Drug delivery via the nose

As more therapeutic peptides and proteins are developed, nasal drug delivery offers an ever more viable alternative to the oral and injectable routes.

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Nasal drug delivery is a rapidly expanding field—paralleling expansion in biotechnology which has seen such an enormous increase in the production of therapeutic peptides and proteins. However, the two fields have seemingly yet to fully discover one another and bring to the market a batch of blockbuster new drug products.

The difficulty could be said to lie on the shoulders of the pharmaceutical scientist, who is presented with the formidable challenge of marrying nasal drug delivery and biotechnology. There is considerable clinical pressure to transform successful nasal drug delivery systems into launched products, primarily to take advantage of the potential benefits that nasal administration has to offer compared with the parenteral or oral route. The benefits for systemically-acting drugs include improved patient compliance, increased cost-effectiveness, rapid onset of action, better bioavailability and avoidance of first-pass metabolism. Some of these potential benefits for systemic drug delivery via the nasal route can also apply at the local level—which is sometimes overlooked; many of the drug technologies and strategies employed for systemic drug action can also be used locally. Interestingly, of the approximately 27 nasal products currently on the market, 17 are prescribed for local effect (1).

This article provides a brief overview of the anatomy of the nose, protein and peptide delivery formulation issues, and generalised nasal drug delivery solutions. Finally, a review is presented of the nasal drug delivery platform that West Pharmaceutical Services has developed in order to improve the efficacy for such chemical entities as small molecules, peptides, proteins and vaccines.

The nose

The exterior nose contains the nostrils and one-third of the nasal cavity, which is dual-chambered and approximately 5 cm high and 10 cm long. Inside the cavities the walls are lined with turbinates, which form the slit-like cavities that maintain the humidification and temperature regulation of inspired air. There are three distinct nasal epithelia lining the cavities: the vestibule, olfactory and airway regions. The airway region epithelium is covered with numerous microvilli, which increase the surface area (2).

The airway epithelium is covered by a dual layer of mucus; this provides a protective barrier against various molecules, protects the mucosa from the
cold and low humidity, and traps and removes inhaled particles via mucociliary clearance or sneezing (3). Mucociliary clearance is the process by which the cilia move the mucus to the back of the throat where it is swallowed. The rate for clearing particles from the nasal passages is between 15 and 20 minutes.

Most low molecular weight drugs (<300 Da) in solution are able to penetrate the nasal epithelium with ease. Hussain has proposed that the mechanism of absorption is via aqueous channels. Some molecules (for example, butorphanol) demonstrate 100 per cent bioavailability compared with intravenous administration. Molecules above 300 Da experience increasing difficulty with absorption – a finding that is similar to that found in the gastrointestinal tract (4). In addition to the size versus absorption issue, there is the additional problem of the mucociliary clearance mechanism to overcome. Higher molecular weight drugs (>1,000 Da) will need some form of drug delivery system to achieve a clinically relevant bioavailability (5).

**Proteins and peptides**

Proteins are highly evolved molecules charged with carrying out essentially all biological processes and reactions. As therapeutic agents, the possibilities for proteins and peptides are immense and are beginning to be felt with the introduction of an increasing number of products onto the market. The future for proteins and peptides as therapeutic and prophylactic drugs looks very bright, considering the completion of the sequencing of the entire human genome and the huge strides being made in proteomics.

However, there are hurdles to overcome. A large molecular weight makes it difficult for some proteins and peptides to cross biological membranes. This is demonstrated by their typically low bioavailability of 1–2 per cent when given nasally (5). The complex architecture of the protein can easily be disrupted or degraded at the site of administration, rendering it impotent. The effective use of proteins does not always follow a familiar sigmoidal dose-response curve, but may need a pulsed rather than continuous release (6). Another factor indirectly related to administration is the fact that, in nature, proteins are synthesised in small amounts when needed and stabilised by the surrounding milieu. As therapeutic agents, proteins will need to be produced in large quantities, purified and concentrated, and have a shelf-life of at least two years. Despite these hurdles, several protein products have reached the market – usually in the form of a lyophilised powder which is then reconstituted before use (7).

**Nasal drug delivery systems**

Currently, there are several diverse nasal drug delivery systems in various stages of development. Most of the systems are made up of bioadhesive materials or absorption enhancers. A universal system for
the nasal delivery of drugs is highly unlikely given the types of material being considered, the different physical and chemical characteristics of drugs, and the various target sites within the body. The effectiveness of a particular delivery system is also affected by its formulation as a liquid, powder, gel, or microsphere (8).

Bioadhesion is defined as the ability of a material to adhere to a biological tissue for an extended period of time. Adherence is accomplished by a number of interactions – physical and chemical – such as electrostatic interaction, hydrogen bonding or hydrophobic intercalation (9). Bioadhesion is useful for both systemic and local delivery because it extends the contact time of the drug in the nasal cavity.

As their name implies, absorption enhancers are used to improve absorption across the nasal membrane. There are a number of ways in which they can act: they may help solubilise or stabilise the drug; they may alter properties of the mucus layer, by opening tight junctions between the cells; or they may increase membrane fluidity. An absorption enhancer may use any number of these mechanisms to promote drug absorption (10).

Systemic delivery
West Pharmaceutical Services (Lionville, PA, USA, and Nottingham, UK) has a balanced platform of nasal drug delivery systems for both systemic and local delivery; these are based on both bioadhesive excipients and absorption enhancing systems.

The company’s leading nasal drug delivery system, ChiSys™, is based on the bioadhesive excipient, chitosan, a polysaccharide derived from the shells of crustaceans. ChiSys is versatile because it can be formulated as a liquid or powder; this is illustrated by the product, ChiSys-leuprolide (Figure 1). Leuprolide is a peptide hormone used for the treatment of prostate cancer in males and various gynaecological conditions in females. Both liquid and powder ChiSys formulations were able to increase bioavailability 10-fold compared with nasal administration of regular leuprolide. The liquid formulation for the treatment of endometriosis was chosen for progression to US Phase I clinical trials – based on the product’s ease of administration, the availability of a delivery device and a lower “cost of goods”.

The ChiSys system has undergone several human trials (pre-clinical through to Phase I) using morphine (Figure 2) and influenza vaccine in addition to leuprolide. To date, all have been successful in that increased bioavailabilities (relative to intranasal delivery without the aid of a drug delivery system) have been achieved; in the case of the formulation for delivering influenza vaccine, the additional benefit of mucosal immunity has also been achieved. The product has been well tolerated by patients with few adverse affects reported to date.

West has also developed a starch microsphere delivery system. Starch microspheres can be combined with drugs to produce a free-flowing bioadhesive powder. This approach has been shown to produce a significant improvement in the systemic absorption of peptides and low molecular weight drug compounds.

Both immediate- and sustained-release properties are combined in West’s ion-exchange delivery system. Unbound drug is available for immediate release, while sustained release is achieved when native ions compete with – and replace – bound drug on the resin base. The ion-exchange delivery system has been shown to be useful for the nasal delivery of various drugs such as nicotine.

Local delivery
For local delivery, West has developed a novel pectin formulation. (Pectin is found in the walls of all green land plants.) The formulation is interesting in that it is formulated as a liquid, but becomes a gel as soon as the droplets come into contact with the nasal mucosa. The contact time of a drug with the nasal membranes has been shown to be improved in a sheep model (Figure 3).
Innovations in Pharmaceutical Technology

Conclusion
As the field of biotechnology continues to advance, nasal drug delivery is increasingly becoming a more viable alternative to oral or injectable routes of administration. The pharmaceutical scientist is confronted with the challenge of successfully bridging these fields as the need for increased patient compliance, cost-effectiveness, rapid onset of action, improved bioavailability and avoidance of first-pass metabolism become more important.

Techniques employing bioadhesion and absorption enhancement remain at the forefront of nasal drug delivery – both systemic and local delivery. Several formulation factors will influence the matching of a drug with a delivery system, including the physical and chemical characteristics of the drug molecule, its molecular weight and desired therapeutic action. Data (including clinical data) shown for West's systemic and local nasal drug delivery platforms demonstrate how the fields of biotechnology and drug delivery can be successfully united.

References