Developments in nasal drug delivery

Intranasal delivery of SYSTEMIC drugs will demand increasingly sophisticated delivery devices to ensure accurate and repeatable dosing.

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Nasal drug delivery - which has been practised for thousands of years - has been given a new lease of life. As the market for the delivery of topical drugs - such as those used in the treatment of nasal congestion - matures, the potential for intranasal administration of systemically-acting drugs is developing at a remarkably fast pace. A number of therapeutic systems have already been marketed and many more nasal drug formulations are at various stages of development.

The advantages of the nasal cavity as a drug delivery route include:

- A highly vascularised sub-epithelial layer allowing for rapid and direct absorption into the systemic circulation, avoiding first-pass hepatic metabolism,
- A less hostile environment than the gastro-intestinal tract, resulting in reduced drug denaturing, and
- Improved patient compliance and comfort compared with intravenous administration.

These advantages of nasal administration are particularly well-suited to the delivery of the new generation of biotechnology drugs, labile drugs and macromolecules, such as proteins or polypeptides, which tend to undergo significant degradation in - or are poorly-absorbed through - the gastrointestinal tract.

Market trends

Locally-acting drugs, including therapies for allergic rhinitis, nasal congestion and infections, account for over 75 per cent of the current nasal drug delivery market, which is estimated to be worth $3,000 million per annum (Figure 1). However, as the market matures, drug development activity in these areas is at a relatively low level and growth is slowing. Conversely, the market for nasal administration of systemically-acting drugs is estimated to be growing at around 33 per cent per annum, and 16 of the 20 major pharmaceutical companies have active nasal drug delivery programmes.

Intranasal delivery is currently being employed in treatments for migraine, smoking cessation, acute pain relief, nocturnal enuresis, osteoporosis and vitamin B-12 deficiency. In 1999, Aviron's intranasal influenza vaccine, FluMist, was first marketed and there is significant activity in the general area of vaccines administered nasally. Other examples of therapeutic areas under development or with potential for nasal delivery include cancer therapy, epilepsy, anti-emetics, rheumatoid arthritis and insulin-dependent diabetes.

The potential size of the intranasal delivery market for a given drug will depend not only on the clinical efficacy of the therapy, but also on the profile of the patients involved, and the acceptability of the dosing regimens and administration methods currently in use. The benefits of nasal delivery must be able to prove their worth against a range of other delivery methods. For example, intranasal administration of insulin will be competing against several other methods including pulmonary delivery, needle-less injectors, and oral, buccal and transdermal delivery.

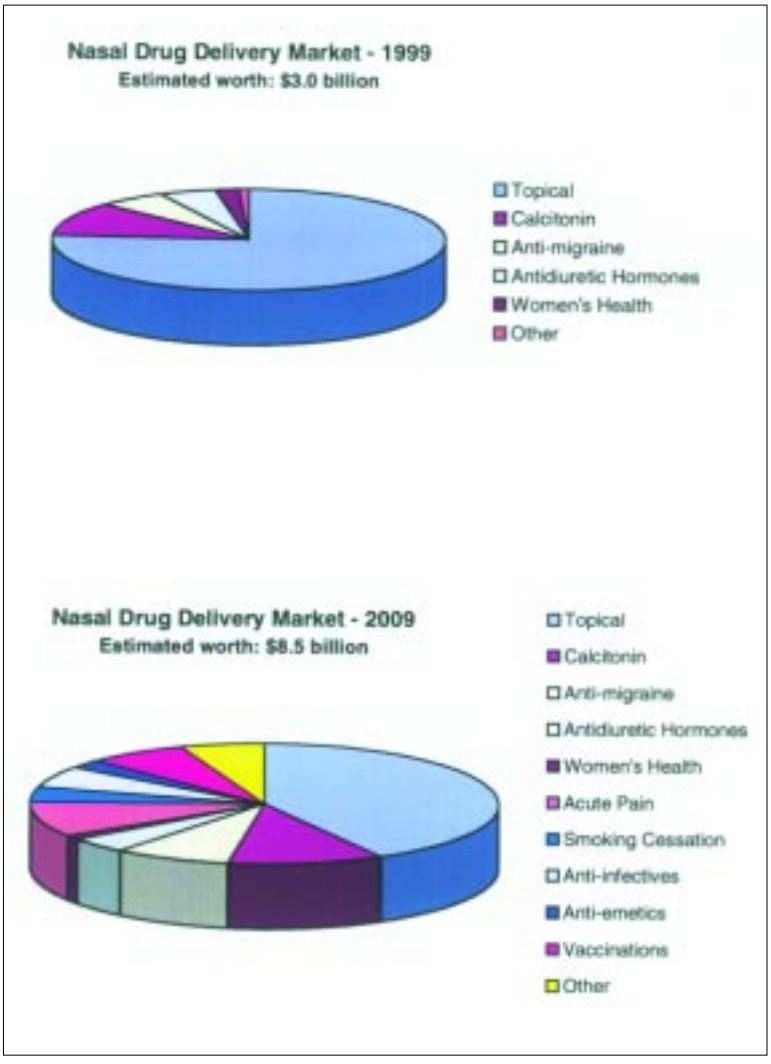

Figure 1. Current and future make-up of the nasal drug delivery market, including estimated worth. Source: Bespak estimates 2000 (8).

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Anatomy of the nasal cavity

Some of the key features of the nasal cavity are shown in Figure 2. The surface area of around 150 cm^2 is made up of two slit-like passages, consisting of regions of varying importance as target sites for systemic drug delivery. The nasal vestibule is bordered at the bottom by the nostril and at the top by the narrow nasal valve. The anterior one-third of the nasal cavity immediately beyond this - which is generally thought to be an area of poor systemic drug absorption - leads to the turbinates, where the sub-epithelial layer is highly vascularised and provides the potential for rapid drug absorption into the systemic circulation. In addition, it is thought that the olfactory region provides a route for absorption into the central nervous system.

The epithelial structure covering the turbinates contains goblet cells which release mucus and is covered with cilia - tiny hair-like structures around 5µm in length and 0.3µm wide (1). This provides an essential physiological defence mechanism for the respiratory system whereby inhaled particles and droplets above around 10µm in size adhere to the mucus and the cilia; these undergo a beating motion, propelling mucus and trapped particulates to the rear of the nasal cavity where they can be cleared via the nasopharynx (a process known as 'mucociliary clearance'). The rate of clearance averages around 5mm per minute and defines a timescale of around 15 to 30 minutes for residence of a drug in the nasal cavity.

It is also important to note that the nasal passages vary significantly in both shape and dimensions, not only between individuals but also at different points in time for a given individual. Overcoming this variability is one of the critical issues in successful delivery device design.

Nasal formulations of systemic drugs

As for any other route of administration, the design of formulations for nasal delivery is aimed at optimising drug bioavailability. The issues that need to be taken into consideration are:

- The rate and efficacy of drug permeation through the nasal mucosa,
- Degradation of the drug in the nasal environment,
- The residence time of the formulation at the required site of delivery, and
- Localised toxicity and the impairment of physiological functions.

The bioavailability of drugs delivered via the nasal mucosa can vary widely, and is related to a number of physicochemical properties, principally molecular weight, polarity, pH and partition coefficient (2). Since, in general, absorption decreases with increasing molecular weight, this poses a potential barrier to the delivery of high molecular weight drugs such as proteins and polypeptides - drugs which also tend to be susceptible to enzymatic degradation.

Several methods are used to enhance the absorption of drugs with sub-optimal nasal bioavailability. These include chemical modification of the drug itself to form salts, which have increased solubility, and esters which can increase the permeability of the nasal mucus membrane. Surfactants may also be incorporated in the formulation to modify the permeability of the mucosa. Other methods involve limiting

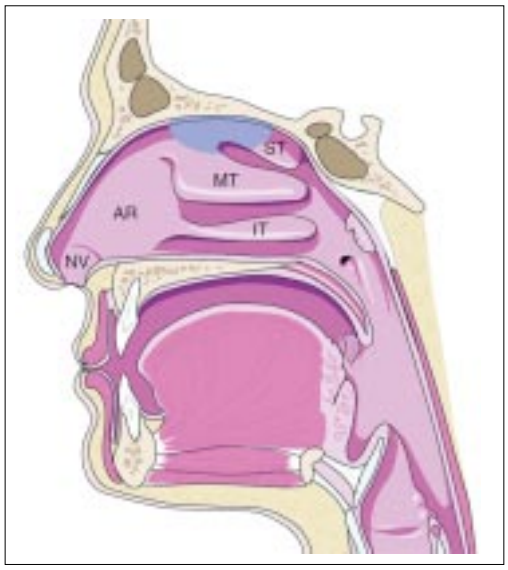

Figure 2. Sectional view showing the lateral wall of the nasal cavity. NV – nasal vestibule, AR – anterior region, ST – superior turbinate, MT – middle turbinate, and IT – inferior turbinate. The blue area indicates the olfactory region.

enzymatic activity - to reduce drug degradation - and the transient modification of the epithelial structure to aid transport mechanisms.

Bio-adhesive polymers are added to formulations in order to increase residence times and allow greater degrees of drug absorption to take place. Compounds, such as those based on cellulose derivatives or polyacrylic acid, swell by absorbing water from mucus to form a gel-like layer of increased viscosity, enhancing contact between the drug formulation and the mucosal membrane.

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Studies have demonstrated the effect that viscosity modification can have in improving retention times (3,4), but the latter investigation also found that this was accompanied by an increase in droplet size and more localised deposition in the anterior region of the nasal cavity. This is an example of how formulation and device characteristics need to be considered together if nasal delivery is to be successful.

Particle design is playing an increasingly important role in absorption enhancement. Microspheres, nanoparticles and liposomes are all systems which can be used as carriers to encapsulate an active drug. The properties of the carrier (for example, its dimensions, structure or surface charge) can be varied to maximise therapeutic efficacy. Overall, this can result in increased absorption efficacy and stability, and reduced toxicity of the active ingredient. Systems can be designed to be muco-adhesive to increase the retention time and facilitate sustained release.

Serious consideration must also be given to the time-scale of any proposed therapy - that is, whether the treatment is for acute or chronic conditions - and the potential for the active drug, absorption-enhancing agents or other formulation excipients to damage the nasal mucosa or have a detrimental effect on mucociliary clearance.

Requirements for nasal drug delivery devices

Intranasal delivery of systemic drugs will demand increasingly sophisticated delivery devices to ensure accurate and repeatable dosing in formats likely to maximise patient compliance. Droppers and squeeze-bottles remain widely-used, but are increasingly being superseded by mechanical pumps and propellant-driven systems. Even these devices have their limitations and future delivery systems will need to be carefully 'tailored' to optimise the delivery of individual drug formulations. The key requirements of intranasal delivery devices include:

- Accurate and repeatable dosing,
- Consistent delivery to the optimal site of action,
- Protection for preservative-free formulations in multi-dose presentations,
- Patient-independent actuation, and
- Compliance monitors and aids.

The site to which the drug is delivered is one of the key parameters, and this is strongly influenced by the size of the droplets or particles emitted by the device and their velocities. The anatomy of the nasal airways enhances inertial impaction, and significant deposition in the anterior region of the nose is common for spray pumps (5) and metered dose inhalers (6) because of, respectively, the relatively large droplet sizes and high aerosol velocities. Optimised delivery requires efficient targeting of the turbinates, whilst avoiding loss of drug to the nasopharynx. A recent study (7) demonstrated that the smaller, lower-velocity droplets delivered by a nebuliser were deposited further back in the nose, but the extent of lung penetration with this method was not verified.

Dosing accuracy is of critical importance for the delivery of potent and/or expensive drugs. Accurate metering systems and careful device design are therefore essential to control not only the overall 'shot' weight or volume, but also the content of active drug per dose throughout the lifetime of the device. Spray pumps and MDIs

both require priming before use and after varying periods of non-use, and this leads to wasted drug and the potential for variable dose levels. The next generation of devices needs to address these - and a whole range of other - design issues.

Drugs formulated as aqueous solutions or suspensions require preservatives to prevent microbiological contamination, unless they are to be used in 'one-shot' devices. Preservatives are incompatible with some active ingredients, and long-term use of such formulations can result in damage to the nasal epithelium and ciliary function. Preservative-free systems require the development of delivery devices that inherently prevent the drug reservoir from being exposed to bacteria.

An alternative approach is to use drugs formulated as dry powders, which can be supplied in pre-metered doses - avoiding the need for preservatives. Peptide and protein drugs are more stable as powders than when formulated as solutions, and degradation of the active ingredient can be avoided. Powders can also produce longer nasal retention times than liquids.

In passive devices, there is a lower limit of 10µm for particle size in order to avoid delivery to the lung (as discussed in the earlier section on nasal anatomy), whereas particle sizes may be somewhat smaller in active devices where the patient's inhalation is enhanced.

As in other areas of drug delivery, there is an increasing need to address issues surrounding patient compliance and monitoring. Taking advantage of the inherent benefits of the nasal administration route demands that devices are easy and reliable to use, and requires that they are compatible with the symptoms of the disease being treated. Dose-counters are important for devices used in long-term therapy, and lock-out systems are required to prevent over-dosing in the delivery of controlled drugs - for example, those used for acute pain relief. In some therapeutic areas - for example, diabetes - there is the requirement for a patient to be able to vary the dose that is administered. Finally, devices used to deliver systemically-acting agents must be able to minimise - or ideally eliminate - intra-patient dosing variability.

Conclusion

Nasal drug delivery is an attractive alternative route of administration for some systemically-acting drugs with poor oral bioavailability, and has advantages in terms of improved patient acceptability and compliance compared with parenteral administration. The successful application of these attributes requires careful design of the characteristics of both the drug formulation and the delivery device, and a clear understanding of the ways in which they impact on each other.

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