Review Article

Intranasal Route : A Putative Strategy for Novel Drug Delivery

Asha Paul, Fathima K.M, Antony Nitheesh, Sreeja C Nair*
Department of Pharmaceutics, Amrita School of Pharmacy, Amrita Vishwa Vidyapeetham, Amrita University, Kochi-682041, India.
***Corresponding author's E-mail:** sreejacnair@aims.amrita.edu

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ABSTRACT

Nasal route due to its highly vascularised nature, porous endothelial membrane, large surface area, avoidance of first pass metabolism seems to be potential and beneficial and a useful convenient route for systemic availability of drug when compared to other routes. The article provide complete information of nasal drug delivery, highlights its importance and summaries its advantages and limitations. It gives a brief description about nasal anatomy, nasal membrane structure, and mechanism of nasal drug delivery. In spite of having few factors affecting nasal absorption the article discuss several approaches for enhancing the absorption of drugs through nasal mucosa by improving nasal residence time and methods of improving bioavailability. Different formulations of nasal drug delivery including conventional dosage forms like nasal sprays, powders etc and noval drug delivery system dealing with nano particles, liposomes etc have been discussed in this article. The drug is protected from enzymatic degradation in nasal secretions and the rate of clearance is controlled by these delivery systems.

Keywords: Nasal drug delivery, olfactory region, trigeminal route, non-invasive route.

INTRODUCTION

The human nose functions as heater and humidifier of inspired air, a filter against airborne particulates, a chemical sensor for environmental irritant and as the principle organ reticulate of olfaction. Nasal route is a promising systemic delivery of drugs when compared with other route of administration and an alternative route in emergency.

It is a painless, non-invasive highly vascularised route of drug delivery.

Through intranasal route, first pass metabolism is avoided. The specialized anatomy and physiology of the nasal cavity and its ready accessibility make the nasal cavity a particularly attractive delivery site for the systemic administration of drugs like other epithelia due to its large surface area.

The permeability of the nasal epithelium to drug molecules varies greatly depending on the chemical and physical properties of the drug[1,2].

Various drugs are having great attraction towards the nasal route as it provides enhanced level of drug absorption with ease of self administration and improved patient compliance.

Scientist have developed many methods to increase bioavailability and developed dosage forms to bypass BBB and enter into central nervous system which became useful in treating CNS related disorders like epilepsy, psychotic disorders etc.

Today nasal cavity is used to deliver large number of drugs ranging from small to large ones including vaccines, proteins, hormones. Steroids like testosterone, corticosteroids, antihypertensive drugs like hydralazine, anlagesics, antibiotics etc have shown enhanced bioavailability when given through nasal route. From the past few decades scientist and physicians have show great interest in the field of nasal drug delivery[3].

Advantages of Nasal Drug Delivery[4-7]

- It is Convenient and easily accessible
- It offers self administration.
- Large surface area for drug absorption (epithelium covered with microvilli)
- Thin porous, highly vascularized epithelium favors rapid absorption of drugs.
- Avoids first pass metabolism.
- Direct delivery into CNS, thereby bypasses BBB.
- Rapid onset of pharmacological action.
- Has limited side effects.
- Reduced enzymatic activity.
- Lower risk of overdose.
- Achievement of controlled release.
- Avoidance of gut wall metabolism.
- Delivery of proteins/peptides, hormones and vaccines
- Higher bioavailability of lipophilic drugs.
- Absorption enhancers are used for improving absorption of hydrophilic drugs.

Limitations of Nasal Drug Delivery

- Mucociliary clearance.

- Delivery of high molecular weight drugs is not possible.
- Surface absorption is less when compared to GIT.
- Pathological condition can minimize drug absorption.
- Certain drugs may irritate nasal mucosa.
- Volume of drug delivered into nasal cavity is limited to 25-200 micro liter.
- Permeability of drugs is affected by enzymatic activity.
- Cough or sneeze can affect the nasal drug delivery.

Nasal Membrane Structure

Nasal cavity is located posterior to external vestibule of the nose and is lined with three types of epithelia

1. Squamous epithelia

2. Olfactory epithelia

3. Respiratory epithelia

The Squamous Epithelium[8]

The squamous epithelium is found in lining the nostril and anterior portion of the cavity up to and partially covering the turbinates with an average surface area of 0.6 cm^2.

This region is also called as nasal vestibule, where permeation of substance is limited due to presence of stratified epithelial cells.

The Olfactory Epithelium[9]

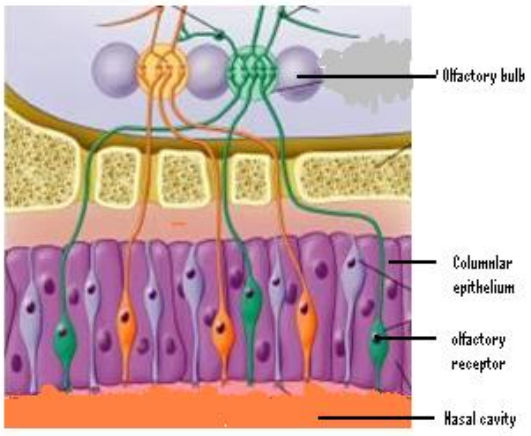


Figure 1: Structure of Olfactory Epithelium

Olfactory epithelium (Figure 1) lines the nasal cavity. The special function of olfactory epithelium is olfaction. It constitutes an area of 10 - 20 cm^2. Receptors for sensing smell are located at this region. The olfactory area is covered by pseudo stratified columnar epithelium.

Olfactory epithelium is composed of 3 cell types:

a. Olfactory cells
b. Supporting cells
c. Basal cells

Olfactory Cells

They are bipolar neurons which comes together to form a cranial nerve.

Olfactory nerve terminate at dendrite cells located at mitral cells of glomeruli by moving through cribiform plate.

Supporting Cells

This cells function as metabolic and physical support for olfactory cells. They are pseudo stratified ciliated coloumnar epithelium.

Basal Cells

Present on the basal lamina of olfactory epithelium. They are stem cells. It is capable of division and differentiation into either supporting or olfactory epithelial cells.

The basal cell layer ensures that every 2-4 weeks, the olfactory epithelium is replaced.

Bowman's Gland

They are tubulo acinar glands lying deep to the basal lamina. The glands deliver secretions via ducts to the surface of mucosa. These secretions trap and dissolve odiferous substances for bipolar cells.

Respiratory Epithelium

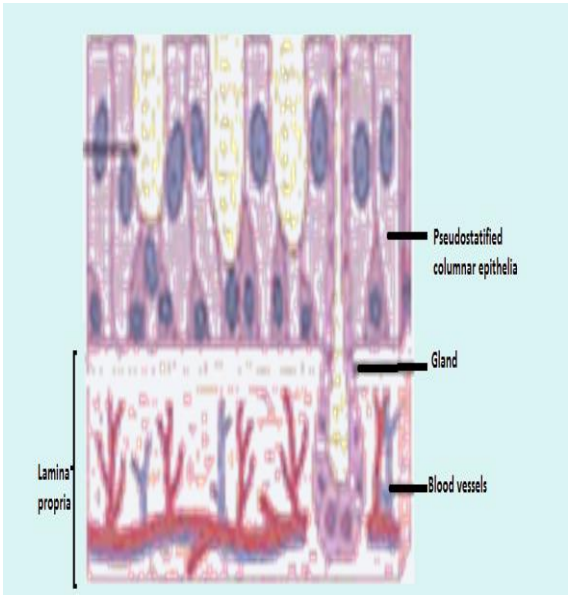


Figure 2: Structure of Respiratory epithelium

Respiratory epithelium (Figure 2) is found in lining of the respiratory tract. It serves to moisten, warm and functions as a barrier to potential pathogens and foreign particles.

The respiratory epithelium lining the upper respiratory airways is classified as pseudo stratified columnar epithelium.

The majority of cells composing the ciliated pseudo stratified columnar epithelium are of three types:

Ciliated Epithelium

The cilia in the nasal cavity are also found in some parts of the respiratory tract. This ciliated epithelium also lines the trachea, bronchi and larger bronchioles.

The cilia present in the respiratory passages and carry out the following functions on incoming air:

- Filtering
- Warming
- Moistening

Goblet Cells

These are columnar epithelial cells that contain membrane-bound mucous granules.

The mucous which is secreted by membrane-bound mucous granules, helps to maintain epithelial moisture and traps particulate material and pathogens moving through the airway.

Basal Cells

Basal cells are a type of cuboidal cells where some have ability to differentiate into other cells types found within the epithelium. It may have cilia in the proximal portion of the bronchiole.

The single layer of simple cuboidal epithelium enables the respiratory bronchioles to create a transitional zone where air conduction and exchange of gases or respiration can take place[9-10].

Histology

Olfactory mucosa consists of:

- Lamina propria
- Basal lamina
- Epithelial layer

Mechanism of Drug Absorption from Nose

There are 2 mechanism for drug absorption from nose.

1. Aqueous route of transport

2. Lipoidal route of transported

Aqueous Route of Transport

Also known as para cellular route. It is slow and passive route and inverse the log-log relationship between molecular weight of water soluble compounds and intra nasal absorption.

This route has poor bioavailability for those drugs which has molecular weight greater than 1000D.

Lipoidal Route of Transport

Also known as trancellular process. This route is responsible for the transport of lipophilic drugs which shows a rate dependency on their lipophilicity. In this route drugs crosses the cell membrane by active transport route via carrier mediated means or through a transporter by opening the tight junctions.

Mechanism for Drug Delivery in to CNS via Intranasal Route (Figure 3)

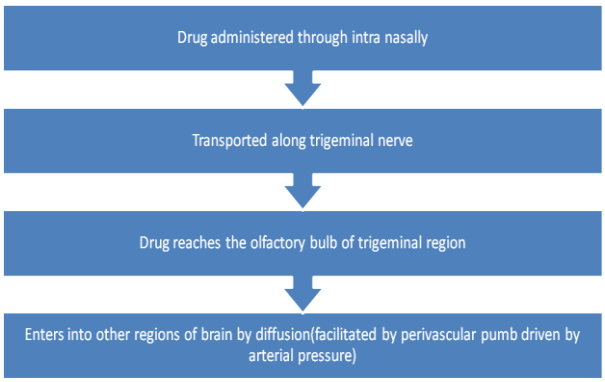
Intracellular Route

Intracellular transport mediated route is slow and it take hours to reach the olfactory bulb.

Extra Cellular Route

The extra cellular transport mediated route causes rapid entrance of drug into the brain (within minutes). There are two mechanism for extra cellular transport (Figure 4).

Mechanism 1



Mechanism 2

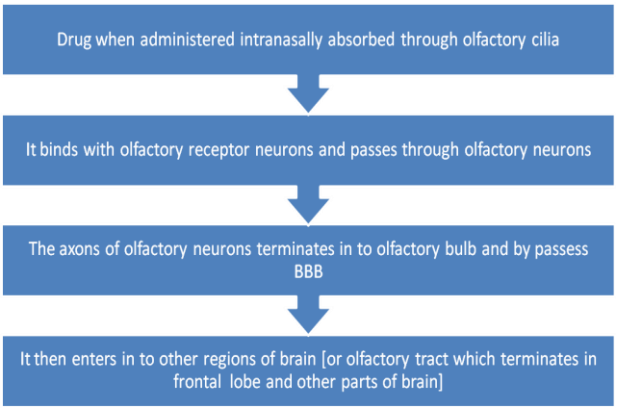


Figure 3: Mechanism 1 and 2 showing Extracellular Transport

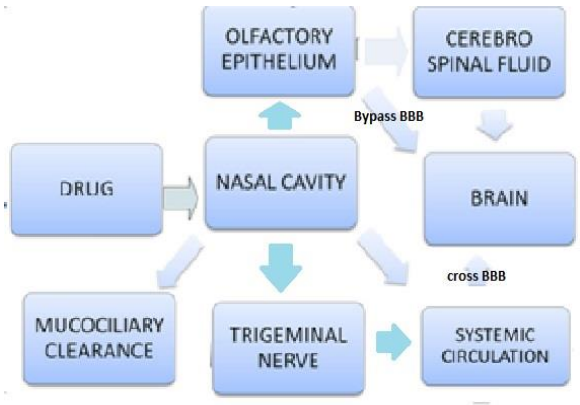


Figure 4: Nasal Drug Delivery Route

Formulations Based on Nasal Delivery System

Liquid Dosage Forms

Nasal Drops

Nasal drops are simple and convenient delivery system. Suspension or solutions are formulated as drops. Dose precision cannot be maintained for nasal drops. The liquid droplet have quick clearance from nasal mucosa and the droplet are easily emptied into nasopharynx.

Nasal Sprays[11-13]

Nasal spray are better alternative to injection or pills. Nasal spray can assimilate the drug substance extremely quickly and directly through the nose. Many drugs in the treatment of migraine osteoporosis and nausea has been used in the form of nasal sprays for systemic administration. Drugs given the form of nasal sprays are absorbed into systemic circulation. Nasal sprays are more efficient way of transporting drugs in crossing the blood brain barrier. Nasal sprays have been commonly used in the local treatment of nasal congestion and allergic rhinitis. To regulate the quantum of the spray metered valve aerosols are available which enable only a certain quantity of spray to be taken out in one go. The main advantage of this system is that, exact dose can be delivered.

Nasal sprays are based on aqueous vehicle, some characterizations of product such as pH, viscosity, osmolarity, surface tensions should be closely monitored. Table 1 shows some examples of drug administered as nasal spray.

Table 1: Examples of Drug Administered as Nasal Spray

S. No	Drug Administered as Nasal Sprays	Therapeutic Use
1.	Insulin	Treatment of Alzheimer's disease
2.	Fluticasone	Reduction in the occurrence of pediatric obstructive apneas and hypopneas
3.	Calcitonin	Treatment of refractory mania
4.	Fentanyl Pectin	Pain relief
5.	Oxytocin	Treatment of autistic or Asperger's disorder
6	Nictotine	Tobacco withdrawal, cognitive enhancer

Nasal Emulsion[14-16]

Microemulsions are mixture of oil, water and surfactants which are used in combination with co-surfactants. Microemulsions have been a noval approach which has resulted in increased bioavailability of poor water soluble drugs. Because of its lipophlic nature & their small size it has shown enchanced drug absorption in the nasal mucosa. The aqueous phase of microemulsion can be salt or other ingredients. Mixture of hydrocarbon and olefins are present in oil phase. Microemulsions are prepared mainly by mixing and stirring with magnetic stirrer or sonicator. Table 2 shows some examples of drugs loaded in microemulsion.

Table 2: Examples of Drugs Loaded in Microemulsion

S. No.	Drugs Loaded in Microemulsions	Uses
1	Nimodipine	Cerebrovascular disorders, Spasm, Stroke and Migraine
2	Mirtazapine	Depression
3	Carbamazepine	Epilepsy
4	Olanzapine	Schizophrenia
5	Diazepam	Anxiety disorder, Alcohol withdrawal symptoms.

Semisolid Dosage Forms

Nasal Gels

Nasal gels are suspensions or thickened solutions with high viscosity. Nasal gels have greater advantage over other formulations. Nasal gels due to its high viscosity and nasal clearance or nasal dripping is reduced. Anterior leakage of drug formulations into mouth is reduced. Drug remains in the gel thus prolonging the duration of action.

Solid Dosage Forms

Nasal Powders[17-19]

Nasal powders are recognized as a better nasal delivery system because of its numerous advantages over liquid dosage forms such as improved stability of formulation, free of preservatives and prolonged contact with mucosa. Stability of formulation depends on the nature of the active drug or excipients, particle size of the drug and its solubility. Table 3 shows some examples of drugs administered as nasal powders.

Table 3: Examples of Drugs Administered as Nasal Powders

S. No.	Drug Administered as Nasal Powders	Therapeutic Use
1.	Sumatriptan	Treatment of migraine and severe head ache.
2.	Curcumin	Anti-inflammatory, anti-oxidant for treating Alzheimers disease
3.	Melatonin	Antihistaminic drug
4.	VenlafaxinE	Treatment of chronic depression
5.	Ropirinole	Dopamine D2 agonist
6.	Midazolam Hydrochloride	Treatment of epilepticus
7.	Lorazepam	Treatment of status epileptics
8.	Triptans	Anti migraine
9.	Vinpocetine	Prevention of Alzheimers disease

Novel Drug Delivery Systems via Intranasal Route

Liposomes[20-22]

Liposomes are simple microscopic phospholipids' vesicles having lipid bilayer membrane composed of lipid molecule which encloses aqueous compartment. The drugs can be encapsulated in the inner aqueous medium or intercalated into the lipid membrane. Smaller or larger molecules with varying hydrophilicity can be encapsulated effectively in the liposomes. Peptides such as insulin and calcitonin have enchanced nasal absorbtion when encapsulated within liposomes. The drugs encapsulated are protected from enzymatic degradation. Table 4 shows some examples of drugs loaded in liposomes.

Table 4: Examples of Drugs Loaded in Liposomes.

S No.	Drugs Loaded in Liposomes	Uses
1	Tacrine hydrochoride	In Alzheimers disease
2	Galanthamine hydrobromide	In Alzheimers disease
3	Olanzapine	In Schizophrenia
4	Rivastigmine	In Alzheimers disease
5	Duloxetine	In depression

Niosomes

Niosomes are the nonionic surfactant vesicles which can entrap both hydrophilic and lipophilic drugs. It is reported of having better stability than liposomes. The drugs are either entrapped in the aqueous layer or in lipid vesicular membrane. The circulation of entraped drugs are prolonged. These system because of its nonionic nature they are useful for targeting drugs for treating cancer, viral and other microbial diseases.

Microspheres[23,24]

Microsphere are small spherical particles, with diameter in range of 1-1000 micrometer, microsphere are also known as microparticles/microbeads etc.

Microsphere play an important role to improve bioavailability of conventional drugs and minimizing side effects. Microsphere are small spherical matrix system where the drugs are incorporated into matrix system.

Microsphere are susceptible to chemical modification and protect the drugs incorporated from enzymatic degradation and produce sustained release thereby prolonging the drug effect.

Microsphere are characteristically free flowing powers consisting of proteins or synthetic polymers which are biodegradable in nature. Microsphere has the ability to incorporate reasonably high concentration of drug.

Table 5 shows some examples of drugs loaded in microsphere.

Table 5: Examples of Drugs Loaded in Microsphere

S. No.	Drugs Loaded In Microspheres	Uses
1	Proteins (vegf & gdnf)	Parkinson's disease
2	Rizatriptan Benzoate	Migraine
3	Carbamazepine	Epileptic seizures
4	n-6 cyclopentyladenosine	Neuronal anti ischemic agents
5	Lorazepam	Status epileptics

Nanoparticles

The nano particles are solid colloidal particles whose size ranges from 10 to 1000nm and drugs may be dispersed, encapsulated or absorbed.

Nano particles are made up of macro molecular material which can be a synthetic or natural origin.

Drugs that are water soluble nano particle approach can be considered[25].

When compared micro and macro particles, nano particles have unique properties. Salient features of nano particles include.[26]

- High surface area
- Small size
- Easy to suspend in liquids
- Variable optical and magnetic properties
- Deep access to cells and organelles
- Particle size smaller than 200nm can be easily sterilized by filtration with 0.22 micro metre filter.

Different Types of Nanoparticles

Polymerised nanoparticles

It is the desired method for drug delivery of biodegradable and biocompatible polymeric nanoparticles.

Gelatin, chitosan, polyglycolic acid, polyethylene glycols, poly lactic-co glycoliacid (PLGA) are the examples of polymerized nanoparticles.

Polymeric coating protect nanoparticle from phagocytosis by reticulo endothelial system which leads to enhanced levels of blood.

It also prevent degradation of drugs as well as to manage drug release from nanoparticles.

Table 6 shows some examples of drugs loaded in polymerized nano particles.

Types

1. Nano Capsules

2. Nanospheres

Solid Lipid Nanoparticles[27-28]

It consist of a monolayer of phospholipid having a rigid core containing hydrophopic lipids present in solid form in room temperature or body temperature. The solid hydrophobic lipid core has dissolved drug molecules. The solid layer is the surrounded by an aqueous solution. It is having a spherical shape.

The lipid core matrix is stabilized by surfactants. Solid lipid nanoparticles are manufactured by high pressure homogenization or microencapsulation.

The surface of SLN is covered with polyethylene glycol which increases the permeability of drug to BBB. The advantages of this solid lipid nanoparticles is that it leads to controlled drug release and these type increases bioavailability of drugs, as well as protect the drug from outer environment. Poor water soluble drugs can be incorporated in the lipid core.

Carbon Nanotubes[29]

Carbon nano tubes are drugs carriers these are having a cylinderical hollow hexagonal nanostructure. The chemical bond present in nanotubes is sp2 bond which is more stronger than sp3 bond and this is responsible for its unique strength ie its high elastic modulus and tensile strength.

Nano Emulsions[30-31]

Nano emulsion are oil water emulsions which are done on nano scale.

Oils such as triglycerids and fatty acids which are biocompactible, combines with surface coating surfactants and water are commonly used for this process. Oils such as omega 3 fatty acids which help in penetrating BBB.

Table 7 shows some examples of drugs loaded in nano emulsion.

Lipid Based Nanoparticles[32]

Lipid based nanoparticles uses liposomes as carriers of drug molecules.

A phospholipid bilayer is present in between interior and exterior environment. Vesicular bilayer of liposomes are made of sphingomyelin, phosphotidylcholine and glycerophollic which are biocompactible and biodegradable lipids.

Chlolesterol improve the stability of liposome and is most widely used in formulation of lipid nanoparticles. Liposome protect the drug from degradation reduces the ADR and toxicity.

Lipid based nanoparticles are manufactured by high pressure homogenization.

Table 8 shows some examples of drugs loaded in lipid nano particles.

Nasal Bioavailability Problems and Solutions[33]

Excipients in Nasal Drug Delivery System[34]

Table 6: Examples of Drugs Loaded in Polymerized Nano Particles

S. No.	Drug Loaded in Polymerized Nano Particles	Uses
1	Paclitaxel	Human cervical carcinoma
2	Cisplatin	Colon adenocarcinoma Prostate cancer Ovarian cancer
3	5-Fluro Uracil	Glioma and breast adenocarcinoma Hepato cellular carcinoma human colon cancer Squamous carcinoma
4.	Doxorubicin	Breast cancer
5.	Tamoxifen	Breast cancer
6.	Gemcitabine	Pancreatic cancer
7.	Epirubicin	Human carcinoma cell lines

Table 7: Examples of drugs loaded in Nano Emulsion

S. No.	Drug Loaded in Nano Emulsion	Uses
1	Rizatriptan Benzoate	Migraine
2	Safranal	Convulsive disorders
3	Risperidone	Psychotic disorders
4	Tacrine	Alzheimer's disease
5	Olanzapine	Schizophrenia

Table 8: Examples of Lipid Loaded Vesicular Nanoparticles

S. No.	Drug in Lipid Loaded Vesicular Nanoparticles	Uses
1	HALOPERIDOL	Schizophrenia
2	5-FLURO URACIL	Brain tumor
3	LORAZEPAM	Antiepileptic
4	RISPERIDONE	Antipsychotic
5	CELECOXIB	Arthritis
6	PACLITAXEL	Metastatic breast cancer

Table 9: Review of Nasal Bioavailability Problems and Solution

Problems	Solutions	Excipients Used
Poor physiochemical properties	Enhance physiochemical properties and drug formulations	Novel drug formulations Cyclodextrins Co solvents
Low permeability of nasal membrane	Enhance drug permeability and dissolution Modify nasal membrane Enhance drug residence time of drug in mucosa	Prodrug Absorption enhancers Co solvents Muco adhesive polymers
Enzymatic degradation	Inhibit nasal enzymes Reduce affinity to nasal enzymes	Enzyme inhibitors
Mucociliary clearace	Reduce mucociliary clearance	Deposit drug on anterior part of nasal mucosa

Table 10: Excipients used in Intranasal Drug Delivery

Excipients	Examples	Function
Permeation enhancers	Liposomes and microsphere Surfactants: Anionic: sodium lauryl sulphate cationic: cetylpyridinium chloride cyclodextrin Fatty acids Cationic compounds chelators Bile salts	Bioavailability of drugs is enhanced Disrupt membrane
Mucoadhesive polymers	carbopol lecithin chitosan thiomers lectin Alginate poly ethylene gycol acrylate Cellulose derivatives polycarbophil	Nasal residential time is enhanced
Viscosity modifiers	Cellulose derivatives	Nasal residence time is improved
Solvents	ethanol polyethylene gycols propylene	Concentration of drug in vehicle is increased. Dose volume is reduced It also act as permeation enhancer
Preservatives	Benzalkonium chloride	For maintaining dosage form sterility
Tonicity modifiers/buffer	Sodium chloride, citrate buffer	Toxicity of nasal epithelium is reduced
Enzyme inhibitors	Bestatin, amastatin	Bioavailability of proteins and peptides is enhanced

CONCLUSION

Intranasal drug delivery system as a novel drug delivery route offers commercial applicability to pharmaceutical industry.

Intranasal drug delivery system bypasses the blood brain barrier hence used for targeting CNS also.

It reduces the systemic exposure of drug thereby minimises peripheral side effects and avoid first pass metabolism. One of the advantages of intranasal drug delivery is that it is a non-invasive method where small drug molecules, peptides, proteins, hormones and biological cells such as stem cells can be delivered by this route.

It can prevent and manage many neurological disorders.

Drug is released from the carrier system and transported to CNS via olfactory/trigeminal nerves. In order to avoid side effects and improving their effectiveness we should

pay more attention to intra nasal drug delivery system based research.

There is a possibility in future that more drugs will be formulated as nasal formulations.

Hence nasal route will have greater potential for future development.

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