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Re-formulating drugs and vaccines for intranasal delivery: maximum benefits for minimum risks?

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The challenges being faced by the pharmaceutical industry in terms of patent expiries and a sparse pipeline of new products are well documented, as are the risks and costs associated with developing new molecular entities. Major pharmaceutical companies are increasingly looking to augment their traditional core expertise in the discovery of small molecules with the development of biologicals (e.g. peptide-based, protein-based, antibody-based and nucleic-acid-based therapies), which are seen as a key element in achieving long-term growth. There is also considerable current interest in vaccines, both in the traditional area of mass immunization against infections and as a novel approach to disease treatment.

Intranasal drug delivery has the potential to transform the administration of new molecular entities (NMEs), especially biologicals and vaccines. Alongside NMEs, the opportunities for further optimizing and thereby maximally leveraging the potential of existing drugs should not be overlooked, and this is where the use of innovative drug delivery systems, especially intranasal, has a key part to play.

Why intranasal delivery?

The nasal route offers many attractions, which have been described in detail elsewhere [1–3]. In brief, the nasal cavity has a large surface area, an excellent blood supply and a highly permeable epithelial membrane, and these features provide the potential for efficient drug absorption. That the drug will reach its site of absorption within seconds of administration means that drugs can be absorbed rapidly and hence the nasal route provides fast onset of action, making it ideal for conditions in which rapid pharmacological intervention is required. Nasal spray devices are familiar to patients, are largely independent of patient technique and are very simple to use. Administration via the nose largely avoids first-pass metabolism, which can dramatically reduce the bioavailability of some orally administered drugs, and also provides a benign environment for peptide and protein compounds compared to the gastrointestinal tract, with a neutral pH and relative absence of destructive enzymes.

Although it is suitable for the administration of numerous chronically used drugs, the nasal route particularly lends itself to acute conditions that require rapid treatment, such as pain, seizures, migraine, nausea and vomiting, seizures, 'off' episodes in Parkinson's disease, and erectile dysfunction. Commercial intranasal products for acute use include dihydroergotamine, sumatriptan and zolmitriptan (migraine), butorphanol and fentanyl (pain), and nicotine (smoking cessation).

Nasal administration might be an option for small-molecule drugs for which oral absorption is low but an injected formulation would not be commercially acceptable, and it has considerable potential as a non-injectable route for macromolecular drugs and vaccines where proof of concept and utility have been proven for antigens including seasonal influenza and diphtheria.

Several proprietary intranasal delivery technologies to enhance or optimize the systemic delivery of drugs and the immunogenicity of vaccine antigens are in clinical development, and these are summarized in Table 1.

New life to old molecules

Although the complexities associated with the development of NMEs are profound, there is a wealth of opportunities in developing innovative pharmaceutical products by applying nasal drug delivery technologies to well-established

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TABLE 1

Proprietary nasal delivery technologies in clinical development or on the market

Company	Proprietary name	Chemical nature	Applications	Therapeutic agent(s)	Development status	Refs.
Aegis Therapeutics	Intravail®	Non-ionic alkyl glycosides	Bioavailability enhancement	Teriparatide	Phase I	[a]
Archimedes	ChiSys®	Chitosan	(i) Bioavailability enhancement	Morphine	Phase III	[30]
			(ii) Vaccine delivery	Norovirus vaccine	Phase II	[b]
Archimedes	PecSys®	Pectin (solution)	Modulated delivery of well-absorbed molecules	Fentanyl	Approved in EU	[31]
CPEX Pharmaceuticals	CPE-215®	Macrocyclic compounds (e.g. cyclopentadecanone)	Bioavailability enhancement	Insulin	Phase II	[13]
Nanotherapeutics	GelVac™	Aloe-derived pectin (powder)	Vaccine delivery	Avian influenza vaccine	Phase I	[c]
Trimel BioPharma	'Intra-nasal gel'	Oil/surfactant based system	Bioavailability/enhancement	Testosterone	Phase II	[d]

[a] http://www.zelostherapeutics.com/news/012810.htm.
[b] http://www.ligocyte.com/downloads/Noro.pdf.
[c] http://www.nanotherapeutics.com/products_pipeline_gelvac.php.
[d] http://www.trimelbiopharma.com/TherapeuticCategories/Endocrinology/Hypogonadism.aspx.

benchmark or gold-standard drugs whose use is limited by current modes of delivery. Such products will have higher patient acceptability or utility and will offer notable and tangible benefits to the patient and wider healthcare system.

The key advantage to this approach is that the drug compound will be well established with proven efficacy and safety in the target indication. As a consequence, there will be a clearly defined pathway to regulatory approval and a lower development risk.

The path to approval can be further enhanced if the nasal delivery platform itself has good regulatory status, in terms of the quality and safety of any excipients, which ideally will have a history of clinical use.

Fentanyl – an excellent case study

The opioid compound fentanyl is probably the best example of a drug whose utility has been maximally exploited through the use of novel drug delivery technologies. Introduced in the 1960s and used for more than 20 years by injection, primarily as a surgical pre-medication and analgesic, a transdermal formulation was introduced in the late 1980s for round-the-clock treatment of chronic pain. A succession of fentanyl products using other routes of administration has arisen more recently for the treatment of a very specific indication, breakthrough cancer pain (BTCP); this is characterized by pain episodes that are unpredictable, severe in intensity and fast in onset (maximum pain intensity in less than five minutes) and that literally break through the existing background opioid medication in cancer patients. Effective treatment of this condition demands easy-to-administer, fast-acting products. Several fentanyl-containing oral transmucosal products for treating BTCP are either on the market or in development; all provide an onset of pain relief in around 15 min [4–6].

Intranasal formulations look set to provide a further advance in the treatment of BTCP, with their key attributes being speed of onset and convenience of use. For example, phase III clinical data for an intranasal fentanyl formulation utilizing a proprietary *in situ* gelling technology (PecSys®, see Table 1) has demonstrated onset of pain relief within five minutes, clinically meaningful pain relief within 10 min, and an excellent safety, tolerability and acceptability profile (http://www.ampainsoc.org/db2/abstract/view?poster_id=4140). This product was recently approved in Europe under the brand name PecFent®.

Rapid treatment of seizures

The treatment of acute seizures has the potential to be greatly enhanced by nasal delivery [7]. The mainstays of treatment for acute seizures are benzodiazepine drugs, such as diazepam and lorazepam. These currently have to be administered by injection and, in the case of diazepam, rectal products are used out of necessity. Early clinical studies on intranasal benzodiazepine formulations have been published and demonstrate the ability to rapidly deliver therapeutically effective amounts of drug into the systemic circulation [8,9].

A particular challenge of delivering benzodiazepines is their poor solubility in aqueous media. It is noteworthy that the previously cited benzodiazepine clinical studies have used non-aqueous delivery vehicles comprising solvents such as propylene glycol and polyethylene glycol, and there are other examples in the patent literature [10,11].

The ability to use non-aqueous vehicles greatly expands the range of drugs suitable for intranasal administration. Indeed, from the authors' experience, the nose is also tolerant of aqueous solutions over a wide range of pH and tonicity, further illustrating its potential as a route for delivering a wide variety of agents. Intranasal products can also be administered as powders, which can be especially advantageous if a drug is unstable in solution, for example.

Macromolecules

Effective delivery of high molecular weight drugs such as peptides and proteins by a route other than injection remains largely elusive. It is noteworthy that the non-injected formulations of peptides currently on the market are primarily nasal sprays (e.g. calcitonin, nafarelin and buserelin). However, these are simple aqueous solutions with low bioavailability (<5%) [12] and might have caused a negative perception of the effectiveness of the nasal route for systemic delivery of large molecules.

Technologies have been developed in recent years to significantly enhance the intranasal bioavailability of macromolecules and thus the feasibility and commercial attractiveness of such products (Table 1). A nasal insulin formulation using CPE-215® technology ('Nasulin') is in clinical development, and a bioavailability in patients with type 1 diabetes of up to approximately 20% has been reported [13]. This represents a considerable improvement over earlier studies and illustrates the advances that have been made in absorption-enhancing technologies; for example, in 1995, Hilsted *et al.* [14]

reported that a nasal insulin formulation containing a phospholipid enhancer required a 20-fold higher dose than subcutaneous injection, implying a bioavailability of around 5%.

Chitosan has been extensively investigated as an agent for enhancing the intranasal delivery of drugs and vaccines [15,16]. Excellent intranasal bioavailability has been reported for several compounds using chitosan, including large molecules such as hGH (molecular weight 22 kDa) [17].

Vaccination

The appeal of needle-free vaccination is evident, especially when mass immunizations are required, and is a very topical subject given the 2009 pandemic H1N1 influenza outbreak. The nose contains the nasal (or nasopharynx)-associated lymphoid tissue, which is an important part of the human immune system and acts as a site to capture infectious organisms entering the body through the respiratory tract [18]. The nasal route, therefore, is particularly attractive for vaccinating against infections that enter the body by inhalation, such as influenza, and has the advantage of eliciting both local (mucosal) and systemic antibody responses [19,20]. There is the added benefit of being able to formulate nasal vaccines for administration as powders, which can enhance stability and avoid cold-chain storage [21]. FluMist® (an intranasal seasonal influenza vaccine) is marketed in the USA, and NASOVAC™ (a nasal H1N1 vaccine) was launched recently in India (http://www.seruminstitute.com/content/products/product_nasovac.htm). The use of mucosal adjuvant technologies, such as chitosan [15,16], can provide an enhanced mucosal antibody response; this might enable the dose of antigen to be reduced and will be central to expanding the number of vaccines given intranasally. Positive preclinical or clinical data have been published for chitosan solution and powders in combination with antigens including influenza [22], diphtheria [23] and anthrax [24]. The use of nanoparticles has been suggested as an advantageous means for delivering antigens by the nasal route [25].

Direct CNS delivery

It has been suggested that the olfactory and trigeminal neural pathways provide a direct route for the transport of therapeutic agents from the nasal cavity into the CNS, thus circumventing the blood–brain barrier [26]. This opens up the possibility of a range of therapeutic opportunities and some potentially interesting applications for well-established compounds; for example, insulin is being investigated as a treatment for Alzheimer's disease [27]. However, the olfactory region is very small in humans and is relatively inaccessible using traditional nasal delivery devices and modes of administration; in the insulin study, medication was delivered into the nasal cavity using a syringe, with the patients lying with the head tilted backwards. A 'bi-directional' delivery device that is claimed to provide a more extensive distribution of drug than conventional devices has been used to deliver sumatriptan [28] and midazolam [29] in clinical studies; it was speculated in these studies that the pharmacokinetic and pharmacodynamic results might have been attributable, at least in part, to direct CNS drug transport.

Are there any downsides?

Although the costs and risks associated with developing a nasal formulation for an established drug are small compared to those of developing a new molecular entity, this process should not be trivialized. Route-specific toxicology studies and a database of patient safety are needed before the approval of products administered by a new route of delivery. If a new indication is being explored then, clearly, extensive clinical trials may be required. Similarly, safety and quality need to be addressed if excipients that are entirely novel or that have not previously been administered intranasally are used.

Dose and solubility are also potential limiting factors within the capacity constraints of the nasal cavity. Enabling excipients might be integral to the success of a nasal protein or vaccine formulation because the efficiency of nasal administration is an important factor when a non-injectable formulation is being considered for a high-value therapeutic agent: for example, a reduction in bioavailability compared to injection means a correspondingly higher dose with corresponding cost implications. Use of appropriate enabling technologies, however, will maximize the efficiency of nasal administration and, together with the lower costs to the healthcare system and improved patient compliance associated with injection-free administration, might provide a strong pharmacoeconomic argument for an intranasal formulation. A strong mucosal antibody response is an important differentiating factor for an intranasal vaccine.

The nasal cavity is more forgiving with respect to droplet and particle size characteristics than the lung, and the efficiency of dose delivery is higher. Nevertheless, regulatory requirements for nasal product and device characterization are similarly demanding and share many attributes with pulmonary formulations.

Finally, intranasal drug delivery is a specialized area and, when contemplating the development of a systemically acting nasal formulation, it is important to partner with organizations experienced in this field to maximize the potential of the drug and to ensure a rapid and efficient path through preclinical and clinical development.

Concluding remarks

Intranasal administration is most commonly associated with treating local conditions, such as rhinitis and congestion. For systemic delivery of drugs and for vaccination, the nose remains underexploited but is arguably among the most attractive routes for non-invasive drug delivery.

The nasal route can be utilized to produce improved treatments for chronic and acute conditions using existing drug compounds, is potentially enabling for drugs that cannot be effectively delivered by other routes and/or for which injection is the only option, and has exciting potential for vaccine administration. New intranasal products such as fentanyl have the potential to transform the perception of nasal delivery and can only help to open up other untapped reformulation opportunities for drugs and vaccines.

Although it presents some considerable challenges, the potential to deliver drugs directly into the CNS via the nose also offers some intriguing therapeutic possibilities. The number of pharmaceutical and drug delivery companies active in the intranasal field has declined (presumably, in part, as a result of the global financial crisis), but there are many potential opportunities for those remaining, and it is the authors' view that the full potential of nasal delivery in producing innovative pharmaceutical products is yet to be realized.

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