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Pharma Research Library
International Journal of Medicine and Pharmaceutical Research
2013, Vol.1 (2): 235-249

ISSN 2321-2624

Review Article

Pharma Research Library

Complete Review on Nasal Drug Delivery Systems

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Abstract

Nasal route for the administration of drugs is used as an alternative route for the systemic availability of drugs restricted to intravenous administration. Intranasal Therapy has been an accepted form of treatment in the Ayurvedic system of Indian Medicine. The absorption of drug at the olfactory region of the nose provides a potential for a pharmaceutical compound to be available to the central nervous system. In this review we discuss the Advantages, Disadvantages, Limitation, Mechanism of nasal drug absorption biological, physicochemical and pharmaceutical Factors Affecting nasal absorption, Bio-availability Barriers, and Strategies to improve nasal absorption, New Developments in Nasal Dosage Form design, Evaluation of Nasal Formulations and Applications of nasal drug delivery system.

Key words: Nasal route, Intranasal drug delivery, Hepatic first pass metabolism

Introduction

Nasal Drug delivery system is used to disperse drug directly central nervous system, through olfactory region. Drug particle are placed inside drug delivery device. The efficiency of the drug delivered to olfactory region located in the Nasal Cavity depends on the size, location of the particle (Pouch) inside device and time of release. Study was carried to trace the particle trajectory for different size particle and concentration of the drug particle in various regions, within the Nasal cavity to evaluate the effectiveness of the device. Based on the data collected, effectiveness of the device can be calculated for different volumes of drug storage (Pouch) with particle of various sizes and design changes are suggested to improve efficiency[1].

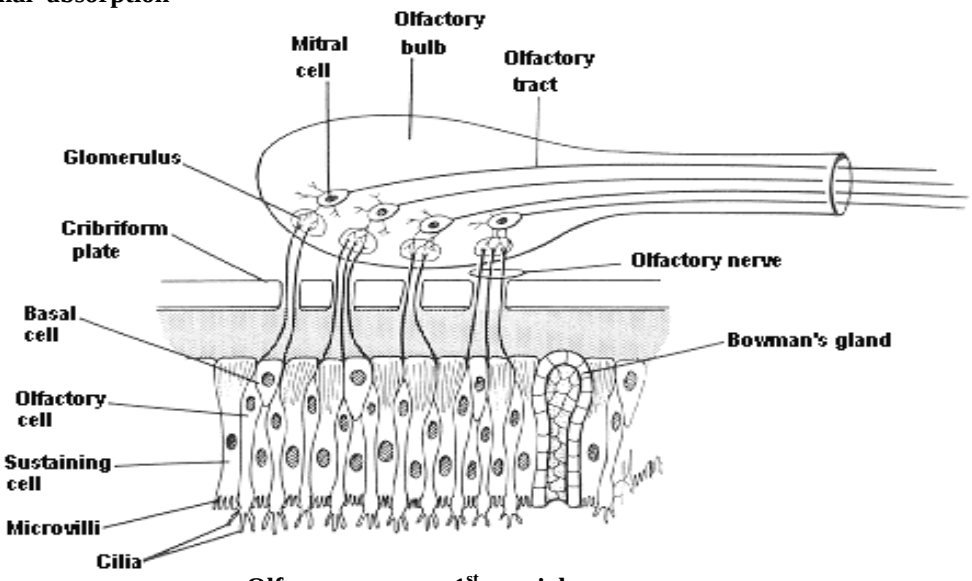
It is a useful drug delivery method for drugs that are active in low doses and show less oral bioavailability such as proteins and peptides. One of the reasons for the low degree of absorption of peptides and proteins via the nasal route is rapid movement away from the absorption site in the nasal cavity due to the mucociliary clearance

mechanism[2]. The nasal mucosa has been considered as a potential administration route to achieve faster and higher level of drug absorption. This is due to the large surface area, porous endothelial membrane, high total blood flow, the avoidance of first-pass metabolism, and ready accessibility. The nasal administration of drugs, including numerous compounds, peptide and protein drugs, for systemic medication has been widely investigated in recent years. In the recent past many researchers have also attempted delivery of drugs to the CNS through the nose. However, the major limitation with nasal route administration is the poor contact of the formulations with the nasal mucosa. In recent years many drugs have been shown to achieve better systemic bioavailability through nasal route than by oral administration. Nasal therapy has been recognized form of treatment in the Ayurvedic systems of Indian medicine, it is also called "NASAYA KARMA"[3]and intranasal drug delivery-which has been practiced for thousands of years, has been given a new lease of life. It is a useful delivery method for drugs that are active in low doses and show no minimal oral bioavailability such as proteins and peptides [3].

Nose brain pathway[4-7]

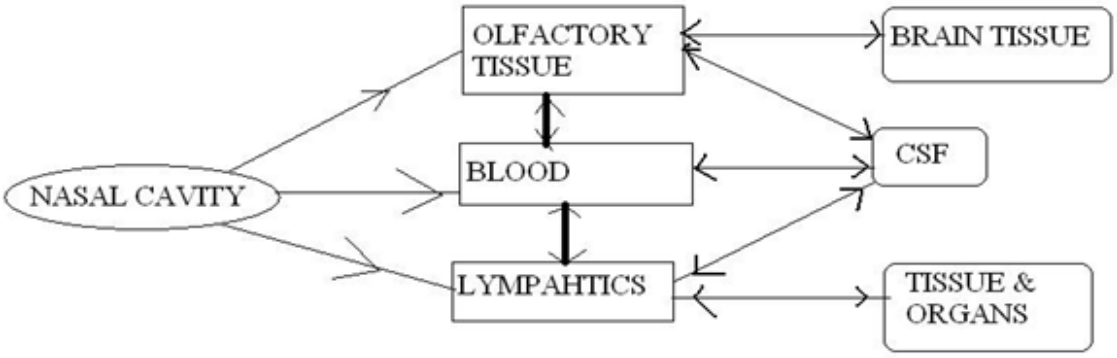
The olfactory mucosa (smelling area in nose) is in directcontact with the brain and CSF.Medications absorbed across the olfactory mucosa directlyenter the brain. This area is termed the nose brain pathway and offers a rapid, direct route for drug delivery to the brain. The olfactory neural pathway provides both intraneuronal and extraneuronal pathways into the brain. The intraneuronal pathway involves axonal transport and requires hours to days for drugs to reach different brain regions. The extraneuronal pathway probably relies on bulk flow transport through perineural channels, which deliver drug directly to the brain parenchymal tissue, to the cerebrospinal fluid (CSF), or to both.

Transneuronal absorption



Olfactory nerve – 1st cranial sensory nerve

Possible drug absorption pathways



Selection of compounds for transmucosal nasal drug delivery[8-38]

Compound	Class	Indication	Investigation/product development/ product and country (example)
Apomorphine	dopamine agonist	Parkinson's disease (on- off symptoms)	product development[8,9]
Buserelin	peptide	prostate cancer	Profact, Germany[10]
Butorphanol	opioid	migraine	Stadol, USA (11)
Calcitonin	protein	osteoporosis	Karil, Germany (12)
Cobalamin (vitamin B12)	vitamin	substitution of vitamin B12	Nascobal, USA (13)
Desmopressin	protein	diabetes insipidus centralis, enuresis nocturna	Minirin, Germany (14)
Diazepam	benzodiazepine	sedation, anxiolysis, status epilepticus	product development (15)
Estradiol	steroid	substitution of estradiol	Aerodiol, UK (16,17)
Fentanyl	opiate	analgesia, postoperative pain and agitation in children	Instanyl, Germany (18)
Gonadorelin	hormone	undescended testicle	Kryptocur, Germany (19)
Human growth hormone	peptide	growth hormone deficiency	Investigation (20)
Influenza vaccine, live attentuated	vaccine	flu prevention	Flu Mist, USA (21)
Insulin	peptide	diabetes mellitus	Investigation (22)
Ketamine	NMDA antagonist	analgesia	product development: Ereska (23)
L- Dopa	nonproteinogenic amino acid	Parkinson's disease	Investigation (24)
Melatonin	hormone	jet lag	Investigation (25)
Metoclopramide	D2 receptor antagonist	antiemesis	Pramidin, Italy (26,27)
Midazolam	benzodiazepine	sedation, anxiolysis, status epilepticus	Investigation (28,29)
Morphine	opiate	analgesia	product development: Rylomine (30)
Nafarelin	hormone	central precocious puberty, endometriosis	Synarel, USA (31)
Nicotine	addictive substance	smoking cessation	NicotrolNS, USA (32)
Oxytocin	hormone	lactation; treatment of social, cognitive and mood disorders	Syntocinon spray, Switzerland (33)
Progesterone	hormone	infertility, amenorrhea	Investigation (17)
Sildenafil	PDE inhibitor	erectile dysfunction	Investigation (34)
Sumatriptan	triptan	migraines	Imigran nasal spray, Switzerland (35)
Testosterone	hormone	substitution of testosterone	Investigation (36)
Zolmitriptan	triptan	migraines	Zomig, Switzerland (37,38)

Advantages of Nasal Drug Delivery System[39-42]

1) Drug degradation that is observed in the gastrointestinal tract is absent.
2) Hepatic first – pass metabolism is absent.
3) Rapid drug absorption and quick onset of action can be achieved.
4) The bioavailability of larger drug molecules can be improved by meansof absorption enhancer or other approach.
5) The nasal bioavailability for smaller drug molecules is good.
6) Drugs that are orally not absorbed can be delivered to the systemic circulationby nasal drug delivery.
7) Studies so far carried out indicate that the nasal route is an alternateto parenteral route, especially, for protein and peptide drugs.
8) Convenient for the patients, especially for those on long term therapy, when compared with parenteral medication.
9) Easy and convenient
10) The nose is a very easy access point for medication delivery
11) No special training is required
12) Painless
13) Lower doses
14) Quicker onset of action
15) Fewer side effects
16) Increased patient compliance
17) Avoidance of hepatic first pass metabolism, gut wall metabolism &biodestruction in GIT
18) Macromolecules like proteins and peptides can be administered
19) Rate and extent of absorption and plasma conc. Vs time profiles have corresponding and comparable values to that obtained by IV route.

Disadvantages[39]

1) Rapid mucociliary clearance.
2) Chances of immunologic reactions
3) Availability of Inadequate toxicity data for penetration enhancement
4) Nasal pathology may adversely affect the product effectiveness

Limitation[43,44]

1) The histological toxicity of absorption enhancers used in nasal drug delivery system is not yet clearly established.
2) Relatively inconvenient to patients when compared to oral delivery systems since there is a possibility of nasal irritation.
3) Nasal cavity provides smaller absorption surface area when compared to GIT.

Mechanism of Nasal Absorption[45-48]

Passage of drug through the mucus is the first step in the absorptionfrom the nasal cavity. Uncharged as well as small particles easilypass through mucus. However, charged as well as large particlesmay find it more difficult to cross. Several mechanisms have been proposed but the following two mechanisms have been considered predominantly.

1. First mechanism:

It involves an aqueous route of transport, which is also known as the paracellular route but slow and passive. There is an inverse log-log correlation between intranasal absorption and the molecular weight of water-soluble compounds. The molecular weight greater than 1000 Daltons having drugs shows poor bioavailability.

2. Second mechanism:

It involves transport through a lipoidal route and it is also known as the transcellular process. It is responsible for the transport of lipophilic drugs that show a rate dependency on their lipophilicity. Drug also cross cell membranes by an active transport route via carrier-mediated means or transport through the opening of tight junctions.

Factors Influencing Nasal Drug Absorption

There are various factors that affect the systemic bioavailability of drugs that are administered through the nasal route. The factors can be affecting to the physiochemical properties of the drugs, the anatomical and physiological properties of the nasal cavity and the type and characteristics of selected nasal drugs delivery system.

Physiochemical properties of drug.
Lipophilic-hydrophilic balance, Chemical Form, Polymorphism, Enzymatic degradation in nasal cavity, Molecular size, Solubility & Dissolution rate
Delivery Effect: Formulation (Concentration, pH, osmolarity),Drugs distribution and deposition, Viscosity
Nasal Effect: Mucociliary clearance, cold, rhinitis, membrane permeability, environmental pH

1. Physiochemical properties of drug
Lipophilic-hydrophilic balance
The HLB nature of the drugs affects the absorption process. By increasing lipophilicity, the permeation of the compound normally increases through nasal mucosa. Although the nasal mucosa was found to have some hydrophilic character, it appears that these mucosae are primarily lipophilic in nature and the lipid domain plays an important role in the barrier function of these membranes. Lipophilic drugs like naloxone, buprenorphine, testosterone and 17a-ethinyl- oestradiol are almost completely absorbed when administered intranasal route.[49,50]

Chemical Form
The chemical form of a drug can be important in determining absorption. For example, conversion of the drug into a salt or ester form can alter its absorption. studied the effect of structural modification of drug on absorption. It was observed that in-situ nasal absorption of carboxylic acid esters of L-Tyrosine was significantly greater than that of L-Tyrosine.(51)

Polymorphism
Polymorphism is known to affect the dissolution rate and solubility of drugs and thus their absorption through biological membranes. It is therefore advisable to study the polymorphic stability and purity of drugs for nasal powders and/or suspensions[52].

Enzymatic degradation in nasal cavity
Drugs like peptides and proteins are having low bio-availability across the nasal cavity, so these drugs may have possibility to undergo enzymatic degradation of the drug molecule in the lumen of the nasal cavity or during passage through the epithelial barrier. These both sites are having exo-peptidases and endo-peptidases, exo-peptidases are mono-aminopeptidases and di-aminopeptidases. These are having capability to cleave peptides at their N and C termini and endo-peptidases such as serine and cysteine, which can attack internal peptide bonds.[53]

Molecular size
The molecular size of the drug influence absorption of the drug through the nasal route**.** The lipophilic drugs have direct relationship between the MW and drug permeation whereas water soluble compounds depict an inverse relationship. The rate of permeation is highly sensitive to molecular size for compounds with MW $\geq$ 300 Daltons.(54)

Solubility & Dissolution Rate
Drug solubility and dissolution rates are important factors in determining nasal absorption from powders and suspensions. The particles deposited in the nasal cavity need to be dissolved prior to absorption. If a drug remains as particles or is cleared, no absorption takes place.[52]
1. Delivery effect factors
Factors that affect the delivery of drug across nasal mucosa such as surfactants, dose pH, osmolarity, viscosity, particle size and nasal clearance, drug structure can be used to advantage to improve absorption.

Formulation (Osmolarity, pH, Concentration)
Osmolarity
The osmolarity of the dosage form affects the nasal absorption of the drug; it was studied in the rats by using model drug. The sodium chloride concentration of the formulation affects the nasal absorption. The maximum absorption was achieved by 0.462 M sodium chloride concentration; the higher concentration not only causes increased bioavailability but also leads to the toxicity to the nasal epithelium[55].

pH
The pH of the formulation and nasal surface, can affect a drug's permeation. To avoid nasal irritation, the pH of the nasal formulation should be adjusted to 4.5–6.5 because lysozyme is found in nasal secretions, which is responsible for destroying certain bacteria at acidic pH. Under alkaline conditions, lysozyme is inactivated and the tissue is

susceptible to microbial infection. In addition to avoiding irritation, it results in obtaining efficient drug permeation and prevents the growth of bacteria.[56]

Concentration

Concentration gradient plays very important role in the absorption / permeation process of drug through the nasal membrane due to nasal mucosal damage. Examples for this are nasal absorption of L-Tyrosine was shown to increase with drug concentration in nasal perfusion experiments. Another is absorption of salicylic acid was found to decline with concentration. This decline is likely due to nasal mucosa damage by the permanent.[57]

Drugs distribution and deposition

The drug distribution in the nasal cavity is one of the important factors, which affect the efficiency of nasal absorption. The mode of drug administration could effect the distribution of drug in nasal cavity, which in turn will determine the absorption efficiency of a drug. The absorption and bioavailability of the nasal dosage forms mainly depends on the site of disposition. The anterior portion of the nose provides a prolonged nasal residential time for disposition of formulation, it enhances the absorption of the drug. And the posterior chamber of nasal cavity will use for the deposition of dosage form; it is eliminated by the mucociliary clearance process and hence shows low bioavailability [(58).]The site of disposition and distribution of the dosage forms are mainly depends on delivery device, mode of administration, physicochemical properties of drug molecule.

Viscosity

A higher viscosity of the formulation increases contact time between the drug and the nasal mucosa thereby increasing the time for permeation. At the same time, highly viscous formulations interfere with the normal functions like ciliary beating or mucociliary clearance and thus alter the permeability of drugs.[52]

1. Nasal effect factors

Mucociliary clearance

Particles entrapped in the mucus layer are transported with it thus, effectively cleared from the nasal cavity. The combined action of mucus layer and cilia is called *mucociliary clearance*. This is an important, nonspecific physiological defence mechanism of the respiratory tract to protect the body against noxious inhaled materials [(59).] The normal mucociliary transit time in humans has been reported to be 12 to 15 minutes [(60).]The factors that affect mucocilliary clearance include physiological factors (age, sex, posture, sleep[(61)]exercise [(62)]common environmental pollutants (sulphur dioxide and sulphuric acid, nitrogen dioxide, ozone, hairspray and tobacco smoke[(63),] diseases (immotile cilia syndrome, primary ciliary dyskinesia- Kartagener.s syndrome, asthma, bronchiectasis, chronic bronchitis, cystic fibrosis, acute respiratory tract infection[(64)] and drugs[(65)] and additives [66].

Cold, rhinitis

Rhinitis is a most frequently associated common disease, it influence the bioavailability of the drug. It is mainly classified into allergic rhinitis and common, the symptoms are hyper secretion, itching and sneezing mainly caused by the viruses, bacteria or irritants. Allergic rhinitis is the allergic airway disease, which affects 10% of population. It is caused by chronic or acute inflammation of the mucous membrane of the nose. These conditions affect the absorption of drug through the mucus membrane due the inflammation.[52]

Membrane permeability

Nasal membrane permeability is the most important factor, which affect the absorption of the drug through the nasal route. The water soluble drugs and particularly large molecular weight drugs like peptides and proteins are having the low membrane permeability. So the compounds like peptides and proteins are main-ly absorbed through the endocytotic transport process in low amounts [(67).] Water-soluble high molecular weight drugs cross the nasal mucosa mainly by passive diffusion through the aqueous pores (i.e. tight junctions).

Environmental pH

The environmental pH plays an important role in the efficiency of nasal drug absorption. Small water-soluble compounds such as benzoic acid, salicylic acid, and alkaloid acid show that their nasal absorption in rat occurred to the greatest extent at those pH values where these compounds are in the nonionised form. However, at pH values where these compounds are partially ionized, substantial absorption was found. This means that the nonionised lipophilic form crosses the nasal epithelial barrier via transcellular route, whereas the more lipophilic ionized form passes through the aqueous paracellular route [68]

Barriers to Nasal Absorption

Low bioavailability

Bioavailability of polar drugs is generally low; about 10% for low molecular weight drugs and not above 1% for peptides such as calcitonin and insulin [69]. The most important factor limiting the nasal absorption of polar drugs and especially large molecular weight polar drugs such as peptides and proteins is the low membrane permeability. Larger peptides and proteins are able to pass the nasal membrane using an endocytotic transport process but only in low amounts [70].

Mucociliary clearance

Particles entrapped in the mucus layer are transported with it and thereby effectively cleared from the nasal cavity. The combined action of the mucus layer and cilia is called mucociliary clearance. This is an important, non-specific physiological defence mechanism of the respiratory tract to protect against noxious inhaled materials. Mucus traps the particles of dust, bacteria and drug substances and is transported towards the nasopharynx at a speed of 5 - 8 mm/min , where it is swallowed. The normal mucociliary transit time in humans has been reported to be 12 to 15 min [71].

Protective barriers

The first step in the absorption of drugs from the nasal cavity passed through the mucus. Uncharged substances with small molecular weight can easily pass through this layer. However, larger or charged particles may find it more difficult to cross. Mucin, the principal protein in the mucus, has the potential to bind to solutes, hindering diffusion. Additionally, structural changes in the mucus layer are possible as a result of environmental changes such as pH, temperature etc. The nasal membrane is a physical barrier and themucociliary clearance is a temporal barrier to drug absorption across the nasal epithelium.

Enzymatic barrier

The role of the enzymatic barrier is to protectthe lower respiratory airways from toxic agents; the nasal mucosa contains many enzymes such as cytochrome P450-dependent monooxygenase, carboxyl esterase and amino peptidase. Although nasal delivery avoids hepatic first-pass metabolism to some extent, the nasal mucosa provides a pseudo-first-pass effect. In addition, there are various barriers in the nasal membrane for protection from the microorganisms, allergens and irritating substances from the environment that must be overcome by drugs before they can be absorbed into the systemic circulation[72].

Table 1: Barriers in nasal drug product development

Nasal barriers	Factors to be considered
I. Physiological barrier	
a. Nasal mucus	Viscosity, pH of mucus and drug/dosage form-mucus interaction
b. Nasal epithelial barrier	Molecular weight, ionization constant and mode of transport
c. Mucociliary clearance	Nasal residential time and nature of dosage form
d. Pathophysiology	Volume of nasal secretion and permeability of epithelium
e. Nasal metabolism	Nature of the molecules (e.g., protein and peptides)
f. Efflux transport system	Nature of drug molecule and duration of therapy
II. Physicochemical barriers	
a. Drug solubility and dissolution	Nature of dosage form, dose, pKa, and polymorphism
b. Molecular weight and size	Less bioavailability with molecular weight more than 1000
c. Compound lipophilicity	Affects the nose to blood and nose to brain absorption
d. pH and pKa	Unionized pH favors for absorption
III. Formulation factors	
a. Drug concentration, dose, and volume	High concentration for better bioavailability, maximum dose in Minimum vehicle (less than 200 µl)
b. Osmolarity	Isotonic solution prevents epithelial damage and toxicity
c. Site of deposition	Site of deposition based on viscosity, position of head, volume, delivery device, deposition at anterior chamber prolong the nasal residential time

Strategies to Improve Nasal Bioavailability[73-78]

Various strategies used to improve the bioavailability of the drug in the nasal mucosa which includes
1. To enhance nasal absorption
2. To improve the nasal residence time
3. To modify drug structure to change physicochemical properties.

Any one or combination of above approaches are used for the enhancing the absorption and bioavailability of the formulations. Several methods have been used to facilitate the nasal absorption of drugs includes:

1. **Nasal enzyme inhibitors**

Absorption enhancers like bile salts and fusidic acid derivatives and Other enzyme inhibitors are tripsin, aprotinin, borovaline, amastatin, bestatin and boroleucin inhibitors.

2. Nasal Permeation enhancers

Some of the chemical penetration enhancers are
Surfactants: Polyozyethylene-9-lauryl ether (Laureth-9), Saponin
Bile salts: Trihydroxy salts (glycol- and taurocholate),Fusidic acid derivatives (STDHF)
Chelators: Salicylates, Ethylenediaminetetraacetic acid (EDTA)
Fatty acid salts: Oleic acid, Caprylate (C8), Caprate (C10), Laurate (C12)
Phospholipids: Lysophosphatidylcholine (lyso-PC), Didecanoyl– PC
Glycyrrhetinic acid derivates: Carbenozolone, Glycyrrhizinate
Cyclodextrins: _, ß, and _- cyclodextrins and their derivatives
Glycols: n- glycofurols and n- ethylene glycols

3. Prodrug approach

Prodrug approach is mainly for improving the nasal bioavailability especially for the proteins and peptides to enhance the membrane permeability along with increased enzymatic stability 44. The absorption of peptides like angiotensin II, bradykinin, caulein, carnosine, enkephalin, vasopressin and calcitonin are improved by pre-pared into enamine derivatives, these agents showed absorption enhancement with prodrug approach.

4. Structural modification

Modification of drug structure without altering pharmacological activity is one of the lucrative ways to improve the nasal absorption.Chemical modification of salmon calcitonin to ecatonin (C-N bond replaces the S-S bond) showed better bioavailability than salmon calcitonin.

5. Particulate drug delivery

Particle design is an increasingly important role in absorption enhancement. Microspheres, nanoparticles and liposomes are all systems which can be used as carriers to encapsulate an active drug. Systems can be designed to be mucoadhesive to increase the retention time and facilitate sustained release. Microspheres are mainly increase the absorption and bioavailability by adhering to the nasal mucosa and increase the nasal residence time of drug.

6. Bioadhesive polymers as delivery systems

Low methylated pectins have been shown to gel and be retained in the nasal cavity after deposition. Chitosan is known to be bioadhesive and also to work as an absorption enhancer. Consequently, two types of pectins, LM-5 and LM-12, together with chitosan G210, can also be used.

Delivery systems:

The selection ofdelivery system depends upon the drug being used, proposed indication, patient population and last but not least, marketing preferences. Some of thesedelivery systems and their importants features are summarized below:

Nasal Drops:[79]

Nasal drops are one of the most simple and convenient systems developed fornasal delivery. The main disadvantage of this system is the lack of the doseprecision and therefore nasal drops may not be suitable for prescription products. It has been reported that nasal drops deposit human serum albumin in the nostrilsmore efficiently than nasal sprays.

Nasal sprays: [80]
Both solution and suspension formulations can be formulated into nasal sprays. Due to the availability of metered dose pumps and actuators, a nasal spraycan deliver an exact dose from 25 to 200 µm.The particles size and morphology(for suspensions)of the drug and viscosity of the formulation determine thechoice of pump and actuator assembly.

Nasal Gels: [81]
Nasal gels are high-viscosity thickened solutions or suspensions. Until therecent development of precise dosing device, there was not much interest inthis system. The advantages of a nasal gel includes the reduction of post-nasaldrip due to high viscosity, reduction of taste impact due to reduced swallowing,reduction of of anterior leakage of the formulation, reduction of irritationby using soothing/emollient excipients and target to mucosa for better absorption.

Nasal Powder: [82]
This dosage form may be developed if solution and suspension dosage forms cannot be developed e.g., due to lack of drug stability. The advantages tothe nasal powder dosage form are the absence of preservative and superiorstability of the formulation. However, the suitability of the powder formulationis dependent on the solubility, particles size, aerodynamic properties andnasal irritancy of the active drug and /or excipients. Local application ofdrug is another advantage of this system.

Evaluation of nasal formulations:

(A) In vitro nasal permeation studies:
Various approaches used to determine the drug diffusion through nasal mucosa from the formulation. The two important methodologies tostudy the diffusion profile of the drug are discussed here,

In vitro diffusion studies [83 84]
The nasal diffusion cell is fabricated in glass. The water-jacketed recipient chamber hastotal capacity of 60 ml and a flanged top of about 3mm; the lid has 3 opening,each for sampling, thermometer, and a donor tube chamber. The 10 cm long donorchamber, and a donor tube chamber has total capacity of 60 ml and a flanged topof about 3mm; the lid has 3 openings, each for sampling, thermometer, and adonor tube chamber the 10 cm long donor chamber tube has internal diameter of1.13 cm. The nasal mucosa of sheep wasseparated from sub layer bony tissues and stoned in distilled water containingfew drops at genatamycin injection. After the complete removal of blood frommuscosal surface, is attached to donor chamber tube. The donor chamber tube is placed such a waythat it just touches the diffusion medium in recipient chamber. Atpredetermined intervals, samples (0.5 ml) from recipient chamber are with drawand transferred to amber colored ampoules. The samples withdrawn issuitablyreplaced. The samples are estimated fordrug content by suitable analytical technique. Through out the experiment thetemperature is maintained at 37 ^{o}C.

(B) In Vivo Nasal Absorption studies[85-90]
Animal models for nasal absorption studiesThe animal models employed for nasal absorption studies canbe of two types, viz., whole animal or in vivo model and an isolatedorgan perfusion or ex vivo model. These models are discussed in detailbelow:

Rat Model
Thesurgical preparation of rat for in vivo nasal absorption study iscarried out as follows: The rat is anaesthetized by intraperitonealinjectionof sodium pentobarbital. An incision is made in the neck and the trachea iscannulated with a polyethylene tube. Another tube is inserted through theoesophagus towards the posterior region of the nasal cavity. The passage of thenasopalatine tract is sealed so that the drug solution is not drained from thenasal cavity through the mouth. The drug solution is delivered to the nasalcavity through the nostril or through the cannulation tubing. The blood samplesare collected from the femoral vein. As all the probable outlets of drainageare blocked, the drug can be only absorbed and transported into the systemiccirculation by penetration and/or diffusion through nasal mucosa.

Rabbit Model[91]
Therabbit offers several advantages as an animal model for nasal absorptionstudies:
1. It is relatively cheap, readily available and easilymaintained in laboratory settings

2. It permits pharmacokinetic studies as with large animals (like monkey)
3. The blood volume is large enough (approx. 300ml)
4. To allow frequent blood sampling (l-2ml)

Thus it permits full characterization of the absorption and determination of the pharmacokineticprofile of a drug. Rabbits (approx. 3 kg) areeither anaesthetized or maintained in theconscious state depending on the purpose ofstudy. In the anaesthetized model, the rabbit is anaesthetized by an intramuscular injection ofa combination of ketamine and xylazine. The rabbit's head is held in an upright position and the drug solution is administered by nasal spray into each nostril. During the experiment the body temperature of the rabbit is maintained at 37°C with the help of a heating pad. The blood samples are collected by an indwelling catheter in the marginal ear vein or artery.

Dog Model[92]

The dog is either anaesthetized or retained hi the conscious condition depending on the drug characteristics and the purpose of experiment. The dog isanaesthetized by intravenous injection of sodium thiopental and the anesthesia is maintained with sodium Phenobarbital. A positive pressure pump through a cuffed endotracheal tube gives the ventilation. The body temperature is maintained at 37-38°C by a heating pad. The blood sampling is carried out fromthe jugular vein.

Sheep Model[93]

The sheep, rabbit and dog models are more practical and suitable for investigating nasal drug delivery from sophisticated formulations. They permit better evaluationof the parameters there involved. The in vivo sheep model for nasal delivery is essentially parallel to that for the dog model. Male in-house bred sheep are employed since they are free from nasal infections.

Monkey Model

Monkeys (approx. 8 kg) are anaesthetized, tranquillized or maintained in the conscious state as per the experimental purpose. The monkey is tranquillized byintramuscular injection of ketamine hydrochloride or anaesthetized by intravenous injection of sodium Phenobarbital. The head of the monkey is held in an upright position and the drug solution is administered into each nostril. Following the administration, the monkey is placed in a supine position in a metabolism chair for 5-10 min. throughout the course of study the monkey breaths normally through the nostrils. The blood samples are collected through an indwelling catheter in the vein.

Ex Vivo Nasal Perfusion Models[94]

Surgical preparation is the same as that is for in vivo rat model. During the perfusion studies, a funnel is placed between the nose and reservoir tominimize the loss of drug solution. The drug solution is placed in a reservoir maintained at 37°C and is circulated through the nasal cavity of the rat with a peristaltic pump. The perfusion solution passes out from the nostrils (through the funnel) and runs again into the reservoir. The drug solution in the reservoir is continuously stirred. The amount of drug absorbed is estimated by measuring the residual drug concentration in the perfusing solution. The drug activity due to stability problems may be lost during the course of experiment. This is especially true for peptide and protein drugs that may undergo proteolysis and aggregation. Rabbit can also be used as the animal model for ex vivo nasal perfusion studies. The rabbit is anaesthetized with parenteral uretliane-acepromazine. Amidline incision is made in the neck and the trachea is cannulated with a polyethylene neonatal endotracheal tube. The oesophagus is isolated and ligated. The distal end of the oesophagus is closed with suture and flexible tygon tubing is inserted into the proximal end and advanced to the posterior part of the nasal cavity. The nasopalatine tract (that connects nasal cavity to the mouth) is closed with an adhesive to avoid drainage of drug solution from the nasal cavity. The drug in isotonic buffer solution is recirculated using a peristaltic pump.

Application of Nasal Drug Delivery System

Local delivery[95,96]

For the natural treatment of topical nasal disorders the drug is administered through nasal route. Among the most common examples are antihistamines and corticosteroids for rhinosinusitis, and nasal decongestants for cold symptoms. In fact, relativelylow doses are effective when administered through nasal route with less systemic toxic effects.

Systemic delivery[95 , 97-108]

The intranasal administration of drugs is an effective way for systemic availability of drugsas compared to oral and

intravascular routes. Actually, it seems to present fast and extended drug absorption, and it has been supported by many studies planned to compare intranasal drug delivery against the oral and parenteral administration.Examples include analgesics (morphine), cardiovascular drugs as propranolol,carvedilol, h ormones such as levonorgestrel, progesterone and insulin, anti-inflammatory agents as indomethacin and ketorolac, antiviral drugs. Some examples which are available in the market include zolmitriptan, sumatriptan for the treatment of migraine and cluster headaches.

Nasal vaccines[95, 109-115]

Nasal mucosa is the first site of contact with inhaled antigens and therefore, its use for vaccination, especially against respiratory
infections, has been extensively evaluated. In fact, nasal vaccination is a promising alternative to the classic parenter al route, because it is able to enhance the systemic levels of specific immunoglobulin G and nasal secretary immunoglobulin A. Examples of the
human efficacy of intranasal vaccines include those against influenza A and B virus, proteosoma-influenza, adenovir us-vectored influenza, group B meningococcal native, attenuated respiratory syncytial virus
and parainfluenza 3 virus.

CNS delivery through nasal route [116]

Intranasal route has promising approaches for delivery of drugs to the brain. The delivery of drugs to the CNS from the nasal route may occur via olfactory neuroepithelium. The transport via trigeminal nerve system from the nasal cavity to CNS has also been described.Drug delivery through nasal route into CNS has been reported for Alzheimer's disease, brain tumors, epilepsy, pain and sleep disorders.

Conclusions

The intranasal route is an accessible alternative to the intravenous route. It is safe and efficaciousformulations which would be useful for a simple, painless and long-termtherapy.It is very likely that in the near future more drugs will come in the market intended for systemic absorption in the formof nasal formulation.
NDDS provides route of drug administration for drugs, which degrade due to first pass metabolism. Though it also poses many challenges such as low absorption, toxicological problems, high dose requirements etc. thus use of absorption enhancers is proving to be useful increasing the absorption.With ongoing efforts to improve bioavailability of protein and peptide drug through nasal route, the nasal route can become the prime route for administration of protein drugs..

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