

## Intranasal Drug Delivery: How, Why and What for?

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### ABSTRACT

Over the recent decades the interest in intranasal delivery as a non-invasive route for drugs is increased. Since the nasal mucosa offers numerous benefits as a target tissue for drug delivery, a wide variety of therapeutic compounds may be administered intranasally for topic, systemic and central nervous system action. We have, herein, outlined the relevant aspects of nasal anatomy, physiology and histology, and the biological, physicochemical and pharmaceutical factors that must be considered during the process of discovery and development of nasal drugs as well as in their incorporation into appropriate nasal pharmaceutical formulations.

### 1. INTRODUCTION

Oral drug delivery is the most desirable route for drug administration whenever systemic effects are intended. Therefore, it is not surprising that the prediction of human oral bioavailability of new drug candidates is currently targeted from the earliest stages of drug discovery and development programmes (1, 2). However, although the oral route remains the most popular for systemic drug administration, low oral bioavailability of some compounds has prompted the search of more effective routes for their systemic delivery (3).

Intranasal drug delivery is now recognized to be a useful and reliable alternative to oral and parenteral routes. Undoubtedly, the intranasal administration of medicines for the symptomatic relief and prevention or treatment of topical nasal conditions has been widely used for a long period of time. However, recently, the nasal mucosa has seriously emerged as a therapeutically viable route for the systemic drug delivery. In general, among the primary targets for intranasal administration are pharmacologically active compounds with poor stability in gastrointestinal fluids, poor intestinal absorption and/or extensive hepatic first-pass elimination, such as peptides, proteins and polar drugs (4). The nasal delivery seems to be a favourable way to circumvent the obstacles for blood-brain barrier (BBB) allowing the direct drug delivery in the biophase of central nervous system (CNS)-active compounds. It has also been considered to the administration of vaccines (5-8).

The widespread interest in intranasal route for therapeutic purposes other than the topically nasal drug delivery arises from the particular anatomical, physiological and histological characteristics of the nasal cavity, which provides potential for rapid systemic drug absorption and quick onset of action. In addition, intranasal absorption avoids the gastrointestinal and hepatic presystemic metabolism, enhancing drug bioavailability in comparison with that obtained after gastrointestinal absorption (9, 10). On the other hand, intranasal administration also offers several practical advantages either from the viewpoint of patients (non-invasiveness, essentially painless, ease drug delivery and favourable tolerability profile) or pharmaceutical industry (unnecessary sterilization of nasal preparations) (11, 12). Hence, bearing in mind the intrinsic value of intranasal route to overcome patient compliance concerns together with its pharmacokinetic advantages, it appears to be an appropriate route for the treatment of not only acute or chronic nasal diseases, but also for a range of acute or chronic conditions requiring considerable systemic drug exposure (4, 12).

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Despite its advantages, the nasal drug administration presents some limitations that must be considered during the discovery of new chemical entities intended for nasal therapy as well as during the development of nasal formulations. First of all, in addition to physicochemical properties of drugs and characteristics of their final formulations, a variety of physiological and pathological conditions related to nasal mucosa may also compromise the extent of nasal drug absorption and therapy efficacy (7, 11, 13). Furthermore, the low volume of nasal cavity restricts the amount of drug formulation administered to about 100-150  $\mu\text{L}$  (13). Consequently, particular problems may appear if nasal delivery of high doses of poorly water-soluble drugs is necessary. Nevertheless, these drawbacks are often overcome making use of medicinal chemistry and/or pharmaceutical technology-strategies involving for instance the synthesis of prodrugs and/or the use of enhancers or bioadhesive polymers to increase drug permeability and residence time in nasal cavity. Enzymatic inhibitors may also be employed to protect drugs against enzymatic degradation in the nasal mucosa. However, care should be taken in the use of such compounds due to their possible risks to develop nasal irritation and/or systemic toxic effects (14).

In the last few years a number of excellent reviews have been published examining in detail some particular aspects concerning to potential therapeutic applications of intranasal route of drug delivery (15-23). However, general reviews gathering together information about special characteristics of nasal mucosa, desirable physicochemical properties of drugs for nasal administration and successful technology-strategies to develop pharmaceutical formulations for topically or systemically intranasal drug delivery are lacking. Accordingly, the present review outlines anatomical, physiological and histological features of nasal cavity and the major factors affecting nasal drug delivery, highlighting simultaneously the properties of drugs and formulation characteristics that determine decisively the pharmacokinetics of nasal preparations. Additionally, the rationale for the extensive research of nasal medicines with current and future drug therapies, as well as their therapeutic benefit, will be also considered whenever appropriated.

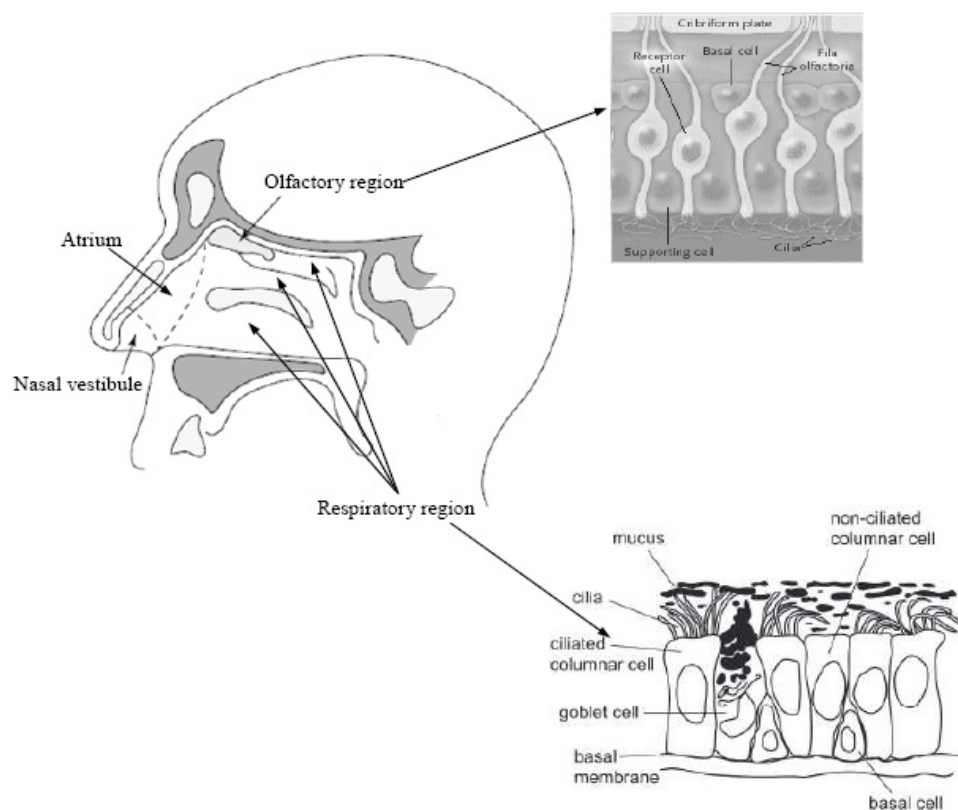
## 2. NASAL CAVITY: ANATOMY, PHYSIOLOGY AND HISTOLOGY

In humans and other animal species the major functions of the nasal cavity are breathing and olfaction (24). However, it also affords an important protective activity once it filters, heat and humidify the inhaled air before reaching the lowest airways. Nasal cavity is lined with mucus layer and hairs which are involved in those functions, trapping inhaled particles and pathogens. Moreover, resonance of produced sounds, mucociliary clearance MMC, immunological activities and metabolism of endogenous substances are also essential functions of nasal structures (25-28).

Anatomic and histological characteristics of the different areas of nasal cavity are such that allow these functions to be performed optimally. Thus, anatomically, human nasal cavity fills the space between the base of the skull and the roof of the mouth; above, it is supported by the ethmoid bones and, laterally, by the ethmoid, maxillary and inferior conchae bones (25). The human nasal cavity has a total volume of 15-20 mL and a total surface area of approximately 150  $\text{cm}^2$  (10, 29). It is divided by middle (or nasal) septum into two symmetrical halves, each one opening at the face through nostrils and extending posterior to the nasopharynx. Both symmetrical halves consist of four areas (nasal vestibule, atrium, respiratory region and olfactory region) that are distinguished according to their anatomic and histological characteristics (Figure 1; Table 1).

### 2.1. Nasal vestibule

Nasal vestibule is the most anterior part of the nasal cavity, just inside the nostrils, and presents an area about 0.6  $\text{cm}^2$  (4). Here, there are nasal hairs, also called vibrissae, which filter the inhaled particles. Histologically, this nasal portion is covered by a stratified squamous and keratinized epithelium with sebaceous glands (4, 27, 28). These nasal vestibular characteristics are desirable to afford high resistance against toxic environmental substances but, at the same time, the absorption of substances including drugs becomes very difficult in this region (30).



**Figure 1.** Anatomy and histology of human nasal cavity.

**Table 1.** Human nasal epithelium characteristics (4, 10, 27, 35).

Nasal Sections	Epithelial Characteristics Cells / Functions	Surface Area	Vascularization	Permeability
Vestibule	<ul style="list-style-type: none"> <li>Stratified squamous and keratinized epithelial cells with nasal hairs / Support and protection</li> </ul>	≈ 0.6 cm <sup>2</sup>	Low	Poor
Atrium	<ul style="list-style-type: none"> <li>Stratified squamous cells / Support</li> <li>Pseudostratified cells / Support</li> </ul>	NF	Low	Reduced
Respiratory region	<ul style="list-style-type: none"> <li>Columnar non ciliated cells / Support</li> <li>Columnar ciliated cells / Support and muciliary clearance</li> <li>Globet cells / Mucus secretion</li> <li>Basal cells / Progenitors of other cell types</li> </ul>	≈ 130 cm <sup>2</sup>	Very high	Good
Olfactory region	<ul style="list-style-type: none"> <li>Sustentacular cells / Support and synthetic</li> <li>Olfactory receptor cells / Olfaction perception</li> <li>Basal cells / Progenitors of other cell types</li> </ul>	≈ 15 cm <sup>2</sup>	High	Direct access to CNS

NF, not found.

## 2.2. Atrium

Atrium is the intermediate area between nasal vestibule and respiratory region. Its anterior section is constituted by a stratified squamous epithelium and the posterior area by pseudostratified columnar cells presenting microvilli (27, 28).

## 2.3. Respiratory region

The nasal respiratory region, also called conchae, is the largest part of the nasal cavity and it is divided in superior, middle and inferior turbinates which are projected from the lateral wall. These specialized structures are responsible for humidification and temperature regulation of inhaled air. Between them there are spaces, called meatus, which are passageways where airflow is created to assure a close contact of the inhaled air with the respiratory mucosal surface. The inferior and middle meatus receive nasolacrimal ducts and paranasal sinuses which are air-filled pockets located inside the bones of the face and around the nasal cavity (31).

The nasal respiratory mucosa, considered the most important section for delivering drugs systemically, is constituted by the epithelium, basement membrane and lamina propria. The nasal respiratory epithelium consists of pseudostratified columnar epithelial cells, goblet cells, basal cells and mucous and serous glands (25, 27, 28). Many of the epithelial cells are covered on their apical surface with microvilli and the major part of them also has fine projections, called cilia (28). Actually, microvilli are important to enhance the respiratory surface area, while cilia are essential to transport the mucus toward the nasopharynx. Under physiological conditions, nasal epithelium is covered with a thin mucus layer produced by secretory glands and goblet cells. These ones secrete granules filled with mucin, a glycoprotein that determines the viscosity of the mucus. The nasal mucus layer is only 5  $\mu\text{m}$  thick and it is organized in two distinct layers: an external, viscous and dense, and an internal, fluid and serous. Overall, nasal mucus layer consists of 95% of water, 2.5-3% of mucin, and 2% of electrolytes, proteins, lipids, enzymes, antibodies, sloughed epithelial cells and bacterial products (32-34). Nasal mucus is indispensable for several physiological functions, such as humidification and warming of the inhaled air, and also offers physical and enzymatic protection

of the nasal epithelium against several foreign compounds, including drugs. The protective action results of the adhesive characteristics of mucus to attract inhaled particles or pathogens, which are removed towards the nasopharynx by nasal MCC (35). The presence of mucin in the nasal mucus layer is crucial because it may trap large molecular weight drugs, such as peptides and proteins (13). The basal cells that exist in the epithelium are progenitors of other cell-types and lie on a thickened layer of collagen called basement membrane. Beneath of it, there is the lamina propria which is richly supplied with blood vessels, including many very permeable fenestrated capillaries, nerves, glands and immune cells. The last ones produce immunoglobulin A antibodies that confer immunological protection against bacteria and virus (36).

## 2.4. Olfactory region

The olfactory region is located in the roof of the nasal cavity and extends a short way down the septum and lateral wall (27). Its neuroepithelium is the only part of the CNS that is directly exposed to the external environment (37). Similarly to the respiratory epithelium, the olfactory one is also pseudostratified but contains specialized olfactory receptor cells important for smell perception (27, 37). In this area there are also small serous glands (glands of Bowman) producers of secretions acting as a solvent for odorous substances (27).

## 3. INTRANASAL DRUG DELIVERY

Over the last years, due to the understanding of the positive attributes and appropriate characteristics of the nasal cavity, intranasal route has been increasingly considered for drug delivery when developing new chemical entities or improving the therapeutic profile of existing drugs. However, to assess the therapeutic viability of intranasal drug delivery several approaches should be considered, attending, specifically, to the nature of pathologic condition (acute or chronic) and intended effects of drug treatment (local, systemic or at CNS). Indeed, for acute disease conditions, the advantages afforded by intranasal drug delivery in terms of patient comfort and compliance may not be much relevant when compared with drug delivery by parenteral route. In contrast, this is particularly

important to treat or control chronic medical conditions (38).

### 3.1 Local delivery

Intranasal administration of medicines is the natural choice for the treatment of topical nasal disorders. Among the most common examples are antihistamines and corticosteroids for rhinosinusitis, and nasal decongestants for cold symptoms (Table 2). In these cases, intranasal route is the primary option for drug delivery because it allows a rapid symptom relief with a more favourable adverse-event profile than oral or parenteral routes. In fact, relatively low doses are effective when administered topically (40), minimizing simultaneously the potential of systemic toxic effects. Recently, for instance, topical antibiotherapy has been considered in chronic rhinosinusitis in an attempt to eradicate biofilm bacteria, often resistant to systemic treatment, and still avoiding systemic toxicity (41-46).

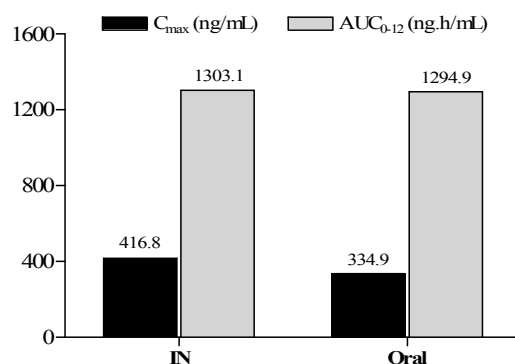
### 3.2. Systemic delivery

The intranasal administration is an effective way to systemically delivery of drugs as an alternative to oral and intravascular routes. Actually, it seems to present fast and extended drug absorption (47), and it has been supported by many studies planned to compare intranasal drug delivery against oral and parenteral administration (Figure 2) (9, 49, 50). Consequently, the number of drugs administered as nasal formulations intended to achieve systemic effects has widely increased. Some prominent examples include analgesics (morphine) (4, 7, 51), cardiovascular drugs as propranolol (52) and carvedilol (53), hormones such as levonorgestrel (48), progesterone (54) and

insulin (49, 55-57), anti-inflammatory agents as indomethacin (58, 59) and ketorolac (60, 61), and antiviral drugs (acyclovir) (62-65). Actually, there are some examples already available in the market (Table 2). These include, for instance, zolmitriptan and sumatriptan for the treatment of migraine and cluster headaches.

### 3.3 Nasal vaccines

Nasal mucosa is the first site of contact with inhaled antigens (4, 13) and, therefore, its use for vaccination, especially against respiratory infections, has been extensively evaluated. In fact, nasal vaccination is a promising alternative to the classic parenteral route, because it is able to enhance the systemic levels of specific immunoglobulin G and nasal secretory immunoglobulin A (58, 66-68). In upper airways, the systemic and local immunological responses are mainly mediated by the nasal associated lymphoid tissue situated underneath the nasal epithelium. The nasal associated lymphoid tissue is composed of agglomerates of dendritic cells, T-cells and B-cells which are involved in the initiation and execution of immune responses (68). Examples of the human efficacy of intranasal vaccines include those against influenza A and B virus, proteosoma-influenza (69), adenovirus-vectored influenza (70), group B meningococcal native (71), attenuated respiratory syncytial virus (72) and parainfluenza 3 virus (72, 73) (Table 2). However, human nasal vaccination is not restricted to the upper airways affections. After nasal immunization secretory immunoglobulin A can also be detected in other mucosal secretions, which may be important against virus transmitted through other mucosal sites, such as human immunodeficiency virus (74) and hepatitis B virus (75).



**Figure 2.** Plasma pharmacokinetic parameters obtained after intranasal (IN) and oral administration of levonorgestrel (500µg) in rats (48).

**Table 2.** Examples of nasal formulations commercially available after prescription (4, 6, 13, 39).

<b>Drug</b>	<b>Brand</b>	<b>Main Excipients</b>	<b>Supplier</b>	<b>Main Indications</b>
<b>Local Delivery</b>				
Azelastine	Astelin	Benzalkonium chloride, edetate disodium, hypromellose	Meda Pharmaceuticals	
Beclometasone	Beconase	Microcrystalline cellulose, carboxymethyl cellulose sodium, benzalkonium chloride	GlaxoSmithKline	
Budesonide	Rhinocort	Microcrystalline cellulose, carboxymethyl cellulose sodium, dextrose anhydrous	AstraZeneca	
Levocabastine	Livostin	Benzalkonium chloride, edetate disodium, disodium phosphate	Jansen-Cilag	Management/treatment of symptoms of seasonal and perennial rhino-sinusitis
Mometasone	Nasonex	Microcrystalline cellulose, carboxymethylcellulose sodium, benzalkonium chloride	Schering-Plough	
Olapatadine	Patanase	Benzalkonium chloride, dibasic sodium phosphate, edetate disodium	Alcon Laboratories	
Sodium cromoglicate	Nasalcrom	Benzalkonium chloride, edetate disodium	Sanofi-Aventis	
Triamcinolone acetonide	Nasacort	Microcrystalline cellulose, carboxymethylcellulose sodium, polysorbate 80	Sanofi Aventis	
Mupirocin	Bactroban	Paraffin and a mixture of glycerin esters (Softisan 649)	GlaxoSmithKline	Eradication of nasal staphylococci
<b>Systemic Delivery</b>				
Estradiol	Aerodiol	Methylbetadex, sodium chloride	Servier laboratories	Hormone replacement therapy
Nicotine	Nicotrol NS	Disodium phosphate, sodium dihydrogen phosphate, citric acid	Pfizer	Smoking cessation
Cyanocobalamin	Nascobal	Sodium citrate, citric acid, benzalkonium chloride	Strativa pharmaceuticals	Vitamin B <sub>12</sub> deficiency
Desmopressin	Desmospray	Sodium chloride, citric acid, benzalkonium chloride	Ferring Pharmaceuticals	Control of dehydration in diabetes insipidus
Oxytocin	Syntocinon	Citric acid, chlorobutanol, sodium chloride	Novartis	Labour induction; lactation stimulation
Salmon calcitonin	Miacalcin	Sodium chloride, benzalkonium chloride, hydrochloric acid	Novartis	Treatment of post-menopausal osteoporosis

Table 2 continued.....

Buserelin	Suprefact	Sodium hydroxide, sodium chloride, sodium dihydrogen phosphate	Sanofi-Aventis	Treatment of prostate cancer
Nafarelin	Synarel	Benzalkonium chloride, glacial acetic acid	Roche Laboratories	Management of endometriosis
Zolmitriptan	Zomig Nasal	Citric acid, disodium phosphate dodecahydrate	AstraZeneca	Treatment of migraine and cluster headaches
Sumatriptan	Imigran	Potassium dihydrogen phosphate, dibasic sodium phosphate anhydrous	GlaxoSmithKline	Treatment of migraine and cluster headaches
Fentanyl	Instany	Sodium dihydrogen phosphate dehydrate, disodium phosphate dehydrate	Nycomed Pharma	Pain management
Butorphanol	Stadol NS	Sodium chloride, citric acid, benzethonium chloride	Bristol-Myers Squibb	Pain management
Live attenuated influenza vaccine	FluMist	Monosodium glutamate, hydrolyzed porcine gelatin, arginine, dibasic potassium phosphate, monosodium phosphate, gentamicin sulfate	MedImmune, Inc.	Flu prevention

### 3.4. CNS delivery through nasal route

The brain is a delicate organ with many vital functions and it is isolated and protected from the outside environment by several intriguing mechanisms. Unfortunately, those are the same mechanisms that prevent the CNS delivery of therapeutic agents. The tight junctions of the BBB surrounding the brain is one of such mechanisms (8), resulting in a greater transendothelial electric resistance ( $1500-2000 \Omega \cdot \text{cm}^2$ ) compared to that of other tissues like skin, bladder, colon, lungs ( $3-33 \Omega \cdot \text{cm}^2$ ) (76). This histological organization impairs, therefore, the systemically delivery of CNS-active drugs. Even though, if drugs or other xenobiotics pass through the BBB, a second line of defence mechanisms, including multidrug efflux protein transporters, may reduce the brain exposure. It is estimated that almost half of drug candidates are substrates to P-glycoprotein (P-gp) efflux pump, presenting reduced potential for systemically CNS penetration (77, 78).

The obstacle imposed by those brain protective mechanisms has increased the interest in developing strategies to overcome them when brain drug exposure is required. In this context,

over the last few years, intranasal route has emerged as a promising approach for brain delivery of drugs. The delivery from the nose to the CNS may occur via olfactory neuroepithelium and may involve paracellular, transcellular and/or neuronal transport (4, 75, 79). Although the olfactory pathway presents potential to bypass BBB, P-gp appears to be also functional on this area (8, 76, 80-82). Graff et al. (81) confirmed that P-gp is present in both the olfactory epithelium and endothelial cells that surround the olfactory bulb. Moreover, the transport via trigeminal nerve system from the nasal cavity to CNS has also been described (83).

Drug delivery into CNS through intranasal route has been reported (84-87) either in humans or animal models of Alzheimer's disease (88, 89), brain tumours (90, 91), epilepsy (92), pain (82) and sleep disorders (93). However, it should be noted that in other cases evidence is lacking supporting the greater brain exposure via intranasal delivery despite the needless of passage BBB and the absence of gastrointestinal and hepatic presystemic elimination (94-97).

## 4. FACTORS INFLUENCING NASAL DRUG ABSORPTION

When a drug is nasally administered to induce systemic effects or to act into CNS it needs to pass through the mucus layer and epithelial membrane before reaching the blood stream or pass directly to the CNS. The passage across the epithelium may occur by transcellular or paracellular mechanisms. The first one includes passive diffusion through the interior of the cell and it is especially involved in the transport of lipophilic drugs (11). However, it seems that compounds with a molecular weight higher than 1 kDa, such as peptides and proteins, are transcellularly transported by endocytic processes (13, 35). Furthermore, transcellular transport can be mediated by carriers that exist in the nasal mucosa, including organic cation transporters and amino acids transporters (76, 80-82). In contrast, paracellular route is involved in the transport of small polar drugs and it takes place between adjacent epithelial cells through hydrophilic porous and tight junctions. Tight junctions are dynamic structures localized between the cells, which open and close accordingly to (in)activation of signalling mechanisms. Nevertheless, it is well known that their size is comprised between 3.9-8.4 Å (98), avoiding the passage of bigger molecules, being this process of transport highly dependent of drug molecular weight (99).

Taking into account previous considerations, it is evident that the molecular weight and lipophilicity of drugs may have a great impact in the rate and extent of its nasal absorption. However, other physicochemical drug properties must be considered as well as the characteristics of drug formulation (7, 11, 13). In this section all these factors will be discussed after a review of the influence of nasal physiological factors on nasal drug absorption.

### 4.1. Nasal physiological factors

#### 4.1.1. Blood flow

Nasal mucosa is richly supplied with blood and presents a large surface area making it an optimal local for drug absorption. The blood flow rate influences significantly the systemic nasal absorption of drugs, so that as it enhances more drug passes through the membrane, reaching the general circulation. Indeed, bearing in mind that

most of drug absorption takes place by diffusion, the blood flow is essential to maintain the gradient of concentration from the site of absorption to blood. Hence, it is well known that vasodilatation and vasoconstriction may determine the blood flow and, consequently, the rate and extent of drug to be absorbed. Several studies were made to evaluate this influence. For example, Huang et al. (100) showed that phenylephrine, a vasoconstrictor agent, inhibited the absorption of acetylsalicylic acid in nasal cavity. More recently, Kao et al. (101) stated that nasal absorption of dopamine was relatively slow and incomplete probably due to its own vasoconstrictor effect. Based on these observations, it was concluded that vasoconstriction decrease nasal drug absorption by diminishing the blood flow.

#### 4.1.2. Mucociliary clearance

MMC also referred to as mucociliary apparatus or mucociliary clearance (MCC) is the self-clearing mechanism of the bronchi. Nasal mucus layer plays an important role in the defence of respiratory tract because it prevents the lungs from foreign substances, pathogens and particles carried by inhaled air. These agents adhere to the mucus layer and, all together, they are transported to the nasopharynx and, eventually, to the gastrointestinal tract. This elimination is designated MCC and it influences also significantly the nasal drug absorption. The MCC system has been described as a "conveyer belt" wherein cilia provide the driving force whereas mucus acts as a sticky fluid that collects and disposes foreign particles (28). The efficiency of MCC thereby depends on the length, density and beat frequency of cilia as so as the amount and viscoelastic properties of mucus. Briefly, all factors that increase mucus production, decrease mucus viscosity or increase ciliary beat frequency may increase the MCC.

In physiological conditions, mucus is transported at a rate of 5 mm/min and its transit time in human nasal cavity is reported to be 15-20 min (4, 35). Values out of these references are abnormal and suggestive of impaired MCC (28). Thus, if MCC decreases, residence time of the drug product in nasal mucosa increase and, therefore, enhances its permeation. The opposite effect is observed when MCC increases. In the last case, a premature discharge of nasally administered drugs from nasal cavity toward the



nasopharynx occurs, decreasing the amount of drug absorbed. The clearance of a drug product from the nasal cavity is also influenced by the site of deposition. A drug deposited in a posterior area of the nose is cleared more rapidly from the nasal cavity than a drug deposited anteriorly. This is because MCC is slower in the anterior part of the nose than in the more ciliated posterior part (28, 102). On the other hand, the site of drug deposition in the nose is highly dependent on the dosage form. Nasal sprays deposit drugs more anteriorly than nasal drops, resulting in a slower clearance for drugs administered from spray formulations (4).

Polar drugs are the most affected by MCC, since they are highly soluble in mucus and their passage across the membrane is very slow. Thus, all factors that influence the efficacy and pace of MCC may modify the drug absorption profile. For instance, environmental factors have a relevant influence in MCC. Temperature and sulphur dioxide seem to cause a significant reduction in MCC, but this the mechanism is not well known. Cigarette smoking also decreases MCC as it enhances the viscosity of the mucus and/or diminishes the number of cilia. In addition, several pathological conditions exist in which MCC does not work properly (28, 103, 104), as shown in Table 3. Furthermore some components of drug formulations may also alter the MCC system, such as preservatives and nasal absorption enhancers (28). Finally, it is interesting to stand out the inter-individual variability observed in MCC and the influence of the menstrual cycle and circadian rhythm. Actually, during the periovulatory period MCC is increased and it is reduced at night.

#### 4.1.3. Enzymatic degradation

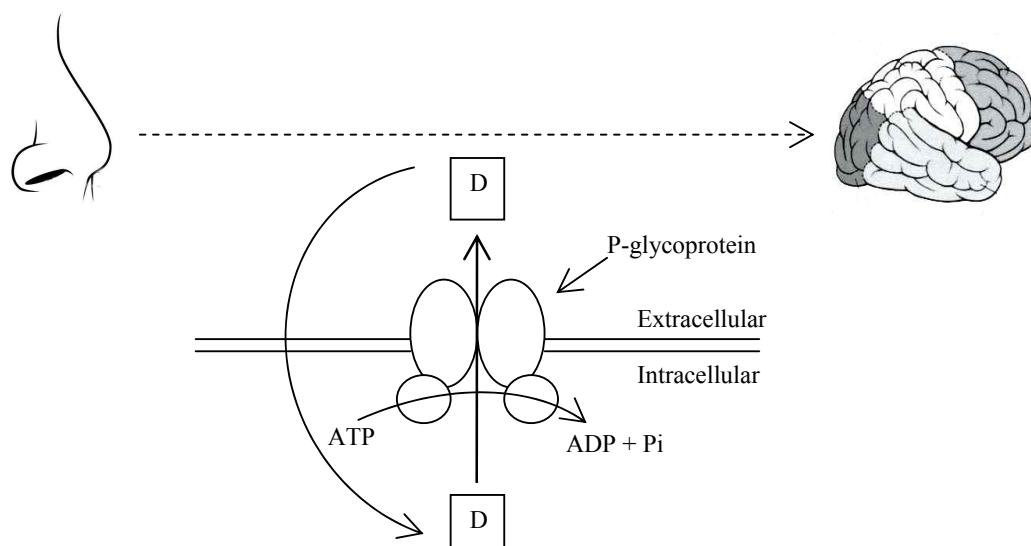
Drugs nasally administered circumvent gastrointestinal and hepatic first-pass effect. However, they may be significantly metabolized in lumen of nasal cavity or during the passage across the nasal epithelial barrier due to the presence of a broad range of metabolic enzymes in nasal tissues. Carboxyl esterases, aldehyde dehydrogenases, epoxide hydrolases and glutathione S-transferases have been found in nasal epithelial cells and are responsible for the degradation of drugs in nasal mucosa (105-107). Cytochrome P450 isoenzymes are also present here and they have been reported as metabolizers of drugs such as cocaine, nicotine, alcohols, progesterone and decongestants (108, 109). Similarly, proteolytic enzymes (aminopeptidases and proteases) were found and they are believed to be the major barrier against the absorption of peptide drugs, such as calcitonin, insulin and desmopressin (110, 111). Thus, xenobiotic-metabolizing enzymes existent in the nasal mucosa may affect the pharmacokinetic and pharmacodynamic profile of nasally applied drugs. In this context, although the nasal first-pass metabolism is usually weaker than hepatic and intestinal ones it cannot be ignored.

#### 4.1.4. Transporters and efflux systems

The study of transporter systems present in the nasal tissue and their effects on the absorption of drugs into systemic circulation and CNS is a research area in development.

**Table 3.** Pathological conditions and their impact in nasal mucociliary clearance (28, 103).

<b>Pathological conditions</b>	<b>Mucociliary clearance</b>
Primary ciliary dyskinesia	• Impaired: absence or dyskinetic beating cilia
Asthma	• Increased: inflammatory process and irritation • Decreased: epithelial damage
Cystic fibrosis	• Impaired: dehydration of mucus
Viral and bacterial infections	• Compromised: loss of cilia and change of mucus properties
Diabetes mellitus	• Impaired: dehydration and microvascular damage



**Figure 3.** P-glycoprotein, an ATP-dependent efflux pump, preventing the influx of a drug (D) from nasal membrane to CNS.

At the moment, multidrug resistance transporters has already been identified in human nasal respiratory and olfactory mucosa, which may be involved in the transport of a wide variety of hydrophobic and amphiphilic drugs (13). P-gp is an efflux transporter that exists in the apical area of ciliated epithelial cells and in the submucosal vessels of the human olfactory region (81). Several studies (80-82, 112) demonstrated that P-gp has an important role in preventing actively the influx of drugs from nasal membrane (Figure 3).

#### 4.2. Physicochemical properties of drugs

The influence of physicochemical characteristics of drug molecules on the rate and extent of gastrointestinal absorption is well understood. Therefore, *in silico* models have been developed to prioritize numerous drug candidates at the early phases of drug discovery. In same way, but with some differences, the physicochemical properties of drugs (molecular weight, lipophilicity, pKa, stability and solubility) can influence nasal absorption.

##### 4.2.1. Molecular weight, lipophilicity and pKa

Lipophilic drugs such as propranolol, progesterone and fentanyl are, in general, well absorbed from the nasal cavity, presenting pharmacokinetic profiles similar to those obtained

after intravenous administration (Figure 4) and a nasal bioavailability near to 100%. Indeed, they are quickly and efficiently absorbed across the nasal membrane through transcellular mechanisms. However, it is important to state that this is true for lipophilic compounds presenting a molecular weight lower than 1 kDa. The extension of nasal absorption of lipophilic drugs bigger than 1 kDa is significantly reduced (99). On the other hand, the rate and degree of nasal absorption of polar drugs is low and highly dependent of the molecular weight. Several studies (99, 114-116) demonstrated that the permeation of polar drugs with a molecular weight of less than 300 Da is not considerably influenced by their physicochemical properties. By contrast, the rate of permeation is highly sensitive to molecular size if it is higher than 300 Da; an inverse relationship exists between rate of permeation and molecular weight (114, 115). For some small polar molecules only a 10% bioavailability is suggested. The value goes down to 1% for large molecules such as proteins (117). The nasal membrane is predominantly lipophilic, hence, drug absorption is expected to diminish with a decrease in lipophilicity (114, 118). Thus, it is evident that polar drugs are not easily transported across nasal membrane thereby enhancing MCC. However, if lipophilicity is too high, the drug does not dissolve easily in the aqueous environment of nasal cavity, hence, with

accelerated MCC the contact time with nasal membrane diminishes resulting in a reduced permeation through the wall (119). In general, the passage across biomembranes is affected not only by lipophilicity/hydrophilicity, but also by the amount of drug existing as uncharged species. This depends on the drug pKa and the pH of the absorption site (5.0-6.5 in human nasal mucosa) (26, 35, 120). According to pH partition theory, the non-ionized fraction of a drug is more permeable than that ionized. For the nasal mucosa, a range of studies evaluating the effect of lipophilicity and pH on the absorption of small drugs were performed (62, 118, 121-123). All of them demonstrated that nasal absorption of weak electrolytes depends on their ionization degree and the largest absorption occurs for the non-ionized species. In this state, they present a higher apparent partition coefficient and, thus, they are more lipophilic. However, drugs such as acetylsalicylic acid (121) and benzoic acid (122) showed some permeability across the membrane even in environments that they are expected to exist as the ionized species. Based on these observations, it was concluded that, for polar drugs, partition coefficient is the major factor influencing the permeability through nasal mucosa.

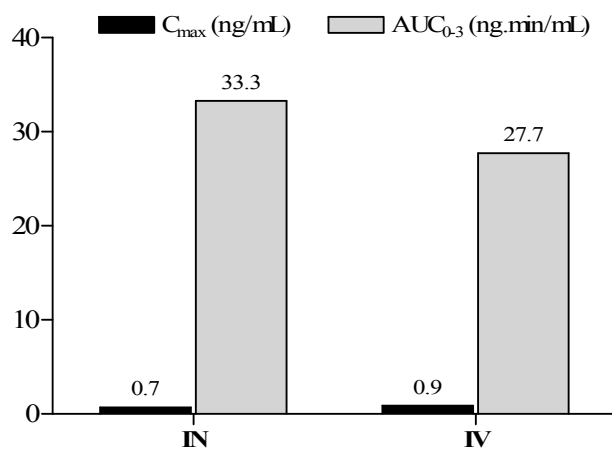
#### 4.2.2. Stability

During the development of new drug formulations biological, chemical and physical drug stability studies must be a matter of the major importance

in all process. As discussed before, the environment of nasal cavity has the ability to metabolize drugs by defensive enzymatic mechanisms, which may reduce the biological stability of nasally administered drugs (105-107). To overcome this difficulty a variety of strategies may be followed, mainly through the use of prodrugs (11, 13, 63, 100) and enzymatic inhibitors (124-126), as it will be discussed later. On the other hand, many drugs may be physicochemically instable due to hydrolysis, oxidation, isomerisation, photochemical decomposition or polymerization reactions (13). The same holds true during the intranasal drug delivery (6).

#### 4.2.3. Solubility

Drug dissolution is a pre-requisite for any drug absorption, since only the molecularly disperse form of a drug at the absorption site may cross the biomembranes. Hence, before nasal absorption the drug must to be dissolved in the watery fluids of the nasal cavity. Thus, of the utmost importance is the appropriated aqueous drug solubility to allow enough contact with the nasal mucosa and posterior absorption (123). However, the absorption profile is influenced not only by drug solubility but also by the nature of pharmaceutical preparations, which have to guarantee the delivery of drug at therapeutically relevant doses. Due to the small size of nasal cavity, the allowable volume of drug solution is low for intranasal drug administration (13).



**Figure 4.** Plasma pharmacokinetic parameters obtained after intranasal (IN) and intravenous (IV) administration of fentanyl (75µg) in man (113).

Thereby, drugs poorly soluble in water and/or requiring high doses may constitute a problem. This can be overtaken enhancing the drug aqueous solubility (6, 11, 13, 101, 127).

### **4.3. Effect of drug formulation**

#### **4.3.1. Viscosity**

As formulation viscosity increases, the contact time between drug and nasal mucosa enhances and, thereby, the potential of drug absorption increases. At the same time, high viscosity of formulations interferes with normal ciliary beating and/or MCC and, thus, increases the permeability of drugs. This has been observed during nasal delivery of insulin (49), acyclovir (65) and metoprolol (52). However, sometimes, enhancing formulation viscosity does not enhance the drug absorption. For example, Zaki et al. (123) performed a study to evaluate the influence of formulation viscosity on the retention time of metoclopramide hydrochloride in nasal cavity and on its absorption. Interestingly, they observed that although the residence time enhanced as viscosity increased the drug absorption diminished. This observation has been attributed to a decrease in the drug diffusion from the formulation. On the other hand, it has also been reported that the viscosity of the solution may provide a larger therapeutic period of nasal formulations (123).

#### **4.3.2. pH**

The extent of nasal absorption depends on the pKa of drug and pH at the absorption site, contributing for that also the pH of formulation. At this point, it should be stated that the pH of formulation must be selected attending to drug stability and if possible should be assured the greatest quantity of non-ionized drug species. However, the pH of formulation can induce nasal mucosa irritation and, hence, it should be similar to that found on human nasal mucosa (5.0-6.5) (26, 35, 120). Besides, the pH often prevents the bacteria growth (11). In order to evaluate the effect of pH solution on the integrity of nasal mucosa, Pujara et al. (128) dissolved drugs in phosphate buffer at different pH values in the range of 2-12. The study was performed in rats whose nasal pH is 7.39 (121) and the results demonstrated that when pH ranged from 3-10

minimal quantities of proteins and enzymes were released from cells, demonstrating no cellular damages. On the contrary, if pH values were below 3 or above 10 damages were observed intracellularly and at membrane level.

#### **4.3.3. Pharmaceutical form**

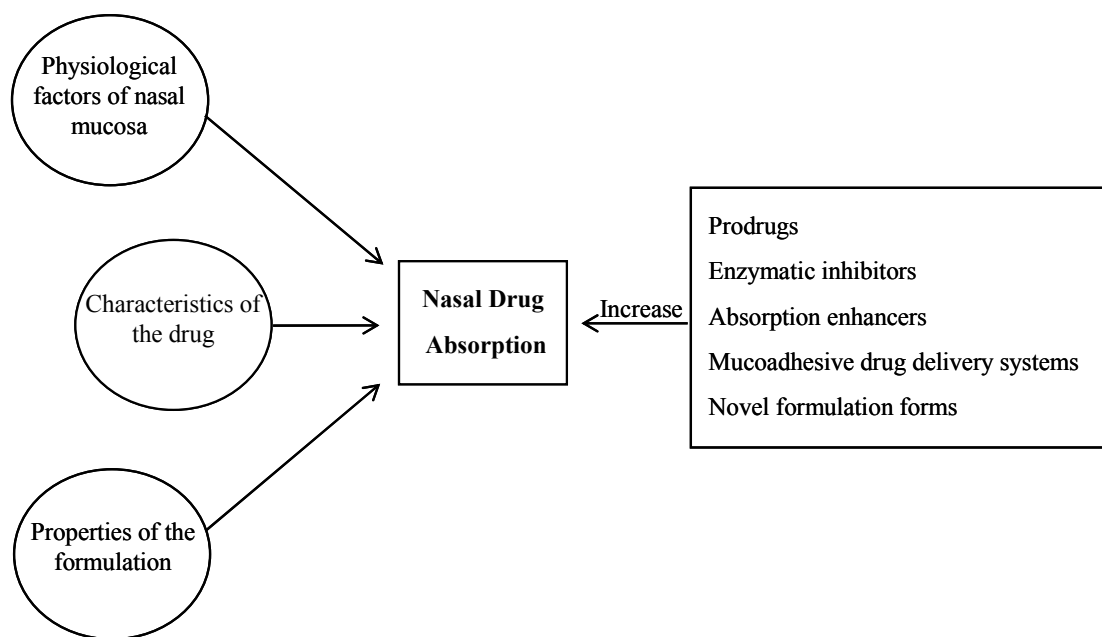
Nasal drops are the simplest and the most convenient nasal pharmaceutical form, but the exact amount of drug delivered is not easily quantified and often results in overdose (6). Moreover, rapid nasal drainage can occur when using this dosage form. Solution and suspension sprays are preferred over powder sprays because the last one easily prompted the development of nasal mucosa irritation (104). Recently, gel-devices have been developed for a more accurate drug delivery. They reduce postnasal drip and anterior leakage, fixing the drug formulation in nasal mucosa. This enhances the drug residence time and diminishes MCC, thereby, potentially increases the nasal absorption. Over the last years, specialized systems such as lipid emulsions, microspheres, liposomes and films have also been developed to improve nasal drug delivery.

#### **4.3.4. Pharmaceutical excipients**

In nasal formulations, a wide variety of pharmaceutical excipients can be found and they are selected accordingly to their functions. Solubilizers, buffer components, antioxidants, preservatives, humectants, gelling/viscosifying agents, and flavoring or taste masking agents are some of the most usual excipients (6). Although they are responsible for several nasal irritations, antioxidants, preservatives, humectants and flavoring or taste masking agents are not expected to alter nasal drug absorption (6).

## **5. STRATEGIES TO INCREASE NASAL DRUG ABSORPTION**

Although the intranasal route is efficient for topic, systemic and CNS delivery of a wide range of drugs, it cannot be applied for many others due to their low nasal bioavailability. Briefly, bioavailability of nasally administered drugs is particularly restricted by low drug solubility, rapid enzymatic degradation in nasal cavity, poor membrane penetration and rapid MCC.



**Figure 5.** Factors affecting nasal drug absorption and practical strategies to overcome them.

**Table 4.** Common problems associated to low nasal bioavailability of drugs, challenges and possible solutions.

<b>Problem</b>	<b>Challenge</b>	<b>Solution</b>
Poor physicochemical properties of drug and/or formulation	Improve physicochemical properties of drug and/or formulation	<ul style="list-style-type: none"> <li>• Prodrugs</li> <li>• Cosolvents</li> <li>• Cyclodextrins</li> <li>• Pharmaceutical excipients</li> <li>• Novel drug formulations</li> </ul>
Enzymatic degradation	Reduce drug affinity to nasal enzymes Inhibit nasal enzymes Protect drugs from nasal enzymes	<ul style="list-style-type: none"> <li>• Prodrugs</li> <li>• Enzymatic inhibitors</li> </ul>
Low permeability through nasal membrane	Increase drug permeability and dissolution Modify nasal membrane Enhance drug residence time in nasal cavity	<ul style="list-style-type: none"> <li>• Prodrugs</li> <li>• Cosolvents</li> <li>• Prodrugs</li> <li>• Cosolvents</li> <li>• Absorption enhancers</li> <li>• Mucoadhesive systems</li> <li>• Gelling/Viscosifying agents</li> </ul>

Several approaches have been suggested to overcome these limitations, including the use of prodrugs, enzymatic inhibitors, absorption enhancers, development of mucoadhesive delivery systems and new pharmaceutical forms (Figure 5 and Table 4).

### 5.1. Prodrugs

The term ‘prodrug’ was coined by Albert in 1951 (129) and it is used to describe compounds that undergo biotransformation prior to exhibiting their pharmacological effect. Over the years, prodrugs have been used to overcome drugs’ bad taste, poor solubility, insufficient stability,

incomplete absorption across biological barriers and premature metabolism to inactive or toxic species (130).

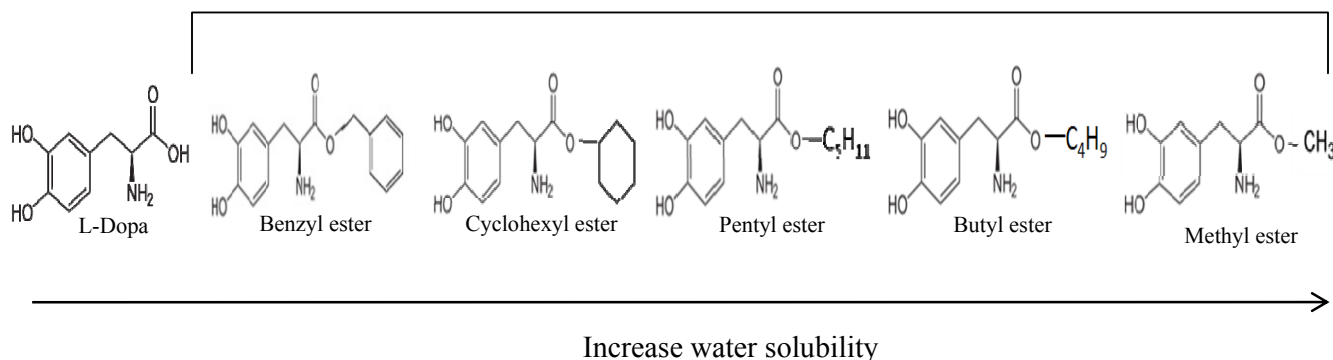
Intranasal drugs are commonly administered as solutions or as powder formulations which need to undergo a dissolution process before absorption. Lipophilic drugs easily pass through biomembranes, however they are poorly water-soluble. In this way, they should be administered as a prodrug with higher hydrophilic character in order to make possible the production of an aqueous nasal formulation with a suitable concentration. Once in the blood stream, the prodrug must be quickly converted to the parent drug. For instance, L-Dopa is poorly soluble in water, so it is very difficult to develop a corresponding intranasal aqueous formulation with an effective dose. Kao et al. (101) produced various prodrugs of L-Dopa and observed that their solubility enhanced significantly in comparison with the parent drug (Figure 6), allowing, hence, the development of adequate nasal formulations. Furthermore, their nasal administration resulted in a rapid and complete absorption to the systemic circulation, where quick conversion to L-Dopa takes place. Similar

results were obtained for testosterone which is also poorly water-soluble (127).

In contrast, very hydrophilic polar drugs may not have ability to cross biomembranes. Thereby, if they are administered as prodrugs with higher lipophilic character, the penetration through the membrane may increase (131). Some researches have also used the prodrug approach for improving enzymatic stability of drugs. For example, Yang et al. (63) stated that L-aspartate- $\beta$ -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 the bioavailability of peptides when intranasally administered (11, 13, 100).

An alternative approach to the use of prodrugs in order to increase drug solubility is the use of co-solvents (13). Co-solvents most used in intranasal formulations include glycerol, ethanol, propyleneglycol and polyethylene glycol and may be of the most importance since they are non-toxic, pharmaceutically acceptable and non-irritant to nasal mucosa.

### L-Dopa prodrugs



**Figure 6.** L-Dopa and its water soluble prodrugs (101).

## 5.2. Enzymatic inhibitors

Nasal mucus layer and nasal mucosa act as enzymatic barriers during nasal drug delivery, because they have a wide variety of enzymes. Various approaches have been used to avoid enzymatic degradation, including the use of proteases and peptidases inhibitors. For example, bestatine and comostate amylase are used as

aminoptidases inhibitors and leupeptine and aprotinin as trypsin inhibitors probably involved in the degradation of calcitonin (125). Furthermore, bacitracin, amastatin, boroleucin and puromycin (124-126) have been used to avoid enzymatic degradation of drugs such as leucine enkephalin (132, 133) and human growth hormone (134). Finally, enzymatic inhibition can also be achieved using certain absorption

enhancers (bile salts and fusidic acid) (13). It is demonstrated that disodium ethylenediaminetetraacetate, an absorption enhancer, reduces enzymatic degradation of beta sheet breaker peptide used for the treatment of Alzheimer's disease (135).

### 5.3. Absorption enhancers

Small and large hydrophilic drugs may be poorly permeable across nasal epithelium and may show an insufficient bioavailability. It is possible to greatly improve their absorption if they are administered in combination with absorption enhancers which induce reversible modifications on the structure of epithelial barrier. In intranasal drug delivery, absorption enhancers most used are surfactants (laureth-9), bile salts, fatty acids (taurodihydrofusidate) and polymeric enhancers (chitosan, cyclodextrins, poly-L-arginine and aminated gelatine) (37, 57, 105, 136-140).

The mechanism of action of absorption enhancers is not well known but, generally, they change the permeability of epithelial cell layer by modifying the phospholipidic bilayer, increasing membrane fluidity or opening tight junctions between epithelial cells and, thus, increasing paracellular transport (58). Although the absorption promoters enhance drug bioavailability, a direct relation between this effect and the damage caused in the membrane may sometimes exist (141, 142). In fact, surfactants, bile salts, fatty acids, phospholipids and lyso-phospholipids modify cell structures, leaching out proteins or even stripping off the outer layer of the mucosa (4, 7). On the other hand, some promoters such as chitosan, cyclodextrins and selected phospholipids present an absorption enhancing effect that greatly outweighs any modification caused in mucosa. Indeed, they act mainly by opening the tight junctions. Moreover, polymeric enhancers present high molecular weight and, hence, they are not absorbed, minimizing systemic toxicity in comparison with enhancers of low molecular weight.

A wide range of absorption enhancers are evaluated in animal models. Special caution is required when interpreting these results as they can be grossly overestimated when compared with human studies. Probably, this results from distinct architectures and morphologies of nasal cavity in different species (4, 7) as resumed in Table 5. Thus, during the choice of an absorption

enhancer to include in an intranasal formulation, it is essential to assure a good absorption enhancing and minimal toxic effects. Considering the wide variety of absorption enhancers that may be used in intranasal administration, this review will only discuss those ones which are more used as a result of their significant enhancing effect and their low toxicity.

#### 5.3.1. Chitosan

Chitosan is a linear polysaccharide biopolymer produced by deacetylation of chitin, the main component of crustacean's exoskeleton (13). Due to its biodegradability, biocompatibility and bioadhesive properties associated to a low toxicity, chitosan is widely used in intranasal formulations. It is believed that it interacts with protein kinase C system and opens the tight junctions between epithelial cells (98), increasing paracellular transport of polar drugs. Moreover, it interacts strongly with nasal mucus layer enhancing the contact time for the transport of the drug across the membrane (4, 143-145). Finally, chitosan also enhances the dissolution rate of low water soluble drugs (120, 128). Consequently, chitosan is used in several intranasal pharmaceutical forms, including powders, liquids, gels, microparticles and microspheres. For some drugs, it is well documented that the addition of chitosan to nasal formulation increases drug bioavailability. Some of the most studied drugs are insulin (7, 55) and morphine (4, 7, 51).

#### 5.3.2. Cyclodextrins

Cyclodextrins are cyclic oligosaccharides composed of glucose units joined through  $\alpha$ -1,4-glycosidic bonds resulted from bacterial digestion of cellulose. Structurally, they have a hydrophilic outer surface and a lipophilic central cavity where apolar drugs can be included (146, 147). Cyclodextrins are used as complexing agents to improve nasal drug absorption by increasing drug solubility and stability. They can also work as absorption enhancers, since they interact with the lipophilic components of biological membranes changing their permeability (13, 35, 148-150). Although widely used in intranasal medicinal preparations, cyclodextrins present some local and systemic toxicity. Moreover, alterations of nasal morphology, ciliary beat frequency, erythrocyte haemolysis and cytotoxic effects have also been reported (151).

**Table 5.** Characteristics of nasal cavity of different animal species (26, 97).

Nasal Cavity	Species				
	Human	Rat	Rabbit	Monkey	Dog
Length (cm)	7.5	2.3	5.2	5.3	10.0
Volume (cm <sup>3</sup> )	20.0	0.4	6.0	8.0	20.0
Surface area (cm <sup>2</sup> )	150.0	14.0	61.0	61.6	220.7
Olfactory area (cm <sup>2</sup> )	10.0	7.0	6.0	NF	NF

NF, not found.

### 5.3.3. Mucoadhesive drug delivery systems

MCC is one of the most important limiting factors for nasal drug delivery, because it reduces the time allowed for drug absorption. Thus, improving nasal drug absorption can also be achieved prolonging the contact time between drug and nasal mucosa. In this way, mucoadhesive drug delivery systems have been developed (65, 89, 152-154). Mucoadhesion implies the attachment of the drug delivery system to the mucus, involving an interaction between mucin and a synthetic or natural polymer called mucoadhesive. The sequential events that occur during this mucoadhesion include several steps. Firstly mucoadhesive systems absorb water from mucus layer and get wet and swelling. Following this, the polymer intimately penetrates into the mucus (155) and, hence, localizes the formulation in nasal cavity, enhancing the drug concentration gradient across the epithelium.

Mucoadhesives mostly used in intranasal drug delivery are chitosan, alginate and cellulose or its derivatives. Some of them may present other important characteristics which also enhance drug absorption. For example, chitosan is mucoadhesive and also causes a transient widening of epithelial tight junctions. Carbacol 934P and polycarbophil are mucoadhesive polymers that inhibit the trypsin proteolytic enzyme and, therefore, they can be used also to increase the stability of peptide drugs (155). Sodium alginate is a water-soluble, natural, linear polysaccharide which is widely used as a polymer matrix due to its non-toxicity, biocompatibility and gel formation stability. Indeed, it has the highest mucoadhesive strength compared with polymers such as polystyrene, chitosan, carboxymethylcellulose and poly(lactic acid) (155).

### 5.4. Novel drug formulations

Several claims have been made in favour of developing nasal formulations containing liposomes, microspheres and nanoparticles for intranasal drug delivery. These systems can include, besides the drug, enzymatic inhibitors, nasal absorption enhancers or/and mucoadhesive polymers in order to improve the stability, membrane penetration and retention time in nasal cavity. In fact, it is not clear 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. However, their use is in widespread growth and the results have been very promising.

#### 5.4.1. Liposomes

Liposomes are phospholipids vesicles composed by lipid bilayers enclosing one or more aqueous compartments and wherein drugs and other substances can be included. Liposomal drug delivery systems present various advantages such as the effective encapsulation of small and large molecules with a wide range of hydrophilicity and pKa values (64). In fact, they have been found to enhance nasal absorption of peptides such as insulin and calcitonin by increasing their membrane penetration (156, 157). This has been attributed to the increasing nasal retention of peptides (157), protection of the entrapped peptides from enzymatic degradation (158, 159) and mucosal membrane disruption (160). Jain et al. (156) incorporated insulin in liposomes coated with chitosan and carbapol and administered them intranasally to rats. The results demonstrated that this formulation was effective and that its mucoadhesive property is a viable option for a sustained release of insulin. The same work has demonstrated the usefulness of novel



mucoadhesive multivesicular liposomes for transmucosal insulin delivery.

Moreover, liposomal drug delivery systems were also reported as useful for influenza vaccine (65) and non-peptide drugs such as nifedipine (161). Liposomes can be incorporated in different formulations. For example, Ding et al. (48) obtained a rapid onset of action and sustained delivery of levonorgestrel when it was intranasally administered as a liposome suspension. Furthermore, positive results were also found during nasal delivery of acyclovir in a liposomal gel (64). The use of a liposomal gel not only promoted the prolonged contact between the drug and the absorptive site, but also facilitated direct absorption through the nasal mucosa. These conclusions were obtained comparing liposomal formulations and free drug suspended in gel.

#### 5.4.2. Microspheres

Microsphere technology has been widely applied in designing formulations for nasal drug delivery (57, 152-154, 162). Microspheres are usually based on mucoadhesive polymers (chitosan, alginate), which present advantages for intranasal drug delivery. Furthermore, microspheres may also protect the drug from enzymatic metabolism and sustain drug release, prolonging its effect (153, 162). Wang et al. (57) have investigated aminated gelatin microspheres as a nasal drug delivery system for insulin. They have observed a significant hypoglycemic effect when administered intranasally in dry powder form to rats, but no significant effect was achieved when given in a suspension. Gavine et al. (152) have analyzed nasal mucosa after its exposure to microspheres of alginate/chitosan containing metoclopramide. They observed open tight junctions in the epithelium and also stated that these spray-dried microspheres have promising properties as mucoadhesive nasal carriers. Many other similar studies have been carried out and positive results are found for nasal delivery of carbamazepine using chitosan microspheres (162), cyclodextrins using chitosan and alginate as mucoadhesive polymers (153) and carvedilol using alginate mucoadhesive microspheres (154).

#### 5.4.3. Nanoparticles

Recently, much attention has been given to nanotechnology in many areas. Nanoparticle systems are being investigated to improve drug

delivery and intranasal drug administration. Nanoparticles are solid colloidal particles with diameters ranging from 1-1000 nm (163). They consist of macromolecular materials and can be therapeutically used as adjuvant in vaccines or as drug carriers, in which the active substance is dissolved, entrapped, encapsulated, adsorbed or chemically attached (163). Nanoparticles may offer several advantages due to their small size, but only the smallest nanoparticles penetrate the mucosal membrane by paracellular route and in a limited quantity because the tight junctions are in the order of 3.9-8.4 Å (98).

Controversial results are found when using nanoparticles in intranasal drug delivery (98, 164-168). In fact, there are few publications wherein nanoparticle formulations don't significantly enhance the drug transport across the nasal cavity (98). The low bioavailability obtained can be due to the fact that particles are probably taken up by M-cells in the nasal associated lymphoid tissue and, therefore, transported into the lymphatic system and blood stream (35, 98). In contrast, other studies have suggested that nanoparticle systems may be ideally suited for the delivery of nasal vaccines (76, 169-171).

## 6. CONCLUSION

Considering the widespread interest in nasal drug delivery and the potential benefits of intranasal administration, it is expected that novel nasal products will continue to reach the market. They will include not only drugs for acute and long-term diseases, but also novel nasal vaccines with better local or systemic protection against infections. The development of drugs for directly target the brain in order to attain a good therapeutic effect in CNS with reduced systemic side effects is feasible.

However, it was also stated that intranasal route presents several limitations which must be overcome to develop a successful nasal medicine. Physiological conditions, physicochemical properties of drugs and formulations are the most important factors determining nasal drug absorption. The use of prodrugs, enzymatic inhibitors, absorption enhancers, mucoadhesive drug delivery systems and new pharmaceutical formulations are, nowadays, among the mostly applied strategies. Each drug is one particular case and, thus, the relationship between the drug characteristics, the strategies considered and the permeation rate is essential.

The era of nasal drug delivery is growing. However, new efforts are needed to make this route of delivery more efficient and popular.

## 7. ACKNOWLEDGEMENTS

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