Nasal Drug Delivery in Humans

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Abstract

Intranasal administration is an attractive option for local and systemic delivery of many therapeutic agents. The nasal mucosa is – compared to other mucous membranes – easily accessible and provides a series of unique attributes, all of which may help to maximize the patient’s safety, convenience and compliance.
Table 1. Selection of compounds for transmucosal nasal drug delivery

<table>
<thead>
<tr>
<th>Compound</th>
<th>Class</th>
<th>Indication</th>
<th>Investigation/product development/product and country (example)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apomorphine</td>
<td>dopamine agonist</td>
<td>Parkinson's disease (on-off symptoms)</td>
<td>product development</td>
<td>3, 4</td>
</tr>
<tr>
<td>Buserelin</td>
<td>peptide</td>
<td>prostate cancer</td>
<td>Profact, Germany</td>
<td>5</td>
</tr>
<tr>
<td>Butorphanol</td>
<td>opioid</td>
<td>migraine</td>
<td>Stadol, USA</td>
<td>6</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>protein</td>
<td>osteoporosis</td>
<td>Karil, Germany</td>
<td>7</td>
</tr>
<tr>
<td>Cobalamin (vitamin B₁₂)</td>
<td>vitamin</td>
<td>substitution of vitamin B₁₂</td>
<td>Nascobal, USA</td>
<td>8</td>
</tr>
<tr>
<td>Desmopressin</td>
<td>protein</td>
<td>diabetes insipidus centralis, enuresis nocturna</td>
<td>Minirin, Germany</td>
<td>9</td>
</tr>
<tr>
<td>Diazepam</td>
<td>benzodiazepine</td>
<td>sedation, anxiolysis, status epilepticus</td>
<td>product development</td>
<td>10</td>
</tr>
<tr>
<td>Estradiol</td>
<td>steroid</td>
<td>substitution of estradiol</td>
<td>Aerodiol, UK</td>
<td>11, 12</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>opiate</td>
<td>analgesia, postoperative pain and agitation in children</td>
<td>Instanyl, Germany</td>
<td>13</td>
</tr>
<tr>
<td>Gonadorelin</td>
<td>hormone</td>
<td>undescended testicle</td>
<td>Kryptocur, Germany</td>
<td>14</td>
</tr>
<tr>
<td>Human growth hormone</td>
<td>peptide</td>
<td>growth hormone deficiency</td>
<td>investigation</td>
<td>15</td>
</tr>
<tr>
<td>Influenza vaccine, live attenuated</td>
<td>vaccine</td>
<td>flu prevention</td>
<td>Flu Mist, USA</td>
<td>16</td>
</tr>
<tr>
<td>Insulin</td>
<td>peptide</td>
<td>diabetes mellitus</td>
<td>investigation</td>
<td>17</td>
</tr>
<tr>
<td>Ketamine</td>
<td>NMDA antagonist</td>
<td>analgesia</td>
<td>product development: Ereska</td>
<td>18</td>
</tr>
<tr>
<td>L-Dopa</td>
<td>nonproteinogenic amino acid</td>
<td>Parkinson's disease</td>
<td>investigation</td>
<td>19</td>
</tr>
<tr>
<td>Melatonin</td>
<td>hormone</td>
<td>jet lag</td>
<td>investigation</td>
<td>20</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>D₂ receptor antagonist</td>
<td>antiemesis</td>
<td>Pramidin, Italy</td>
<td>21, 22</td>
</tr>
<tr>
<td>Midazolam</td>
<td>benzodiazepine</td>
<td>sedation, anxiolysis, status epilepticus</td>
<td>investigation</td>
<td>23, 24</td>
</tr>
<tr>
<td>Morphine</td>
<td>opiate</td>
<td>analgesia</td>
<td>product development: Rylomine</td>
<td>25</td>
</tr>
</tbody>
</table>
(d) the application device (pharmaceutical considerations) have to be addressed, e.g.:

(a) Is the drug designated for local or systemic delivery, for single or repetitive administration, is the therapeutic target concentration known?

(b) Are the physicochemical properties of the drug suitable for intranasal administration, can clinically relevant bioavailability be achieved?

(c) Can the vehicle provide prolonged drug stability, ideal characteristics during (ejection) and after application (prolonged residence time on the mucosa) and support drug delivery to local target tissues or to the blood vessels for systemic delivery?

(d) And finally, is the application device easily deployable and does it allow adequate drug/formulation deposition within the nose?

These issues are addressed below with a view to their impact on the development of products for nasal application.

**The Nose – Anatomy and Function**

The nose is a complex multifunctional organ. The major functions of the nasal cavity comprise cleansing the inhaled air and olfaction. Moreover, it exerts important protective and supportive activities; it filters, heats and humidifies the inhaled air before it reaches the lower parts of the airways. Nasal hairs and mainly the nasal mucosa with its sticky mucus blanket help to prevent xenobiotics like allergens, pathogens or foreign particles from reaching the lungs. It represents a most efficient

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<tr>
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<th>Indication</th>
<th>Investigation/product development/product and country (example)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nafarelin</td>
<td>hormone</td>
<td>central precocious puberty, endometriosis</td>
<td>Synarel, USA</td>
<td>26</td>
</tr>
<tr>
<td>Nicotine</td>
<td>addictive substance</td>
<td>smoking cessation</td>
<td>Nicotrol NS, USA</td>
<td>27</td>
</tr>
<tr>
<td>Oxytocin</td>
<td>hormone</td>
<td>lactation; treatment of social, cognitive and mood disorders</td>
<td>Syntocinon spray, Switzerland</td>
<td>28</td>
</tr>
<tr>
<td>Progesterone</td>
<td>hormone</td>
<td>infertility, amenorrhea</td>
<td>investigation</td>
<td>12</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>PDE inhibitor</td>
<td>erectile dysfunction</td>
<td>investigation</td>
<td>29</td>
</tr>
<tr>
<td>Sumatriptan</td>
<td>triptan</td>
<td>migraines</td>
<td>Imigran nasal spray, Switzerland</td>
<td>30</td>
</tr>
<tr>
<td>Testosterone</td>
<td>hormone</td>
<td>substitution of testosterone</td>
<td>investigation</td>
<td>31</td>
</tr>
<tr>
<td>Zolmitriptan</td>
<td>triptan</td>
<td>migraines</td>
<td>Zomig, Switzerland</td>
<td>32, 33</td>
</tr>
</tbody>
</table>

NMDA = N-methyl-D-aspartate; PDE = phosphodiesterase.
first line of defense for the body’s airway as it copes with more than 500 liters of air that are filtered hourly into the lung. During this time it is thought that more than 25 million particles are processed by this epithelium [34, 35]. Mucociliary activity removing mucus towards the nasopharynx, immunological activities involving a variety of immunocompetent cells and metabolism of endogenous substances are further essential functions of the nasal structures. The nasal cavity connected to other cavities such as the frontal and maxillary sinus and the ear also serves as a resonant body.

There are 3 distinct functional areas (fig. 1) in the nasal cavity, the vestibular, olfactory and respiratory zones. The vestibular area (approx. 0.6 cm²) serves as a first barrier against airborne particles with low vascularization comprised of stratified squamous and keratinized epithelial cells with nasal hairs. The olfactory area (approx. 15 cm²) enables olfactory perception and is highly vascularized. The respiratory area (approx. 130 cm²) serves with its mucus layer produced by highly specialized cells as an efficient air-cleansing system [36]. The surface of this zone is enlarged by the division of the cavity by lateral walls into 3 nasal conchae or turbinates and by the magnification of the mucosa by microvilli and cilia. The magnification in terms of square centimeters is unknown. The zone is highly vascularized. The posterior region of the nasal cavity is the nasopharynx. Its upper part consists of ciliated cells, the lower part contains squamous epithelium. The area is also part of the mucosal immune system.

Due to the rich vascularization, the olfactory and in particular the respiratory zone may serve as an efficient absorption surface for topically
applied drugs. The olfactory region with its vicinity to the cerebrospinal fluid and direct nervous interface to the brain has attracted research interest for possible nose-to-brain delivery.

The respiratory epithelium as well as other parts of the nasal cavity and airways are lined by superficial epithelium (fig. 2) consisting primarily of 2 types of cells: mucus-producing goblet cells (20%) and ciliated cells (80%). The various cell types of the epithelium are joined together by tight junctions. Mucus continuously produced by goblet cells traps inhaled particulate and infectious debris while the propulsive force (about 1,000 strokes/min) generated by ciliated cells transports the mucus towards the nasopharynx and the gastrointestinal tract for elimination. This effective cleansing mechanism is called mucociliary clearance (MCC) [37]. The MCC time is approximately 20 min but is subject to great inter-subject variability. The MCC is dependent on the function of the cilia and the characteristics of the covering mucus, which can be influenced by acute or chronic illnesses like common cold or allergic rhinitis. Many substances can influence the MCC of the airways, either by stimulation or inhibition. A stimulatory effect of drugs on the MCC is of clinical importance, because these substances can possibly be used to improve pathological conditions of the MCC. Components (drug, ingredient) of nasally administered formulations with a too pronounced MCC-impairing activity may limit their use.

Nasal Delivery

The intranasal administration represents a viable option for local and systemic delivery of many therapeutic agents. Therapeutic and pharmaceutical considerations direct the development of nasal products [38].

Therapeutic Considerations
Answers to key questions whether the drug is intended for (a) local or systemic delivery or for (b) single or repetitive administration and (c) patient-related issues (e.g. adults, children) define the development strategy for the nasal product. An idea of the clinically effective drug concentration in the target site should exist in order to estimate the feasibility of the nasal application route.

![Cell types of the nasal epithelium with covering mucous layer.](image)
Local Delivery
Prominent examples for locally acting intranasally administered drugs are decongestants for nasal cold symptom relief, antihistamines and corticosteroids for allergic rhinitis. Due to the fact that relatively low doses are effective when administered topically, the intranasal administration of antihistamines and corticosteroids has a weak potential for systemic adverse effects as opposed to systemic therapy. Intranasal administration is therefore a logical delivery choice for the topical (local) treatment of nasal symptoms.

Systemic Delivery
The nasal mucosa provides a practical entrance portal for systemically acting molecules. Intranasal administration offers a rapid onset of therapeutic effects, avoids the first-pass effect or gastrointestinal degradation of drugs, is noninvasive, essentially painless and finally easily administered by patients or by physicians in emergency settings. The intranasal administration provides a true alternative route for systemic drugs presently delivered more conventionally by oral or parenteral routes.

Single versus Repetitive Administration
The disease, the therapeutic goal and the therapeutic agent predefine the dosing regimen. Dosing frequencies of currently marketed intranasally administered products range from weekly dosing to multiple times daily. To avoid multiple parenteral applications, repetitive intranasal administration may be practical for the situation of chronic application with orally insufficient drug bioavailability.

The delivery target (local, systemic) as well as the intended dosing schedule govern the development strategy and therefore predefine the drug form (dissolved, ionized etc.), the vehicle form (solid, semisolid, liquid) including the specific ingredients to form the vehicle system (powder, gels, microspheres, solution etc.) and the application device, which determines the drug deposition within the nose.

Patient-Related Issues
The nasal physiology and anatomy have a potential impact on intranasal administration. Temperature, humidity, airflow and the nasal cycle – an alternating congestion and decongestion of the nasal mucosa – may change the absorption area. Any impairment of the physiological and anatomical situation – whether natural (nasal cycle) or pathological (inflammation, nosebleed, alterations as a result from smoking, snuffing, decongestant addiction or nasal drug abuse) – may have a potential impact on intranasal absorption. The extent of this impact is unknown.

Even though the epithelial tissue within the nasal cavity provides an ideal absorption area, the natural permeation barrier and the efficient cleansing mechanism confine the total amount of drug that can be absorbed. Therefore the clinically effective drug concentration at the target site requires a therapeutic agent with sufficient potency.

Pharmaceutical Considerations
Once the therapeutic goal and the therapeutic agent have been defined, the formulation scientist is challenged to incorporate the drug into a vehicle system that provides prolonged drug stability, ideal dispensing characteristics from a tailor-made delivery device during (ejection) and after application (prolonged residence time on the mucosa) which supports drug delivery to a local target site (penetration; e.g. antihistamines such as levocabastine) or to the blood vessels for systemic delivery (permeation; e.g. benzodiazepines such as midazolam).

Thoughtful consideration of all elements in a formulation triad – comprising drug, vehicle form/system and delivery device – is the basis of a successful formulation development (fig. 3). Based on the properties of the drug molecule, the vehicle form/system (solid; powder, semisolid; gel, emulsion or liquid; solution) is determined first; second, the device is chosen, and third the ingredients are chosen to create an optimal vehicle. Skillful selection of vehicle form/system
and ingredients bypasses natural attributes of the mucus blanket as a protective layer (i.e. increase drug absorption) and of the MCC as an effective cleansing mechanism (i.e. increase resident time of formulation on the mucous layer).

Drug Characteristics
The influence of physicochemical characteristics [38–40] of drug molecules on the rate and extent of absorption through biological membranes is generally well explored. In numerous predominantly animal studies, the influence of the drug characteristics in nasal absorption was studied. Lipophilic drugs are in general well absorbed from the nasal cavity, presenting pharmacokinetic profiles often similar to those obtained after intravenous administration. Lipophilic molecules with molecular weights less than 1 kDa
are rapidly and efficiently transcellularly absorbed across the nasal membrane. The extent of absorption for lipophilic molecules larger than 1 kDa is significantly lower. Absorption of hydrophilic drugs is generally low and highly dependent on the molecular weight. Absorption through membranes is not only affected by lipophilicity/hydrophilicity or molecular weight, but also by the amount of drug existing as uncharged species. This depends on the drug pKₐ and the pH at and in the absorption site – the nonionized fraction of the drug is more permeable than the ionized one. The pH of the nasal epithelium is 5.5–6.5. A pH lower than 5.5 or higher than 6.5 combined with a buffer capacity higher than that of the nasal epithelium may cause local adverse effects and may therefore affect drug permeation. Only the molecularly disperse form of a drug at the absorption site may cross the nasal epithelium. Therefore sufficient drug solubility is a prerequisite for any drug absorption. Due to the limited amount of vehicle that can be lastingly applied to the nasal cavity without losing drug through vehicle runoffs via the nasopharynx including subsequent ingestion or via the vestibular area of the nose, the solubility of the drug must guarantee sufficient bioavailable molecules to achieve a clinical effect. Some characteristics are important when choosing a drug candidate for transmucosal nasal drug delivery in an aqueous formulation (table 2).

Against this background it becomes obvious that selecting drug candidates for transmucosal nasal application may become challenging. The biopharmaceutical drug classification system [41] reveals that drug candidates that fit into class I (high permeability, high solubility) have the highest potential for nasal delivery. To further refine the selection criteria for small molecules in aqueous solution, one may – in the style of the Rule of Five defined by Lipinski et al. [42] – establish the following rule of thumb:

- drug characteristics: molecular weight <500 Da, logP <5;
- dose per spray puff (left and right nostril): potency <5 mg/dose;
- volume maximally 100 μl/spray puff: solubility >50 mg/ml;
- drug in solution: pH approximately 5.5, osmolality <500 mosm/kg.

Vehicle System
The assignment of a pharmaceutical vehicle is to provide prolonged drug stability, ideal characteristics during (e.g. ejection) and after application (e.g. prolonged residence time on the mucosa) and to support drug delivery to local target tissues or to the blood vessels for systemic delivery.

It is obvious that drug stability is a basic prerequisite for a marketable product. Referring strategies and modalities are discussed elsewhere.

To support drug absorption through the nasal mucosa, 2 natural protective functions have to be bypassed – the MCC and the barrier properties of the tissue.

The MCC mechanism efficiently removes product from the application site, by reducing product contact (time and adhesion) in the potential absorption area. Skillfully chosen ingredients that form the vehicle are able to temporarily modulate the MCC and may therefore eventually increase drug absorption. Mucoadhesive ingredients enable the vehicle encasing the drug an intimate and prolonged contact with the mucosa [43].

Adhesion provided by polymers such as carbomers, chitosans, cellulose or starch derivates results from van der Waals, hydrogen, hydrophobic and electrostatic forces (wanted) and chemical bonds (unwanted). Concurrently they increase viscosity of the formulation and prevent loss of product towards the nasal vestibule or the nasopharynx. However, very high product viscosities will stimulate the cleansing mechanism. The relevance of viscosity for bioavailability of nasal drug products is still unknown.

It is possible to significantly improve the absorption of molecules if they are applied in
Table 2. Characteristics to consider when choosing a small-molecular-weight drug candidate for transmucosal nasal drug delivery in an aqueous formulation

<table>
<thead>
<tr>
<th>Sequence of importance</th>
<th>Character of drug candidate</th>
<th>Envisaged target range</th>
<th>Comments/suggestions for improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>+++</td>
<td>potency</td>
<td>max. 20 mg/dose</td>
<td>nasal bioavailability of drug has to be considered to reach the therapeutic target dose/none</td>
</tr>
<tr>
<td>+++</td>
<td>local mucosal toxicity</td>
<td>no toxicity and tissue damage</td>
<td>minor damage tolerable for emergency or single-application use, no toxicity or damage for chronic use/none</td>
</tr>
<tr>
<td>+++</td>
<td>solubility</td>
<td>&gt;100 mg/ml (for a potency of 20 mg/dose)</td>
<td>none/solubility can be improved by means of prodrugs, solubility enhancers, other salt forms, polymorphic forms</td>
</tr>
<tr>
<td>+++</td>
<td>solubility and spray volume</td>
<td>maximal 100-200 μl (1 or 2 puffs with 100 μl)</td>
<td>spray volumes may be increased by means of mucoadhesive formulations up to 150 μl for a puff without runoff problems/none</td>
</tr>
<tr>
<td>+++</td>
<td>stability in solution</td>
<td>≥2 years</td>
<td>prerequisite for reasonable shelf life/ stability of solution can be improved by solubility enhancers, stabilizers and prodrugs</td>
</tr>
<tr>
<td>+++</td>
<td>molecular weight</td>
<td>&lt;1,000 Da</td>
<td>smaller size is an advantage/permeability enhancers like chitosan can boost the paracellular absorption</td>
</tr>
<tr>
<td>++</td>
<td>compatibility with adjuvants</td>
<td>prerequisite</td>
<td>choose appropriate excipients, the triad of nasal drug delivery (drug, vehicle and device) has to be in balance, slight changes may alter clinical effects/none</td>
</tr>
<tr>
<td>++</td>
<td>logP</td>
<td>1–5</td>
<td>none/permeability enhancers like chitosan can boost the paracellular absorption of hydrophilic drugs, very lipophilic drugs need special vehicle systems</td>
</tr>
<tr>
<td>++</td>
<td>pH of solution</td>
<td>(3.5) 4–7.5</td>
<td>slightly acid is recommended, impairment of ciliary function possible at very low and very high pH, avoid buffers/none</td>
</tr>
<tr>
<td>+</td>
<td>osmolality of solution</td>
<td>290–500 mosm/kg</td>
<td>higher values tolerable for emergency or single-application use, isotonic conditions for chronic use, hypotonic solutions should be avoided/if solution is hypertonic, revise formulation</td>
</tr>
</tbody>
</table>

+ = Moderate; ++ = high; +++ = very high. The character of each drug candidate is ranked according to its importance. An envisaged target range and concomitant comments and suggestions for formulation improvements are presented (see also the section on pharmaceutical trends and perspectives).
combination with absorption-enhancing ingredients. They reversibly modify the barrier properties of the nasal epithelium. In intranasal drug delivery, surfactants, bile salts, fatty acids and polymeric enhancers have been proposed for absorption enhancement [44]. However, their local tolerance is often awkward and has therefore to be carefully evaluated. Local or systemic intolerance after ingestion or inhalation or impairment of the MCC has to be avoided by all means. The addition of dexamethasone as excipient proved to be an option to avoid cytotoxicity [45]. The knowledge of the mechanism of action of absorption enhancers is still incomplete but they change the permeability of the epithelial cell layer by increasing the fluidity of the bilayers (increasing transcellular transport) or by weakening the cellular junctions (increasing paracellular transport). Unfortunately a correlation between enhancing bioavailability and damaging the membrane does exist for many enhancer molecules. This is particularly important to remember when designing products for chronic use.

Chitosan – a linear polysaccharide biopolymer – has emerged as an optimal molecule that reveals mucoadhesive properties and opens transiently the tight junctions increasing paracellular transport of polar drugs [46].

Osmolality and pH of the vehicle affect local tolerance and the current state of the drug (ionized, nonionized). Osmolality and pH should whenever possible be adapted to the physiological situation.

Application Device
The intended use and the pharmaceutical form of a nasal product (lavages, drops, squirt systems, sprays) predetermine the character of the application device. The dose (volume per puff normally only 100 μl), the dosing options (single vs. multiple), the users (consumer, patient, children, elderly individuals, any involved healthcare professionals) and a patient’s state of health predetermine the character of the application device.

Material and design of application devices for lavages, drops and squirt systems are straightforward whereas in recent years for sprays (liquid, powder) dedicated material and ingenious designs have been chosen to attain optimal and specific clinical effects (see the section on pharmaceutical trends and perspectives). Earlier it was revealed that the application mode as a consequence of the pharmaceutical form and the application device influence product deposition within the nose [47, 48]. Furthermore the suitability of an application device frequently depends on a patient’s position (supine vs. upright).

Today the range of devices one can choose from is huge. Due to the ubiquitous reports on preservative-mediated intolerance, the goal of any evaluation should be to find a device that allows the use of a preservative-free formulation. Preservative-free single- and bi-dose devices filled under sterile conditions are directly disposed of after use. But even modern multidose device systems prevent formulation contamination under multiple-use conditions. This allows also for multidose device systems to be filled with preservative-free formulations. In addition to a better tolerance, the formulation development becomes simplified.

With single- or bi-dose device systems (2 puffs for each nostril, e.g. with Bidose Liquid from Aptar; http://www.pfeiffer-group.com), the patient’s position is less essential (supine vs. upright) whereas with multidose device systems the upright position is essential for correct dosing. Single or bi-dose device systems allow drug and dose accountability which make them suitable for narcotic drugs.

Requirements concerning device performance such as plum geometry or droplet size are strictly regulated. The clinical relevance of some of these parameters remains unknown; however, for the development and registration of generic drug products it is apparently a prerequisite.
**Trends and Perspectives**

**Therapeutic Trends and Perspectives**

**Nose-to-Brain Delivery**

The olfactory region located in the upper remote parts of the nasal passages offers the potential for certain compounds to circumvent the blood-brain barrier and enter the brain. Although the clinical potential of this delivery route is the subject of controversial debates, there is considerable interest [49] in exploring the route for the treatment of common intracerebral diseases such as Alzheimer's [50] or obesity [51].

Vasoconstriction/Vasodilatation

Vasoconstrictors have been used to reduce nasal congestions by reducing blood vessel diameter, blood flow and by increasing blood pressure. In combination – in ophthalmology or anesthesiology – with other drugs to prevent adverse systemic effects by reducing systemic absorption or to prolong the duration of action by reducing clearance from the delivery site. Vasodilators have also been used to enhance the systemic bioavailability of drugs. Documented only recently in animal experiments, the vasoconstrictor phenylephedrine in a nasal formulation enhanced intranasal targeting of neuropeptide therapeutics to the central nervous system (CNS) [52]. Nasal formulations with vasoconstrictors may have particular relevance for CNS therapeutics with adverse side effects where it would be advantageous to limit systemic exposure. However, any pharmacological exertion of influence holds – particularly in the olfactory region – many dangers, e.g. infections.

**Efflux Transport Proteins**

It is known from oral absorption investigation that gastrointestinal drug absorption can be diminished due to efflux transporters, e.g. P-glycoproteins [53]. There are relatively few reports regarding the importance of transporter systems for drug transport across the nasal epithelium. Newer papers have focused on the role of P-glycoproteins in the olfactory epithelium [54]. Uptake into the brain was enhanced when drugs were administered in combination with the P-glycoprotein efflux inhibitor rifampicin. Deeper understanding of the role of these systems in achieving therapeutically relevant concentrations of drug in the CNS may have an important impact on future development of nose-to-brain delivery.

**Nasal Vaccination**

The vast majority of disease-causing bacteria, viruses and parasites reach the body through the mucosal surfaces. It is obvious, therefore, that most of the immune system is either located in, or in direct contact with, mucosal membranes, thus providing a 'first line of defense' system against harmful microorganisms. Among other mucosal sites, nasal delivery is especially attractive for immunization, as the nasal epithelium is characterized by reasonable permeability, low enzymatic activity and by the presence of an important number of immunocompetent cells [16]. Despite these encouraging characteristics, free antigens alone are usually unable to elicit protective responses following their intranasal administration. The physical properties of a vaccine can greatly influence its performance. Nasal vaccines must be specifically formulated and optimized to achieve a good immune response and at the same time prevent local irritation and other potential adverse effects. In order to enhance the potency of the nasal vaccines, adjuvants (i.e. immunostimulatory molecules) such as Toll-like receptor ligands, toxin-based adjuvants or cytokines [55] need to be included in the formulation [56]. Based on current insights, encapsulation of antigens into bioadhesive (nano)particles is a further approach towards improved nasal vaccine delivery. These antigen-loaded particles – some of which are in clinical investigation – can be tailor made by supplying them with targeting ligands, adjuvants or endosomal escape mediators to form the desired vaccine that provides long-lasting protective immunity [57].
Currently only very few nasal vaccine products are approved for human use, indicating that advances towards new effective vaccines are still slow. Opportunities in nasal vaccination are not in a single research field but require the integration of many research fields including immunology, biotechnology, microbiology and pharmaceutical sciences. A concerted approach, combining various targeting techniques including the use of particulate antigen carriers furnished with distinct functionalities such as mucoadhesive polymers, cell-specific targeting ligands, adjuvants and endosomal escape promoters will eventually yield new nasal vaccine products [58].

The Role of Surface Chemistry
It has been observed that some capsid viruses freely diffuse through mucus [59, 60]. The external surface of the virus proteins are coated with equal densities of positive and negative charges, and have no exposed patches of hydrophobic surfaces. Thus, some capsid viruses appear well designed to permeate mucus by being small enough, neutral in net surface charge and coated densely with charged groups that prevent hydrophobic bonding to mucins. Moreover, they have evolved effective methods for adhering selectively to, and entering, their target cells.

Due to the fact that particles usually get trapped and wrapped in mucus, making them less suitable as efficient vehicles, the virus-mimetic nanoparticles may offer some promise for increasing delivery efficiency [60].

Pharmaceutical Trends and Perspectives
Drug Characteristics
More recent drug discovery processes resulted in a high prevalence of potential drug candidates of increased molecular weight and lipophilicity. Such drug candidates represent considerable challenges to formulate therapeutically effective products, since they often have poor bioavailabilities due to their poor dissolution or poor permeability to achieve sufficient and consistent local or systemic exposure.

To address issues of low aqueous solubility, solubilization and micronization have commonly been used to increase dissolution and hence bioavailability of such drugs. Using salt formation, co-solvents, micellar solutions or inclusion complexes with cyclodextrins, there have been attempts to solubilize and stabilize these drugs. Unfortunately the increased amount of ingredients required to formulate the poorly water-soluble molecules may raise the potential for adverse effects.

Micronization of poorly water-soluble drugs increases their dissolution rate by increased surface area. For drugs with very low aqueous solubility, the achieved increase in dissolution rate may remain limited and still insufficient to provide a significant enhancement of bioavailability.

Several studies predicted from thermodynamics the potential impact of polymorphs on bioavailability [61, 62]. The amorphous form of a drug has a higher thermodynamic chemical potential than its crystalline counterpart [63]. The higher thermodynamic activity of the drug can form supersaturated solutions [64], thereby providing an opportunity to enhance absorption and bioavailability. Only recently [65] was it shown that the supersaturation produced by inhaled (pulmonary dosing of rats) amorphous nanoparticles of a poorly water-soluble drug produced a higher systemic absorption and thereby enhanced bioavailability. It is very likely that a similar observation will be made with nasal dosing.

The prodrug concept is a well-established means to overcome unfavorable qualities of a drug such as bad taste, poor solubility, insufficient stability and incomplete absorption across biological barriers. For example, the nasal bioavailability of poorly soluble L-Dopa was enhanced using this concept [19], and it was stated [66] that the aspartate ester prodrug of acyclovir was more permeable and less labile to enzymatic hydrolysis than its parent drug. In addition, the potential use of prodrugs to protect peptide drugs from nasal enzymatic
degradation has been discussed and suggested as a powerful strategy to increase bioavailability of peptides when administered intranasally.

Vehicle System
A drug is infrequently applied to an application site in the form of a pure chemical but, instead, is normally incorporated into a carrier system – the vehicle. The vehicle is built from a series of ingredients to create a 3-dimensional matrix (e.g. gel, liposome). In clinical and experimental situations, most vehicle systems (structural matrix and ingredients) undergo considerable changes after being applied to the absorptive area. This process has been described as ‘metamorphosis of the vehicle’ [67]. Subsequently, the initial structural matrix and the quantitative composition of the vehicle will most likely change after application of the product (e.g. changed pH, dilution with body fluids, evaporation of ingredients). As a consequence of these processes, the thermodynamic activity of the drug within the formulation may change and hence affect bioavailability. The awareness of this phenomenon and its consequences is still low and rarely included in the development of new formulations.

Only recently has the use of an in situ gelling pectin formulation, which exploits this phenomenon of metamorphosis, been developed to deliver fentanyl intranasally. The nasal spray droplets are deposited as a thin layer on the nasal mucosa where they come into contact with calcium ions present in the mucosal fluid at a sufficient concentration to gel the pectin. The jelled formulation will increase the residence time on the mucosal surface and will release the drug in a controlled manner, e.g. delayed maximum time, lowered maximum concentration while maintaining a clinically sufficient area under the curve. Other delivery systems have been described where gel is administered to the nasal cavity. Examples of thermoresponsive formulations that undergo a sol-to-gel transformation when exposed to the temperature found in the nasal cavity include systems based on chitosan and polyethylene glycol and poloxamer and carbopol.

Nasal formulations containing liposomes, microspheres or nanoparticles have been the object of many research efforts. These systems can contain, besides the drug, enzymatic inhibitors, nasal absorption enhancers and/or mucoadhesive polymers in order to improve the stability, membrane permeation or/and retention time in the nasal cavity. However, it is not entirely elucidated if those formulations increase drug absorption by transporting encapsulated drug across the membrane or just because they enhance the nasal retention time and stability of the drug. Moreover, it is doubtful whether the integrity of the liposome at the application site is preserved after application. An observed effect can therefore not be attributed to the liposome itself but may be rather an effect of the ingredients used.

Several pharmaceutical ingredients (glycerol, ethanol, propylene glycol, polyethylene glycol) that are regularly used to formulate vehicles are suitable for mixed solvent systems or as cosolvents and are therefore ideal to increase solubility [68]. In addition to increasing solubility, such cosolvents may provide permeation enhancement across tissue membranes. Local intolerance may be limiting.

Application Device
Numerous delivery devices are available for intranasal administration. Devices vary in accuracy of delivery, dose reproducibility, cost and ease of use. Currently, metered-dose systems provide the greatest dose accuracy and reproducibility. Differences also exist in force of delivery, spray patterns and emitted droplet size. The latter is of the utmost importance for drug deposition within the nasal cavity. The challenge is to optimize deposition while limiting the fraction of small particles able to bypass the nose and enter the lungs. Several companies have proposed new delivery technologies, which can provide a more uniform particle size distribution and therefore improve the nasal deposition pattern.

Recently, a Norwegian company developed an interesting delivery concept for improved
systemic drugs and vaccines. The following 2 aspects of the nasal anatomy are of importance. Firstly, during exhalation the soft palate closes automatically, separating the nasal and oral cavities. Consequently, it becomes possible to use smaller particles in a nasal spray and still avoid lung deposition. Secondly, during closure of the soft palate there is a communication pathway between the two nostrils, located behind the walls separating the two passages. Under these circumstances, it is possible for airflow to enter via one nostril and leave by the other. This bidirectional delivery concept combines the two anatomical facts into one fully functional device. The device is inserted into one nostril by a sealing nozzle, and the patient blows into the mouthpiece. The combination of closed soft palate and sealed nozzle creates an airflow which enters one nostril, turns 180° through the communication pathway and exits through the other nostril (bidirectional flow). Since delivery occurs during exhalation, small particles cannot enter the lungs. Particle size, flow rate and direction can be optimized for efficient delivery to the nasal mucosa. By adding an exit resistor to give additional control of the input pressure, it is possible to optimize distribution to the sinuses and the middle ear. Manipulation of the flow pattern enables delivery to the olfactory region, thereby possibly achieving direct ‘nose-to-brain’ delivery. The 180-degree turn behind the septum will trap particles still airborne, allowing targeted delivery of vaccines and drugs to the adenoid. Provided that patient capability and cooperation are present, the flexibility of the bidirectional delivery concept offers a range of new and attractive nasal destinations not reached by traditional nasal pump sprays [69].

Conclusions

Nasal drug delivery offers an attractive alternative to invasive drug delivery for small- and large-molecular-weight drugs. The major advantages are the straightforward and needle-free application mode and the permeable application site in the nasal cavity that allow a rapid onset of local and systemic drug actions. Appropriate indications are therefore breakthrough pain or emergency conditions such as status epilepticus. Transmucosal nasal absorption prevents drugs from gastrointestinal destruction and hepatic first-pass metabolism. The limited area (150 cm²) in the nasal cavity that offers an optimal absorption environment is perpetually cleansed (MCC) removing all particles including vehicle. Furthermore, the tissue is vulnerable and therefore limits the use of ingredients that form the vehicles.

Nonetheless a considerable number of products for intranasal administration have been developed in recent years. This underlines the continuous attractiveness of the nasal administration mode. Clinical and pharmaceutical considerations predict that the potential of this administration route has not been exhausted yet. Careful and concurrent considerations of all elements in the formulation triad – drug, vehicle system and delivery device – are the basis of successful formulation development.

References


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