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NOVEL FRONTIERS IN NASO-BRAIN DRUG DELIVERY;CHALLENGES AND OPPORTUNITIES: AN OUTLOOK

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ABSTRACT

Delivery of drugs through nasal route has been potentially explored as an alternative route for administration of vaccines and bio molecules such as proteins, peptides and non peptide drugs, hence it has attracted the interest of scientific community. Nasal route is beneficial for the drugs which are unstable on oral administration because they are significantly degraded in GIT or metabolized by first pass effect in liver. It is thought that olfactory route of drug transport, by pass the blood-brain barrier and allows the direct transport of drug from the nose to the brain. This Nasal route is alternative to parentral therapy and also useful for long term therapy. Nasal mucosa is highly vascularised and most permeable giving rapid absorption and onset of action. Nasal route is non invasive, widely used for the local treatment may also be used for systemic therapy as drug directly goes in systemic circulation. Nasal route gives good absorption of small molecules, than that of large molecules can be increased by absorption promoters. In this article is an overview of intranasal drug delivery with its various aspects like factors affecting nasal absorption, strategies to improve bioavailability are discussed.

KEYWORDS: *Intranasal drug delivery, Bioavailability, Nano-technology, Permeation enhancers.*

1. INTRODUCTORY NOTES

Despite tremendous advances occurring in brain research, brain and central nervous system disorders like schizophrenia, meningitis, migraine, Parkinson's disease and Alzheimer's disease remains the world's leading cause of disability and account for more hospitalizations

cases and prolonged care than accounted for almost all other diseases combined.[1] The major problem in drug delivery to brain is the presence of the BBB. Brain is tightly segregated from the circulating blood by a membranous barrier called the Blood Brain Barrier (BBB).[2-4] For decades, the BBB has prevented the use of many therapeutic agents for treating Alzheimer's disease, Parkinson's disease, glioma, stroke, head injury, schizophrenia, anxiety and other CNS disorders etc. Various techniques and attempts were made to deliver the drug across the BBB such as modification of therapeutic agents, altering the barrier integrity, carrier-mediated transport, invasive techniques etc. Describe number of possibilities that could explain the mechanism of the delivery of nanoparticulate formulations across the BBB. As compared to the pure drugs, there is an increased retention of the nano formulations in the brain blood capillaries combined with more adsorption to the capillary walls. These retention and adsorption create a higher concentration gradient that would enhance the transport across the endothelial cell layer and result in better delivery.[10]

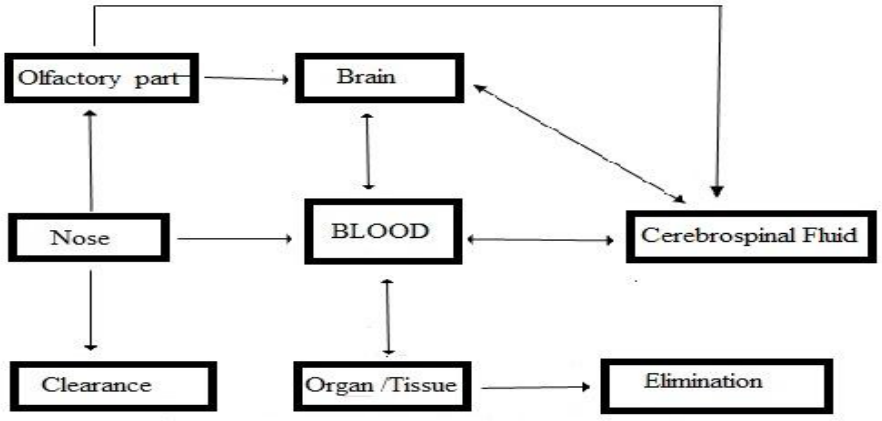

Fig 1: Different pathway for Naso-Brain administration.[6]

Nasal route has been explored as the conventional route, for the local delivery of drugs for treatment of local diseases like nasal allergy, nasal infections, rhinitis and nasal congestion. Since last few decades, nasal route had attracted a wide attention for researchers as a convenient, reliable and a safe route to achieve faster and higher levels of absorption.[6]

2. ANATOMICAL RELEVANCY FOR NOSE-TO-BRAIN TRANSPORT

In the next paragraph the anatomical organization of the nasal cavity will be discussed, in particular the structures that are necessary for understanding nose-to-brain transport. This topic has already been the subject of several excellent reviews. Therefore only a summary is present here, underlining the key-points in the anatomical organization in the nasal cavity

relevant for intranasal transport to the CNS. First, the possible pathways that are responsible for an effective nose-to-brain transport will be discussed. Next, a closer look will be provided into the anatomical structures that decide whether the applied substance can undergo nose-to-brain transport.[4]

2.1. Macroscopical Anatomy

2.1.1. Olfactory Pathway/Olfactory Region

The exact mechanisms underlying nose-to-brain transport are not yet fully understood, but the olfactory pathway seems to play a pronounced role. The olfactory region in humans accounts for <10% of the nasal cavity. Pharmaceutical agents can gain fast access to the CNS along the olfactory nerve fibers of the olfactory bulb, which is the only anatomical structure of the CNS that is in direct physical contact with the environment. This was well-illustrated by Jansson *et al.* by intranasal administration of a fluorescent dye and subsequently monitoring of the route of transport along the olfactory nerves.

2.1.2 Other Possible Pathways

Perineural transport along the olfactory and trigeminal nerves is probably the major determinant of the nose-to-brain pathway. However, other connections between the nasal cavity and the CNS are also possible candidates. It is not unlikely that, for instance, the facial nerve or the Grueneberg ganglion are also entry points towards the CNS. Beside the neural pathways, the vasculature pathways are also gaining interest. The olfactory region's vascularization originates from small branches of the ophthalmic artery, while the respiratory region receives blood supply from branches of the maxillary artery. Intranasaly administered drugs can reach the systemic circulation via this vascularisation and pass the BBB to enter the brain, especially if the applied drugs are small and lipophilic. More likely, molecules can also travel perivascularly along the channels associated with blood vessels, located between the outermost layer of blood vessels and the basement membrane of surrounding tissue. Perivascular transport is not only driven by diffusion but also by bulk flow and arterial pulsation, which might explain the rapid distribution in the CNS of intranasally administered drugs. Direct transport from the nasal cavity to the cerebrospinal fluid (CSF) has been reported, but is a rather unclear mechanism. Absorption of the applied substance in the lymphatic vessels, located just under the basal lamina and draining the deep cervical lymph nodes of the neck, has also been reported.

2.2. Microscopical Anatomy

In this paragraph, the hurdles and entry points that need to be overcome for an intranasally applied substance, to travel along the proposed routes to the CNS will be discussed.

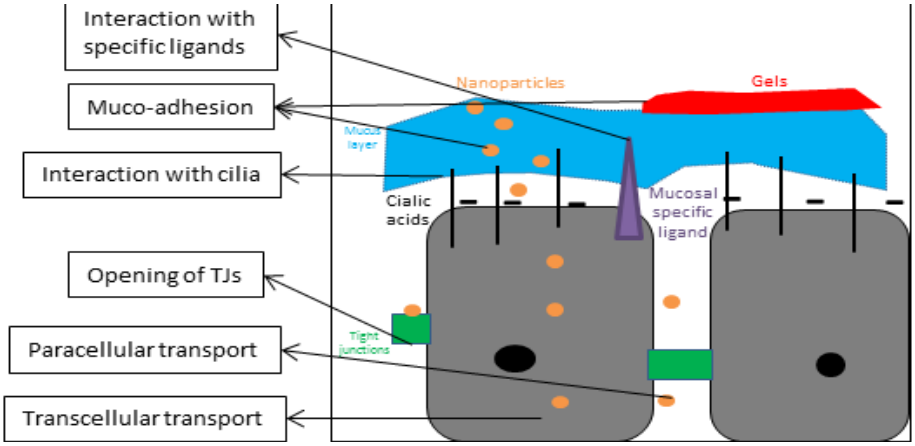

Fig. 2: Drug transport through nose-to-brain pathway[2]

2.2.1. Nasal Mucosa and Mucus

The first barrier that a pharmacological agent will encounter upon intranasal administration is the mucus layer covering the olfactory and respiratory mucosa. Mucus is a complex mixture secreted by the goblet cells in the mucosa and consists out of 95% water, 2% mucin, 1% salt, 1% albumin, lysozymes, lactoferrin, immunoglobulines, and lipids. The resulting pH of mucus in the nasal cavity is close to neutral or slightly acidic (pH 5.5–6.5) .The mucus layer is propelled towards the pharynx by the cilia. It should be noted that only the cilia on the respiratory mucosa can move the mucus because the cilia on the olfactory mucosa lack the dynein arms which are necessary for motion. These cilia can beat with a frequency of 1,000 beats per min and propel the mucus 5 mm per min. If a pharmacological agent successful reaches the nasal cavity, this is the first barrier to cross. Next, the drug can travel between cells, paracellularly or through cells, *i.e.*, transcellularly.

2.2.2. Tight Junctions (TJs)/Paracellular Transport between Nasal Mucosa

When the applied substance needs to travel between epithelial cells, it will have to cross several barriers. Two epithelial cells can be in close approximation with each other using several junctions: TJs, adhering junctions, desmosomes, and gap-junctions. The intactness of these junctions will determine the success of the paracellular transport. There is also a size limitation: the hydrophilic channel between two epithelial cells is about 8 A^{o}. Questions about the integrity of these junctions remain, due to the constant renewal of the olfactory

receptor cells, and the integrity of the entire mucosa. Certain formulations can temporarily open these junctions and therefore promote nose-to-brain transport, as discussed later. This transport route is rapid and can occur within 30 min after application.

2.2.3. Endocytosis /Transcellular Transport across Nasal Mucosa

An applied substance larger than 20 nm is believed to travel transcellularly. Many possible mechanisms are described in the literature and depend on the nature of the substance: clathrin-dependent or independent, caveolae-dependent or independent, macropinocytosis or phagocytosis. It is reported than substances smaller than 200 nm prefer caveolae-mediated endocytosis, while substances in a range of 200–1000nm prefer clathrin-mediated endocytosis. Transcellular transport is generally rather slow, ranging from hours to several days. Substances entering an olfactory receptor neuron will undergo intraneuronal transport in the anterograde direction towards the olfactory bulb.

2.2.4. Organization Nerves/Filia Olfactoria

In the lamina propria, just underneath the olfactory mucosal layer, the different axons of olfactory receptor neurons conjoin and are ensheathed by Schwann cells. These structural organizations are called filia olfactoria. Typically 20 axons are bundled together in fascicles. One Schwann cell can easily ensheathe 5–10 fascicles, and thereby contain >100 axons. Perineuronal channels of 10–15 nm are present here and act as ionic reservoirs. Mesaxons are also present within the filia olfactoria and are pores that allow the passage of extracellular fluids. Transneuronal transport is dependent of the diameter of the axons, which in human ranges from 100 nm to 700 nm.

3. MACHANISM OF DRUG ABSORPTION THROUGH NASAL CAVITY:

The principal step in the absorption of a drug from the nasal cavity is the passage through the mucus. Fine particles easily pass through the mucus layer; however, large particles may find some difficulties. Mucus contains mucin, a protein with the potential to bind with solutes and thus affect the diffusion process. Structural changes can occur within the mucus layer as a result of environmental or physiological changes. Subsequent to a drug's passage through the mucus, there are numerous mechanisms for absorption through the mucosa. These include transcellular or simple diffusion across the membrane, paracellular transport via movement between cell and transcytosis by vesicle carriers. Several mechanisms have been proposed, but paracellular and transcellular routes dominate. Paracellular transport is slow and passive. There is an inverse correlation between intranasal absorption and the molecular weight of

water-soluble compounds. Poor bioavailability was reported for drugs with a molecular weight greater than 1000 Da. The second mechanism involves transport through a lipoidal route that is also known as the transcellular process and is responsible for the transport of lipophilic drugs that show a rate dependency on their lipophilicity. Drugs also cross cell membranes by an active transport route via carrier-mediated means or transport through the opening of tight junctions. Obstacles to drug absorption are potential metabolism before reaching the systemic circulation and inadequate residence time in the nasal cavity.[7]

4. FUTURESTIC FORMULATIONS FOR NASO-BRAIN DELIVERY

Numerous nanoformulations have been investigated successfully for better brain delivery which includes nanoparticulate systems (polymeric/solid lipid), liposomes, dendrimers, nanoemulsions, nanosuspensions, and ligand mediated nanosystems.

1. Polymeric nanoparticles

Nanoparticles (NPs) are colloidal particles, less than 1000 nm, that can be used for better drug delivery and prepared either by encapsulating the drug within a vesicle and or by dispersing them drug molecules within a matrix. Nanoparticulate drug delivery systems have been extensively studied in recent years for spatial and temporal delivery, especially in tumour and brain targeting.

2. Solid lipid nanoparticles

Solid lipid nanoparticles (SLN) are colloidal particles composed of biocompatible/biodegradable lipid matrix that is solid at body .Temperature and exhibit size in a range of 100 to 400 nm. SLN offer several advantages such as controlled drug release, targeted delivery, increased drug stability, high drug payload, least biotoxicity, large scale production and ease of sterilization.

3. Liposomes

Liposomes or lipid based vesicles are microscopic (unilamellar or multilamellar) vesicles that are formed as a result of self-assembly of phospholipids in an aqueous media resulting in closed bilayered structures. Since lipid bilayered membrane encloses an aqueous core, both water and lipid soluble drugs can be successfully entrapped into the liposomes. Lipid soluble or lipophilic drugs get entrapped within the bilayered membrane whereas water soluble or hydrophilic drugs get entrapped in the central aqueous core of the vesicles.[8]

4. Microsphere

Microsphere technology has been widely applied in designing formulations for nasal drug delivery. 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.[1]

Advantages of Nasal microsphere

- ✓ Degradation of drug does not occur.
- ✓ Absence of Hepatic first-pass metabolism.
- ✓ Rapid drug absorption.
- ✓ Quicker onset of action.
- ✓ Better nasal bioavailability for larger drug molecules as well as for smaller drug molecules.
- ✓ Nasal drug delivery system provides an alternative route for the Drugs which cannot be absorbed orally.

Disadvantages of Nasal microspheres

- ✓ Dose is limited because of relatively small area available for the absorption of drug.
- ✓ Time available for drug absorption is limited.
- ✓ Diseased condition of nose impairs drug absorption.[8]

5. Micelles

Polymeric micelles obtained from block copolymers as colloidal carriers for drug and gene targeting have been receiving much attention in the field of drug delivery and targeting because of the high drug-loading capacity. A variety of drugs with diverse characteristics, including genes and proteins, can be incorporated into the core.

6. Chitosan nanoparticles

Currently, NPs prepared from cationic polysaccharide chitosan (CS) have shown promising results in nose to brain drug delivery because of its excellent intrinsic properties like low toxicity, excellent biocompatibility, high loading and entrapment efficiency and ability of delivering hydrophilic molecules. Bromocriptine loaded chitosan nanoparticles (BRC-CS NPs) by an ionic gelation with tri-polyphosphate (TPP; 0.175% w/v) as anion. The chitosan used was of medium Mw and with degree of deacetylation of about 85%, prepared in acetic acid (2% v/v; pH 3.5). The concentration of chitosan used was 0.175% w/v. Bio-distribution

and pharmacokinetic studies revealed the higher brain/blood ratios of intranasal BRC-CS NPs compared to intranasal BRC solution and intravenous BRC-CS NPs, indicating the direct nose to brain transport of BRC along olfactory or trigeminal nerve pathways bypassing the BBB. The enhanced direct nose to brain drug delivery effect of chitosan formulations is suggested to be attributable to a combination of passive targeting ability of chitosan by mucoadhesion resulting in increased residence time of formulation over the olfactory region. The increased permeability of nasal epithelia to drug due to tight junction opening between apical cells.

7. Nanoemulsions and mucoadhesive nanoemulsions

Nanoemulsions (NEs), by virtue of their lipophilic nature and low globule size, are widely explored as a delivery system to enhance uptake across the nasal mucosa. The addition of mucoadhesive agents such as polyelectrolyte polymers help in the retention of formulation on the nasal mucosa, thereby providing an extended delivery of the drug to the olfactory region and henceforth to the brain. The NEs modified with mucoadhesive agents are referred to as Mucoadhesive nanoemulsions (MNEs).The formulation and development of ropiniroleloaded NE and MNE for in. administration as a better management option for the treatment of PD. The formulation was characterized, primarily, by physico-chemical investigations like particle size (58.61 ± 5.18), Polydispersity index (0.201), viscosity (31.42 ± 6.97), stability, dilution capability and ability to improve in. flux. The ex-vivo studies showed a significant higher drug translocation in different parts of the wistar rat brain. From the *in vitro*, *ex-vivo* and *in vivo* evaluation, it concluded that the NEs and MNEs could be a promising approach for the delivery of ropinirole hydrochloride and utilized as a better treatment option for PD.[10]

5. RATIONALE FOR INTRANASAL DRUG DELIVERY

Advantages of Intranasal Drug Delivery

- Rapid drug absorption via highly vascularized mucosa.
- Ease of administration, non-invasive.
- Improved bioavailability.
- Improved convenience and compliance.
- Self-administration.
- Large nasal mucosal surface area for dose absorption.
- Avoidance of the gastrointestinal tract and first-pass metabolism.

- Rapid onset of action.
- Lower side effects.
- Drugs which cannot be absorbed orally may be delivered to the Systemic circulation through nasal drug delivery system.
- Convenient route when compared with parenteral route for long term therapy.
- Bioavailability of larger drug molecules can be improved by means of absorption enhancer or other approach.[10]

Disadvantages of Intranasal Drug Delivery

- Some drugs may cause irritation to the nasal mucosa.
- Nasal congestion due to cold or allergies may interfere with absorption of drug.
- Drug delivery is expected to decrease with increasing molecular weight.
- Frequent use of this route leads to mucosal damage.
- The amount of drug reaches to different regions of the brain and spinal cord varies with each agent.[10]

Enhancement of Drug Transport across BBB by means of Nanoparticles.

- Nanoparticles are preferably absorbed on the wall of the brain blood vessels without transport of particles across the endothelium.
- The fluidization of the endothelium by the surface activity of the surfactant polysorbate 80 is known to enhance the drug transport across the brain.
- Opening of the tight junction between the endothelial cells lining the brain.
- Endocytic uptake by the endothelial cells
- Lining of the brain blood vessels with or without degradation of the nanoparticle.
- Trancytosis across the brain endothelial cells. After the uptake of the nanoparticleby the endothelial cells, the nanoparticles and adsorbed drug may be delivered to the brain cells by trancytosis.[4]

Many drugs having high water solubility have poor permeability across nasal epithelia and may present insufficient bioavailability. To enhance their permeation and bioavailability permeation enhancers are frequently employed. In principle, permeation enhancers induce reversible modifications on the structure of the epithelial barrier. Although the exact mechanism of drug absorption/permeation enhancement is not well known, it is widely

accepted that these materials modify the permeability of epithelial cell layer by modifying the phospholipid bilayer.[7]

Physiochemical properties of drugs

1. Chemical forms

The chemical form of a drug is an important factor in determining absorption. For example, conversion of the drug into a salt forms can also alter its absorption. The effect of structural modification of drug on absorption was observed that in-situ nasalabsorption of carboxylic acid esters of L-Tyrosine was significantly greater than that of LTyrosine.

2. Polymorphism

Polymorphic nature of drug molecules is known to affect the dissolution rate and solubility of drugs and thus their absorption through biological membranes.

3. Molecular weight

A linear inverse correlation exists between the absorption of drugs and molecular weight up to 300 Da. Absorption decreases significantly if the molecular weight is greater than 1000 Da. Absorption can be enhanced with the use of absorption enhancers.[6]

4. Effect of perfusion rate

Absorption depends on the perfusion rate up to certain extent beyond that perfusion rate has no effect on the absorption.

5. Effect of perfusate volume

It also effect the absorption of the drug administered through nasal drug delivery system.

6. Effect of solution P^H

PH also influences the nasal absorption. As the P^H increases the nasal absorption decreases. The rate of nasal absorption depends on the P^H and ionization of penetrate molecule. Ex: Insulin nasal absorption decreased or increased based on the P^H of the insulin solution administered through the nasal drug delivery system.

7. Effect of drug lipophilicity

Lipophilicity cannot show greater variability in nasal absorption of drugs. It can be studied using a series of barbiturates at P^H 6.0.

8. Effect of drug concentration

As the concentration increases the absorption also increases. It can be studied using the ex vivo nasal perfusion technique in rats.[11]

Formulation Factors

1. pH of the formulation: The pKa of drug and pH at the absorption site plays important role in absorption of drug through nasal route. Thus the stability can achieve by proper selection of pH of formulation. However, the pH of formulation should be near on human nasal mucosa (5.0-6.5) to prevent the sneezing.[3]

2. Buffer capacity

Nasal formulations are generally administered in small volumes ranging from 25 to 200µL. Hence, nasal secretions may alter the pH of the administered dose. This can affect the concentration of unionized drug available for absorption. Therefore, an adequate formulation buffer capacity may be required to maintain the pH in-situ.

3. Viscosity

Higher the viscosity of the formulation greater is the contact time between the drug and the nasal mucosa thereby increases the time for permeation. At the same time, highly viscous formulations may interfere with the normal functions like ciliary beating, mucociliary clearance and thus alter the permeability of Drugs.

4. Role of absorption enhancers

Absorption enhancers are used when a drug exhibits poor membrane permeability, large molecular size, lack of lipophilicity and enzymatic degradation by amino peptidases. Absorption enhancers improve absorption through many different mechanisms, such as increasing membrane fluidity, increasing nasal blood flow, reducing mucus viscosity, and enzyme limitation.[6]

6. BIOADHESIVE POLYMERS USED FOR NASAL DRUG DELIVERY

Bioadhesive polymer: To improve the nasal residence and absorption of the drug bioadhesive polymers are used. They improve the retention time of the drug inside the nasal cavity is increased by making an adhesive force between formulation and nasal mucosa, which leads to minimization of mucociliary clearance of formulation.[1]

Table-1: Characteristics of various polymers employed in Intra-nasal delivery.

Polymer	Characterstics
Cellulose derivatives- Soluble:hydroxypropylmethylcellulose, hydroxypropylcellulose,methyl cellulose, Carboxymethyl Cellulose, Insoluble:ethylcellulose, microcrystalline cellulose.	-Prolong the residence time of drug in nasal cavity -Sustain the release of drug due to high viscosity -Act as absorption enhancer -Effectively increase intranasal bioavailability
Polyacrylates -Carbomers -Polycarbophils	Excellent mucoadhesive and gel forming capability, capable of attaching to mucosal surfaces hence ensure intimate contact between the formulation and membrane surface
Starch -Maize starch -Degradable starch microspheres (DSM)	Effectively improve absorption of both small hydrophobic and hydrophilic macromolecular drugs. Mostly used in mucoadhesive microparticulate nasal delivery system
Chitosan	Insoluble at neutral and alkaline P^H, It can form water soluble salts with inorganic and organic acids, low cost, Biodegradable and Biocompatible

Table 2: Drugs used in Naso-Brain delivery system.

Category	**Drugs**	**Drug delivery system**
Anti-Parkinsonism	Tacrine	Nanoparticles
Anti-alzheimer	Estradiol	Nanoparticles
Antipsychotics	Risperidone	Nanoparticles
Anti-Parkinsonism	Odorranalectin	Nanoparticles
Anti-alzheimer	Rivastigmine	Nanoparticles
Anticonvulsant	Midazolam	Microspheres
Hypnotic's , Sedative	Clonazepam	Microemulsion
Anti-Migraine	Sumtriptan	Microemulsion
Antipsychotics	Olenzapine	Nanoemulsion
Antiepileptic	Gabapentine	Microspheres
Anti-migraine	Rizatriptan benzoate	Nanoemulsion
Antipsychotics	Risperidone	Nanoemulsion

Table 3: Proteins and peptides marketed products for systemic delivery.[10]

Drug substance (product name)	**Indication**	**Dosage form**	**Manufacturer**
Salmon calcitonin (Karil 200 I.E.)	Osteoporosis	Solution (spray)	Novartis Pharma
Desmopressin (Minirin Nasenspray)	Antidiuretic hormone	Solution (spray)	Ferring Arzneimitted
Buserelin (Profact nasal)	Buserelin	Solution (spray)	Aventis Pharma
Nafarelin (Synarela)	Endometriosis	Solution (spray)	Pharmacia
Oxytocin (Syntocinon)	Lactation	Solution (spray)	Novartis Pharma

Table 4: Non-peptide marketed nasal products for systemic delivery[10]

Drug substance (product name)	Indication	Dosage form	Manufacturer
Zolmitriptan (AscoTop Nasal)	Migraine	Solution (spray)	Astra Zeneca
Sumatriptan Imigran Nasal	Migraine	Solution (spray)	Glaxo SmithKline
Dihyfroergotamin (Migranal NasalSpray)	Migraine	Solution (spray)	Novartis Pharma
Estradiol (Aerodiol)	Migraine	Solution (spray)	Servier

7. CONCLUDATORY COMMENTS

The treatment of brain diseases is particularly challenging because the delivery of drug Molecules to the brain is often precluded by a variety of physiological, metabolic and Bio chemical obstacles that collectively comprise the BBB, BCB and BTB. The nasal mucosa offers several advantages for controlled drug delivery. The mucosa is well supplied with both vascular and lymphatic drainage. First-pass metabolisms in the liver and pre systemic elimination in the GI tract can be avoided drainage. First-pass metabolisms in the liver and pre systemic elimination in the GI tract can be avoided. Drug delivery directly to the brain interstitium has recently been markedly enhanced through the rational design of polymer-based drug delivery systems. Substantial progress will only come about, however, if continued vigorous research efforts to develop more therapeutic and less toxic drug molecules are paralleled by the aggressive pursuit of more effective mechanisms for delivering those drugs to their brain targets. It is expected that in the following years, neurosurgeons, oncologists and neurologists will meet the pharmaceutical sciences. This cross-talk could lead to the development of a new therapy concept regarding the intranasal administration route, and might ultimately lead to a better prognosis for brain diseases.

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