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REVIEW ARTICLE

NASAL ANATOMY AND ABSORPTION THROUGH NASAL ROUTE

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ABSTRACT

The nasal cavity is covered by a thin mucosa which is well vascularised. This facilitate to quick transfer of drug molecules across the single epithelial cell layer directly to systemic blood circulation without first-pass hepatic and intestinal metabolism. In this way the effect of a smaller drug molecule can be achieved in five minutes. The nasal administration therefore can be used a better route than oral drug administration. The present study is all about the compilation of existing knowledge about nasal anatomy and mecahahis routnism of absorption through nasal rout nase. The study is also about the present formulations for nasal administration.

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INTRODUCTION

The nasal drug delivery is an ancient therapy system of drug for psychological problems. But in modern pharmaceutics, this route has been as better route of drug administration for local ailments. Recently the formulations through this route are being discovered to give in systemic circulations. Advent of biotechnology, molecular boil endogenousogy and pharmacology has provided lot of endogenous peptide molecules and proteins for therapeutic use the delivery of such molecules is possible through nasal drug delivery. The greater permeability of nasal mucosa with large surface area provides a fast onset of therapeutic drug effect [1]. Drug candidates ranging from small metal ions to large macromolecular proteins have also been tested in various animal models. Complete absorption of certain steroids and hormones for nasal administration have also been reported by nasal drug administration [2]. The better and complete absorption of drug through nasal route in nasal solution formulation or other suitable formulations is possible after only complete absorption of such drugs. The present work is thus focused on nasal anatomy and drug delivery system through this route.

Anatomy of the nose [3-14]

The total surface area of human nasal cavities is about 150 cm2 and the total volume is about 15ml. The nasal cavity is divided into two halves by the nasal septum.

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The volume of each cavity is approximately 7.5 ml, having a surface area around 75 cm2. The anatomy and histology of the nasal cavity is shown in Fig. 1. The nasal cavity consists following three main regions:

The vestibular region: It is located at the opening of nasal passages and is mainly responsible for restricting entry of air borne particles. It is considered to be less important of the three regions with regard to drug absorption.

The respiratory region: The respiratory region is the largest having the highest degree of vascularity. The respiratory region contains three nasal turbinates: superior, middle, and inferior which project from the lateral wall of each of the nasal cavity. The presence of these turbinate creates a turbulent air flow through the nasal passages ensuring a better contact between the inhaled air and the mucosal surface. The respiratory region is considered as the major site for drug absorption into systemic circulation. The mucosa consists of an epithelium resting on a basement membrane and a lamina propria. The anterior part of respiratory region is covered with squamous epithelium, while the posterior part covered by a pseudo stratified columnar epithelium. The cells of respiratory epithelium are covered by about 300 microvilli per cells.

The olfactory region**:** Olfactory mucosa lines the roof of the nasal cavity and superior turbinates (= *nasal conchae*) an is structurally modified to detect odor-producing chemicals (= odorants).

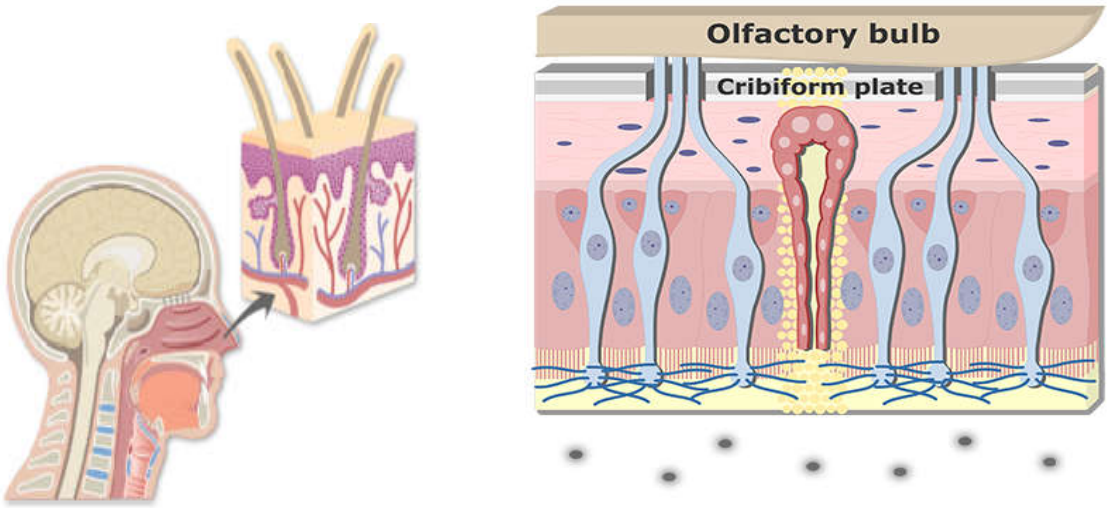

Fig. 1. Showing structure of olfactory mucosa

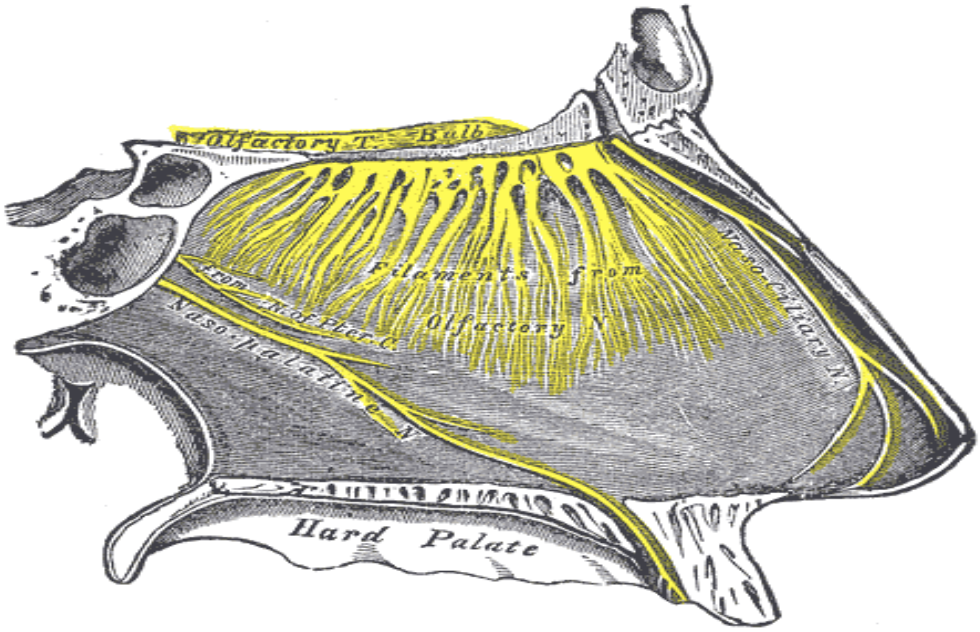

Fig. 2. Showing nasal section with olfactory mucosa

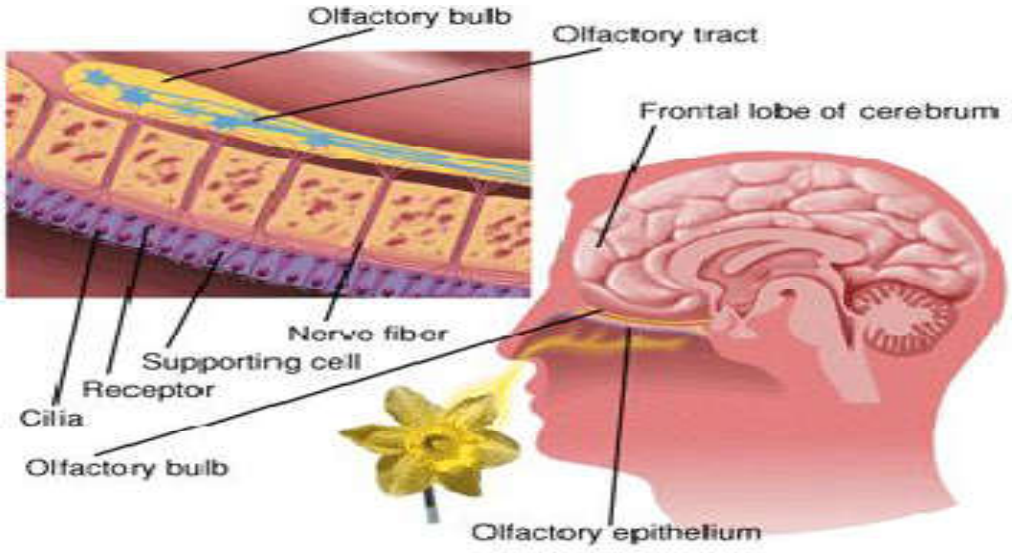

Fig.3:Showing absorption from nose to brain

In the epithelium layer are millions of specialized nerve cells referred to as olfactory receptor odorant-sensitive tips of the receptors protrude into the nasal cavity from the free surface of the epithelium. Several non-motile cilia extend from each bulbous tip. Along the cilia are many binding sites for odorants. Surrounding the receptors are many elongated supporting cells or sustentacular cells. A thin layer of watery mucus made by the supporting cells and Bowman's (olfactory) glands covers the receptor cilia and microvilli. During inhalation, odorants are drawn into this fluid layer, where they dissolve and then bind to the cilia receptors. The human nasal cavity has a total volume of about 16 to 19 ml, and a total surface area of about 180 cm2, and is divided into two nasal cavities by the septum. The volume of each cavity is approximately 7.5 ml, having a surface area approximately 75 cm2. Post drug administration into the nasal cavity, a solute can be deposited at one or more of anatomically distinct regions, the vestibular, respiratory and olfactory regions showing in figure below.

Moreover it is explained by another researchers as, the olfactory region is situated between the nasal septum and the lateral walls of each of the two nasal cavities and just below the cribriform plate of the ethmoid bone separating the cranial cavity from nasal cavity. The olfactory epithelium is a pseudostratified epithelium, comprising olfactory sensory neurons and two types of cells; basal cells that are able to differentiate neuronal receptor cells and sustentacular cells (supporting cell) that provide mechanical support by unsheathing neuronal receptor cells and maintain the normal extracellular potassium level for neuronal activity. The olfactory epithelium is covered by a dense and viscous layer of mucus, which is secreted from the tubuloalveolar Bowman's glands and the supporting cells. The olfactory epithelium constitutes only about 5% of the total area of the nasal cavity in man. It is about 10 cm2 in surface area, and it plays a vital role in drug delivery because it bypasses the BBB, delivering therapeutic drugs to CNS. It should be noted that the blood supply to the nasal mucosa is pertinent with regards to systemic drug delivery. The arterial blood supply to the nasal cavity is derived from both the external and internal carotid arteries.

The blood that is supplied to olfactory region by anterior and posterior ethmoidal branches come from the ophthalmic artery supply, which is branch of carotid artery. These vessels supply the anterior portion of the nose. When the drug is administered intranasally, it can enter into the brain via three different paths. The first one is the systemic pathway by which the drug is absorbed into the systemic circulation and subsequently reaches the brain by crossing BBB (especially lipophilic drug). The others are the olfactory region and the trigeminal neural pathway by which drug is transported directly from the nasal cavity to CNS (cerebrospinal fluid and brain tissue). The trigeminal nerve receptors which are present in the nasal cavity are responsible for most chemoperception and are suggested to transport the drug directly to CNS of drugs to the brain and the CNS. The deep and superfacila cervical lymph nodes were of special interest in intranasal drug delivery because they are known to receive lymphatic afferents from portions of the nasal passages and nasolabial areas, respectively. This pathway is thought to mediate the efflux of large molecules and/or immune cells from sites within the CNS to the lymphatic system. The connection between the brain and nasal lymphatics may offer a direct pathway from the brain interstitial fluid to the nasal submucosa that excludes direct conact with the cerebrospinal fluid.There are different mechanism by which the drugs across the olfactory membrane to reach CNS. The first mechanism involves direct transfer of the drug to primary neurons of the olfactory epithelium and transport to the olfactory bulb by intracellular axonal transport with subsequent possible distribution into more distant brain tissues. The second mechanism depends on the drug permeation across the olfactory sustentacular epithelial cells, either by transcellular or par cellular mechanisms followed by uptake into CNS. The last one employs pinocytosis by olfactory neurons. The drug can cross olfactory lobe by one or combination of pathways. Absorption for displaying systemic effects. Important candidates are the compounds, generally administered by injection and hardly absorbed after oral administration, due to their instability in the gastrointestinal tract, poor absorption properties, and their rapid and extensive biotransformation.

Nose to brain

If the nasally administered medication contacts the olfactory mucosa, there is good evidence that suggests molecule transport can occur directly across this tissue and into the cerebral spinal fluid. The olfactory mucosa is located in the upper nasal cavity, just below the cribriform plate of the skull. It contains olfactory cells which traverse the cribriform plate and extend up into the cranial cavity. When medication molecules come in contact with this specialized mucosa they are rapidly transported directly into the brain, skipping the blood-brain barrier, and achieving very rapid cerebrospinal fluid levels (often faster than if the drug is given intravenously). This concept of transfer of molecules from the nose to the brain is referred to as the nose-brain pathway and has implications when centrally acting medications such as sedatives, anti-seizure drugs and opiates are delivered nasally. Multiple authors demonstrate that the nose-brain pathway leads to nearly immediate delivery of some nasal medications to the cerebral spinal fluid, by-passing the blood brain barrier.

The unique relationship between nasal cavity and cranial cavity tissues in anatomy and physiology makes intranasal delivery to the brain feasible. An intranasal delivery provides some drugs with short channels to bypass the blood–brain barrier (BBB), especially for those with fairly low brain concentrations after a routine delivery, thus greatly enhancing the therapeutic effect on brain diseases. In the past two decades, a good number of encouraging outcomes have been reported in the treatment of diseases of the brain or central nervous system (CNS) through nasal administration. In spite of the significant merit of bypassing the BBB, direct nose-to-brain delivery still bears the problems of low efficiency and volume for capacity due to the limited volume of the nasal cavity, the small area ratio of olfactory mucosa to nasal mucosa and the limitations of low dose and short retention time of drug absorption. It is crucial that selective distribution and retention time of drugs or preparations on olfactory mucosa should be enhanced so as to increase the direct delivery efficiency. In this article, we first briefly review the nose-to-brain transport pathways, before detailing the impacts on them, followed by a comprehensive summary of effective methods, including formulation modification, agglutinant-mediated transport and a brain-homing, peptide-mediated delivery based on phage display screening technique, with a

view to providing a theoretic reference for elevating the therapeutic effects on brain diseases (Illum *et al.,* 1999).

Liophilicity-[16-30]

Lipid loving" - implies that the molecule will easily absorb and cross a lipid membrane. Cell membranes are made of lipids. A molecule with high lipophilicity will easily cross cell membranes (mucous membranes, vascular membranes, blood brain barrier) and enter the blood stream and cerebral spinal fluid.

Mechanism of nasal absorption [16-30]

The absorbed drugs from the nasal cavity must pass through the mucus layer; it is the first step in absorption. Small, unchanged drugs easily pass through this layer but large, charged drugs are difficult to cross it. The principle protein of the mucus is mucin; it has the tendency to bind to the solutes, hindering diffusion. Additionally, structural changes in the mucus layer are possible as aresult of environmental changes (i.e. pH, temperature, etc.) (Illum *et al.,* 1999). So many absorption mechanisms were established earlier but only two mechanisms have been predominantly used, such as

a) 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 com-pounds. The molecular weight greater than 1000 Daltons having drugs shows poor bioavailability.
b) 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 which is showing in figure- 5

For examples: chitosan, a natural biopolymer from shellfish, opens tight junctions between epithelial cells to facilitate drug transport

Barriers to nasal absorption: Nasal drug delivery system is considered has a profitable route for the formulation scientist because it has easy and simple formulation strategies. Intra-nasally administered drug products therapeutic efficacy and toxicities are influenced by number of factors. Following factors are the barriers to the absorption of drugs through nasal cavity.

i. **Low bioavailability**: Lipophilic drugs are generally well absorbed from the nasal cavity compared to polar drugs. The pharmacokinetic profiles of lipophilic drugs are often identical to those obtained after an intravenous injection and bioavailability approaching 100%. A good examples of this is the nasal administration of Fentanyl where the Tmax for both intravenous and nasal administration have been shown to be very rapid (7 min or less) and the bioavailability for nasal anterior part of the nasal cavity can decrease clear administration was near 80%. 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. Drugs can cross the epithelial cell membrane either by the transcellular route exploiting simple concentration gradients, by receptor mediated or vesicular transport mechanisms, or by the paracellular route through the tight junctions between the cells. Polar drugs with molecular weights below 1000 Da will generally pass the membrane using the latter route. Larger peptides and proteins havebeen shown to be able to pass the nasal membrane using an endocytotic transport process but only in low amounts

ii. **Low membrane transport:** Another importance factor is low membrane transport is the general rapid clearance of the administered formulation from the nasal cavity due to the mucociliary clearance mechanism. This is especially the case for drugs that are not easily absorbed across the nasal membrane. It has been shown that for both liquid and powder formulations, that are not mucoadhesive, the half life of clearance is in the order of 15–20 min. It has further been suggested that the deposition of a formulation in the anterior part of the nasal cavity can decrease clearance and promote absorption as compared to deposition further back in the nasal cavity.

iii. **Enzymatic Degradation**: Another contributing (but normally considered less important) factor to the low transport of especially peptides and proteins across the nasal membrane is the possibility of an enzymatic de-gradation of the molecule either within the0 lumen of the nasal cavity or during passage across the epithelial barrier. These sites both contain exo-peptidases such as mono- and di-aminopeptidases that can cleave pep-tides at their N and C termini and endo peptidases such as serine and cysteine, which can attack internal pep-tide bonds. The use of enzyme inhibitors and/or saturation of enzymes may be approaches to overcome this barrier.

Physicochemical properties of drugs which affect their nasal delivery

Drug molecular weight and size

The permeation of drugs having molecular weight less than 300 Da is not significantly influenced by the physicochemical properties of the drug as they will mostly permeate hrough aqueous channels of the membrane. On the other hand, the rate of permeation is highly sensitive to molecular weight for compounds more than 300 Da. The bioavailability of intranasally administered peptides and proteins including insulin may be low because of high molecular weight and hydrophilicity.

Drug solubility and dissolution rate

Like other routes of administration, the nasal absorption can take place only after the drug's dissolution. The dissolution rate is important in determining nasal absorption of powder and suspensions dosage forms. Rapid dissolution is very crucial for the drug particles after nasal administration otherwise the particles will be subjected to rapid clearance from the airway with subsequent reduction of the bioavailability.

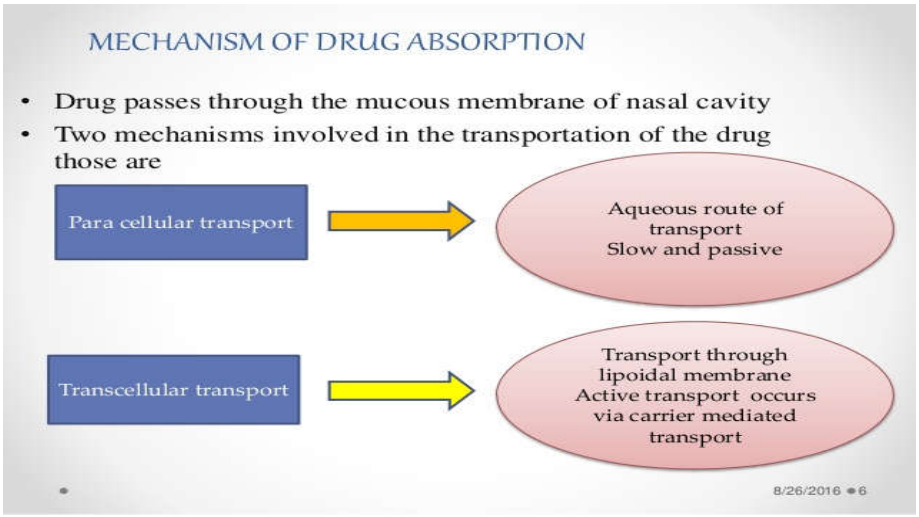

Fig.4. Showing mechanism of drug absorption through nasal route

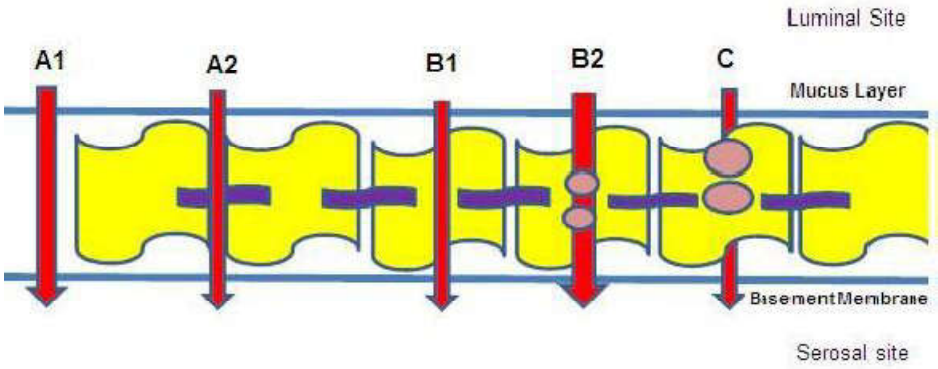

Fig .5 : Showing drug absorption through nasal route. (A1) Intercellular spaces, (A2) Tight junctions, (B1) Passive diffusion, (B2) ,Active transport, (C) Transcytosis

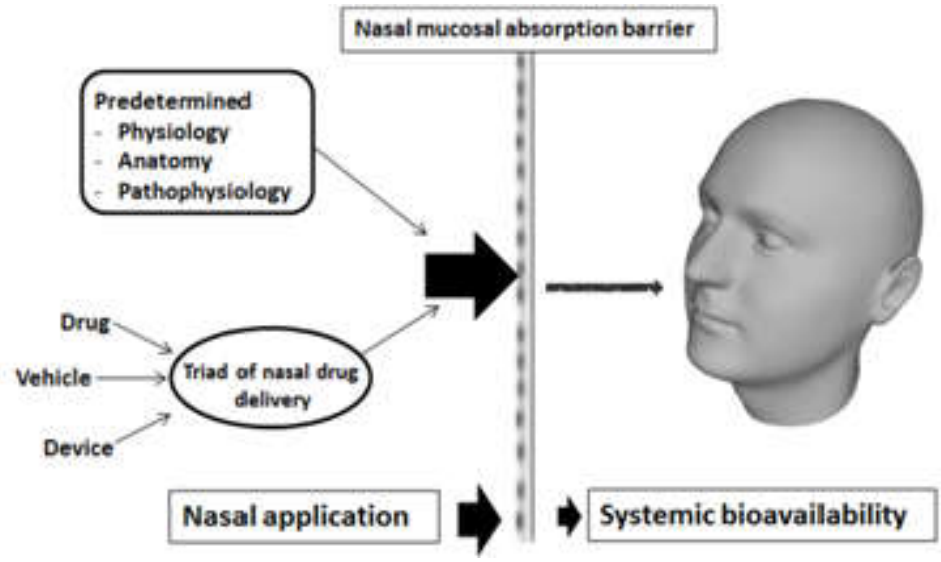

Fig. 5. Showing nasal absorption

pKa and the partition coefficient of drug

The nasal membrane is predominantly lipophilic, hence, the rate and extent of absorption of a drug across a biological membrane is influenced by its lipophilicity. Normally, the permeation of material through the compound through nasal mucosa increases with increasing lipophilicity. Low molecular weight lipophilic drugs are absorbed quite efficiently across the nasal epithelium, whereas larger hydrophilic drugs, such as peptides and proteins, have substantially lower bioavailability because they are not easily transported across nasal membrane thereby enhancing mucociliary clearance. However, if lipophilicity is too high, the drug does not dissolve easily in the aqueous environment of nasal cavity, hence, with accelerated mucociliary clearance the contact time with nasal membrane diminishes resulting in a reduced permeation through the wall. In general, the passage across biomembrane is affected not only by lipophilicity/hydrophilicity, but also by

the amount of drug existing as uncharged species. This depends on the drug pKa and the pH of the absorption site. According to pH partition theory, the non-ionized fraction of a drug is more permeable than that ionized. The nasal absorption of week electrolytes depends on their ionization degree and the largest absorption occurs for the non-ionized species. For polar drugs partition coefficient is the major factor influencing the permeability through nasal mucosa.

Chemical state: Prodrugs

The chemical form in which a drug is presented at the nasal mucosa can be important in determining its absorption. If a drug does not have the desired absorption properties, several options can be considered to improve the drug's delivery. Prodrug technique has been employed to increase the lipophilicity. The aliphatic prodrug of acyclovir provides a classical example of this process, which resulted in an increased drug bioavailability. However, it should be noted that the 140-fold increase in partition coefficient of the drug was only associated with 30% increase in bioavailability. It should also be emphasized that the ester form of the prodrug can show greater increase in transnasal drug transport but premature hydrolysis of such ester in the nasal cavity provides the main limitation of this technique. Water-soluble prodrugs of 17β-estradiol have been evaluated after intranasal administration. These prodrugs were capable of producing high levels of estradiol in the cerebrospinal fluid (CSF), compared to an equivalent intravenous dose. These data suggest that the drug can reach the CSF via a direct pathway through the nasal cavity and as a result may have a significant value in the treatment of Alzheimer's disease.

Physical state: particle size and morphology

Particle size and morphology of drug particles constitute important properties for particulate nasal drug products. Particle size and morphology are related to the drug dissolution and should be controlled to obtain suitable drug dissolution properties in the nostrils.

products. Generally, particles in the 5-10 micron range are deposited in the nostrils.

Polymorphism

An evaluation and study of the polymorphic forms of drugs administered in particulate form is an important parameter to be considered in nasal drug product development. Polymorphism is known to affect dissolution of drugs and their absorption through biological membranes. The effect of polymorphism on the nasal drug absorption has not been explored to date. However, in view of the information available on other biological membranes, this factor should be considered.

Nasal permeation enhancers [121-125]

Permeation enhancers have been employed for improving the absorption of poorly absorbed and large molecular weight compounds. Complete mechanism of drug absorption enhancement through nasal mucosa is not known. Cyclodextrins act as a solublizer and permeation enhancer for nasal drug delivery and they are well tolerated in humans.

Strategies to improve nasal bioavailability

1. Nasal enzyme inhibitors
   e.g., bestatin, amastatin, boroleucine, fusidic acids, and bile salts
2. Nasal permeation enhancers
   e.g., cyclodextrins, surfactants, saponins, fusidic acids, and phospholipids
3. Prodrug approach
   e.g., cyclic prodrug, esters, and derivatization of C and N termini
4. Nasal mucoadhesives in nasal drug delivery
   e.g., carbopol, polycarbophil, cellulose derivatives, lecithin, and chitosan
5. Particulate drug delivery
   e.g., microspheres, nanoparticles, and liposome

Barriers in nasal drug product development

Nasal barrier	Factors to b consider
I. **Physiological barrier [31-85]**	
a. Nasal mucus Viscosity, pH of mucus and drug/dosage form-mucus interaction	Viscosity, pH of mucus and drug/dosage form-mucus interaction.
b. Nasal epithelial barrier Molecular weight, ionization constant and mode of transport	Molecular base ionization
	Nasal residential time and nature of dosage form
c. Mucociliary clearance Nasal residential time and nature of dosage form	Volume of nasal secretion and permeability of epithelium
d. Pathophysiology Volume of nasal secretion and permeability of epithelium	Nature of the molecules (e.g., protein and peptides)
e. Nasal metabolism Nature of the molecules (e.g., protein and peptides)	Nature of drug molecule and duration of therapy
f.. Efß ux transport system Nature of drug molecule and duration of therapy	Nature of dosage form, dose, pKa, and polymorphism
II. **Physicochemical barriers [86-107]**	
a. Drug solubility and dissolution	Less bioavailability with molecular weight more than 1000
b. Molecular weight and size	Affects the nose to blood and nose to brain absorption
c. Compound lipophilicity d. pH and pKa	High concentration for better bioavailability, maximum dose in Minimum
III. Formulation factors[108-120]	
a. Drug concentration, dose, and volume.	Isotonic solution prevents volume vehicle (less than 200 µl)
b. Osmolarity	Site of deposition based on viscosity, position of head, volume,delivery device, deposition at anterior chamber prolong the nasal residential time
c. Site of deposition	

In vitro dissolution rates in suitable simulated fluid(s) should be considered. Particle size and morphology are also important to minimize the feel of grittyness and possibly irritation to the nasal cavity. Too fine particles, below five microns may be inhaled into the lungs and should be avoided for nasal

Olfactory transfer

The olfactory transfer of drugs into the brain is thought to occur by either slow transport inside the olfactory nerve cells to the olfactory bulb or by faster transfer along the perineural

space surrounding the olfactory nerve cells into the cerebrospinal fluid surrounding the olfactory bulbs and the brain. Olfactory transfer could theoretically be used to deliver drugs that have a required effect in the central nervous system such as those for Parkinson's or Alzheimer's diseases, its advantages, if used for stem cell delivery in neurodegenrerative diseases like multiple sclerosis [16] has been proposed. Studies have been presented that show that direct transfer of drugs is achievable [17][18] but the possibility of olfactory delivery of therapeutically relevant doses to humans remains to be demonstrated.

Nasal mucoadhesive drug delivery system

Although nasal enzyme inhibition and incorporation of permeation enhancers are the two popular approaches, these approaches hinder the normal physiological process and drug delivery system Although nasal enzyme inhibition and incorporation of permeation enhancers are the two popular approaches, these approaches hinder the normal physiological process and hence are prone to cause toxicity of nasal mucosa. Designing bioadhesive drug delivery system is a novel approach in nasal drug delivery, which enhances the nasal residential time of the drug molecule and hence enhances the absorption and bioavailability of nasally administered drug products. Bioadhesion is the ability of synthetic or natural material to adhere to a biological tissue or membrane for a prolonged period of time. Bioadhesive drug delivery implies attachment of drug delivery system to a specific biological tissue, which increases the local residential time of the delivery system. If biological tissue is covered by mucus, the attachment of drug delivery system to the mucus is called as mucoadhesive drug delivery system. Mucoadhesive system is the ideal choice of drug delivery system for systemic nasal drug delivery because it improves the nasal residential time. Intimate contact of drug delivery system to the nasal mucosa not only prolongs the duration of action but also increases extent of absorption. Pharmaceutical excipients which improve the mucoadhesion are called as mucoadhesive materials.

The mucoadhesive synthetic and natural polymers are called as first generation mucoadhesive material. Apart from these polymers, lecithin\ a new second generation promising mucoadhesive material is widely used in drug delivery systems. Lecithin is a non immunogenic compound, basically constructed by protein or glycoprotein moiety capable of specific and reversible binding with mucin and other carbohydrate moiety. Mucoadhesive drug delivery has been used to improve the therapeutic efficacy of local as well as systemic drug delivery. The bioavailability of nasally administered drugs was improved with all kinds of therapeutic substances such as small organic molecules, antibiotics, vaccines, DNA, proteins, and other macro molecules. Intranasal bioavailability of aqueous solution of apomorphine was found to be 45%.The nasal bioavailability of apomorphine is rate limited by drainage of aqueous solution through nasopharynx and rapid oxidation in aqueous solution. Highest nasal bioavailability of 98% of apomorphine was achieved by using mucoadhesive polymer like polyacrylic acid, carbopol, and carboxymethylcellulose. Nasal mucoadhesive gels are the lucrative ways of improving the nasal residential time. Chitin and chitosan nasal gel formulations were prepared using indomethacin and papaverine as model drugs. Chitin nasal gel increased the nasal residential time of both drugs than nasal powder dosage form. Similar study showed that cationic chitosan was fairly mucoadhesive in comparison to polycarbophil as a reference substance. Nasal absorption of nifidipine gel has been studied in rats.Nasal administration of PEG/ carbopol system resulted in rapid absorption and high Cmax. However, the rapid rate of elimination was also found in the same study. Plasma concentration of nifedipine after nasal administration in aqueous carbopol gel formulation was very low.

The usage of PEG in nasal formulation should be carefully optimized, because it is irritant to nasal mucosa if concentration exceeds 10%. The effect of insulin loaded polycarbophil gel on nasal bioavailability was studied in animal models. Low concentration of polymer favors absorption and hence better bioavailability. Carbopol, pluronic, chitosan and its derivatives, polycarbophil and cellulose derivatives are widely studied as gelling agents in nasal drug delivery. Mucoadhesive powder dosage form not only offered increased nasal residential time but also reduced the oxidation of apomorphine in nasal cavity. In addition to apomorphine, other small molecular weight compounds including budenoside, caffeine, ketorolac, nicotine, pentazocine, and ondansetron have been characterized for nasal administration with mucoadhesives. The airway diseases such as rhinitis and asthma are commonly associated with inflammation. The systemic administration of steroidal drugs produces low drug concentration at the targeted site. Moreover, it has been associated with systemic toxicity such as immunosuppression, fluid retention, and hyperacidity. Nasal delivery of steroid is one of the meaningful approaches to improve the therapeutic efficacy with minimum systemic toxicity. However, nasal residential time of such dosage form determines the duration of action; nasal mucoadhesive dosage form improves the duration of action of steroidal drugs along with patient compliance. Petersen and coworkers studied the pharmacokinetics of budenoside loaded bioadhesive grafted copolymers of polymethacrylic acid and polyethylene glycol.

The result stated that the bioadhesive drug delivery system offered relatively quick absorption (Tmax ~ 45 min) with steady state plasma drug concentration that lasted more than 8 h. Continuous release of the drug could be possible because carboxylic group of polymers strongly adhered to the epithelial mucosa. The physical interaction of mucoadhesion may be due to hydrogen bonding at acidic pH. Nasal mucoadhesive vaccine loaded microparticles induced both systemic as well as mucosal immunity. Vila and coworkers studied the nasal immunization of tetanus toxoid by encapsulating and administration in the form of PEG coated polyacetic acid mucoadhesive nanospheres. The results indicated high level of tetanus toxoid in the blood as compared to non bioadhesive nasal drug delivery system. The protein and peptide molecules bioavailability is rate limited by short nasal residential time of the formulation in nasal cavity, which impaired the uptake of the macromolecules from nasal epithelial cells. Insulin is one of the most widely studied proteins with respect to nasal delivery using mucoadhesive dosage forms.The strategies adopted to improve the nasal bioavailability of insulin are mucoadhesive micropartcles and nanoparticles, mucoadhesive gels and powders. Mucoadhesive polymers also act as permeation enhancer by opening the TJs of the nasal epithelium and hence it improves the bioavailability. New generation mucoadhesive polymers such as chitosan derivatives and polycarbophil derivatives are in developmental stage. If these polymers get regulatory approval, we can expect few nasal mucoadhesive drug delivery systems in market.

Table 1. List of prescription nasal product currently on the market

No.	Product	Drug	Indication	Manufacturer
1	BeconaseÒ AQ Nasal Spray	Beclomethasone dipropionate monohydrate	Symptomatic treatment of seasonal and perennial allergic rhinitis	Allen and Hanbury's/ Glaxo Wellcome Inc.
2	VancenaseÒ AQ Nasal Spray	Beclomethasone dipropionate monohydrate	Symptomatic treatment of seasonal or perennial allergic rhinitis	Schering Plough Corp
3	RhinocortÒ Nasal Inhaler	Budesonide	Management of symptoms of seasonal and perennial allergic rhinitis and non-allergic perennial rhinitis	Astra USA, Inc.
4	Stadol NSÒ Nasal Spray	Butorphanol tartrate	Management of pain including migraine headache pain	Bristol Myers Squibb
5	MiacalcinÒ Nasal Spray	Calcitonin—salmon	Post-menopausal osteoporosis	Sandoz PharmaceuticalCorp.
6	NasalcromÒ Nasal Solution	Cromolyn sodium	Symptomatic prevention and treatment of seasonal or perennial.	Fisons Corp. Prescription
7	DDAVPÒ Nasal Spray	Nasalide Ò NasalSolution	Prevention and control of polydipsia, polyurea, and dehydration in patients with diabetes insipidus	Rhone Poulenc mRorer
8	StimateÒ Nasal Spray	Desmopressin Acetate	Hemophilia A, von Willebrand's disease (type 1)	Rhone Poulenc Rorer
9	DecadronÒ Phosphate TurbinaireÒ	Dexamethasone	Treatment of inflammatory nasal conditions or nasal polyps	Merck and Co., Inc.
10	NasalideÒ Nasal Solution	Flunisolide	Symptomatic prevention and treatment of seasonal or perennial rhinitis	Roche Laboratories
11	FlonaseÒ Nasal Spray	Fluticasone propionate	Management of seasonal and perennial rhinitis	Allen and Hanbury's/ Glaxo Wellcome Inc.
12	Synarel Ò Nasal Solution	Nafarelin ace	Central precocious puberty; endometriosis	Roche Laboratories
13	Syntocinon Ò Nasal Spray	Oxytocin	Promote milk ejection in breast feeding mothers	Sandoz Pharmaceutical Corp.
14	Nasacort Ò Nasal Inhaler	Triamcinolon Acetonide	Treatment of seasonal and perennial allergic rhinitis	Rhone Poulenc Rorer

Particulate drug delivery system

The classical approach to improve the bioavailability of nasal formulations is particulate systems such as microspheres, nanoparticles, and liposomes. The microspheres used in nasal drug delivery are water insoluble but absorb water into the sphere matrix, resulting in swelling of sphere and the formation of gel. The gel formation improves the nasal residential time and hence it improves the bioavailability. Another mechanism stated for improving nasal bioavailability is improving the nasal permeation by opening of the tight junctions of the nasal epithelium. A wide variety of materials were investigated to construct the microspheres including starch, dextran, albumin, hyaluronic acid, carbopol, chitosan, etc. Dextran microspheres have been used as a delivery system of nicotine, insulin, and octreotide. Illum Mand coworkers introduced well characterized bioadhesive dextran microspheres for prolonging residence time in the nasal cavity. The slowest clearance was detected for DEAE-dextran, where 60% delivery dose was present at the deposition site after 3 h. However, the microspheres did not successfully improve the bioavailability of insulin. In later study, the same insulin dose administered with dextran microsphere of particle size less than 45 μm, which showed 52% decrease in plasma glucose in rats. Degradable starch microspheres (DSM) are the most frequently used nasal drug delivery systems for absorption of insulin, gentamicin, human growth hormone metclopromide, cynacobalamin, and desmopressin. The safety and efficacy of nasal microspheres have been demonstrated by many researchers. Insulin loaded DSM resulted in a rapid dose dependent decrease in blood glucose. The histopathological studies in rabbit have demonstrated that DSM does not induce a series of morphological change in nasal mucosa. Moreover, the DSM was well tolerated by human volunteers with absence of nasal irritation and did not cause significant changes in nasal mucociliary clearance. DSM was used as a carrier for delivery of human growth hormone. DSM loaded human growth hormone was prepared with and without permeation enhancer. The relative bioavailability of human growth hormone in sheep model is 3%, whereas it increased to 14% with permeation enhancer (lysophophatidylcholine) incorporated microsphere.

Chitosan loaded microspheres are extensively used as drug delivery vehicle for nasal drug administration. Chitosan microspheres were fabricated to improve the bioavailability and achieve the prolonged release profile of gentamicin. Chitosan microspheres showed better adhesion to nasal mucosa because of its cationic nature and opening of the TJ, hence it showed prolong release profile and improved bioavailability, respectively. Hydroxypropyl methylcellulose, gelatin, polyacrylic acids, polycarbophils, carbopol, gelatin, and albumin are the polymers widely used to formulate the microspheres for nasal drug delivery. Liposomes have been delivered by nasal route; the amphiphilic nature of liposome is well characterized for favorable permeation of drugs through biological membranes. The permeability of liposome entrapping insulin through nasal mucosa of rabbits has been studied with and without incorporating sodium glychoate as a permeation enhancer. The comparative pharmacokinetics in rats showed high permeability of liposome pretreated with permeation enhancer than solution containing the same quantity of permeation enhancer. The loading and leakage character of desmopressin loaded liposome and the effect of liposome on permeability of desmopressin on nasal mucosa was studied. High permeability of liposome was achieved than solution dosage form. In liposome formulation, cationic liposomes are prone for higher permeability than negatively charged liposomes.

Advantages with nasal systemic drug delivery. 126-128

The nasal cavity is covered by a thin mucosa which is well vascularised. Therefore, a drug molecule can be transferred quickly across the single epithelial cell layer directly to the systemic blood circulation without first-pass hepatic and intestinal metabolism. The effect is often reached within 5 min for smaller drug molecule. Nasal administration can therefore be used as an alternative to oral administration of for example tablets and capsules if a fast effect is desired or if the drug is extensively degraded in the gut or liver. Drugs which are poorly absorbed orally can also be given by this route.

Limitations with nasal systemic drug delivery

Nasal administration is primarily suitable for potent drugs since only a limited volume can be sprayed into the nasal cavity. Drugs for continuous and frequent administration may be less suitable because of the risk of harmful long-term effects on the nasal epithelium. Nasal administration has also been associated with a high variability in the amount of drug absorbed. Upper airway infections may increase the variability as may the extent of sensory irritation of the nasal mucosa, differences in the amount of liquid spray that is swallowed and not kept in the nasal cavity and differences in the spray actuation process. However, the variability in the amount absorbed after nasal administration should be comparable to that after oral administration [129-135].

CONCLUSION

After collecting and studying about the nasal physiology mechanism and the importance of nasal physiology in drug delivery system it is concluded that this route may be a better route of drug administration.

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