUTURE – ELECTRONICS AND POWER

With the US FDA advocating dose counting and compliance monitoring, new methods of nasal drug delivery are a must for the device industry. Physician monitoring and web-based downloads also are under discussion. With built-in electronics and power, the ViaNase device offers these functions upon request.

## CONCLUSION

From its inception, CPD was designed as a technology platform. With its many controllable parameters, CPD offers pharmaceutical partners a nasal drug delivery device that meets industry needs – today and tomorrow.

Although used for 25 years, the spray pump, was never a viable system. When 90 percent of the drug delivered is swallowed, nasal drug delivery is at best, a misnomer. Spray pumps in fact use the nose as an alternative route to the stomach. Most of the devices available today are simply variations on this single theme – and most of the compound still ends up in a region other than the nasal cavity.

Based on the CPD technology platform, ViaNase is a truly viable nasal drug delivery device, demonstrating that the key to effective nasal drug delivery is a flexible technology platform upon which a product line can be built and expanded. After 25 years of falling far short of the intended target – saturation of the entire nasal cavity – the future of nasal drug delivery brings change. This much needed paradigm shift is Controlled Particle Dispersion.

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## NASAL DELIVERY OF ANALGESICS

A number of high-profile drugs important to the management of pain have received negative press in the past few months, from the withdrawal of COX-2 inhibitors to the withdrawal of Palladone. The unfortunate demise of these agents has left a short-term void in the marketplace. Overlooked in this spate of bad publicity, though, is the crucial long-term story that the pain market will experience significant, sustained growth due to the current under-treatment of acute, chronic and cancer-related pain and the need to close these gaps. In this article, Michael Sheckler, MBA, Vice-President, Business Development; Fred Mermelstein, PhD, President; Douglas Hamilton, BSc, MBA, Chief Operating Officer and Chief Financial Officer; and Daniel Carr, MD, Chief Executive Officer and Chief Medical Officer, all of Javelin Pharmaceuticals (formerly Innovative Drug Delivery Systems), describe the important place that intranasal analgesics have in this growing market.

Valued at nearly US\$21 billion in 2004, the entry of new drugs for the treatment of neuropathic pain, acute and breakthrough cancer pain, and postoperative pain, will grow the pain management market to US\$30 billion by 2008, says Navigant Consulting. Like the pain management market, nasal drug delivery is also projected to grow significantly over the next few years. Greystone Associates is forecasting 24% annualised growth from 2004 to 2007, which will increase the value of the nasal drug delivery market from slightly less than US\$2 billion to US\$4.3 billion. More specifically, the global 2007 forecast for analgesics delivered nasally is US\$535 million, up from US\$110 million in 2003.

A number of small, innovative companies are now addressing the unmet need for nasal analgesics. In the July 2005 update of BioPharm Insight (Infinata), 16 INDs were cited for nasally delivered pain drugs. This activity speaks to the attractiveness of the nasal delivery of analgesics. With ease of administration, rapid absorption and onset of action, generally low dose requirements, and safety, it is easy to understand why so much attention is being paid to this route of administration.

Two nasally delivered analgesics are the focus of this article – morphine and ketamine. Morphine remains the gold standard of opioids and is often considered the prototype  $\mu$ -agonist. With its good safety profile, widespread usage and historical record of efficacy, it is highly unlikely that it will ever be withdrawn from the market. It has been used extensively in the management of both acute and chronic pain. Ketamine, a non-opioid, is an

N-methyl D-aspartate, or NMDA, receptor antagonist that has been in clinical use as a general anesthetic for the past 30 years. It has been administered to tens of thousands of patients and has an established safety record.

### INTRANASAL MORPHINE

With a successful track record as an intramuscularly (IM) and intravenously (IV) delivered drug (oral preparations are available, but have a slow onset of pain relief and variable bioavailability), why do we need or want a nasal form of morphine?

As can be seen in figure 1, there are several advantages to intranasal morphine, perhaps the most significant of which is getting rid of the requirement for a needle and syringe.

Of the advantages outlined in figure 1, perhaps the most important is that the pharmacokinetic performance of nasal formulations approaches that of IV administration. After all, IV delivery offers the most rapid absorption and onset of action of all routes of administration. Figure 2 clearly depicts the kinetic superiority of intranasal morphine to oral morphine and its similarity to that of injectable kinetics.

Several other advantages are available to both the patient and healthcare professional. There is patient/staff familiarity with both morphine (as a “gold standard” in pain management) and the nasal route. The duration of action makes it ideal for large target markets, including, orthopaedic, post-operative, procedural and burn pain. There is a low risk of misuse of residual controlled substances, such as the scavenging of residual materi-



Michael T. Sheckler, MBA  
Vice-President, Business Development  
T: +1 212 554 4550  
F: +1 212 554 4554  
E: msheckler@javelinpharmaceuticals.com

Fred Mermelstein, PhD  
President  
E: fmermelstein@javelinpharmaceuticals.com

Douglas A. Hamilton, MBA  
Chief Operating Officer & Chief Financial Officer  
E: dhamilton@javelinpharmaceuticals.com

Daniel Carr, MD  
Chief Executive Officer & Chief Medical Officer  
E: dcarr@javelinpharmaceuticals.com

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Rapid Onset	➔	Onset of action in under 10 min
Immediate release of morphine	➔	<ul style="list-style-type: none"> <li>• 1st order delivery comparable to IV morphine</li> <li>• Easy to calculate equi-analgesic doses to layer on top of baseline medication</li> </ul>
Ease of Administration	➔	Patient controlled dose titration
Bypasses GI metabolism	➔	<ul style="list-style-type: none"> <li>• Fewer GI side-effects</li> <li>• Lower levels of metabolites involved in side-effects (M6G, M3G)</li> </ul>
Desirable Safety Profile	➔	<ul style="list-style-type: none"> <li>• No nasal irritation or deposition on lungs</li> <li>• Can be used in opioid naïve patients</li> </ul>

Figure 1: Intranasal morphine product profile

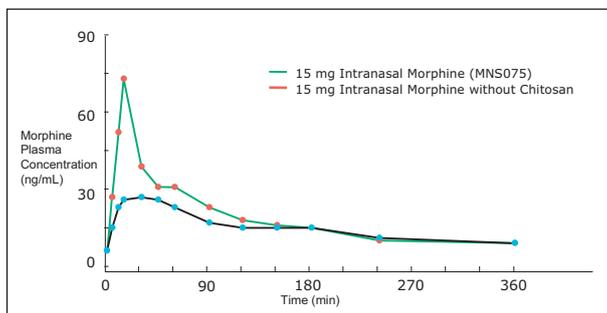


Figure 2: Phase I Trial - Mean plasma concentration curves of 15mg intranasal morphine with and without chitosan

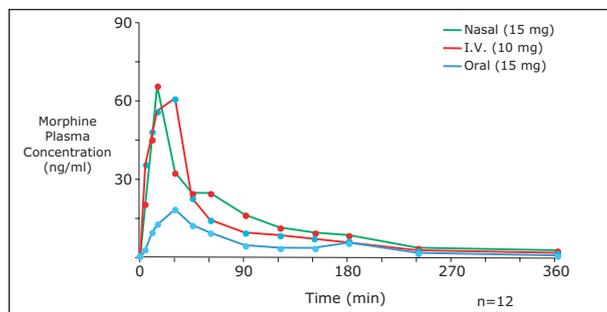


Figure 3: Intranasal morphine - intranasal kinetics similar to injectable kinetics

	Javelin Intranasal morphine	Oral morphine sulphate	I.V. Morphine	Actiq®
Onset of action	<10 min	20-40 min	<10 min	15 min PD <sup>2</sup>
Time until peak efficacy	30 min	60 minutes	30 min	45 min
Ability to titrate	Easy titration	Difficult titration	Easy titration	Difficult titration
Patient ease of use	Easy to use	Easy to use	Requires a nurse	Easy to use
Duration of effect	2 to 2.5 hrs	4 to 6 hrs	4 hrs	4 hrs

<sup>1</sup> Physicians' Desk Reference, 58th edition, 2004  
<sup>2</sup> PD = post dose, on average it takes 15 minutes to consume a single dosage unit

Figure 4: Competitive product comparison<sup>1</sup>

is seen in figure 3, where the greater mean plasma concentration curves of 15 mg intranasal morphine with chitosan is clearly demonstrated.

Given the uniqueness of route of administration and the advantages of intranasal morphine, how does it compare with competitive products? Figure 4 outlines the comparison using the criteria set forth in the product profile found in figure 1.

## INTRANASAL KETAMINE

With the documented success of ketamine as an anaesthetic, one can ask the same question as that for morphine: Why the need for an intranasal form? Low doses (one sixth the dose needed to induce anaesthesia) of intranasal ketamine have been found to be effective in the treatment of moderate-to-severe acute pain. It has a rapid onset of action (4-8 minutes) and its duration (up to 2.5 hours of analgesia) matches the timeframe for breakthrough pain & procedural pain episodes.

Ketamine enjoys a wide margin of safety. It is not physically addictive, does not cause respiratory depression, hypotension or gastro-intestinal or genito-urinary dysfunction and, at lower doses, is not associated with the dissociative side effects such as hallucination or psycho-mimetic effects sometimes associated with higher doses. Like intranasal morphine, it is easily titrated for effective nasal dosing.

Ketamine can be used as an alternative to opioids, yet can be used in combination. In so doing, the compound becomes a valuable tool to healthcare providers, enabling them to minimise opioid side effects, and treat opioid dependent/tolerant patients and patients unable to take opioids.

An additional benefit that can be conferred is that when ketamine is used in a multimodal regimen, post-operative pain and analgesic consumption are both reduced. The US Department of Defense is very interested in intranasal ketamine as an alternative to IM morphine for battlefield analgesia and a variety of severe pain indications such as trauma, burn wound care and procedural pain. It is financially supporting the development of intranasal ketamine.

As an example of the pain relief intranasal ketamine can provide, the following graphs outline the plight of a hypothetical patient with breakthrough cancer pain. Figure 5 shows the several episodes/day of breakthrough pain. Regardless of the reason, it can be seen that the pain overcomes the baseline medicine.

In figure 6, we see that if there is an increase in the opioid regimen, meaning an increase in the controlled release form, it will blanket more of the pain episodes, but will only do so at the expense of opioid side effects, such as constipation, respiratory depression sedation and an overall decrease in the quality of life.

Lastly, in figure 7, we see the introduction of intranasal ketamine. This is the approach that most guidelines recommend where the baseline regimen stays as it was and the physician adds a quick-onset, short-duration medication for those episodes. Baseline opioid consumption is reduced and quality of life improves.

## A CLOSER LOOK AT SAFETY AND RISK MANAGEMENT

At the heart of the delivery of any opioid or non-opioid analgesic is the consideration of safety and risk and how to ensure the former and minimise the latter. In the case of intranasal morphine, the drug's developer has taken numerous steps to accomplish both.

A valuable lesson learned early on in the nasal delivery of potentially addictive drugs was that of the abuse of butorphanol.

Sold in a multidose sprayer (up to 12-13 doses after priming) with no lock-out mechanism, this product was easily abused. Regrettably, it required the death of the child of a high-profile individual to draw attention to the dangers of an abusable drug in a multidose sprayer. While such dosage forms are still available, prescription drugs that are being delivered today are more likely to be found in unit dose sprayers such as that used for Imitrex and Zomig nasal migraine products.

This device is the same one chosen by the developer of intranasal morphine and ketamine. Because it contains only 120µL of drug and the delivered amount is 100µL, there is very little residual to scavenge after actuation.

An intrinsic safety mechanism is the capacity of the nasal passages. Each nostril can hold only 150-200µL of administered drug. It requires approximately 15 minutes for the drug to clear the nasal passages, so attempting to introduce additional drug will result in either the drug being swallowed or dripping out of the nose.

Ketamine, even as a non-opioid and with its wide safety profile, is not immune to abuse and will have to be handled and managed as a controlled substance. However, when one examines trend data from the Drug Abuse Warning Network (DAWN) that reports those drugs associated with emergency department visits, the ketamine-related visits occur at only 1% of the rate of visits related to hydrocodone.

Both intranasal morphine and ketamine have been shown to be non-irritating to the nasal mucosa. Chitosan, the naturally occurring bio-adhesive that improves the mean plasma concentration of intranasal morphine, is also a non-irritant. It would seem that the preferred bio-adhesive would be an agent like chitosan, that is generally recognised as safe, rather than unproven agents

that may cause irreversible damage to the nasal mucosa.

## CONCLUSION

The fields of pain management and nasal drug delivery clearly combine to meet the needs of a growing and underserved marketplace. Helping to drive the growth will be the approval of new nasal products for pain management, a trend toward self-administration, an aging population, managed healthcare initiatives and growth in the home healthcare population.

The convergence of pain management and nasal drug delivery may prove to be very fortuitous to those who are suffering with acute, moderate-to-severe and breakthrough pain. In an era when people are recognising that they can talk with their healthcare provider about their pain rather than simply try to ignore and live with it, nasal delivery of analgesics will offer a non-invasive, fast-acting, efficacious means to relieve that pain.

## FOOTNOTE

Javelin Pharmaceuticals has been awarded government contracts from the US Department of Defense, which are used to subsidise the company's research and development projects.

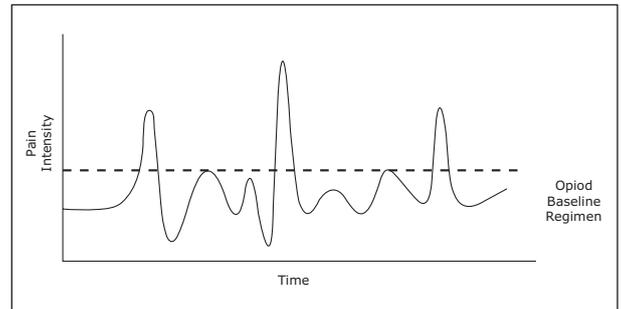


Figure 5: Cancer pain = baseline plus breakthrough episodes

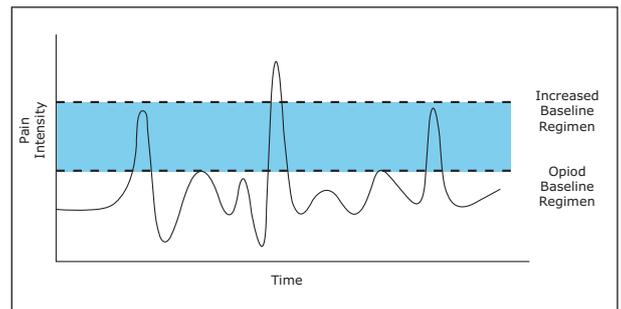


Figure 6: Controlling breakthrough pain episodes by increasing the fixed-dose, baseline opioid regimen increases side effects (sedation, constipation, respiratory depression...) and decreases quality of life

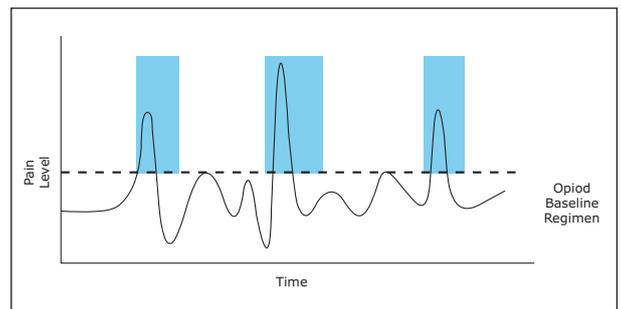


Figure 7: Adding ketamine as needed for breakthrough pain episodes avoids the need to increase the fixed-dose, baseline opioid regimen and improves quality of life.

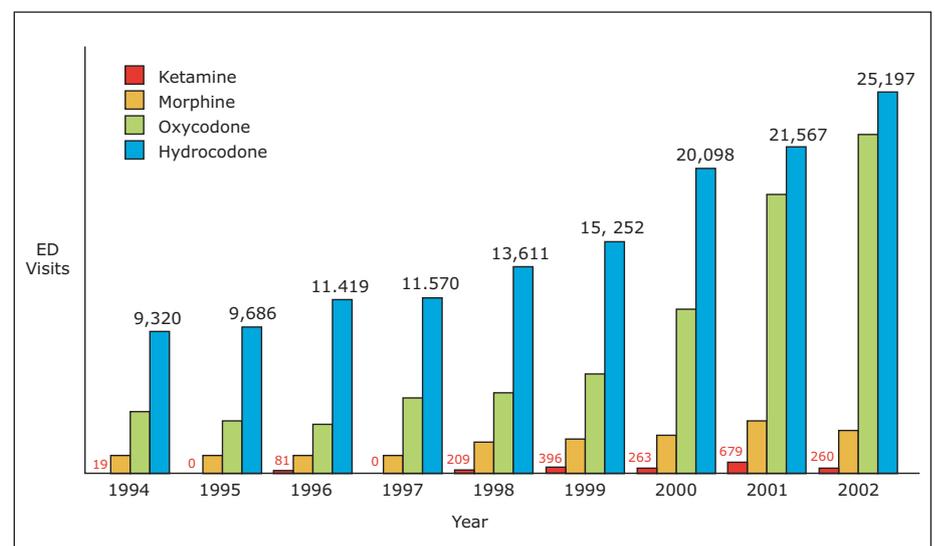


Figure 8: DAWN trends for selected drugs - emergency department visits 1994-2002



# 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-



Per Gisle Djupesland, MD, PhD  
Chief Scientific Officer

T: +47 22958015  
F: +47 22958098  
E: [pgd@optinose.no](mailto:pgd@optinose.no)

OptiNose AS  
Oslo Innovation Center  
Gaustadalleen 21  
0349 Oslo  
Norway

Jon Watts  
Commercial Development Director

T: +44 1793 834 929  
M: +44 7788 414 917  
E: [jw@optinose.com](mailto:jw@optinose.com)

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South Marston Park  
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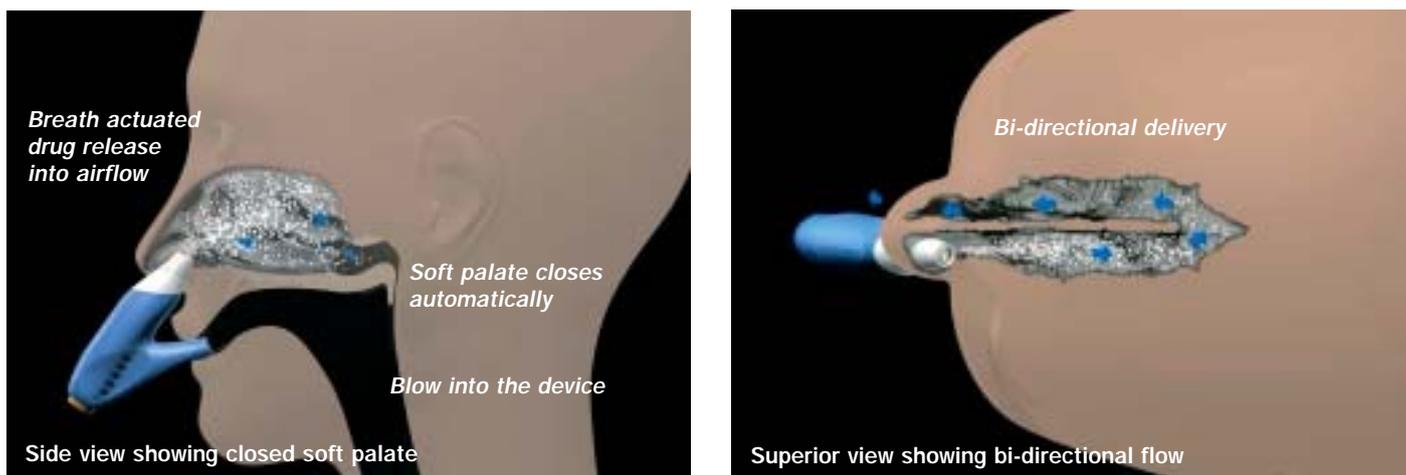


Figure 1: Two interlinked anatomical principles underlying bi-directional drug delivery

dritic 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.<sup>1</sup>

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  $180^\circ$  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  $99\text{mTc}$ -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.<sup>2</sup>

### 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

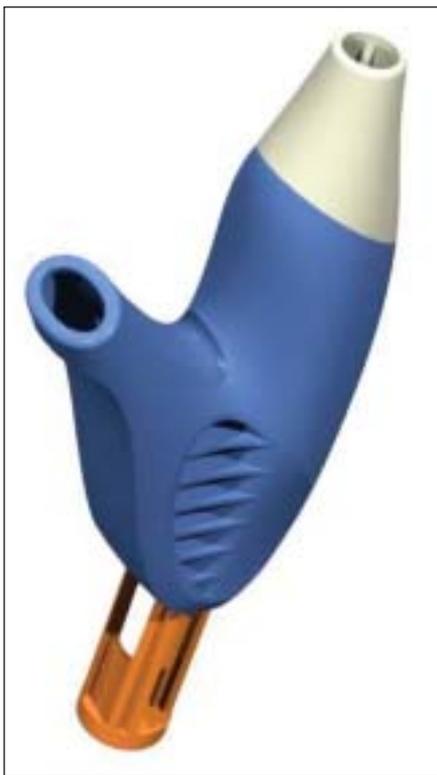


Figure 2: The single-use device

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 nosepiece 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.

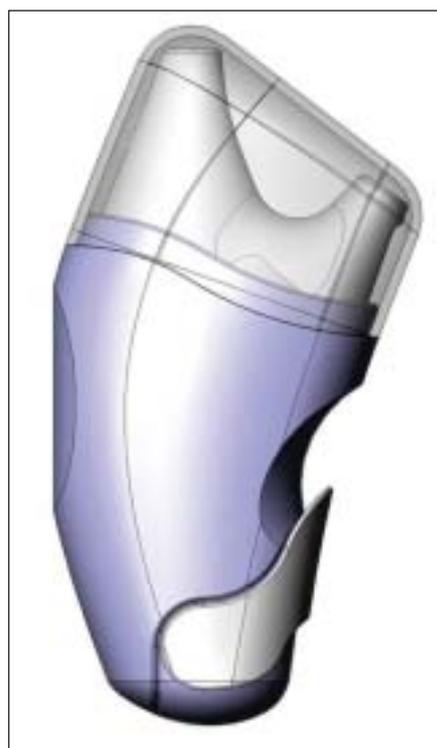
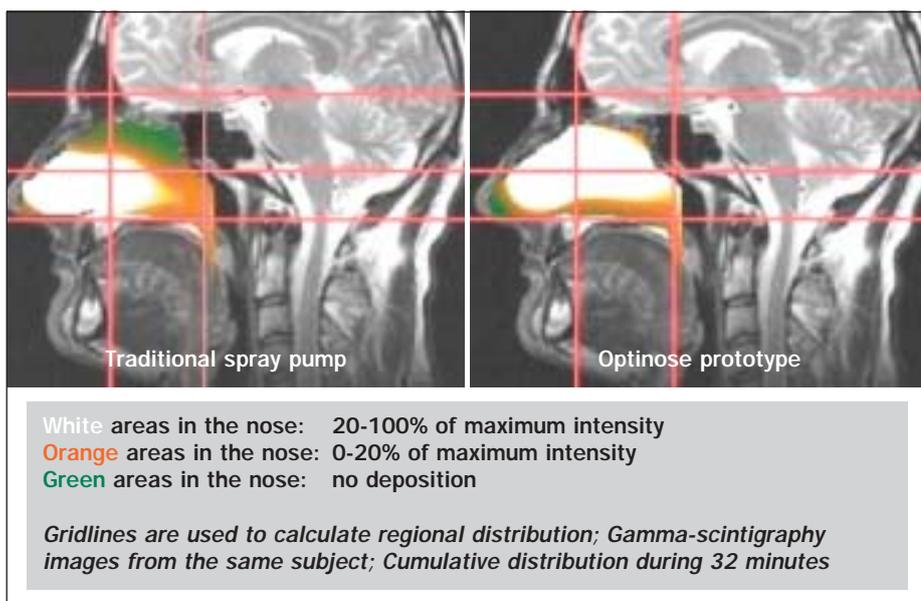


Figure 3: The multi-use liquid reservoir device



**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.”<sup>4</sup>

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 Cmax comparable with the formulation delivered by OptiNose’s device with the same dose.<sup>5</sup>

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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