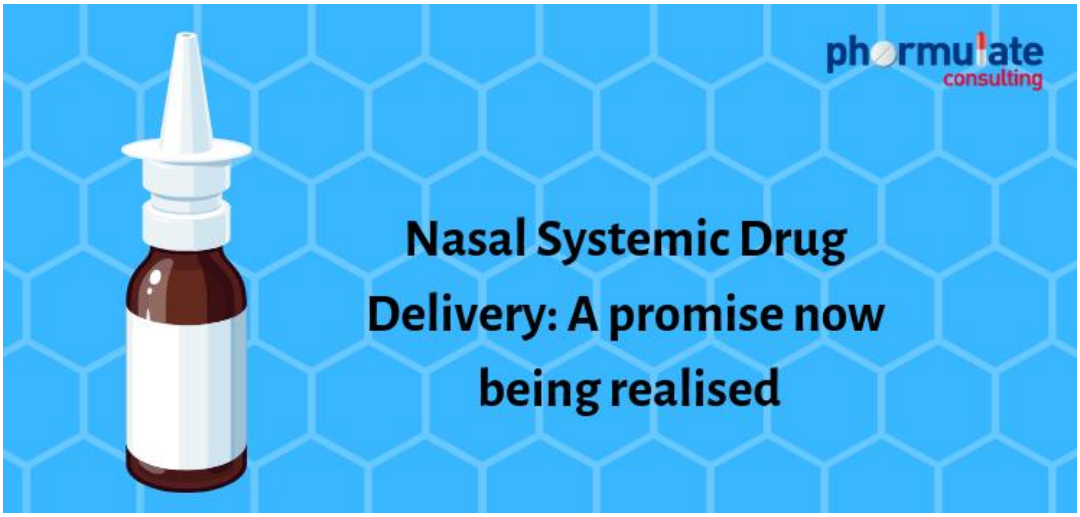

Having worked in the field of nasal drug delivery for more than 20 years and with drug candidates ranging from small molecules through to proteins and possessing a multitude of development challenges, I thought it would be timely to write this brief overview of where the field currently is, specifically using the nose to administer drugs for systemic effect (I'm not covering locally-acting drugs or vaccines in this piece). This is an area of the pharmaceutical sciences which appears to be undergoing something of a renaissance.

A short history

It was first realised that the nose might offer a viable route of entry into the systemic circulation for challenging molecules, notably peptides, more than thirty years ago. Pioneering companies such as DanBioSyst and Nastech set about developing technologies to enable the nasal systemic delivery of a diverse range of molecules. While simple solution formulations of peptide compounds had low intranasal bioavailability, it was considered adequate by the originator companies, and products such as desmopressin, GnRH agonists and calcitonin reached the market. A few small molecule products for nasal systemic delivery also began to be commercialised around this time, including the migraine treatments dihydroergotamine, sumatriptan and zolmitriptan (all simple aqueous solutions).

Revolutions are infrequent in the field of drug delivery and technologies come into and go out of favour based not only on clinical success(es) but perceived patient acceptance, developability and cost. New innovations and hype inevitably go hand in hand and innovative formulation and drug delivery technologies often over-promise and under-deliver (literally!). In those early years the full potential of nasal delivery was never realised, and the pharma industry to a large extent lost interest in using this route for systemic drug delivery.

The search for new product opportunities that demonstrate an improved clinical outcome and positive patient experience at a cost that healthcare systems are willing to reimburse is becoming ever more challenging. In the past few years there has been a renewed interest in the advantages of using the nose as a route for systemic delivery, which has doubtless been energised by that search for innovative new product opportunities. This revival has resulted in a remarkable number of new nasally-administered products currently in development or recently launched across a wide range of therapeutic areas.

Solves many delivery challenges

Using the nose for systemic drug delivery offers many advantages, comprehensively reviewed elsewhere: Fast absorption; good bioavailability for many drugs (especially lipophilic ones);

avoidance of needles; easy administration for carers and healthcare providers; potential to directly access the central nervous system.

Importance of the device

The administration device is of critical importance. The inherent delivery characteristics of the device will be a key contributor to clinical effectiveness but the interaction between the device and user must not be overlooked; a device which is poorly designed and difficult to use from a patient perspective has the potential to negatively impact clinical outcomes and promote a negative perception of the administration route.

Devices exist for administering single and multiple doses of liquids and powders and for targeting specific anatomical areas of the nasal cavity, notably the olfactory region for accessing the CNS.

Some examples

Examples of products which are in clinical development, filed for approval or recently launched are listed in the tables below (current as of November 2018). I have categorised them according to the primary advantage which is achieved by using nasal administration, although many of the products would fit into multiple categories.

Enabling needle-free administration of complex drugs with negligible oral bioavailability e.g. peptides, proteins

Active	**Indication**	**Company**	**Status**
Carbetocin	Prader-Willi syndrome	Levo Therapeutics	Phase 2/3
Glucagon	Hypoglycaemia	Eli Lilly	Awaiting approval
Merotocin	Lactation failure	Ferring	Phase 2
Octreotide	Acromegaly + others	Dauntless Pharmaceuticals	Phase 1

Fast action without IV injection

Many of these products are likely to be given by carers, hence the ease of dosing offered by nasal administration is attractive.

Active	**Indication**	**Company**	**Status**
Epinephrine	Anaphylaxis	INSYS Therapeutics	Phase 2
Etripamil	PSVT*	Milestone Pharmaceuticals	Phase 3
Nalmefene	Opioid overdose	Opiant Pharmaceuticals	Phase 1
Naloxone	Opioid overdose	Adapt Pharma	Approved
Midazolam	Acute seizures	UCB	Awaiting approval
Olanzapine	Agitation	Impel NeuroPharma	Phase 1
Diazepam**	Acute seizures	Neurelis	Awaiting approval
PH94B	Social anxiety	Vistagen	Phase 2/3

* Paroxysmal supraventricular tachycardia; ** Existing product administered rectally

Overcoming impaired or delayed oral absorption e.g. due to nausea/vomiting, gastric stasis

Active	Indication	Company	Status
Dihydroergotamine†	Migraine	Impel NeuroPharma*	Phase 3
Metoclopramide	Gastroparesis	Evoke Pharma	Awaiting approval
Sumatriptan†	Migraine	Avanir* Promius Pharma**	Approved Awaiting approval

† Second generation product(s): * advantaged delivery device; ** utilises absorption enhancer

Access to olfactory and trigeminal nerve pathways

Active	Indication	Company	Status
Insulin	Alzheimer's	Impel NeuroPharma	Phase 3
OC-01 and OC-02	Dry eye disease	Oyster Point Pharma	Phase 2

Low oral bioavailability (high first pass metabolism)

Active	Indication	Company	Status
Esketamine	Depression	Janssen	Awaiting approval
Naltrexone	Alcohol misuse	Opiant Pharmaceuticals	Phase 1

There are challenges but many solutions

As with any route, nasal delivery has its drawbacks and many drug candidates may appear, at least on first inspection, to be unsuitable for administration via the nose for a variety of reasons. However, there are creative solutions to deal with many of these issues.

- Hydrophilic and high molecular weight drugs generally have low absorption
    - Absorption enhancers exist although there are safety, tolerability and cost considerations, including potential licensing fees (there's further discussion below)
- There are dose limitations in terms of drug solubility and the maximum spray volume or powder mass which can feasibly be administered
    - There is the possibility of using non-aqueous solvents for solubility enhancement, but toxicology will need to be assessed
- Tolerability – irritation and taste disturbance need to be considered both for the drug and delivery vehicle (product draining from the nasally cavity encounters taste receptors)
- Manufacturing and packaging costs are relatively high, especially for single dose presentations
- Limited number of CDMOs
- Relatively complex CMC data requirements

Absorption promoters

From the very early days of nasal drug delivery it became apparent that systemic absorption of many compounds would be inadequate without using enabling excipients. While aggressive surfactants were found to be effective enhancers by disrupting the nasal epithelial membrane, the extent of tissue damage they caused was unacceptable; a fine balance was needed between tissue disruption and safety i.e. any disturbance of the cell membrane needed to be mild and transient. Bioadhesive agents were also of interest since they had the potential to enhance bioavailability by prolonging drug residence at the absorption site.

For nasal products currently in development, the favoured enhancer is Aegis Therapeutics' Intravail® technology, which is based around alkylsaccharides, a class of compounds which have surfactant properties. The companies using Intravail® in their nasal products include Promius Pharma (sumatriptan), Neurelis (diazepam), Dauntless Pharmaceuticals (octreotide) and Opiant Pharmaceuticals (nalmefene and naltrexone).

Chitosan, a bioadhesive polymer, also deserves a mention. There is undoubtedly a larger database of preclinical and clinical data on chitosan than any other nasal enhancer technology. Proof-of-principle studies have been conducted for numerous drugs and many clinical trials have been completed during the past three decades. None of these products have yet been commercialised; it could be argued that many were ahead of their time and the market for them would now be more compelling. Chitosan should remain an excipient to be considered when contemplating nasal delivery of challenging molecules, and although it presents its own set of challenges, individuals and organisations with expertise on its use in intranasal delivery are available to assist in navigating the development pathway.

Where next?

While the versatility of nasal systemic drug administration is clear, the reality is that oral delivery will always reign supreme. The pull is such that there are orally-administered peptide medicines under development which could be more feasibly delivered via the nose; clearly some negative perceptions of the nasal route remain.

However, the many interesting and attractive attributes of the nasal route mean there are a multitude of pharma product opportunities which can take advantage of them, particularly in the speciality space. Increasing patient familiarity and acceptance can only further encourage the adoption of nasal products. There's significant potential for paediatric use since this patient population is particularly averse to needles; there are already several drugs which are instilled into the nose as the injection solution in hospital settings. Many of these injection preparations will be sub-optimal for nasal use and consequently present product development opportunities.

Nasal drug administration as a means of targeting the central nervous system is still in its infancy and has the potential to yield interesting new products in the future.

The development of new absorption-promoting compounds and continued advances in device technologies will only act to enhance the attractiveness of nasal systemic drug delivery.