DDT Vol. 7, No. 23 December 2002

Nasal drug delivery: new developments and strategies

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The use of the nasal route for the delivery of challenging drugs has created much interest in recent years in the pharmaceutical industry. Consequently, drug delivery companies are actively pursuing the development of novel nasal drug-delivery systems and the exploitation of these for administration of conventional generic drugs and peptides, both in-house and with partners in the pharmaceutical industry. This review sets out to discuss some new developments and strategies in nasal drug delivery. An exiting discovery that drugs can be transported directly from nose to brain via the olfactory pathway is discussed and examples of proof-of-concept in man are given.

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▼ In the past decade, the use of the nasal cavity as a route for drug delivery has been an area of great interest to the pharmaceutical industry, especially for systemically acting drugs that are difficult to deliver via routes other than injection. The possibilities for the use of the nasal cavity for drug delivery are outlined in Box 1. The nasal route could be important for drugs that are used in crisis treatments, such as for pain, and for centrally acting drugs where the putative pathway from nose to brain might provide a faster and more specific therapeutic effect [1].

The world market has seen an increasing number of systemically acting drugs being marketed as nasal formulations. For example, sumatriptan (GlaxoSmithKline, http://www.gsk.com), zolmitriptan (AstraZeneca, http://www.astrazeneca.com), ergotamine (Novartis, http://www.novartis.com), butorphanol (Bristol-MyersSquibb, http://www.bms.com), all with the indication for treatment of migraine, where a rapid onset of action is beneficial; estradiol (Servier, http://www.servier.com), where an improved bioavailability as compared to oral delivery has been achieved; and desmopressin (Ferring, http://www.ferring.se), buserelin (Aventis, http://www.aventis.com) and calcitonin (Novartis), all peptides normally only administered by injection because of low membrane permeability and susceptibility to degradation by enzymes in the gastrointestinal tract. A range of companies specializing in the development of innovative nasal delivery systems and formulation problems has come to the fore: Nastech (http://www.nastech.com), Britannia Pharmaceuticals (http://www.britannia-pharm.co.uk), Intranasal Technologies (http://www.intranasal.com), Bentley Pharmaceuticals (http://www.bentleypharm.com) and West Pharmaceutical Services (http://www.westdrugdelivery.com) are actively developing novel nasal formulations for conventional generic drugs (e.g. apomorphine, triptans, morphine, midazolam, fentanyl, non-steroid anti-inflammatory drugs), as well as for peptides and proteins (e.g. leuprolide, parathyroid hormone, insulin, interferon) in situations where the nasal route would be beneficial for the therapeutic efficacy of the drug.

Furthermore, the use of the nasal cavity for vaccination, especially against respiratory infections, is being pursued by vaccine companies. This is because it is possible to obtain, by the nasal route, not only a systemic immune response, but also a local mucosal immune response that should provide a much higher level of protection against these diseases. The first nasal influenza vaccine from Berna Biotech [(CH) http://www.bernabiotech.com] based on an antigen–adjuvant system, reached the European market in 2001 (but has been withdrawn from the market because of possible toxicological problems) and a second influenza vaccine from Aviron (http://www.aviron.com) (cold adapted virus system) is expected to be launched in 2003 [2,3]. This review will discuss new developments and strategies for nasal drug delivery and also touch upon the

PII: S1359-6446(02)02529-1

Box 1. Nasal delivery – what are the possibilities?

- **Local delivery**
  Nasal allergy
  Nasal congestion
  Nasal infection
- **Systemic delivery**
  Crisis treatments – rapid onset is needed
  Long term treatment – daily administration
  Peptides and proteins – difficult to administer
- **Vaccine delivery**
  Antigens (whole cells, split cells, surface antigens)
  DNA vaccines
- **Access to CNS**
  To reach local receptors
  To circumvent the blood-brain barrier

physicochemical and physiological factors to be considered when entering into the development of novel nasal formulations.

Nasal absorption

Nasal physiology

The general architecture and morphology of the human nasal cavity are shown in Figure 1. The nasal absorption of drugs is considered mainly to take place in the respiratory region comprising the turbinates and part of the nasal septum. As is the case for all biological membranes, drugs can cross the nasal mucosal membrane using two different pathways; transcellularly – across the cell – and paracellularly – between the cells. Lipophilic drugs are transported transcellularly by an efficient concentration-dependent passive diffusion process, by receptor or carrier mediation and by vesicular transport mechanisms. Polar drugs are believed to pass through the epithelium via the gaps or pores between the cells (the tight junctions). Although, the tight junctions are dynamic structures that can open and close to a certain extent, the size of these channels is less than 10 Å [4,5]. Hence, the paracellular route will be less efficient for large molecules and is dependent upon the molecular weight of the drug with a general molecular size cut-off of ~1000 Da [4].

Lipophilic drugs, such as propanolol, progesterone, pentazocine and fentanyl, generally demonstrate rapid and efficient absorption when given nasally. For such drugs, it is possible to obtain pharmacokinetic profiles similar to those obtained after an intravenous injection with bioavailabilities for some drugs approaching 100% [1]. Figure 2 shows the pharmacokinetic profiles obtained after intravenous and intranasal delivery of pentazocine in simple formulations. The figure illustrates the high bioavailabiliy

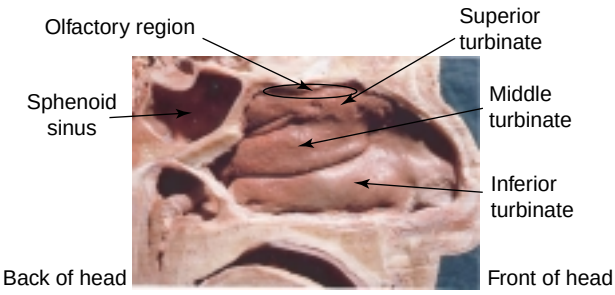

Figure 1. The human nasal cavity shown as a vertical slice through the head from the tip of the nose to the back of the nose. Slide produced by Nick Jones, Ear Nose and Throat Dept, Queen's Medical College, Nottingham (http://www.qmc.nhs.uk)

achieved after nasal administration of this lipophilic drug. The nasal absorption of more polar compounds is poor, with bioavailabilities not exceeding 10% for small molecular weight drugs (e.g. alniditan, morphine, sumatriptan) and less than 1% for peptides such as insulin, calcitonin and leuprolide. For higher molecular weight proteins, the nasal absorption has been shown to be even lower, although there is some evidence that even large proteins, such as horseradish peroxidase, can pass the membrane, albeit to a small extent [6]. It is believed that the transport mechanism in this case is one of transcellular vesicular transport.

The poor transport of polar drugs across the nasal mucosa can be associated with three major factors; (1) low membrane permeability, especially for the larger molecular weight drugs, (2) a rapid clearance of the drug formulation

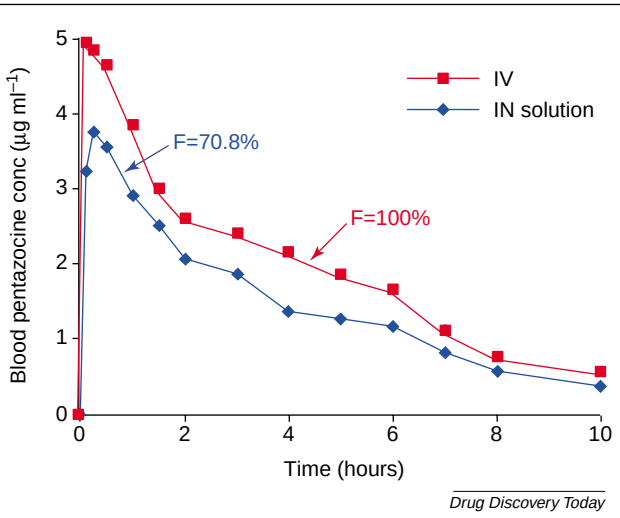

Figure 2. The nasal and intravenous administration of pentazocine in simple solution formulations in man. After Sankar *et al.* [34]. Abbreviations: IN, intranasal; IV, intravenous.

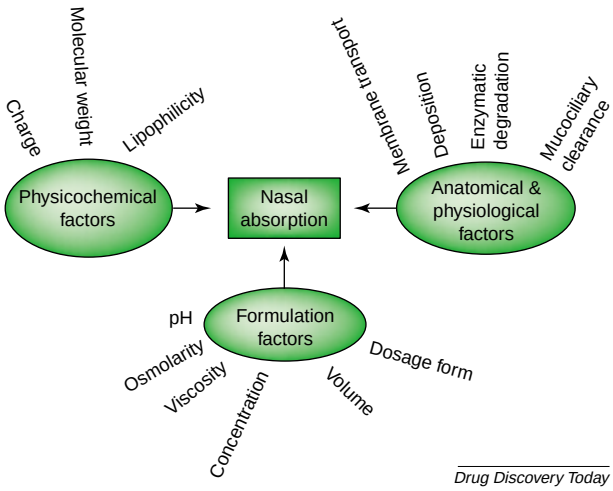

Figure 3. The physicochemical, anatomical, physiological and formulation factors affecting the nasal absorption of drugs.

from the nasal cavity as a result of the mucociliary clearance mechanism and (3) a possible enzymatic degradation of the drug in the nasal cavity. The third factor could be important for peptide and protein drugs but so far has not been shown to be of significant importance for the absorption process and will not be discussed further here [1]. The main reasons for the poor transport of polar drugs across the nasal membrane are discussed previously and are size and poor membrane permeability. Figure 3 summarizes the various physicochemical, formulation, anatomical and physiological factors that can to some extent affect the nasal absorption of drugs.

The mucociliary clearance system provides the human organism with an efficient defence system, which protects the respiratory system against inhaled bacteria, irritants and particles. It transports such agents (sticking to the viscous mucus) backwards in the nose and down into the throat. The transport of mucus is closely correlated to the beat of the cilia present on the respiratory epithelial cells. The tips of the outstretched cilia carry the viscous mucus forward with the forward stroke while on the backward stroke the cilia are bent and the movement is solely in the pericellular fluid underneath the viscous mucus. With a beat of ~1000 strokes per min, the cilia transport the mucus with a speed of 5 mm per min and formulations administered on the human respiratory epithelium has been found to be cleared from the nasal cavity with a half-life of clearance of about 15 min [7]. It is evident that for polar drugs, which are not easily transported across the nasal membrane, the mucociliary clearance mechanism can quickly move the drug away from the absorption site in the nasal cavity into the oesophagus, whereby the drug is swallowed and the absorption minimized [8]. A good example of this is for the marketed nasal spray of sumatriptan (Imigran®; GlaxoSmithKline, http://www.gsk.com), which has a bioavailability of 15.8% [9]. Comparing the nasal pharmacokinetic profile with that for oral administration, it is evident that only a minor part of the nasally administered formulation is absorbed through the nasal cavity and that most of the reported bioavailability is a result of the drug being swallowed or cleared from the nasal cavity and subsequently absorbed via the gastrointestinal tract [8]. The sumatriptan spray is formulated as a simple aqueous solution and hence should be cleared rapidly from the nasal cavity. However, even the small quantity absorbed nasally is apparently able to promote a more rapid relief of the migraine as compared to the oral tablet formulation [9].

Nasal absorption enhancement

It is possible to greatly improve the nasal absorption of polar drugs by administering them in combination with an absorption enhancer that promotes the transport of the drug across the nasal membrane. Furthermore, a nasal drug-delivery system that combines an absorption enhancing activity with a bioadhesive effect, which increases the residence time of the formulation in the nasal cavity, has been shown to be even more effective for improving the nasal absorption of polar drugs. A wide range of absorption enhancer systems has been evaluated in animal models (and some in man). Certainly in animal models, they have been shown to improve significantly the nasal absorption of drugs. However, two aspects of the use of absorption enhancers should be given particular note. First, caution is required when interpreting results obtained in animal models for the transport promoting effect of nasal absorption enhancers. Especially with the rat model (*in situ*, anaesthetized and otherwise), the effect obtained by enhancers can be grossly overestimated. However, other animal models, such as the rabbit and even the dog, can give misleading results, most probably a result of the different architecture and morphology of the nasal cavity and also the use of anaesthetics or sedating procedures that can affect the mucociliary clearance mechanism [10]. As an example, some years ago Merkus *et al.* [11] published results from a study on the nasal delivery of insulin using the rat model with dimethyl-β-cyclodextrin as the absorption enhancer. They obtained an astonishing bioavailability of 100% when compared with a subcutaneous injection of insulin. Later, when the same formulation was tested in rabbits and in man the resulting bioavailability in both animal species was almost 0%. Second, enhancers, such as surfactants, bile salts, fatty acids and most phospholipids and lysophospholipids, can work by modifying the phospholipid bilayer

structure of cells, leaching out proteins or even stripping off the outer layer of the mucosa, thereby promoting the observed improved transcellular transport of drugs. Generally, for such enhancer systems there is a direct correlation between the bioavailability obtained and damage caused to the membrane [8]. For other enhancers, especially those that work by transiently opening the tight junctions between the cells (e.g. chitosan, see later) and selected cyclodextrins and phospholipids, the absorption enhancing effect can greatly outweigh any modifications caused to the mucosa.

Novel nasal delivery systems

Chitosan and other positively charged polymers

In recent years, the polysaccharide material, chitosan has attracted much interest as a nasal delivery system that is able to efficiently deliver polar drugs (including peptides) to the systemic circulation and provide therapeutically relevant bioavailabilities. Chitosan is produced, by a process of deacetylation, from the chitin found in crustacean shells. The resultant free amino groups enable the formation of positively charged chitosan salts with organic and inorganic acids. A pharmaceutically acceptable chitosan salt (GMP grade) for nasal drug delivery is chitosan glutamate. This has a mean molecular weight of ~250,000 Da and a degree of deacetylation of >80% [1]. We have found [12] that in the sheep model the addition of chitosan to a nasal formulation of insulin resulted in an increase in the peak plasma insulin levels from 34 mIU l^{-1} to 191 mIU l^{-1} and a sevenfold increase in the area under the curve (AUC). Later studies in human volunteers confirmed these results with a nasal bioavailability in the order of 9–15% compared to a subcutaneous injection. Further studies in man on a nasal insulin formulation based on chitosan powder have been reported to be in progress in Type 2 diabetics [13,14]. Similarly, chitosan powder formulations have been shown to enable an efficient nasal absorption of goserelin in a sheep model where bioavailabilities of 20–40% were obtained dependent on the nature of the formulation [15].

A novel nasal morphine product containing chitosan as an absorption promoter is expected to reach the market within the next few years. Morphine is a polar drug and, consequently, is not readily absorbed via the nose using simple formulations (bioavailability of ~10% in humans) [16]. Recently published Phase I clinical trial data have demonstrated that a nasal solution formulation of morphine containing chitosan gave rapid absorption of the drug with the peak plasma concentration within 10 min, and the absorption increased about sixfold to provide a bioavailability of 60% compared with intravenous injection. Figure 4 shows a comparison between the plasma peak concentrations after intravenous, intranasal and oral formulations of morphine. The impressive increase in nasal morphine absorption with the addition of chitosan to the nasal formulation is especially notable. The metabolic profile of morphine after nasal administration was similar to the one obtained after an intravenous administration showing a much lower degree of metabolism to glucorunides to that seen after oral administration. Later studies, with further optimized formulations, have given bioavailabilities in the region of 80% [13]. A pilot Phase II clinical trial in cancer patients using a candidate morphine–chitosan system showed a rapid decline in breakthrough pain intensity and a rapid pain relief after nasal administration of the nasal morphine formulation [17].

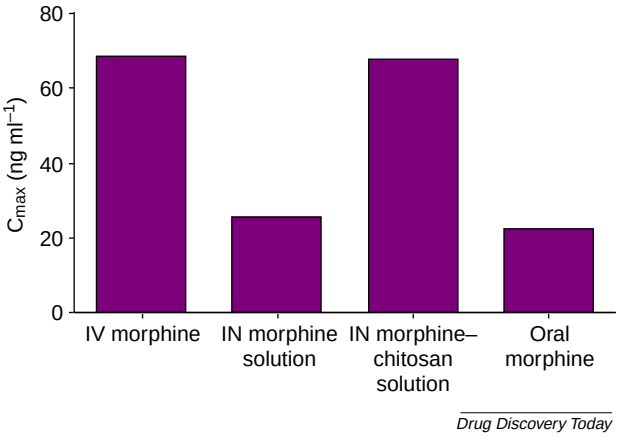

Figure 4. A comparison of the peak plasma levels obtained after intravenous, oral and intranasal administration of morphine in man. The intranasal formulations comprise a simple morphine solution and a morphine-chitosan formulation. Dose of morphine 15 mg for nasal and oral administration and 10 mg for intravenous administration. Abbreviations: IN, intranasal; IV, intravenous.

The nasal epithelium, as discussed previously, is poorly permeable to hydrophilic drugs that are larger than the gap junctions or tight junctions that are part of the intercellular junctional complexes. These molecules cannot diffuse across the cell by a transcellular pathway. The mechanism of action of chitosan in improving the transport of polar drugs across the epithelial membrane is believed to be a combination of bioadhesion and the transient opening of the tight junctions in the cell membrane to enable the passage of polar drugs [18–20]. Extensive toxicological and tolerance studies in animals and man have shown chitosan to be non-toxic and non-irritant to the nasal membrane [8].

Other cationic polymers, such as poly-L-arginine and aminated gelatin have been investigated for their use as nasal absorption enhancers. These polymers work in a similar way to chitosan, at least in animal models, and have been

found to provide good absorption of fluorescein isothiocyanate (FITC)-dextran and insulin with only negligible nasal toxicity [21–23].

Cyclodextrins

The work of Merkus and others [24,25] on the use of cyclodextrin derivatives for nasal absorption enhancement has shown early promise in animal models but, unfortunately, this has not been confirmed in humans. These cyclodextrin systems are, however, still used in nasal formulations but mainly as a means of providing drug solubilization as, for example, with the nasal oestradiol product marketed recently by Servier in Europe.

Phospholipids and lipids

The development of a nasal insulin product by Novo-Nordisk (DK) (http://www.novonordisk.com) in the 1990s, using the phospholipid material didecanoyl-L-α-phosphatidyl choline (DDPC) as an absorption enhancer, was halted as a result of low bioavailability obtained in diabetic patients and insufficient metabolic control when compared with a conventional subcutaneous injection of insulin [26]. Irritation problems were also reported. Interestingly, the reported results obtained in the Phase I clinical trials had been promising [27]. Recently, Bentley Pharmaceuticals has announced promising results for their nasal insulin formulation in the dog model with a quoted bioavailability of 35% [28]. However, it is difficult to deduce from such press releases whether the quoted bioavailability is calculated in terms of pharmacodynamic or pharmacokinetic parameters and the exact nature of their absorption enhancer. It is described as 'a powerful lipid (CPE 215)' that, according to Bentley, works by 'saturating the tissue and causing a fast, temporary and reversible phase separation'. Time will show whether this product will provide therapeutic benefit in diabetics when compared with the conventional treatments and novel approaches using the pulmonary route and buccal membrane for delivery of preprandial doses of insulin.

Nose to brain delivery

It is well known that the euphoria derived from the sniffing of cocaine in conscious subjects occurs rapidly (within 3–5 min). It has been suggested that the reason for such rapid effects is, apart from a rapid nasal absorption, the presence of a direct pathway from the nasal cavity to the CNS and the capacity of the drug to concentrate selectively in specific regions in the brain. Various studies in animal models have confirmed that, at early time points after nasal administration, the concentration of cocaine in the brain was higher after nasal administration than after intravenous injection, thereby showing the existence of the pathway from nose to brain [29,30]. Similar results have been found for many other drugs. This could be especially interesting for polar drugs that are not normally transferred across the blood–brain barrier. By being administered nasally they might be able to reach a target in the brain to a higher extent than by other routes of administration [29]. For example, it was shown in a mouse model that [^{3}H]-dopamine reached the olfactory lobe after nasal administration and that at 4 hours after administration the concentration in this tissue after nasal administration was 27-times higher than after intravenous injection [31,32]. However, it should be stressed that, for most drugs investigated, the overall quantity appearing in the brain tissue normally amounts to less than 1% of the dose given to the nasal cavity.

Evidence of direct nose to brain transport of drugs has also been gathered in man, mostly in terms of pharmacodynamic effects on the CNS, such as effects on event-related potentials during a subject's performance of an oddball task comparing drug administration via nasal and intravenous routes of delivery [1]. Recently, experiments have been conducted in man, not only studying the effect on brain potentials but also investigating the drug transport into the cerebrospinal fluid (CSF) after nasal and intravenous administration by sampling CSF from a spinal tap. A list of the drugs studied in man is given in Box 2. Fehm [33] reported a significant accumulation of insulin in the CSF after a single administration of 40 IU insulin, whereas no increase was seen in insulin plasma levels. Similarly, recent work suggests that apomorphine, when given nasally, reaches the CSF to a higher degree than after subcutaneous injection (Nastech, unpublished data). A nasal product containing apomorphine is being developed by Nastech for the indication of erectile dysfunction.

Box 2. Drugs used in nose to brain drug transport studies in man

Functional evidence in man of facilitated transport to the brain was provided by changes in event related potential during performance of an oddball task

- Arginin-vasopressin (n=15)
- Cholecystokinin-8 (n=20)
- Angiotensin II (n=12)
- Insulin (n=18)
- Adrenocorticotropin 4-10 (n=54)
- Insulin (n=12)

Direct evidence in man of nose to cerebrospinal fluid uptake

- Insulin (n=8)
- Apomorphine (n=5)
- Melatonin/hydroxycobalamin (n=2)

Drugs have been shown to reach the CNS from the nasal cavity by a direct transport across the olfactory region situated at the loft of the nasal cavity. It is the only site in the human body where the nervous system is in direct contact with the surrounding environment. The drug can cross the olfactory epithelium by one or a combination of mechanisms. There is a transcellular route through the cells as well as a paracellular route between the cells, as is the case for the normal nasal epithelium. Furthermore, the drug can be transported through the olfactory neuron cells by intracellular axonal transport primarily to the olfactory bulbs. The intracellular axonal pathway is a slow pathway that can take hours to deliver drugs to the CNS, whereas the two other pathways are fast and enable drug transport to happen within minutes. Thus, this last pathway is often evident in the experimental settings.

It is clear that, in many therapeutic situations where a rapid and/or specific targeting of drugs to the brain would be beneficial, such as for the treatment of Parkinson's disease, Alzheimer's disease or pain, these results, demonstrating direct nose to brain transport, are of great interest. To exploit these results, efforts should now be given to the development of nasal delivery systems capable of increasing the fraction of the drug that will reach the CNS after nasal delivery.

Conclusion

Considering the wealth of activity and interest in the area of nasal drug delivery, together with the potential benefits from this route of administration, we should expect to see a range of novel nasal products reaching the market in the near future. These products will, in the first instance, most probably comprise products for crisis treatments, such as erectile dysfunction, sleep induction, acute pain (migraine), panic attacks, nausea, heart attacks and Parkinson's disease because of the ability to provide rapid absorption of drug from the nasal cavity into the systemic circulation. On a longer term, novel nasal products for treatment of long-term illnesses, such as diabetes, growth deficiency, osteoporosis, fertility treatment and endometriosis, will also be marketed. Most of the new drugs used for these treatments are peptides and proteins and, hence, normally are only given by injection. It will also be interesting to follow the developments in the area of nose to brain delivery of drugs and whether it will prove possible to develop nasal delivery systems that will enable a rapid and efficient concentration of drug in the brain necessary for the treatment of selected diseases of the brain or the CNS and to circumvent the blood–brain barrier.

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