

Getting systemic treatments into the bloodstream via the nasal mucosa

In this fourth article in our series looking developments in drug technologies, **Jenny Bryan** describes development of techniques for getting drugs into the body, and even the brain, via nasal inhalation

The nasal mucosa has been the subject of research in drug delivery for at least a decade

For an emerging pharmaceutical company, Seattle-based Natestch hit the jackpot last month. It will be paid \$5m by Merck for rights to its novel obesity nasal spray — a formulation containing PYY3-36 — and, if clinical trials go well, the company stands to make hundreds of millions more in sales and royalties. All this is happening on the basis of three small phase I clinical trials involving PYY3-36, a gut-derived hormone that is released postprandially in proportion to the calories ingested. The trials show that intranasal delivery of PYY3-36 increases plasma levels of the peptide, makes healthy volunteers feel less hungry, and does not make them feel sick, unless they inhale too much.

Industry goal

Getting systemic treatments into the bloodstream via the nasal mucosa has been a goal of many pharmaceutical companies for at least a decade. In principle, nasal delivery should provide fast onset of activity, comparable to intravenous delivery, and avoid gastric breakdown of peptide-based treatments. But only a handful of products, including nicotine, sumatriptan, nafarelin and calcitonin nasal sprays, have made it to the market.

Lisbeth Illum, chief scientific officer at Phaeton Research, and associate to the School of Pharmacy at Nottingham University, explains that, although lipid soluble molecules cross the nasal membrane into the bloodstream with a bioavailability of up to 100 per cent, the figure falls to 10 per cent for small, polar molecules and to less than 1 per cent for large peptide molecules.¹

A major barrier is the tight junctions between the epithelial cells of the nasal mucosa which need to be prised apart to gain access to the systemic circulation. Early attempts at opening the junctions with permeation enhancers, for example, for intranasal insulin products ran in to toxicity problems (see *PJ*, 31 July, p161). However, recent developments in permeation enhancers are proving more promising.


Chitosan is a linear polysaccharide, produced by alkaline hydrolysis (deacetylation) of chitin from crustacean shells. It is bioadhesive and interacts strongly with the nasal mucus and with nasal epithelial cells. It prolongs the period of time that a drug stays on the nasal membrane and *in vitro* studies suggest that it opens tight junctions so that hydrophilic drugs can pass through. Most importantly, explains Professor Illum, who developed the substance, chitosan is non-toxic and non-irritant.

“We started looking for positively charged materials that were abundant and cheap, and came across chitosan,” she says. “We then used it for nasal delivery of insulin in rat studies and found that it was very effective. For nasal drug delivery, chitosan is really the only enhancer that has been fully developed so far.”

The chitosan system has been shown to increase bioavailability of morphine from less than 10 per cent without permeation enhancers to over 60 per cent with chitosan. In Nottingham, West Pharmaceuticals will soon start a clinical study of nasal leuprolide with chitosan as permeation enhancer for the treatment of endometriosis. Nasal formulations of calcitonin and parathyroid hormone are expected to follow, when the company finds pharmaceutical partners to complete development and market its products.

Nasal vaccines are another area of interest for West's chitosan delivery system. Alan Smith, vice-president for research and development, explains that, although conventional injected vaccines stimulate production of systemic antibodies, the aim of nasal vaccines is to stimulate immunoglobulin A antibodies in the nasal mucosa.

“A nasal vaccine against influenza is very attractive because it provides local immunity at the site where the virus gains access to the body,” he says.

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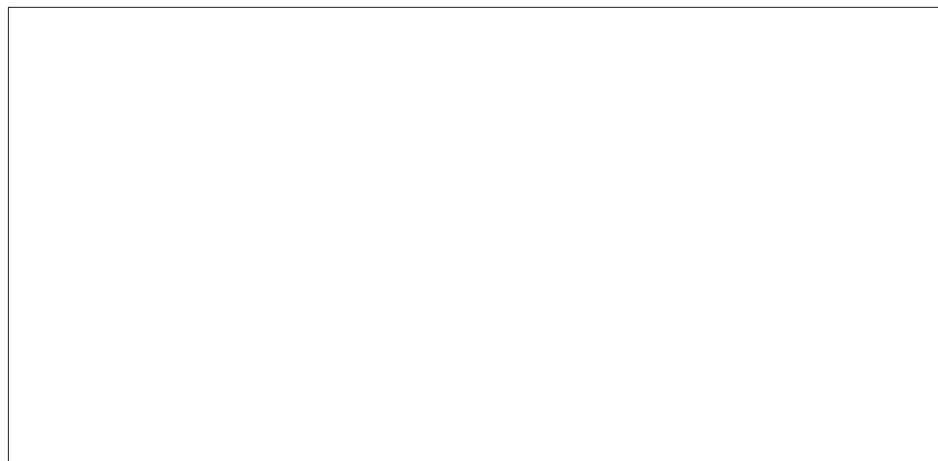
Less is known about how Nastech is optimising the bioavailability of its new nasal anti-obesity treatment. Peptide YY is a naturally occurring hormone produced by L-cells in the gut after a meal to trigger feelings of satiety. L-cells are distributed throughout the intestine facing the gut lumen, which suggests that they sense the luminal concentration of lipids and carbohydrates directly. Nastech has used the 34 amino acid C-terminal fraction, PYY3-36, in its phase I studies. At a US congress in June, the company reported bioavailability of approximately 16 per cent in healthy volunteer studies. The elimination half life of 35–49 minutes with the three highest doses of PYY3-36 (100µg, 150µg and 200µg) compared favourably with the nine minutes seen with intravenous dosing, and is thought to reflect prolonged wash-in from the nasal mucosa.

Also focusing on improved bioavailability from the nasal route is Icelandic drug delivery company Lyfjathroun Biopharmaceuticals, which last month announced promising phase I results from an intranasal formulation of sumatriptan to rival that of GlaxoSmithKline. The company is claiming 17-fold greater bioavailability for its formulation compared with the GSK product during the first 20 minutes after administration. Maximal blood levels were 75 per cent of those achieved with an injectable sumatriptan product.

Further away — but with significant potential for the treatment of neurological disorders — is the prospect of nasal drug delivery, not for systemic absorption through the nasal mucosa in the front and middle parts of the nose, but as a means of bypassing the blood-brain barrier.

In the roof of the nasal cavity, some 7cm back from the nostrils, lies the olfactory region from which nerve pathways, including the trigeminal pathway, have the potential to carry drugs to distant parts of the brain, with no need to cross the blood-brain barrier.

Another option for nose-to-brain drug transport is to improve absorption of drugs



A newly developed bidirectional nasal drug delivery device

through the olfactory epithelia into the cerebral circulation and cerebrospinal fluid — also providing faster and potentially more efficient access to brain tissues.

A key problem for enthusiasts of nose-to-brain transport is the difficulty of getting drugs as far as the olfactory region. Conventional nasal sprays do not attempt to get drugs beyond the areas of the nose affected by rhinitis. Reducing particle size improves deposition to the further recesses of the nose, but increases the likelihood that large amounts of each dose will go down the throat.

New device

Norwegian company OptiNose has recently unveiled a unique bidirectional nasal drug delivery device which, it believes, propels drugs to parts of the nasal cavity that other products have never reached — and avoids the problem of drug being lost down the throat.

Users blow into a mouthpiece to release drug which is then delivered through a sealing nozzle into their nose. Blowing into the device automatically closes the soft palate, so that drug will not be lost down the throat, and a combination of particle size and device design ensures that drug passes up one nostril,

reaches the olfactory area, does a U-turn and exits the nose through the other nostril. Gamma-scintigraphy images confirm the coverage at the back of the nose that can be achieved with OptiNose, and further adaptations to the device are planned to target specific parts of the olfactory area more precisely.

Rod Hafner, operations director at the newly established OptiNose UK, explains that the company will start by showing that the bidirectional device is superior to conventional nasal sprays for delivering nasal steroids for the treatment of rhinosinusitis. It then hopes to acquire business partners to test the device for nose-to-brain delivery of drugs for neurological disorders.

As Mr Hafner points out: “Previous nasal delivery technology has only considered parts of the nose that people can see. But there is a much larger volume of interest which is buried behind the nose. With different nozzles, airflows and spray plumes, we can go much further and higher than before.”

Reference

1. Illum L. Is nose-to-brain transport of drugs in man a reality? *Journal of Pharmacy and Pharmacology* 2004;56:3–17/