Review Article

Drug Delivery through Nose: A Noninvasive Technique for Brain Targeting

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Abstract

Majority of drugs are usually introduced through oral or intra-venous route for fast action, better patient compliance and ease of drug administration. However, the low bioavailability and limited brain exposure of orally administered drugs pose a huge challenge to treat neurodegenerative and psychiatric disorders. So, the situation demands for targeting the drug to brain. For brain targeting, a number of factors are considered viz. molecular weight, route of administration, lipophilic character of drug and blood brain barrier (BBB). These factors limit the movement of drug into brain tissue through BBB. To overcome these problems, intranasal drug administration is one of the promising routes that bypasses BBB and cuts down the dose to be administered with better brain exposure to drug. Nasal route has been used for the administration of antihistamines, local analgesics and corticosteroids intended for local drug delivery in nasal allergy, nasal congestion and nasal infection. However, systemic drug delivery through this route has also been explored in recent times. For nose to brain drug delivery, olfactory and respiratory region are utilized which also enable delivery of larger molecules to reach brain tissues. Such delivery systems are generally pH or temperature dependent. Certain diseases of nervous system like migraine, dementia, parkinsonism, epilepsy and Alzheimer's disease can be successfully treated through this route. This review attempts to highlight the anatomy of nose, mechanisms of drug delivery from nose to brain, critical factors in the formulation of delivery systems, nasal formulations and applications of nasal route for delivery of various drugs.

Keywords: *Nose, Drug, Brain targeting, Blood brain barrier, Olfactory region, Respiratory region*

Introduction

Central nervous system (CNS) is one of the most complex systems in our body. Majority of functions and movements of human body are controlled by CNS. The blood–brain barrier (BBB)/tight junction is the major barrier for the delivery of drugs to the brain. The drugs used to treat CNS disorders must pass through BBB to reach at target site.[1]

The role of BBB is principally regulated by different endothelial cells present at tight junction of BBB. The tight junction offers a very high electric resistance of about 1500–2000 Ohm cm^2, which is very high as compared with other tissues such as skin, colon, bladder, and lungs offering an electric resistance in a range of 3–33 Ohm cm^2. This electrical resistance significantly affects physical absorption of drugs by brain tissues. There are some certain drugs, such as benzodiazepines, because of their highly lipid soluble nature, that are able to cross the BBB easily. Another barrier that is also present in the path of systemically administered drug is called as blood–cerebrospinal fluid barrier (BCB). The BCB barrier is accomplished by the presence of double-layered membrane called as arachnoid membrane. It serves as a barrier for the movement of drug between blood and cerebrospinal fluid (CSF). Consequently, the BBB is most important rate-limiting/rate-determining barrier for the transport of drug to the brain. For taking drug molecules across BBB, physicochemical characteristics of drugs are the main factors to be considered during designing of delivery system for brain tissue targeting. A number of scientific approaches such as receptor-mediated transport, BBB disruption, targeted delivery through prodrug, and cell-penetrating peptides have been studied for brain targeting. Among all the delivery systems for brain targeting, nasal drug delivery system is the most reviewed system because of its uniqueness to bypass BBB. In this system, transport of drugs to brain tissue takes place through olfactory nerve endings present in nose.[2]

Nevertheless, intranasal drug delivery would be effective, only when the drug is in contact with olfactory nasal epithelium for prolonged/sufficient period of time to allow diffusion into the olfactory nerve ending

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projections. Thermosensitive gels and pH-responsive gels are very promising approaches for the delivery of drugs through nasal route, which stop clearance of drug by ciliary movement. The polymers used in the formulation of nasal thermosensitive gels are hydroxy propyl methyl cellulose (HPMC), poloxamer, and carboxymethylcellulose; the pH-responsive gels are formulated using polymers such as carbopol 934, carbopol 940, and carbomer. In addition, mucoadhesive polymers such as chitosan, guar gum, and sodium alginate are added to further enhance the nasal drug residence time and promote maximum diffusion of the drug molecule across nasal epithelium.[3]

Brain Targeting through Nasal Route

Poor brain tissue distribution of drugs in the presence of BBB leads to the development of other approaches. There is a unique connection between nose and CNS, because of which nasal route can distribute drug molecules to the brain tissues bypassing the BBB. The olfactory nerve endings present in brain provide an alternate pathway for the delivery of drugs into CNS. On the basis of the literature available, it has been observed that on drug administration through nasal route in rats, the resultant concentration was found to be higher than normal.[4]

Advantages of Nasal Drug Delivery System

Large surface area. Nasal mucosa offers large surface area for the accommodation of drug or dosage form, which allows greater absorption of drugs.

High vascularity. Nasal mucosa is highly rich in blood vessels, which promotes large uptake of drugs.

Rapid onset of action. Because of high vasculation and large surface area offered by the nasal mucosa, drug gets absorbed quickly and shows its action promptly.

Noninvasive. Administration of drug by nasal route is easy. Patients can administer drug by their own.

Bypass BBB. Drugs that fail to pass through BBB can be given through nasal delivery system. Transport of drug from nasal mucosa to brain and CSF takes place through olfactory region of the nose bypassing the BBB.

Better drug use with less side effects. The drugs introduced through nasal route do not undergo hepatic first pass metabolism; hence, less dose of drug can be effective to treat specific condition and side effects are also minimized.

Systemic effect and CNS drug delivery. Administration of drugs through nose may result in systemic effects in addition to which the delivery of drug localized to brain tissues can also be achieved. Drugs show systemic effects once get absorbed from the respiratory region of nose and brain delivery is associated with absorption of drug through olfactory nasal epithelia.[5]

Limitations of Nasal Drug Delivery

Limited dose size. The biggest limitation of nasal drug delivery is that only limited size of dose can be administered at a time. The drugs where high dose is required to show their therapeutic effect cannot be given through this route. Only 50–250 µL of dose can be introduced per nostril.

Delivery of macromolecules. Molecules having molecular weight more than 1000 Daltons cannot be absorbed through nasal mucosa.

Pathological conditions. The pathological conditions such as cold, flu, nasal allergy, and nasal infection lead to alteration in nasal secretions and pH. In such cases, efficient delivery of drug is not possible through nose.

Ciliary movement. Ciliary movements lead to removal of mucus from nasal surface. It can decrease the residence time of drug at the surface of nasal mucosa and hence permeability of drug may be altered/ decreased.

Enzymatic degradation of proteins and peptides. Enzymes exonuclease (mono and diamino peptidases) and endonuclease (serine and cysteine) present at the inner nasal surface break the peptide molecules from N- and C-terminal residue and also at the center of molecules.[5]

Anatomy of Nose

Human nose comprises two lobes, separated by a flexible septum. Volume of each lobe is about 7.5–9 mL and about 16–19 mL in total for both the lobes. The internal surface area of nose is about 180 cm^2. From the drug administration point of view, nose is divided into three major regions as shown in Figure 1.[6]

1. Vestibular region
2. Respiratory region
3. Olfactory region

When drug is administered by nasal route in various forms such as nasal drop, nasal spray, or nasal emulsion, it gets deposited in aforementioned regions from where absorption of drug takes place.

Vestibular region

It is present at the opening of the nostrils. It comprises fine nasal hair. The main function of nasal hair is to filter out air born particulates. It has no significant impact on absorption of drugs.

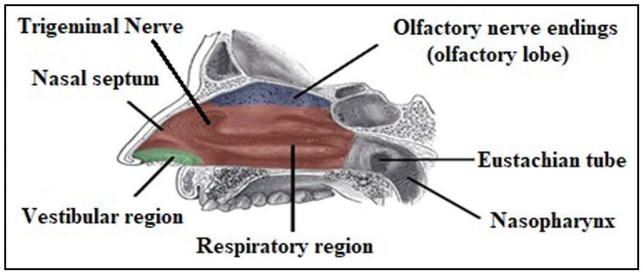

Figure 1: Anatomy of nose

Respiratory region

Respiratory region is mainly responsible for drug absorption. It comprises high degree of blood vessels in respiratory mucosa. Most of the drugs are absorbed through respiratory region to systemic circulation.[7]

Olfactory region

It comprises about 10–11 cm^2 surface area and plays an important role in drug absorption directly into the brain tissues and CSF. Olfactory region comprises a number of olfactory nerve endings. Although this region is responsible for delivery of drug to brain, the exact mechanism involved therein is still unknown.[7]

The epithelium of nose is covered by the mucus layer whose function is to sooth the epithelial cells and entrap foreign particles. Mucus over the epithelium is cleared by the ciliary movement. It takes about 15–20 min to move cilia through a distance of 1 cm. The pH of mucosal secretions in healthy adult is about 5.5–6.5, whereas in children it ranges from 5.0 to 6.7.[4]

Mechanism of Drug Delivery from Nose to Brain

In olfactory region of nose, the drug communicates with the nerve endings present at the olfactory receptor and also with trigeminal neurons to some extent. After interaction with nerve endings, drug moves toward brain by the extracellular and intracellular transport mechanism and follows the nerve channels of olfactory cells. Finally, drug arrives at the cribriform plate and then enters into the olfactory bulb and CSF. Once the drug arrives at the CSF, it gets mixed with the spinal fluid and distributed to the brain and throughout the CNS. Clearance of the drug from CNS to PNS occurs in reverse direction by the same mechanism.

When drug is absorbed from the respiratory region of the nose, sometimes it is retained in the venous supply instead of entering into systemic circulation in nasal passage and quickly transfers to the arteries of CNS and brain. This process of drug transfer is known as counter current transfer.[8]

Pathways Followed by the Drug

Despite the lack of understanding about exact mechanisms behind nose-to-brain delivery of drugs, there is much evidence that shows the pathways involved in nerves connection between nasal mucosa to the brain/spinal cord. In addition, various other pathways such as lymphatic system and CSF have been involved in transport of drug molecules from nasal mucosa to CNS, as shown in Figure 2. Usually, combination of these pathways is responsible for the drug transport, where one pathway may or may not predominate, depending upon the characteristics of the therapeutic agent, the characteristics of dosages form, and the delivery device used.[9,10]

Olfactory nerve pathway

Olfactory nerve pathway is a major route followed by the drug in for brain targeting through intranasal delivery. Olfactory

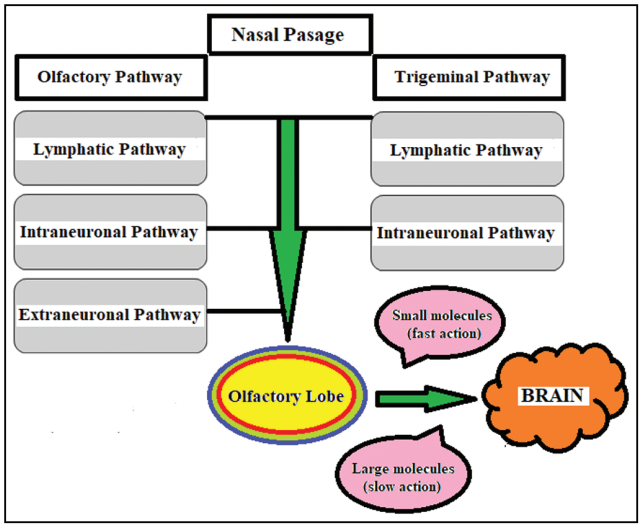

Figure 2: Pathways representing nose-to-brain drug delivery

pathways are present at the upper portion of nasal cavity. In olfactory region, olfactory receptor neurons (ORNs) are present along with supporting cells that are also called as sustentacular cells/basal cells/microvillar cells. ORNs convey sensory information (sense of smell) from the peripheral surrounding to the CNS. Just beneath the epithelium layer, it comprises bowman's glands (mucus secretion), axons, lymphatic vessels, blood vessels, and connective tissue. The dendrites of olfactory neurons extend in the mucous layer over the olfactory epithelium, whereas axons of these neurons extend centrally in the cribriform plate of ethmoid bone, where it separates the cranial cavity and nasal cavity. The stem (axon) of the olfactory neuron passes through the subarachnoid space, which comprises CSF. From this region, neuronal projections extend toward the multiple brain regions such as olfactory tract, piriform cortex, anterior olfactory nucleus, amygdale, and hypothalamus.[11]

In general, three different pathways can be involved for drug transport across olfactory epithelium: (1) transcellular (especially across sustentacular cells) pathway where transport generally takes place by endocytosis or passive diffusion (majorly responsible for transport of lipophilic drugs); (2) paracellular (between sustentacular cells) pathway. This route accounts for transport of hydrophilic drugs the rate of which depends upon molecular weight of drug. Good bioavailability can be achieved from drugs with molecular weight up to 1000 Da or more (with absorption enhancer) through this route; (3) olfactory nerve pathway, where endocytosis is involved in taking up of drug into the neuronal cell and further transportation is carried out to olfactory bulb by intracellular axonal transport.[12]

Trigeminal nerve pathway

Trigeminal nerve provides an important pathway for brain drug delivery through nasal drug administration. These nerves pass through olfactory and respiratory epithelium and enter CNS at pons region.

The respiratory region varies from olfactory region in cellular composition. It comprises ciliated epithelium, which is distributed among goblet cells that play an important role to remove mucus (mucocilliary clearance) along with foreign material from the nasal pathway. The function of trigeminal nerve is to convey sensory information from oral cavity, nasal cavity, eyelids, and cornea to CNS through the ophthalmic division, the maxillary division, and the mandibular division of trigeminal nerve.

The trigeminal nerve is unique in contrast to olfactory nerve as from respiratory region it enters the brain at two sites near the olfactory bulb through cribriform plate and at the pons region. Some other nerves such as facial nerves and sensory structures in nasal passage passing through the facial and head region may provide points for the entry of drug molecules in to CNS.

Obstacles in Brain Targeting through Nasal Drug Administration

The main problem in brain targeting through nasal administration involves poor drug permeability, enzymatic degradation of drug, mucocilliary clearance, and low drug retention at the site of absorption.[9]

Along with these problems, the nature of the excipients, drug, and potency of the drug are also considered. The total volume of nasal cavity is low (17–20 cm^3), which allows only a fixed and small amount of formulation (100–500 µL) administration at a time. In the case of higher doses, larger volumes should be divided (i.e., half dose in each nostril). It means only potent drugs are considered suitable for intranasal drug delivery for brain targeting. The excipients used in these formulations must be biocompatible. The pH (5.0–6.5), viscosity, and tonicity of the formulation must be optimum.[13]

Factors to be Considered in Development of Nasal Drug Delivery System

There are a number of factors that are considered critical in the development of nasal drug delivery system. These are considered so because small change in these factors may alter the therapeutic effectiveness of dosage forms up to greater extent [Table 1].[14] These factors are tabulated below.

Chemical form of drug

Chemical form of drug is having greater importance in the designing of intra nasal dosages forms. It affects the absorption of drug as well as stability. Some drugs show better solubility in their salt form or complex form rather than pure drug alone.[15,16]

Molecular weight

Molecular weight is one of the most important factors for brain targeting because only the molecules with less molecular weight can be used for brain targeting. When we talk about brain targeting through intranasal drug administration, drugs up to molecular weight of 1000 Da can be delivered. Drugs having molecular weight less than 300 Da can penetrate freely through the nasal epithelium without getting affected significantly by physicochemical factors.[17]

Table 1: Critical factors in the formulation of nasal drug delivery system

Physicochemical factors	Chemical form
	Molecular weight
	Polymorphism
	Lipophilicity
Formulation-related factors	pH of formulation
	Osmolarity
	Gel forming carrier used
	Solubilizers
	Dose concentration
Physiological factors	Nasal blood flow
	Mucocilliary clearance
	Enzymatic degradation
	Pathological conditions

Polymorphism

In general, a number of chemical substances exist in nature in more than one form. These are present in different states such as unstable, metastable, and stable. For the formulation of dosage forms, metastable form of drug is used because of maximum solubility and suitable stability as well.[18]

Lipophilicity

Lipophilic character of drug determines its ability to get absorbed from the surface of mucosa. Generally, it depends on the hydrophilic lipophilic balance (HLB) of drug.[19] To reach in brain or systemic circulation, drug has to go across phospholipid bilayer membrane. Hence, highly lipophilic drugs can easily pass through this membrane.[13]

pH of formulation

The pH of nasal mucosa ranges from 5.5 to 6.5. The formulations developed for intranasal administration should be within this pH range. Nasal mucosa comprises lysozyme, an enzyme which is responsible for destroying variety of microbes. Lysozyme remains activated at acidic pH and if any drug alters the pH of nasal cavity, it may lead to infection in nasal cavity.[15] The following are the major functions where nasal pH plays an important role:

- Makes drug available for absorption in unionized form.
- Prevents microbial growth and infection in the nasal cavity.
- Preserves properties and functions of excipients.
- Avoids irritation to nasal mucosa.
- Maintains normal ciliary movement.

Tonicity

Tonicity is the measure of concentration of solution with respect to body fluids. Tonicity can affect the absorption of drug from nasal mucosa. It has been observed from previous studies that the hypertonic solutions of drug cause shrinkage of nasal mucosa and lead to better absorption. Hypertonic solutions

also decrease the natural ciliary movement and provide long time for drug residence.[20]

Gelling agent

Gelling agents are the substances that enhance the viscosity of formulation. The more is the gelling capacity, the more will be the residence time of drug inside the nasal cavity. Studies show that the dosage forms with high viscosity and less molecular weight, which are intended to be administered through intra nasal route, are better absorbed from nasal mucosa, whereas drugs with high molecular weight do not show a significant increase in the absorption.[21]

Solubilizers

Ideally, the soluble form of drug is considered better for absorption but high aqueous solubility of drugs is not desirable. The drugs should have sufficient lipid solubility when intended to be absorbed through nasal cavity. For this purpose, aqueous solvents along with cosolvents such as alcohol, glycerol, medium chain glycerides, and labrasol can be used. Other techniques to overcome this problem include use of surfactants (nonionic) and cyclodextrin complexation. While using these ingredients, nasal irritancy must be kept into consideration.[22]

Drug concentration

Some studies showed an increase in absorption of drug with increasing drug concentration but not all the times. If drug absorption takes place according to concentration gradient, there is an increase in the absorption of drug with an increase in concentration but when absorption is carrier mediated, there is no any significant increase in absorption with an increase in concentration.[23]

Nasal blood flow

The nasal mucosa is highly rich in blood vessels. It plays an important role in humification of inhaled air. The presence of blood vessels promotes fast absorption of drug molecules from nasal mucosa.[15]

Mucocilliary clearance

Mucocilliary clearance is a natural phenomenon of removing dust, allergens, and other foreign materials from the nasal passage. The residence time of dosage forms is affected by this clearance and absorption process is affected indirectly. To overcome this, certain bioadhesive polymers such as chitosan, carbopol, and HPMC are used in formulations.[24,25]

Enzymatic degradation

Nasal passage comprises a variety of enzymes that may degrade the drugs during administration through nasal cavity; proteins are mainly degraded by the protease enzyme, which break the protein structure into peptones. Exopeptidase such as mono and diamino peptidases break the protein molecule from C- and N-terminal and endopeptidase such as serine and cysteine proteases break the internal structure of peptide molecule rendering the drug ineffective.

Pathological conditions

Pathological conditions such as nasal allergy, allergic rhinitis, nasal infection, and nasal surgery affect the mucocilliary clearance of drug and tendency of drug to get absorbed. Intranasal route cannot be used during cold or flu because of increased drainage from nasal cavity. Pathological conditions may alter the pH of the nose as well and thus may affect the drug absorption.[15]

Nasal Formulations

There are a variety of nasal formulations available in the market. Depending on the purpose of drug administration, they are classified as follows [Figure 3].[26-28]

Nasal drops

Nasal drops are one of the simplest dosage forms that are introduced through nasal route. Usually, nasal drops are used for local effect (nasal congestion, allergic rhinitis) and systemic effect (migraine pain, osteoporosis, nausea). Nasal drops offer very less residence time in the nasal cavity because of postnasal dripping. The main limitation of nasal drops is lack of precision.[26]

Nasal spray

Nasal solutions and nasal suspensions can be sprayed into nasal cavity by using actuator and metered-dose pumps. These pumps and actuator with different size and shape are available for different particle sizes of dosage forms and spray patterns. Selection of actuator depends on the nature of dosage forms such as viscosity and droplet size. Exact dose of formulation ranging from 25 to 250 µL can be delivered with this system.[27]

Nasal emulsion

Nasal emulsions were developed with application of enhanced residence time for better absorption and for the treatment of local infections. There are some issues with the drug delivery in the form of nasal emulsions such as postnasal dripping, poor dose precision, and their stability.[28]

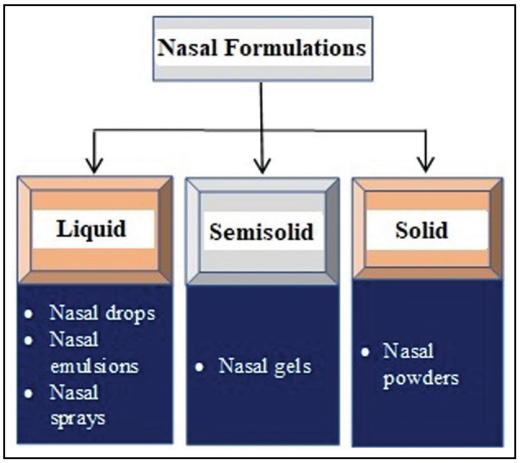

Figure 3: Classification of nasal drug delivery system

Nasal gels

Nasal gels are semisolid type of nasal drug delivery systems. They are solutions or suspensions with high viscosity. In these systems, polymers such as carbopol 934, carbopol 940, carbomer, and chitosan are used, which get converted into gel at particular pH or at particular temperature. Because of high viscosity of these systems, postnasal dripping can be avoided, residence time of dose at the surface of mucosa can be enhanced, and taste factor can be avoided due to reduced swallowing.

Nasal powders

Nasal powder dosage forms are formulated where suspension or solution dosage forms cannot be developed because of their poor stability. To check the suitability of the dosage forms and excipients, some properties such as particle size, solubility of drug, irritancy studies, and aerodynamic properties are evaluated. These powders offer several advantages such as stability, absence of preservatives, and local action. The major challenges in this delivery system are delivery of accurate dose and nasal irritation.[27]

Nanomedicines

A triad of nanomedicine delivered through nasal route for neurotherapeutics (3"N") is currently a relevant topic in research. These three nouns put together have a potential to become a single solution for drug targeting to brain. Nano formulations have a particle size less than 1000 nm and are obtained from different raw materials such as phospholipids (liposomes), lipids (solid lipid nanoparticles, nanostructured lipid carriers), and polymers (nanocapsules, nanospheres, micelles). Different types of nanosystems were investigated in preclinical studies, from screening of a suitable formulation to reach the brain intra-nasally to *in vitro*, *ex vivo*, and *in vivo* studies on the health or pathological model of animals.[29]

There are two important parameters that need to be determined to have an evidence of direct transport of molecules after intranasal drug administration. These parameters are drug targeting efficiency (DTE%) and direct nose-to-brain transport percentage (DTP%). DTE represents the time average partitioning ratio and can be calculated as follows:

$$DTE\%IN = \frac{\left(AUC_{brain} / AUC_{blood}\right) IN}{\left(AUC_{brain} / AUC_{blood}\right) IV} X\ 100 \qquad (1)$$

$$DTP\% == \frac{(BIN - BX)}{BIN} X\ 100 \qquad (2)$$

that is, [BX = (BIV/PIV) × PIN].

Here, B_{IN} is the AUC_{max} (brain) following IN administration; B_X is the brain AUC fraction contributed by systemic circulation through the BBB following intranasal (IN) administration; B_{IV} is the AUC_{max} (brain) following IV administration; P_{IV} is AUC_{max} (blood) following IV administration; and P_{IN} is AUC_{max} (blood) following IN administration. El-Zaafarany *et al.*[30] used these parameters as proof of concept to evaluate brain-targeting efficiency of oxcarbazepine-loaded nano-tryglyceride carrier-defined emulsomal vesicles followed by oxcarbazepine-loaded emulsome-loaded poly(lactic acid-co-glycolic acid)-poly(ethylene glycol)-poly(lactic acid-co-glycolic acid) (PLGA-PEG-PLGA, triblock polymer) thermogel solutions.[31]

Applications of Nasal Drug Delivery Systems

Vaccine delivery through intra nasal administration

Vaccine delivery through nasal administration is used for both systemic and local immune response in nasal pathway. In addition, it also provides barrier for protection. The majority of foreign antigens enter the body through mucosal surface.[32] Nasal mucosa acts as a first barrier or protective layer to the microbes as well as a filter for pathogens because of mucocilliary clearance. Nasal secretion comprises antibodies, that is, immunoglobulin (IgA, IgG, IgM, IgE), and the production of which gets stimulated by vaccines and is responsible for first line of defense.[33] Table 2 shows some of the intranasal vaccines available for commercial applications.[34-36]

Brain targeting through nasal drug administration

The major challenge in the delivery of drugs to the brain tissue is the development of suitable dosage forms, which may overcome BBB. Penetration of the drug across BBB is based on several properties of materials, such as molecular size, lipophilicity, and specificity. In the beginning of 1900s, the direct connection between brain and the nose via olfactory neurons was discovered and transport of CSF from olfactory neurons was observed, which led to generation of new idea that transport can exist in reverse direction and access to brain tissues can be achieved through nasal cavity.[37] A list of drugs that have been tested on laboratory animals[38,39] is given in Table 3.

Table 2: Vaccines available for intra nasal drug administration in market

Brand name	Vaccine	Dosage form	Manufacturer
Nasalflu Berna	Human influenza vaccine	Virosomes spray	Berna Biotech
Flu Avert	Equine influenza vaccine	Drops	Heska
FluMist	Human influenza vaccine	Spray	Medlmmune
StrepAvax	Human streptococcus—a vaccine	Proteosomes nanoparticulate	ID Biomedical
MaxiGuard Nasal Vac	Porcine bordetella bronchiseptica vaccine	Drops	Addison Biological Laboratory

Table 3: Intranasal drug administration reported in lab animals

Drug	Animal used	Target	Method of analysis
Bupivacaine	Rat	CSF	High-performance liquid chromatography (HPLC)
Chlorpheniramine	Rat	CSF	HPLC
Dihydroergotamine	Monkey	Brain tissue	Radioactivity counting
Fibroblast growth factor	Mouse	CSF	Motor activity, dopamine activity
β-Alanine	Hamster mouse	Brain tissue, CSF	Autoradiography, biochemical analysis

Table 4: Proteins and peptide nasal formulations for systemic effect

Brand name	Drug	Dosage form	Indications	Manufacturer
Syntocinon	Oxytocin	Solution (spray)	Lactation inducer	Novartis Pharma
Synarela	Nafarelin	Solution (spray)	Endometriosis	Pharmacia
Profact nasal	Buserelin	Solution (spray)	Prostate cancer	Aventis Pharma
Karil	Salmon calcitonin	Solution (spray)	Osteoporosis	Novartis Pharma

Table 5: Non-peptide nasal formulations for systemic effect

Brand name	Drug	Dosage form	Indications	Manufacture
Aerodiol	Estradiol	Solution (spray)	Hormone replacement	Servier
AscoTop Nasal	Zolmitriptan	Solution (spray)	Migraine	Astra Zeneca
Migranal Nasal	Dihydroergotamine	Solution (spray)	Migraine	Novartis Pharma

Protein and peptide drug delivery

Most of the proteins and peptides are hydrophilic in nature with high molecular weight. These polar molecules are poorly absorbed and have less bioavailability with concentration around 1%–2%. The poor bioavailability is not considered as a major problem for drugs such as desmopressin, and calcitonin because of wide therapeutic index, but in some cases where therapeutic index is narrow, novel strategies must be followed.[40]

To enhance the bioavailability of these drugs, various researches have been carried out using bioadhesive agents and absorption enhancers. Some examples of absorption enhancers are surfactants, cyclodextrin, and glycols. A list of protein and peptide drugs available in the market is given in Table 4. Table 5 shows nonpeptide products[41,42] administered through the nasal route for systemic effects.

Conclusion

Intranasal drug delivery provides an easy and noninvasive way to deliver drug molecules to brain tissues bypassing the BBB. This method is mainly applicable when delivery of drugs to brain tissue is not possible from systemic circulation. The route offers certain clinical benefits to the user such as lesser side effects by reduction in dose and less systemic exposure. In addition to these advantages, there are also certain limitations that are required to be overcome. Some of these limitations include pathological conditions, physiology of nose, and certain drug-related factors that determine the absorption of drug. To overcome these, some approaches such as minimization of mucocilliary clearance, use of permeability enhancers, and increasing residence time of drug can be used.

Intranasal delivery provides an alternate route to parenteral and oral delivery of drugs such as vaccines, nonpeptide, and peptide drugs; however, exhaustive research is still needed to establish the actual potential of this route.

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Conflicts of interest

There are no conflicts of interest.

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