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### REVIEW ARTICLE ON NASAL DRUG DELIVERY SYSTEM

D. Anish Kumar\*<sup>1</sup>, G. Mohanranga Reddy<sup>1</sup>, D. Saidarao<sup>1</sup>

<sup>1</sup>\*Department of Pharmaceutics, A. M. Reddy Memorial College of Pharmacy, Narasaraopet, Guntur, Andhra Pradesh, India.

#### ABSTRACT

The administration of drugs through the nasal cavity is not a new method of delivering drugs. Intranasal Therapy has been an accepted form of treatment in the Ayurvedic system of Indian Medicine. It has been used for the delivery of psychotherapeutic compounds in the ancient era, particularly for the systemic effects. The drug delivery through the nasal mucosa provides a number of advantages like a large surface area for absorption, overcomes the first pass effect. The increasing research in the field of novel drug delivery system has led to the development of novel forms like the intranasal route which has been shown to have an equivalent efficacy to the intravenous route. The nasal drug delivery system is very advantageous in the delivery of proteins, peptides and the novel research in the field has led to the development of nose to brain drug delivery systems. We discuss here the relevant aspects of biological, physicochemical and pharmaceutical factors of nasal cavity that must be considered during the process of discovery and development of new drugs for nasal delivery as well as in their incorporation into appropriate nasal Pharmaceutical formulations and the marketed formulations.

#### KEYWORDS

Nasal route, Nasal mucosa, Novel drug delivery system and Intranasal Therapy.

#### Author for Correspondence:

D. Anish Kumar,  
Department of Pharmaceutics,  
A. M. Reddy Memorial College of Pharmacy,  
Narasaraopet, Guntur (Dt), Andhra Pradesh,  
India.

**Email:** anishbujji@gmail.com

#### INTRODUCTION<sup>1, 2</sup>

Intranasal Therapy has been an accepted form of treatment in the Ayurvedic system of Indian Medicine. Nowadays many drugs have better systemic bioavailability through nasal route as compared to oral administration. The oral administration of protein and peptide drug is not possible because they are significantly degraded in

the gastrointestinal tract or considerably metabolized by first pass effect in the liver. Intranasal drug delivery offers a promising alternative route for administration of such drugs. Nasal route has also been considered for the administration of vaccines. The interest in intranasal route for therapeutic purposes arises from the anatomical, physiological and histological characteristics of the nasal cavity, which provides rapid systemic drug absorption and quick onset of action.

#### **Advantages<sup>1</sup>**

1. Avoidance of hepatic first pass elimination, gut wall metabolism.
2. To increase the bioavailability of drugs.
3. Rich vasculature and highly permeable structure in nasal cavity facilitates more and rapid drug absorption.
4. Quick onset of action.
5. The bioavailability of larger drug molecules can be improved by means of absorption enhancer or other approach.
6. Better nasal bioavailability for smaller drug molecules.
7. Drugs which cannot be absorbed orally may be delivered to the systemic circulation through nasal drug delivery system.
8. It is easy to administrate.

#### **Limitations<sup>3</sup>**

1. The absorption enhancers used to improve nasal drug delivery system may have histological toxicity which is not yet clearly established.
2. Absorption surface area is less when compared to GIT.
3. Once the drug administered cannot be removed.

#### **Physiological aspect of Nose<sup>1</sup>**

In humans and other animal species the major functions of the nasal cavity are breathing and olfaction. However, it also affords an important protective activity once it filters, heat and humidity the inhaled air before reaching the lowest airways. Nasal cavity is lined with mucus layer and hairs which are involved in those functions like trapping inhaled particles and pathogens. Moreover, resonance of produced sounds, mucociliary clearance MCC, immunological

activities and metabolism of endogenous substances are also essential functions of nasal structures. Anatomic and histological characteristics of the different areas of nasal cavity are designed in such a way that allows these functions to be performed optimally. Thus, anatomically human nasal cavity fills the space between the base of the skull and the roof of the mouth. Above mouth, it is supported by the ethmoid bones and laterally by the ethmoid, maxillary and inferior conchae bones. The human nasal cavity has a total volume of 15-20 mL and a total surface area of approximately 150 cm<sup>2</sup>. It is divided by middle (or nasal) septum into two symmetrical halves, each one opening at the face through nostrils and extending posterior to the nasopharynx. Both symmetrical halves consist of four areas (nasal vestibule, atrium, respiratory region and olfactory region) that are distinguished according to their anatomic and histological characteristics.

Some drugs shows adverse effects when they administered through nasal route.

Ex: cocaine, Atropine, Anti histamines, Propranolol and Bile salts.

During common cold or any pathological condition there is decrease in the therapeutic efficacy of many drugs due to dysfunction of mucociliary action which is necessary for nasal clearance.

Several factors should be considered to optimize the nasal drug delivery of drugs.

Method of technique of administration, Site of deposition, Rate of clearance, Minimization of pathological conditions.

Absorption promoters have been used to achieve a better systemic bioavailability.

Long term use of absorption promoters leads to tolerance and local toxicity.

#### **Fundamentals of Nasal Absorption<sup>4-10</sup>**

##### **Physical and chemical parameters**

Effect of molecular size, Effect of perfusion rate, Effect of perfusate volume, Effect of solution P<sup>H</sup>, Effect of drug lipophilicity, Effect of drug concentration, Mechanism and pathways, Distribution and deposition, Enhancement in absorption, Effect of delivery system.

### **Physical and Chemical Parameters**

Physical and chemical properties of a drug should be evaluated before the development of nasal drug delivery system.

#### **Effect of molecular size**

Molecular weight of a drug up to 1000 daltons shows more absorption where as oral absorption fall even molecular weight goes beyond 400 daltons.

#### **Effect of perfusion rate**

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

#### **Effect of perfusate volume**

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

#### **Effect of solution pH**

$P^H$  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.

#### **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.

#### **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.

### **MECHANISM AND PATHWAYS**

#### **Mechanism**

The mechanism of nasal drug delivery was investigated in rats. It is studied by using a protein molecule SS-6. It is an octapeptide and horseradishpeorxide. In this two mechanisms are involved. A fast rate of nasal absorption which is lipophilicity dependant. Slower rate which is sensitive to the variation in molecular weight. Based on this data a good systemic bioavailability can be achieved by for molecules with a molecular weight up to 1000 daltons when no enhancer is used. With the enhancer the molecular weight up to 6000 daltons gives good systemic bioavailability. Water

soluble compounds such as Sodium cromoglycolate absorption based on diffusion through aqueous pores. Transport of Insulin involves passive diffusion where as transport of Aminoacids involves active diffusion.

#### **Pathways**

The main transport pathway is

Olfactory epithelium → CNS → Peripheral circulation → Nasal absorption.

Nasal cavity, subarachnoid space, between the lymphatic plexus in the nasal mucosa and subarachnoid spaces.

The process of drug transport across the nasal membrane involves either the diffusion of drug molecule through the pore channels in the nasal mucosa (or) participation of some non passive pathways before they reaches in to blood stream.

#### **Distribution and Deposition**

The distribution of drug delivered in transnasally in the nasal cavity is one of the most important factor that could affect the efficiency of nasal absorption. Mode of administration also effects the distribution. Different types of administrations are there, they are Nose drops, Plastic bottle nebulizer, An atomized pump, Metered dose pressurized aerosols Among these atomized pump delivers the drug effectively than other dosage forms. Nasal deposition of drug depends on the nasal resistance to airflow and the particle size. Particles with aerodynamic size of 10-20 $\mu$ m are often found to be deposited on nasal mucosa. In the poorly absorbed regions like anterior atrium and posterior nasopharyngeal region the deposition is poor. The deposition of aerosols also depends on particle size, density, shape, hygroscopicity of the particles. Pressurized gas propellant gives uniform distribution throughout the nasal mucosa. A metered dose delivery system gives a constant deposition rate.

#### **ENHANCEMENT IN ABSORPTION**

Several methods have been used to facilitate the nasal absorption of drugs. Those are

**Structural modification** - chemical modification of molecular structure modify the physic chemical properties of drugs which enhances the absorption.

**Salt (or) ester formation**- conversion of drug in to salt or ester formation will increase the solubility which increases the nasal membrane permeability.

**Formulation design** - proper selection of excipients could improve the solubility and enhances the nasal absorption of drugs.

Ex: Surfactant-surfactants modify the permeability of nasal mucosa which facilitates nasal absorption of drugs.

**Bile salts act by the following mechanisms**

1. Inhibit the amino peptidase activity in nasal mucosa.
2. Formation of transient hydrophilic pores in the membrane bilayer.
3. Reduces the viscosity of mucus.
4. Effect of delivery systems.

Several types of drug delivery systems have been used for delivering drugs to the nasal cavity

Ex:

Nasal spray, Nose drops, Aerosol spray, Saturated cotton pled get, Insufflators

Metered dose nebulizers (MDN) have recently been introduced as a potential nasal drug delivery device. It delivers a predetermined volume of drug with a precision in to the nasal cavity.

It works by mechanical actuation and the dose of API depends up on the volume of drug solution delivered at each actuation.

Many topically administered drugs are changed in to metered dose nebulizers.

1. Ex:
  - a. Corticosteroids
  - b. Beclomethasonedipropionate
  - c. Tramazoline
2. Some systemically active drugs changed in to MDN's.
3. Ex: Enviroxime, Insulin, Nitroglycerine etc.

**PHARMACOKINETICS AND BIOAVAILABILITY**

Factors that can affect the pharmacokinetics and bioavailability of drugs which are administered through nasal route. Those are

**Physiological factors**

Speed of mucus flow, Change in physiological state, Atmospheric conditions in nasal cavity.

**Dosage form factors**

Physicochemical properties of the drug, Concentration of active drug, Physicochemical properties of pharmaceutical excipients Density, viscosity, pH of the formulation and Toxicity of the dosage form.

**Administration factors**

Size of dose, Site of deposition

The bioavailability may be expressed in terms of absolute nasal bioavailability i.e absolute nasal absorption

$$B_n = (AUC)_{IN} (DOSE)_{IV} / (AUC)_{IV} (DOSE)_{IN}$$

Two types of kinetics profiles involved in transnasal permeation of drug

Zero- order trans nasal permeation kinetics

First order trans nasal permeation kinetics

**Zero order transnasal permeation kinetics**

When a drug under goes zero order kinetics when it administered as transnasal delivery system i.e. for example a controlled delivery of a drug at a constant rate of absorption, the plasma profile of the drug may be described as

$$d X_B/dt = K_o - K_e X_B$$

Here

$K_o$  – Absorption rate constant

$K_e$  – Overall rate constant

$X_B$  – amount of drug absorbed in to the body

Then the plasma concentration may be expressed as

$$C_p = K_o / C_L \cdot 1 - e^{-k_e t}$$

$C_L$  – total body clearance

First order transnasal permeation kinetics:

If the absorption of drug follows first order kinetics, the plasma profile can be described as

$$d X_B/dt = F_a X_{IN} K_a - K_e X_B$$

$K_a$  – 1<sup>st</sup> order rate constant

$F_a$  – fraction of dose absorbed

$X_{IN}$  – Amount of dose administered through intra nasal route.

The plasma concentration may be expressed as

$$C_p = F_a X_{IN} K_a / V_d (K_a - K_e) (e^{-k_e t} - e^{-k_a t})$$

$X_{IN}^0$  – Initial drug dose delivered at zero time

$V_d$  – Volume of distribution.

**Bio medical applications of nasal drug delivery system**

**Nasal delivery of Organic based pharmaceuticals**

Drugs with extensive presystemic metabolism, such as progesterone, estradiol, Testosterone, Hydralazine, Propranolol, cocaine, Nalaxone, and nitroglycerine can be rapidly absorbed through the nasal mucosa with a systemic bioavailability of approximately 100%.

**Nasal delivery of peptide based pharmaceuticals**

These have physicochemical instability and susceptibility to hepatogastro intestinal first pass elimination, so these pharmaceuticals have generally a low bioavailability and are normally administered by parenteral route. Most nasal formulations of peptide and protein pharmaceuticals have been simply prepared by simple solution with preservatives.

**Table No.1: Epithelial Characteristics cells/functions in Nasal sections**

S.No	Nasal Section	Epithelial Characteristics cells/functions	Surface area	Vascularization	Permeability
1	Vestibule	Stratified squamous and keratinized epithelial cells with nasal hair	≈ 0.6 cm <sup>2</sup>	Low	Poor
2	Atrium	Stratified squamous cells/ support Pseudo stratified cells / support	NF	Low	Reduced
3	Respiratory region	Columnar non ciliated cells/ support Columnar ciliated cells/ support and muciliary clearance Goblet cells/ mucus secretion Basal cells / progenitors of other cell types	≈ 130 cm <sup>2</sup>	Very high	Good
4	Olfactory region	Sustentacular cells / support and synthetic Olfactory receptor cells/ olfaction perception Basal cells / progenitors of other cell types	≈ 15 cm <sup>2</sup>	High	Direct access to CNS

**Table No.2: Some absorption promoters**

S.No	Drug	Promoters
1	Atropine	Sodium lauryl sulfate
2	Calcitonin	Poly acrylic acid
3	Gentamycin	Sodium glycol ate
4	Hydralazine	Sodium Glycocholate (bile salt)

**Table No.3: Bio pharmaceutical data for some organic based pharmaceuticals**

S.No	Pharmaceuticals	Animal model	t <sub>max</sub>	Relative bioavailability	
				Nasal (%)	Other (%)
1	Buprenorphine	Rat	2 -5 min	95	9.7 (ID)
		Human	5 min	48	
2	Clofiliumtysolate	Rat	< 10 min	69.6	1.3 (PO)
3	Diazepam	Humans	60 min	72-84	-----
4	Ergotamine tartrate	Rat	2 min	62	12.7 (ID)

ID- Intra duodenal administration PO- post oral administration

**Table No.4: Bio pharmaceutical Data for Nasal Delivery of some Peptide based pharmaceuticals**

S.No	Pharmaceuticals	Animal model	t <sub>max</sub>	Relative bioavailability %
1	Alsactide (ACTH-17)	Rat	1 hr	12%
2	Glucagon ( with Na glycocholate)	Human	10 min	50%
3	Na glycocholate	Rat	10-15 min	7-8 %
4	Na caprate	Rat	5 min	98%

**Table No.5: Various Intranasal Drug Delivery Systems and Their Purpose**

S.No	Drug	Delivery system	Purpose
1	Pentazocine	Microspheres	Avoid first pass effect
2	Ketorolac trimethamine	Microspheres	Avoid gastric complications
3	Sildenafil citrate	Microspheres	Avoid first pass metabolism
4	Metaclopramide HCl	Microspheres	Permeation enhancement
5	Propranolol HCl	Microspheres	Open tight junction without cell damage
6	N- cyclopentyladenosine	Microspheres	Selective brain targeting
7	Propranolol HCl	Microspheres	Avoid first pass effect
8	Ondansetron	Microspheres	Avoid first pass effect and improve therapeutic efficacy
9	Domperidone	Microspheres	Selective brain targeting
10	Sumatriptan succinate	Microspheres	Avoid hepatic first pass metabolism and brain targeting
11	Clonazepam	Microspheres	Brain targeting
12	Clonazepam	Micro emulsion	Brain targeting

**Table No.6: Examples of Nasal Formulations Commercially Available**

S.No	Drug	Brand	Main Excipients	supplier
<b>Local Delivery</b>				
1	Azelstine	Astelin	Benzalchonium chloride, Edetate disodium, Hypromellose	Meda pharmaceuticals
2	Beclomethasone	Beconase	Microcrystalline cellulose, Car boxy methyl cellulose sodium.	Galaxosmithkline
3	Levocabastine	Livostin	Benzalchonium chloride, Edetate disodium, Disodium phosphate	Jasen-Cilog
4	Olapatadine	Patanase	Benzalchonium chloride, Dibasic sodium phosphate, Edentate disodium	Alcon laboratories
5	Mupirocin	Bactroban	Paraffin and mixture of glycerine esters	Galaxosmithkline
<b>Systemic delivery</b>				
1	Estradiol	Aerodiol	Methyl betadex. sodium chloride	Servier laboratories
2	Nicotine	Nicotrol NS	Disodium phosphate, Sodium dihydrogen phosphate, citric acid	Pfizer
3	Cyanocobalamin	Nascobal	Sodium citrate, citric acid, benzalkonium chloride, sodium chloride	Strativa pharmaceuticals.
4	Oxytocin	Syntocinon	Citric acid, Chlorbutanol, sodium chloride	novartis



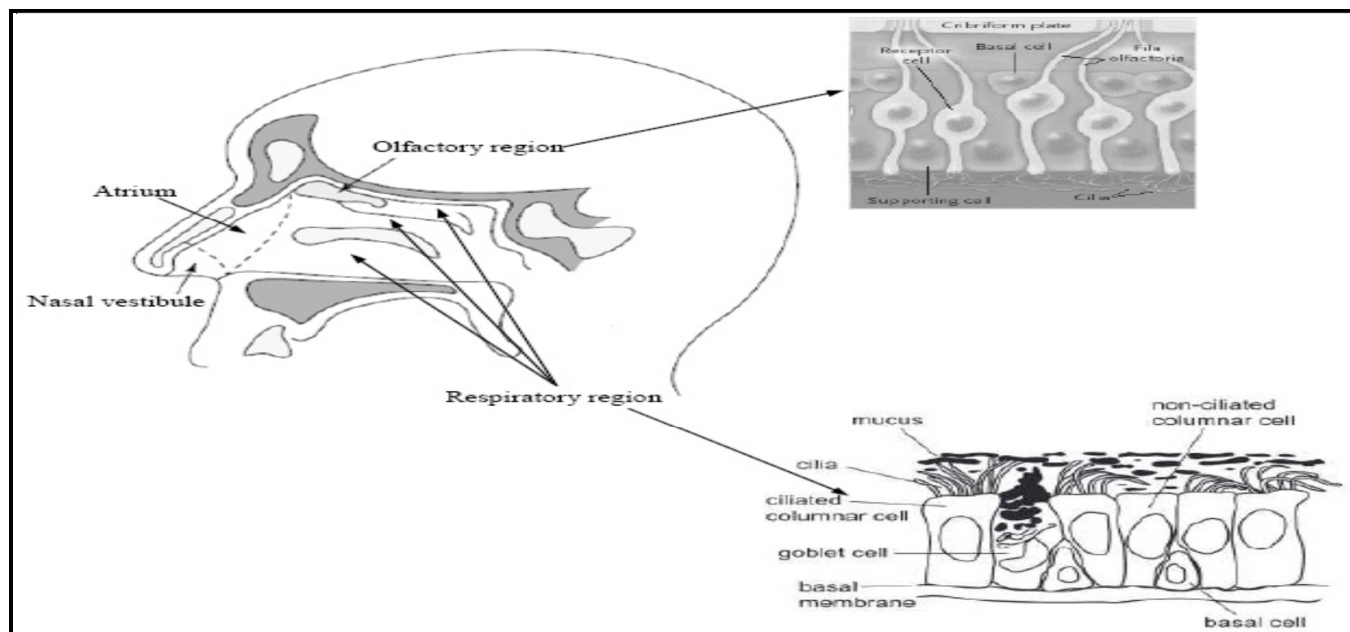


Figure No.1: Physiological aspect of nose

## CONCLUSION

The increasing research in the field of novel drug delivery system has led to the development of novel forms like the intranasal route which has been shown to have an equivalent efficacy to the intravenous route. The nasal drug delivery system is very advantageous in the delivery proteins, peptides and the novel research in the field has led to the development of nose to brain drug delivery systems. Nasal product will include drugs for acute and long term diseases and also vaccines with better local or systemic protection against infections. From this route drugs can be directly target to the brain in order to attain a good therapeutic effect in CNS with reduced systemic side effects. Nasal drug absorption mainly depends on the physiological conditions of the nose and also physicochemical properties of drugs. Much has been investigated and much more are to be investigated for the recent advancement of nasal drug delivery system.

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## CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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