

Compiled by CINDY H. DUBIN

**NASAL DRUG DELIVERY**



## Nothing to Sneeze At

*Often overlooked and long neglected, the nose has become one of the most viable drug delivery pathways for treating everything from the flu to erectile dysfunction.*

**T**HE PORTAL TO OUR BLOOD SYSTEM IS how nasal drug delivery experts view the nose. With the continuous development of more potent and complex molecules and the imminent expiration of many patents for major brands, novel delivery systems offer opportunities for developmental and marketed compounds alike. Nasal delivery is ideal for potent drugs that are to be delivered in small doses, as low as tens of milligrams.

Although modified oral delivery is the dominant delivery method for potent drugs—comprising nearly half of drug delivery projects in the major pharmaceutical companies—there are many cases when oral delivery is not applicable. For example, many compounds, particularly macromolecules, are not adequately bioavailable when delivered orally or are associated with adverse gastrointestinal effects. Nor is oral medication appropriate if the patient suffers from nausea or vomiting or has difficulty swallowing tablets or capsules, as is often the case with children and the elderly. Additionally, the orally administered drug takes longer to reach the bloodstream than a nasally absorbed drug.

Traditionally, many drugs have been administered intranasally for localized treatment of conditions such as rhinitis and nasal congestion. Pharmacokinetic concerns have caused formulators to overlook nasal delivery. These include true nasal absorption, acute or long-term mucosal irritation and the need for prolonged

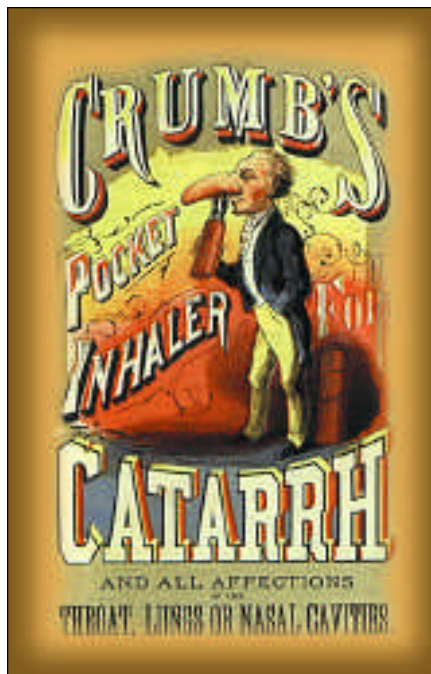
high blood levels. Nasal inflammation and mucosal swelling due to infection, allergies and environmental irritants and physiological changes may affect nasal drug distribution. Studies are needed to clarify how such conditions will influence nasal bioavailability.

However, the nasal cavity provides a large and easily accessible area of highly permeable and vascularized tissue through which drugs can be absorbed rapidly and directly into systemic circulation. By avoiding the gastrointestinal tract and the effects of first-pass metabolism, the nasal route offers the opportunity to administer low-dose medications—from tens to hundreds of milligrams of powder or solution volumes up to 150 mL per nostril. Nasal route administration for certain medications may also offer reduced side effects.

Nasal drug delivery can present a convenient and patient-friendly alternative for drugs that otherwise would require injectable administration. This improves patient compliance, may allow patients to self-medicate and avoids exposing health workers to the risks of needle-stick injuries and biohazardous waste.

Nasal drug delivery offers a quick onset of action, similar to injectables. Relief from chronic pain and migraine headaches can come within minutes.

For these reasons, the exploration of the nasal route for the delivery of drugs to systemic circulation is growing. A number of small and macromolecules,



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administered systemically via the nasal cavity, are now on the market (see Table 1 on page 43).

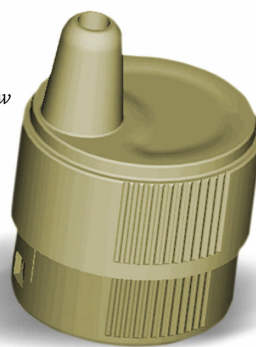
### POWDERS VS. SPRAYS

London-based Britannia Pharmaceuticals is one company developing treatments for nasal delivery, including apomorphine for the treatment of Parkinson's disease and erectile dysfunction. Initial trials show Britannia's proprietary nasal powder formulation yields a bioavailability equal to or greater than what is delivered through injection or other forms of drug delivery, as well as increased speed of onset and low potential for irritation.

Britannia claims the nasal powder is a "rescue drug," providing relief for patients suffering an "off"<sup>2,5</sup> period or episode of immobility. The nasal powder is marketed as a solution for uncomfortable, subcutaneous injection/infusion.

While administration of liquid intranasal apomorphine has been shown to be effective in Parkinson's disease (Dewey et. al., van Laar et. al.)<sup>3</sup> local side-effects—in the form of nasal crusting, inflamma-

Britannia's new six-dose nasal device



tion and infection—have been evident. In addition, apomorphine is subject to rapid oxidation in solution, presenting pharmaceutical challenges in developing such a product. The nasal-powder approach was developed to overcome these problems.

Intranasal products currently available are generally formulated as a liquid, delivered by a metered pump spray. While liquid is effective for many compounds, this formulation approach can be limited by the solubility of the drug in the vehicle, the limited capacity of the nasal cavity to hold liquid without drainage to the throat or from its anterior portion, and stability of the formulation.

The delivery of drugs to the nasal cavity as a powder has clinical and pharmaceutical advantages over liquid administration. The administration of powder ensures

localized distribution of particles on the surface of the mucosa, in contrast to a widespread coating of the nasal cavity that occurs with liquid administration. This provides two benefits: First, the surface area exposed to the formulation is reduced, minimizing potential for irritation. Second, localized delivery presents areas of high drug concentration, facilitating rapid absorption and reducing the residence time in the nose. Therefore, based on the assumption that a powder formulation will be exposed to a lower surface area for a reduced time, it is expected that this formulation will be tolerated better than a liquid formulation. Rapid absorption may also increase bioavailability resulting in the possibility of dosage reduction. Ugwoke<sup>4</sup> demonstrated this by comparing the pharmacokinetics of apomorphine formulations administered intranasally as both powder and liquid, and as a subcutaneous injection. This study showed the powder formulation had a more rapid absorption rate and greater availability than the liquid.

Others, however, believe that one of the major problems with traditional spray pumps in use today is the localized deposition in the anterior one-third of the

### Nasal Insulin Delivers More While scientists have spent years researching alternatives to insulin injections, nasal delivery is still in the early stages of evaluations.

Companies are seeking to develop inhaled insulin, which currently exhibits low absorption and bioavailability.

Scientists and regulators are concerned that flooding the lungs with insulin particles will eventually cause life-threatening side

effects. Further complicating the process, some inhaled insulin never reaches the lungs because it settles in the mouth or throat, making it difficult to ensure that the patient is getting the correct drug dosage.

The historic challenge of delivering insulin has been to find a way to enhance hormone absorption without irritating the nasal passages. Other obstacles include low payload delivery and variability.

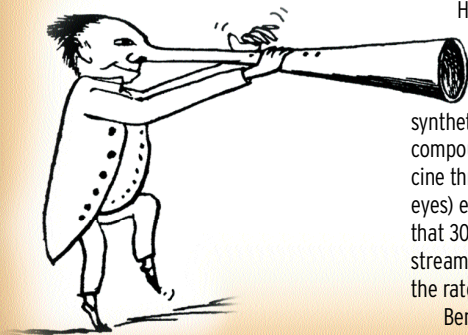
Bentley Pharmaceuticals, Inc. of North Hampton, NH claims to have overcome these issues with high bioavailability, lack of irritation and low variability. Animal tests of its CEP-215 (a synthetic version of a naturally occurring compound that enhances absorption of medicine through the skin, nasal passages and eyes) enhanced intranasal insulin indicate that 30% of the hormone reaches the bloodstream without significant irritation, triple the rate of inhaled insulin.

Bentley plans to formulate CPE-215 into an insulin that diabetics would spray into

their noses. This year, the company plans to begin human trials of nasal insulin. If the technology proves viable, nasal insulin would tap a US insulin market currently worth about \$1.3 billion.

Pfizer Inc. has partnered with Bentley after independently studying CPE-215. The agreement calls for Bentley to formulate Pfizer compounds using CPE-215 and Pfizer would develop the drugs.

East Norriton, PA-based Auxilium Pharmaceuticals Inc. is researching a nasal formulation of an existing opiate pain drug using CPE-215. The expectation is that the nasal pain drug would begin working more quickly than pills while avoiding injections. Human testing has yet to begin, suggesting that the drug is at least three years from reaching market.



#### Bentley Pharmaceuticals, Inc.

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nose. Considerable efforts are underway to achieve a more widespread distribution. The anterior segment is predominantly lined by squamous epithelium, and not by mucose. Thus, for both topical and systemic substances, the goal is to reduce the deposition to this anterior area. Substances delivered to the mucosal site will be cleared along the lower parts of the nasal airway.

### LEADING WITH THE NOSE

The nose has a number of roles, one of which is to act as a protective organ, filtering particles from inhaled air prior to entry into the lungs. Most inspired particles will be retained in the nasal cavity, although very small particles (<5-10µm) have the potential to pass through the nasal cavity and enter the pulmonary region. Particles retained in the nasal cavity have a very short residence time as the process of mucociliary clearance will send particles to the throat within 5-15 minutes of deposition. Therefore, the physico-chemical properties of a nasal powder are key to its safety and efficacy.

A limitation of liquid nasal administration can be its solubility. Each nostril has the capacity to hold a maximum vol-

ume of 100-150µL before the formulation drains to the back of the throat. Therefore, the drug delivered must be therapeutically active in an amount soluble in 200-300µL of liquid. There is also a limit to the amount of powder that can be safely and comfortably delivered into the nose so all intranasal administration must be limited to relatively potent compounds. However, the potential exists to deliver larger powder doses of compounds that have limited solubility.

In addition, many compounds are not sufficiently stable as a liquid. In these cases, powder formulation may offer an alternative approach that confers a greater degree of stability on the compound.

West Pharmaceutical Services of Lionville, PA has developed a nasal drug delivery technology that can be used either in liquid or powder form, depending on the drug's solution stability. The patented ChiSys nasal delivery system uses a naturally occurring substance, chitosan, derived from crustacean shells. Chitosan

is a bioadhesive that allows a nasally administered compound to reside in the nose longer by bonding with mucus, resulting in increased bioavailability.

ChiSys-morphine has been approved for clinical trials to treat pain in cancer patients and other analgesia indications, and ChiSys-leuprolide has been approved for clinical trials for the treatment of endometriosis and other gynecological conditions. West and Brussels-based Solvay Pharmaceuticals are developing Influvac, an influenza vaccine.

### Intranasal Drugs Administered for Systemic Effect

COMPOUND	COMPANY
Nicotine	Pharmacia
Dihydroergotamine	Novartis
Sumatriptan	GSK
Oestradiol	Servier
Calcitonin	Novartis
Desmopressin	Ferring, Norgine
Buserelin	Shire
Narafrelin	Pharmacia

Table 1 SOURCE: Britannia Pharmaceuticals

### The Results Are In

#### A non-invasive alternative to injectable Interferon beta may be on the horizon for multiple sclerosis sufferers.

Nastech Pharmaceutical Co. Inc. of Hauppauge, N, has received the results of its Phase I pharmacokinetic, pharmacodynamic, safety and tolerance study demonstrating the nasal delivery of Interferon beta-1a. The single-dose, open-label study, involving healthy male volunteers, required each to receive either a 60-mcg dose of Interferon beta-1a as an intramuscular injection or a 30-60 mcg nasally administered Interferon beta-1a spray of either Nastech's formulation or a standard formulation without absorption enhancers. The subjects were evaluated at various time intervals after dosing.

Administration of the standard nasal formulation did not result in detectable elevations in biologic markers for Interferon beta-1a, however, subjects receiving Nastech's formulation showed elevations in

biologic markers similar to those produced by the intramuscular product, suggesting a pharmacologic effect. In addition, the Nastech formulation was well tolerated with fewer reported side effects than for the injected product. No nasal irritation was observed during the study.

"Having previously demonstrated the successful nasal delivery of Interferon alpha, we consider these results a further validation of our core technology," says Steven C. Quay, MD, PhD, chairman, president and CEO of Nastech.

"Nasally administered Interferon beta may potentially provide MS patients with a more convenient alternative to Interferon-beta injections."

Interferon beta is a drug used to reduce the frequency and severity of

relapses afflicting MS patients. The market for Interferon beta is more than \$1.4 billion.

Nastech has also recently received a \$2 million development milestone payment from Pharmacia Corp. under their collaboration and licensing agreement for intranasally administered apomorphine for sexual dysfunction.



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West expects to receive FDA approvals to begin clinical trials for additional therapeutic products using ChiSys within the coming year.

Pharmacokinetic studies of Britannia's apomorphine powder show the formulation is absorbed at least as quickly as the injected product and equally available. Acute- and short-term chronic use Phase II studies have shown the product is effective with no evidence of the local side-effects associated with the liquid formulation. Long-term safety and efficacy studies are on-going. In addition, Phase I studies are underway in developing a second apomorphine product for the treatment of male erectile dysfunction (MED). Known to be an effective treatment of MED, the drug is marketed by other companies for this indication as a sublingual tablet. However, the nasal-powder formulation is expected to be superior to the sublingual product, providing a more rapid effect at a reduced dose with fewer associated side-effects.

Liquid and powder formulations are of particular interest to Oslo, Norway-based OptiNose, which is developing

devices for nasal delivery of vaccines and drugs with topical or systemic action. Through manipulation of the particle size profile and nasal aerodynamics, the patented OptiNose concept allows optimized delivery of liquids and powders to the nasal mucosa (widespread and targeted), while at the same time eliminating the risk of inhalation of small particles to the lungs.

The work of these companies, and others like them, demonstrates that the nasal cavity is a promising administration route that has long been neglected. It is a viable and relatively safe method for drug delivery; the products coming to market reflect this sentiment. **-PFQ**

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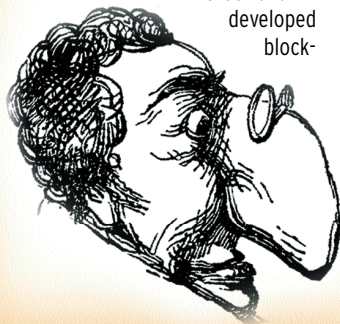
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	Good	Fair	Poor
Usefulness	351	352	353
Style	354	355	356

### Flu Spray Returns to DC Gaithersburg, MD-based MedImmune Inc. hopes to win FDA approval just in time for the 2002-2003 flu season with FluMist, an experimental vaccine, the first to be delivered as a nasal spray.

The 14-year-old biotech company is pinning its hopes on the promise that FluMist pushes the company into the elite group of biotech firms that have developed block-



buster drugs, bringing in \$1 billion in annual sales.

While patient trials have found the needle-alternative vaccine to be highly effective, an FDA advisory panel recommended against FluMist's approval last July, raising questions about its safety. In January, the company resubmitted its FDA application with additional data to address FDA's concerns. PFQ tried calling MedImmune several times to learn why the biotech company expects approval this time around, but the company did not return the calls. Wall Street analysts believe FluMist will win approval this time for several reasons, one of which is that the company hired a former FDA official to help review the vaccine.

Intranasal vaccination offers local mucosal immune protection for many vaccines. Some health experts support FluMist because it offers doctors

another tool to fight influenza and makes up for recent shortages of the flu vaccine.

Others believe, however, that there is not a pressing need for a nasally delivered flu vaccine. Even if FluMist wins approval, industry insiders question how many people would be willing to pay as much as \$20 or more for a nasal-spray vaccine when the current needle vaccine works just fine. In addition, they say FluMist will be less accessible to the public because the vaccine must be stored at cool temperatures.

"MedImmune has a solution to a problem that doesn't exist," said David Hines, president of Avalon Research Group Inc., of Boca Raton, FL, in a March 18, 2002 Washington Post article. "It's too expensive and inconvenient. If it's important to vaccinate children for flu, give them a \$10 shot. It's safe and effective, tried and true."