Intranasal Drug Delivery: An Approach for Brain Targeting

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Abstract

Many drugs are not being effectively and efficiently delivered using conventional drug delivery approach to the brain or central nervous system (CNS) due to its complexity. The brain and the central nervous system both have limited accessibility to blood compartment due to a number of barriers. Rich vasculature and a highly permeable structure of the nasal mucosa along with several other benefits promises intranasal drug delivery system as an interesting alternative for achieving therapeutic drug effects. If the drug is administered in the olfactory region of the nasal cavity, it can bypass the blood brain barrier (BBB) and target the brain. Various models have been designed and studied by scientists to establish the qualitative and quantitative transport through nasal mucosa to brain, which promises the existence of a direct pathway between nose and brain as studies suggests. However, the development of nasal drug products for brain targeting is still faced with enormous challenges. A better understanding in terms of properties of the drug candidate, nose to brain transport mechanisms, and transport to and within the brain is of utmost importance. In the future, this can be used for treatment of brain and CNS diseases like Alzheimer's disease. This review will discuss some pertinent issues to be considered and challenges to brain targeted intranasal drug delivery.

Keywords: Intranasal drug delivery, olfactory pathway, brain targeting, nasal drug formulation

1. Introduction

Drugs such as cocaine have been snorted by the human beings since centuries, which shows existence of nasal cavity as a route for drug administration. The world market is seeing an increasing number of therapeutic drugs being marketed as nasal formulations. Oral drug delivery is the most popular and the most desirable route for drug administration. However low oral bioavailability of some compounds has prompted the search of more effective routes for their systemic delivery. The parenteral route is invasive and can be inconvenient. Intranasal drug delivery offers a reliable and interesting alternative for achieving the desired therapeutic effect, in particular for proteins and peptides. 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. The BBB represents an insurmountable obstacle for a large number of drugs, including antibiotics, antineoplastic agents and a variety of CNS-active drugs, especially neuropeptides. This barrier system is a perfectly logical arrangement, since the brain is the most sensitive and complex organ in the human body and it would not make sense for it to become the battleground of infection and immune response. 98% of all small-molecule drugs do not cross the BBB, and nearly 100% of large-molecule drugs do not cross the BBB. The usual noninvasive approach to solving the brain drug delivery problem is to lipidize the drug as the water -soluble parts of the drugs restrict BBB transport. Conversion of water-soluble drug into lipid-soluble pro drug is the traditional chemistry driven solution to the BBB problem. In another approach, the BBB is disrupted momentarily. Intraventricular / Intrathecal delivery can be used to cross the BBB. However, all these pathways are not feasible and presents many challenges. The nasal delivery seems to be a favourable way to circumvent the obstacles for BBB allowing the direct drug delivery in the biophase of CNS-active compounds. This is achieved by the olfactory pathway. When a nasal drug formulation is delivered deep and high enough into the nasal cavity, the olfactory mucosa may be reached and drug transport into the brain and/or CSF via the olfactory receptor neurons may occur. This review is an attempt to understand the nasal drug delivery system, advantages of this system & physiochemical and formulation factors for development of dosage. Exploitation of this drug delivery for brain targeting, challenges underlying and the future perspective will also be discussed.

2. Advantages of Intranasal Drug Delivery System

- Rapid absorption –rapid onset of therapeutic effect.

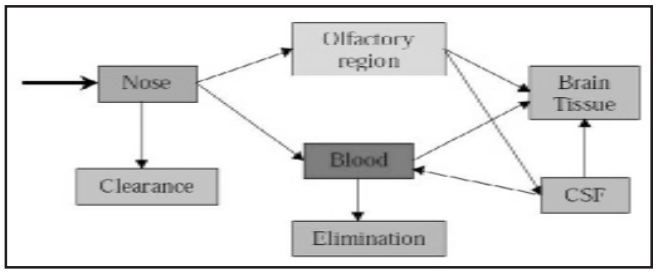
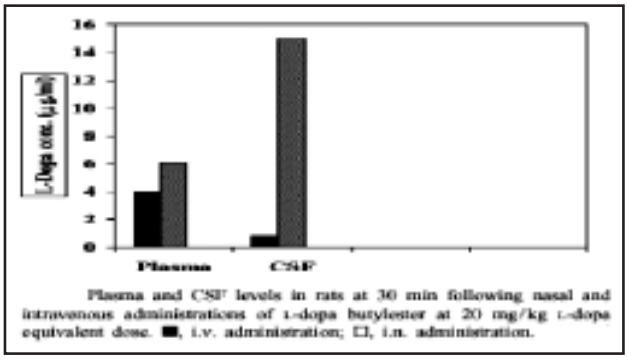


Figure 1 : Fortune of Drug after Adminstered to Nose for Brain Targeting.
Source: Behl C R, Targeting Brain via Nasal RouteReality or Myth? Pros and Cons, Practical Considerations; Conference of Behl Holding Corp., Inc., June 9, 2005.

- Its easy, convenient and painless.
- The nose is a very easy access point for medication delivery.
- It can be self administered.
- Allows for a dual product concept for better therapy.



Plasma and CSF levels in rats at 30 min following nasal and intravenous administrations of L-dopa butylester at 20 mg/kg L-dopa equivalent dose. ■, i.v. administration; □, i.n. administration.

Graph 1 : Plasma conc. of Nimopidine in rats

Source: Zhang QZ, Xin-guo JIANG & Chun-hua WU. Distribution of nimodipine in brain following intranasal administration in rats Acta Pharmacol Sin 2004 Apr; 25 (4), (2004 Apr) 522-527

- Avoidance of gut and liver first pass metabolism.
- Lower dose is required and hence lower side effects.
- More optimal therapeutic effect of existing drugs.
- Additional intellectual property and commercial benefits.
- Needleless: Intranasal Medication administration offers a truly "Needleless" solution to drug delivery.
- Superior: Intranasal medication administration generally results in superior drug delivery to the blood stream compared to other transmucosal routes.[1,2,3]

3. Nasal Anatomy, Physiology and Histology

In humans and other animal species, the major functions of the nasal cavity are breathing and olfaction. However, it also affords an important protective activity once it filters, heat and humidifies 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. 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. The human nasal cavity has a total volume

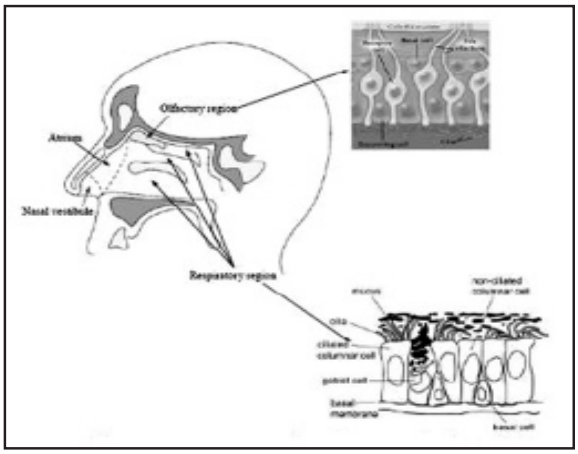


Figure 2 : Anatomy and Histology of human nasal cavity

Source: Anaísa Pires, Ana Fortuna, Gilberto Alves and Amílcar Falcão. Intranasal Drug Delivery: How, Why and What for? J Pharm Pharmaceut Sci 12(3), (2009) 288 - 311,

of 15-20 mL and a surface area of approximately 150 cm^2. It is divided by middle (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 that are distinguished according to their anatomic and histological characteristics. [4, 5]

Nasal Vestibule is the most anterior part of the nasal cavity, just inside the nostrils. Here, there are nasal hairs, also called vibrissae, which filter the inhaled particles. 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. [3,5]

Atrium is the intermediate area between nasal vestibule and respiratory region. [3, 5]

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. The nasal respiratory mucosa, considered the most important section for delivering drugs systemically, is constituted by the epithelium, basement membrane and lamina propria. 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. Actually, microvilli are important to enhance the respiratory surface area, while cilia are essential to transport the mucus toward the nasopharynx. 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 Mucociliary clearance (MCC). The presence of mucin in the nasal mucus layer is crucial because it may trap large molecular weight drugs, such as peptides and proteins. [3, 5]

The Olfactory Region is located in the roof of the nasal cavity and extends a short way down the septum and lateral wall. Its neuroepithelium is the only part of the CNS that is directly exposed to the external environment. The olfactory one is also pseudostratified but contains specialized olfactory receptor cells important for smell perception. In this area, there are also small serous glands (glands of Bowman) producers of secretions acting as a solvent for odorous substances. [3,5,6]

3.1. Anatomy of Olfactory Receptors

The nose contains 10-100 million receptors for the sense of smell or olfaction. The total area of olfactory epithelium is 5 cm^2. The olfactory epithelium consists of three kinds of cells: olfactory receptors, supporting cells, and basal stem cells.

Olfactory Receptors which are first order neurons of the olfactory pathway, are bipolar neurons whose exposed tip is a nose shaped dendrite. The sites of olfactory transduction are the olfactory hairs, which are cilia that project from the dendrite. Olfactory receptors respond to the chemical stimulation of an odorant molecule by producing a generator potential, thus initiating the olfactory

response. From the base of each olfactory receptor, a single axon projects through the cribriform plate and into the olfactory bulb.

Supporting Cells are columnar epithelial cells of the mucous membrane lining the nose. They provide physical support, nourishment, and electrical insulation of the olfactory receptors, and they help them detoxify the chemicals that come in contact with the epithelium.

Basal Stem Cells lie between the bases of the supporting cells and continually undergo cell division to produce new olfactory receptors, which live for only a month or so before being replaced. This process is remarkable because olfactory receptors are neurons, and in general, mature neurons are not replaced.

Within the connective tissue that supports the olfactory epithelium are olfactory (Bowman's) glands, which produce mucous that is carried to the surface of the epithelium by ducts. The secretion moistens the surface of the olfactory epithelium and dissolves odorants. Both supporting cells of the nasal epithelium and olfactory glands are innervated by the branches of the facial nerve, which can be stimulated by certain chemicals.

3.2. Physiology of Olfaction

Olfactory receptors react to odorant molecules in the same way that most sensory receptors react to their specific stimuli: A generator potential develops and triggers one or more nerve Impulses. The result is the following chain of events:
Opening of sodium ion (Na^+) channels → inflow of Na^+ → depolarizing generator potential → nerve impulses.

3.2.1. Olfactory Pathway

On each side of the nose, bundles of the slender, unmyelinated axons of olfactory receptors termed, the "olfactory nerves", terminate in the brain in paired masses of grey matter called the olfactory bulbs. Axons of olfactory bulb neurons extend posteriorly and form the olfactory tract. Because many olfactory tract axons terminate in the lateral olfactory area, it is considered the primary olfactory area, where conscious awareness of smell begins. Connections to other limbic system regions and to the hypothalamus probably account for our emotional and memory-evoked responses to odours. From the lateral olfactory area, pathways also extend to the frontal lobe, both directly and indirectly via the thalamus. [4,5]

4. Nose to Brain Pathways

When a nasal drug formulation is delivered deep and high enough into the nasal cavity, the olfactory mucosa may be reached and drug transport into the brain and/or CSF via the olfactory receptor neurons may occur. The olfactory pathways may be broadly classified into 3 possible mechanisms (Fig 3). [10, 19]

The extraneural Pathway is a significantly faster route for direct nose-to-brain transfer, whereby compounds pass paracellularly across the olfactory epithelium into the perineural space, which is continuous with the sub-arachnoid space and in direct contact with the CSF. Then the molecules can diffuse into the brain tissue or will be cleared by the CSF flow into the lymphatic vessels and subsequently into the systemic circulation. The extraneuronal pathway allows therapeutic agents to reach the CNS within minutes.[6]

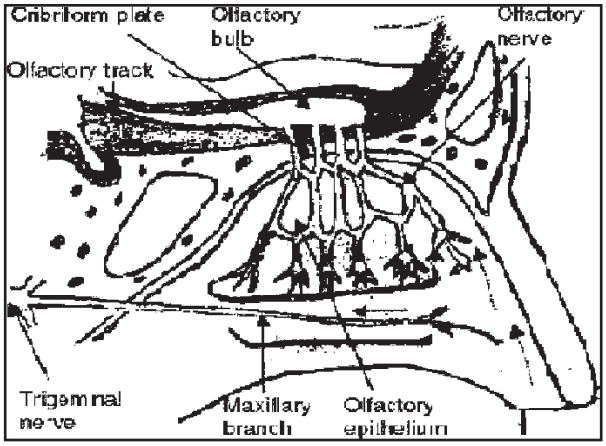


Figure 3 : Pathways of Nose to Brain
Source: S. Talegaonkar, P. R. Mishra. Intranasal delivery: An approach to bypass the blood brain barrier. Indian J Pharmacol, 36(3), (2004) 140-147.

The Intraneuronal Pathway involves axonal transport for drugs to reach different brain regions. Axonal transport is considered a slow route whereby an agent enters the olfactory neuron via endocytotic or pinocytotic mechanisms and travels to the olfactory bulb by utilizing the same anterograde axonal transport mechanisms the cell uses to transport endogenous substances to the brain. [19] Depending on the substance administered, axonal transport rates range from 20-400 mm/day to 0.1-4 mm/day.

The Trigeminal Neural Pathway may also be involved in rapidly delivering protein therapeutic agents, such as insulin-like growth factor-1 to the brain and spinal cord following intranasal administration. [10]

Intranasal delivery of agents to the CSF is not surprising as CSF normally drains along the olfactory axon bundles as they traverse the cribriform plate of the skull and approach the olfactory submucosa in the roof of the nasal cavity, where the CSF is then diverted into the nasal lymphatics.

5. Distribution of Drug in Nasal Cavity

Drug distribution in the nasal cavity is a key factor that affects the efficiency of nasal absorption. The mode of drug administration may affect this distribution, which in turn, can help determine the extent of absorption of a drug. Nasal deposition of particles is related to the individual's nasal resistance to airflow. [7] With nasal breathing, nearly all the particles having an aerodynamic size of 10-20 mm are deposited on the nasal mucosa. The deposition of particles in the respiratory tract is a function of size and respiratory patterns. The deposition of the particle is influenced by various factors as density, shape, and hygroscopicity of particles, and the pathological conditions in the nasal passage. Whereas particle size distribution determines the site of deposition and affects the subsequent biological response in animals and humans. [8] Three mechanisms are usually considered in assessing particle deposition in the respiratory tract, i.e., inertia, sedimentation and diffusion, the first being the dominant mechanism in nasal deposition. [9] Any particle with an aerodynamic diameter of 50 mm or greater does not enter the nasal passage. It was demonstrated that 60% of aerosolized particles of 2-20 mm are deposited in the anterior regions of the nostrils, 2-3 mm from the external nares. The site of drug deposition within the

nasal cavity depends on the type of delivery system and the technique used in application. [10]

6. Absorption of Drug

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. 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. It is well known that their size is comprised between 3.9-8.4 Å avoiding the passage of bigger molecules. [10,3]

7. Factors Affecting Absorption

7.1. Nasal Physiological Factors

7.1.1. Mucociliary Clearance

MCC is the self-clearing mechanism of the bronchi. This elimination is designated MCC and it significantly influences the nasal drug absorption. [2] If MCC decreases, residence time of the drug product in nasal mucosa increases and, therefore, enhances its permeation. The opposite effect is observed when MCC increases. [12]

7.1.2. Enzymatic Degradation

The drug may be 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. [2,13]

7.1.3. Transporters and Efflux Systems

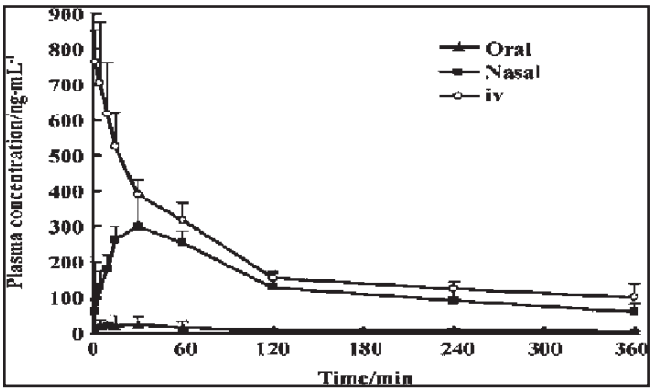
The study of transporter systems present in the nasal tissue and their effects on the absorption of drugs into systemic circulation and CNS is a research area in development. At the moment, multidrug resistance transporters have already been identified in human nasal respiratory and olfactory mucosa. [14] P-glycoprotien (Pgp) is an efflux transporter that exists in the apical area of ciliated epithelial cells and in the submucosal vessels of the human olfactory region. Several studies including Graff CL (2005) demonstrated that Pgp has an important role in preventing actively the influx of drugs from nasal membrane. [2,38]

7.2. Physicochemical Properties of Drugs

7.2.1. Molecular Weight, Lipophilicity, Partition Coefficient & pKa

Molecular weight still presents the best correlation to absorption. The nasal membrane is predominantly lipophilic. Lipophilic drugs such as propranolol, progesterone and nimopidine are, in general, well absorbed from the nasal cavity, presenting pharmacokinetic profiles similar to those obtained after intravenous administration and a nasal bioavailability near to 100%.

The extension of nasal absorption of lipophilic drugs bigger than 1 kDa is significantly reduced. Drug absorption is expected to diminish with a decrease in lipophilicity. However, 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



Graph 2 : Drug conc. in CSF by IN and IV Route
Source: Kao (1995) from Ref No. 40

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. For some small polar molecules only a 10% bioavailability is suggested. The value goes down to 1% for large molecules such as proteins. [1]

It also depends on the drug pKa and the pH of the absorption site (5.0-6.5 in human nasal mucosa). Both the pH of the nasal cavity and pKa of a particular drug need to be considered to optimize systemic absorption. Nasal irritation is minimized when products are delivered with a pH range of 4.5 to 6.5. According to pH partition theory, the non-ionized fraction of a drug is more permeable than that ionized. Nasal absorption of weak electrolytes depends on their ionization degree and the largest absorption occurs for the nonionized species. In this state, they present a higher apparent partition coefficient and, thus, they are more lipophilic. However, drugs such as acetylsalicylic acid and benzoic acid 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. [1,15,16]

7.2.2. Solubility

Drug dissolution is a pre-requisite for any drug absorption, since only the molecularly dispersed form of a drug at the absorption site may cross the biomembranes. 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. 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. Due to the small size of nasal cavity, the allowable volume of drug solution is low

for intranasal drug administration. Thereby, drugs poorly soluble in water and/or requiring high doses may constitute a problem. This can be solved by enhancing the drug aqueous solubility. An upper limit of 25 mg/dose and a volume of 25 to 150 mL/nostril have been suggested. [14, 17]

7.2.3. Stability

The environment of nasal cavity has the ability to metabolize drugs by defensive enzymatic mechanisms, which may reduce the biological stability of intranasally administered drugs [14]. Many drugs may be physicochemically instable due to hydrolysis, oxidation, isomerisation, photochemical decomposition or polymerization reactions.

8. Formulations of Dose

The absorption profile is highly influenced by the formulation of the pharmaceutical drug. This in turn, determines the therapeutic effect of the drug.

8.1. Factors of Formulation in Absorption Profile

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. While pharmaceutical preparation is formulated, several properties are considered.

8.1.1. 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, cyclovir and metoprolol. However, sometimes, enhancing formulation viscosity does not enhance the drug absorption, for eg. Zaki (2006). [40] Although the residence time enhanced as viscosity increased the drug absorption diminished. This can be 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. [20]

8.1.2. pH

The extent of nasal absorption depends on 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). Besides, the pH often prevents the bacteria growth. In order to evaluate the effect of pH solution on the integrity of nasal mucosa, Pujara (1995) [21] 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 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. [3, 20]

8.1.3. 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. Moreover, rapid nasal drainage can occur when using this dosage form. Solution and suspension sprays are preferred over powder sprays as they prompted the development of nasal mucosa irritation. Recently, gel devices have been developed for a more accurate drug delivery. They reduce post nasal drip and anterior leakage, fixing the drug formulation in nasal mucosa. Over the last years, specialized systems such as lipid emulsions, microspheres, liposomes and films have also been developed to improve nasal drug delivery. [3, 21]

8.1.4. Pharmaceutical Excipients

In nasal formulations, a wide variety of excipients can be found and they are selected accordingly to their functions. Solubilizers, buffer components, antioxidants, preservatives, humectants, flavoring or taste masking agents are some of the most usual excipients. 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. [3, 11]

8.2. Strategies to Increase Nasal Drug Absorption

Briefly, for many drugs, bioavailability is particularly restricted by low drug solubility, rapid enzymatic degradation in nasal cavity, poor membrane penetration and rapid MCC. [22] Several approaches have been suggested to overcome these limitations.

8.2.1. Prodrugs

The 'prodrugs' are those compounds that undergo biotransformation prior to exhibiting their pharmacological effect. Intranasal drugs are commonly 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 CNS, the prodrug must be quickly converted to the parent drug. An alternative approach to the use of prodrugs in order to increase drug solubility is the use of co-solvents. Co-solvents most used in intranasal formulations include glycerol, ethanol, and may be of the most importance since they are nontoxic, pharmaceutically acceptable and nonirritant to nasal mucosa. [3, 23]

8.2.2. Enzymatic Inhibitors

Various approaches have been used to avoid enzymatic degradation in nasal mucosa, including the use of proteases and peptidases inhibitors. Enzymatic inhibition can also be achieved using certain absorption enhancers. 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. [3, 21]

8.2.3. Absorption Enhancers

It is possible to greatly improve their absorption, if drugs 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, bile salts, fatty acids and polymeric enhancers (chitosan, cyclodextrins). 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. [18] Although the absorption promoters enhance drug bioavailability, a direct relation between this effect and the damage caused in the membrane may sometimes exist. Thus, during the choice of an absorption enhancer to include in an intranasal formulation, it is essential to assure good absorption enhancing and minimal toxic effects. [3, 24]

8.2.4. Mucoadhesive Drug Delivery Systems

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. 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. Firstly, mucoadhesive systems absorb water from mucus layer and get wet and swelling. Following this, the polymer intimately penetrates into the mucus and, hence, localizes the formulation in nasal cavity, enhancing the drug concentration gradient across the epithelium. [25] Mucoadhesives mostly used in intranasal drug delivery are chitosan and cellulose or its derivatives. [3]

8.3. Novel Drug Formulations

Several claims have been made in favour of developing nasal formulations. 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. [26]

8.3.1. 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. [23] In fact, they have been found to enhance nasal absorption of peptides such as insulin and calcitonin by increasing their membrane penetration. This has been attributed to the increasing nasal retention of peptides, protection of the entrapped peptides from enzymatic degradation and mucosal membrane disruption. They also facilitate direct absorption through the nasal mucosa.[3] These conclusions were obtained comparing liposomal formulations and free drug suspended in gel.

8.3.2. Microspheres

Microsphere technology has been widely applied in designing formulations for intranasal drug delivery. Microspheres are based on mucoadhesive polymers. Microspheres may also protect the drug from enzymatic metabolism and sustain drug release, prolonging its effect. [3, 25,26]

8.3.3. Nanoparticles

Nanoparticle systems are being investigated to improve intranasal drug administration. 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. 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. Studies have suggested that nanoparticle systems may be ideally suited for the delivery of nasal vaccines. [3,26]

9. Applications of Intranasal Drug Delivery

9.1. For Small and Large Molecules

Intranasal drug delivery system has several advantages over other routes, specially for CNS drug delivery. A large number of molecules have been studied and many market preparations are available. [3, 27] Few of these drugs are listed below.

9.2. Insulin for Treating Alzheimer's Disease

Excessive production of β-amyloid (Aβ) peptides from proteolytic cleavage of amyloid precursor protein is believed to play a central role in the pathogenesis of Alzheimer's disease (AD). Evidence shows that both extracellular and intracellular Aâ-derived diffusible ligands (ADDLs) can compromise insulin signaling. Abnormal insulin/

TABLE 1. Various Drugs being Studied for Nasal Drug Delivery System

SMALL MOLECULES	
Antibiotics	Gentamicin, Cephalosporin, Penicillins, Tyrothricin
Antiviral drug	Enviroxime
Cardiovascular drugs	Nitroglycerin,Propranolol, Verapamil, Hydralazine
Central nervous system drugs	
a. Stimulants	Cocaine, Lidocaine
b. Depressants	Diazepam, Lorazepam
Autonomic nervous system drugs	
a. Sympathomimetics	Dopamine, Dobutamine, Ephedrine, Epinephrine,
b. Parasympathomimetics	Methacholine, Nicotine
c. Parasympatholytics	Prostaglandins, Ipratropium, Scopolamine
Narcotics and antagonists	Buprenorphine, Naloxone

	LARGE MOLECULES
Amino acids	
Peptides	Calcitonin, Secretin, Cerulein, Enkephalin Thyrotropin-releasing hormone (TRH),
	Mekephamid, Cholecystokinin Pentagastrin, SS-6, Substance P, Kyotorphin,
Polypeptides and proteins	a. Albumins
	b. Anterior pituitary hormones - Adrenocorticotropic hormone, Gonadotropinreleasing
	hormone, Growth hormone
	c. Biological products - Interferon, Vaccines
	d. Horseradish peroxidase
	e. Pancreatic hormones - Insulin, Glucagon
	f. Posterior pituitary hormones - Oxytocin, Vasopressin

Source: Anaísa Pires, Ana Fortuna, Gilberto Alves and Amílcar Falcão. Intranasal Drug Delivery: How, Why and What for?. J Pharm Pharmaceut Sci 12(3), (2009) 288 - 311.

Insulin Receptor (IR) levels and activities are seen in Alzheimer's dementia, whereas administration of insulin significantly improves the cognitive performance of these patients. At the molecular level, insulin/IR participates in regulation of learning and memory via activation of specific signaling pathways.

In healthy adults and patients with Alzheimer's disease, raising plasma insulin levels while maintaining euglycemia can improve memory; however, raising plasma glucose while suppressing endogenous insulin secretion may not, suggesting that adequate levels of insulin and glucose are necessary for memory facilitation.

The advantage of using intranasal rather than intravenous insulin, however, is that it does not cause systemic side effects like hypoglycemia.

Gender is a critical factor in brain insulin signaling that affects both food intake and cognitive functions. Intranasal Insulin shows better memory improvement among the women. [31,32] Collectively, these findings support an association among Alzheimer's disease, impaired glucose metabolism, and reduced insulin sensitivity. [28-30]

10. Limitations of Intranasal Drug Delivery System

- Nasal drug delivery is convenient and easy, but it may not always be effective.
- Nasal drug delivery cannot completely replace the need for injections.
- It can irritate nasal mucosa and their histological toxicity is not clear.
- Not all drugs can be delivered via the nasal mucosa and the surface available is small.
- The absorption of many drugs is very very low.
- There may not be the contact of drug formulation with the olfactory region (Figure 4).
- In most of the studies, animal models and methods are used. However, there exists a large change in properties and area of the olfactory region of the human and animals.
- The pharmacokinetics and pharmacodynamics of the drug uptake in CSF is different for different drugs, so can't be predicted. [35-37]

11. Conclusion

Keeping in the mind the potential benefits of intranasal drug delivery

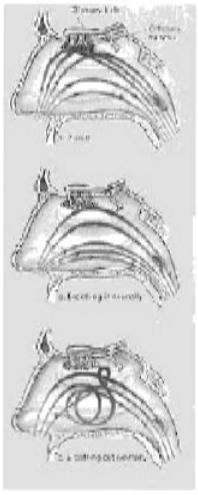


Figure 4 : Site of Administration of Drug

Source: Behl C R, Targeting Brain via Nasal RouteReality or Myth? Pros and Cons, Practical Considerations; Conference of Behl Holding Corp., Inc., June 9, 2005.

to administer drugs to CNS and numerous advantages of nasal route, there is a widespread interest in this field and it is expected that the market will grow enormously and will see many novel nasal products. Rapid and non invasive approach to target the brain with reduction in systemic side effects seems to be promising.

The use of novel drug formulations such as mucoadhesive drug delivery, microsperes and nanotechnology is coming up. In the near future, these techniques should be properly exploited for its use to treat brain tumors, parkinson's and other neurological diseases.

However, the route is yet to prove its usefulness from practical point of view though it has potential from technical considerations. Most of all the study is carried on different animals and there are several other problems that need to be addressed. Each drug is one particular case and, thus, the relationship between the drug characteristics, the strategies considered and the permeation rate is essential. Intranasal drug delivery has a long way to cover.

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