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Intranasal Drug Delivery System

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ABSTRACT
Delivery of drugs through nasal route has been potentially explored as an alternative route for administration of vaccines and biomolecules such as proteins, peptides and non-peptide drugs, hence it has attracted the interest of scientific community. Intranasal therapy has been accepted form of treatment in the Ayurveda system of medicines. Nasal route is beneficial for the drugs which are unstable on oral administration because they are significantly degraded in GIT or metabolized by first pass effect in liver. Nasal route is alternative to parenteral therapy and also useful for long term therapy. Nasal mucosa is highly vascularized and most permeable giving rapid absorption and onset of action. Nasal route is non-invasive, widely used for the local treatment may also be used for systemic therapy as drug directly goes in systemic circulation. Nasal route gives good absorption of small molecules, then that of large molecules can be increased by absorption promoters. In this article an overview of intranasal drug delivery with its various aspects like factors affecting nasal absorption, strategies to improve bioavailability are discussed.

Keywords: Intranasal drug delivery, Bioavailability, Permeation enhancers.

INTRODUCTION

Oral route is the desirable and convenient method of drug administration as their ease of manufacture and administration. Failure of adequate absorption through the gastrointestinal tract led to research on alternate routes of drug delivery. [1]

Therapy through intranasal administration has been accepted form of treatment in the Ayurvedic system of Indian Medicine. In recent years many drugs have been shown to achieve better systemic bioavailability through nasal route by oral administration. [2]

In nasal mucosa high permeability, high vascularity and low enzymatic environment of nasal cavity are well suitable for systemic delivery of drug molecules. The non-invasiveness and self-administrative nature of nasal also attract the formulation scientist to deliver protein and peptides compounds

NASAL ANATOMY AND PHYSIOLOGY

In studying drug absorption from the nasal mucous membrane, it is necessary to have a clear understanding of anatomy and Physiology of the nose and how it relates to the characteristics of the delivery system used. The nasal passage which runs from the nasal vestibule to the nasopharynx has a depth of approximately 12-14 cm. In this passage the nasal cellular apparatus is in close contact with mucus which protects the mucosa from the inspired air. [1] There are three separate functional zones in the nasal cavities, vestibular, respiratory and olfactory region.[2]

The human nasal cavity has a total volume of about 16-19ml and total surface area of about 180cm2. It is divided into two nasal cavities via the septum. Some of the regions are described as follows.

1) The Respiratory Region [2] The respiratory region is the largest having the highest degree of vascularity and is mainly responsible for systemic drug absorption.

2) The Vestibular Region [2] It is located at the opening of nasal passage and is responsible for filtering out the air borne particles. It is considered to be the least important of the three regions with regards to drug absorption.

3) The Olfactory Region It is of about 10cm2 in surface area and it plays a vital role in transportation of drugs to the brain and the CSF. Human olfactory region comprises if thick connective tissue lamina propria, upon which rests the olfactory epithelium. Lamina propria has axons, Bowen's bundle and blood vessels whereas epithelium consist of three different cells i.e., basal cells, supporting cells and olfactory receptor cells etc. Neurons are interspersed between supporting cells. The olfactory receptor cells are bipolar neurons with a single dendrite and extending from

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the cell body to the free apical surface where it ends in an olfactory knob carrying non-motile cilia, which extend above the epithelium.[2] The epithelium of the nasal passage is covered by a mucus layer, which entraps particles. The mucus layer is cleared from the nasal cavity by cilia and is renewed every 10-15 minutes the pH of the mucosal secretions ranges from 5.5-6.5 in adults. Numerous enzymes for instance, Cytochrome P-450, Carboxyl esterase and Glutathione S-transferees are present in nasal cavity.

ADVANTAGES OF NASAL DRUG DELIVERY SYSTEM [4,9,10,11,]

- Rapid absorption, higher bioavailability therefore lower dose.
- Fast onset of therapeutic action.
- Avoidance of liver first pass effect.
- Avoidance of metabolism by gastrointestinal tract.
- Reduction risk of overdose.
- Non-invasive therefore reduced risk of infectious disease transmission.
- Improved patient compliances
- Absorption of drug is rapid via highly vascularized mucosa.
- Availability of large nasal mucosal surface area for dose absorption.
- Onset of action is rapid.
- Noninvasive and easy for administration.
- Bypass the BBB.
- Degradation of drug observed in GIT is avoided.
- Hepatic first pass metabolism is absent.
- Nasal bioavailability of small drug molecules is good.
- Bioavailability of large drug molecules can be increased by means of absorption enhancers.
- Unsuitable drug candidates for oral route can be successfully given via nasal route.
- Alternate to parenteral route especially for proteins and peptides.
- Convenient route for the patient on long term therapy.
- Improved bioavailability.
- Side effects are reduced due to low dose.
- Patient convenience and compliance is improved.
- A self-administration is possible.
- Direct transport into systemic circulation and CNS is Possible.
- Offers lower risk of overdose
- Does not have any complex formulation requirement

LIMITATIONS OF NASAL DRUG DELIVERY SYSTEM [1,13]

1. There is a risk of local side effects and irreversible damage of the cilia of nasal mucosa, both from substances and from constituents added to the dosage form.
2. Certain surfactants used as chemical enhancer may disrupt and even dissolve membrane in high concentration.
3. There could be a mechanical loss of the dosage form into the other parts of the respiratory tract like lungs because of the improper technique of administration.
4. Delivery volume in nasal cavity is restricted to 25–200 µL.
5. High molecular weight compounds cannot be delivered through this route (mass cut off ~1 kDa).
6. Adversely affected by pathological conditions.
7. Large interspecies variability is observed in this route.
8. Normal defense mechanisms like mucociliary Clearance and ciliary beating affects the permeability of drug.
9. Irritation of nasal mucosa by drugs like Budesonide, Azilactine.
10. Limited understanding of mechanisms and less developed models at this stage.
11. Systemic toxicity occurring due to absorption enhancers is yet not established.
12. Smaller absorption surface compared with GIT.
13. Possibility of nasal irritation hence inconvenient compared with oral route.
14. Enzymatic barrier to permeability of drug.

1. PROFILE OF AN 'IDEAL' DRUG CANDIDATE FOR NASAL DELIVERY [16]

An ideal nasal drug candidate should possess the following attributes:

- Appropriate aqueous solubility to provide the desired dose in a 25–150 ml volume of formulation administration per nostril.
- Appropriate nasal absorption properties.
- No nasal irritation from the drug.
- A suitable clinical rationale for nasal dosage forms, e.g. rapid onset of action.
- Low dose. Generally, below 25 mg per dose.
- No toxic nasal metabolites. • No offensive odors/aroma associated with the drug.
- Suitable stability characteristics.

MECHANISM OF NASAL ABSORPTION [14]

The initial step in the absorption of drug from the nasal cavity is passage through the mucus; large or charged particles may find it more difficult to cross. But small unchanged particles easily pass

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through this layer, the mechanisms for absorption through the nasal mucosa. These include paracellular transport via movement between cell and transcytosis by vesicle carriers, trans cellular or simple diffusion across the membrane. [14]

1. The first mechanism includes aqueous route of transport, which is also called as the paracellular route. This is slow and passive route, inverse log-log relationship between intranasal absorption and the molecular weight of water-soluble compounds. Poor bioavailability was observed for drugs with a molecular weight greater than 1000 Daltons.[1]

2. The second mechanism is transporting a lipoidal route is known as transcellular process and is responsible for the transport of lipophilic drugs that show a rate dependency on their lipophilicity. Drugs also cross membrane by an active transport route via carrier mediated means or transport through the opening of junctions. For example, Chitosan, a natural biopolymer opens tight junctions between epithelial cells to facilitate drug transport. [1, 14]

DIFFERENT FACTORS AFFECTING NASAL DRUG ABSORPTION [4, 14,]

Various factors affect bioavailability of nasally administered drugs as follows;

I Biological Factors [4]
• Structural features
• Biochemical changes

II Physiological factors
• Blood supply and neuronal regulation
• Nasal secretions
• Mucociliary clearance and ciliary beat frequency
• Pathological conditions
• Environmental conditions.
• Membrane permeability.

III Physicochemical Properties of Drugs [4]
• Molecular weight
• Size
• Solubility
• Lipophilicity
• pka and Partition coefficient
• Chemical form of drug.
• Polymorphism.
• Chemical state.
• Physical state.

IV Physicochemical Properties of Formulation
• Physical form of formulation
• pH
• Osmolarity
• Volume of solution applied and drug concentration
• Viscosity.

I Biological factors

1] Structural features There are five different sections of nasal cavity: nasal vestibule, atrium, respiratory area, olfactory region and the nasopharnyx. These structures and the type of cells, density and number of cells present in that region influence the permeability. Absorption enhancers used in combination with drugs increase the permeation of compounds. [15]

2] Biochemical changes Enzymatic barrier to the delivery of drugs is nasal mucosa because of the presence of a large number of enzymes, which include oxidative and conjugative enzymes, peptidases and proteases. These enzymes are responsible for the degradation of drugs in the nasal mucosa and result in creation of a pseudo-first-pass effect. Metabolism of nasal decongestants, alcohols, nicotine and cocaine IS due to p450 dependent monoxygenase system. Protease and peptidase were responsible for the pre systemic degradation and subsequent lower permeation of various peptide drugs, such as calcitonin, insulin, LHRH and desmopressin.. To overcome these degradations various approaches have been used. These include the use of protease and peptidase inhibitors such as bacitracin, amastatin, boroleucin and puromycin [16].

II Physiological factors

Blood supply and neuronal regulation

Nasal mucosa is highly permeable site. High blood supply due to parasympathetic stimulation gives congestion and low blood supply due to sympathetic stimulation gives relaxation, regulate the rise and fall in the amounts of drug permeated, respectively [17]. Based on the above observations, we can conclude that the increased permeability of a compound is due to parasympathetic stimulation.

Nasal secretions

Nasal secretions are produced by anterior serous and seromucus glands. Mucus production is approximately 1.5–2 l ml daily. The permeability of drug through the nasal mucosa is affected by:

• Viscosity of nasal secretion

The viscous surface layer will inhibit the ciliary beating if the sol layer of mucus is too thin and mucociliary clearance is impaired if sol layer is too thick, because contact with cilia is lost. Permeation of the drug is affected due to impairment of mucociliary clearence by altering the time of contact of drug and mucosa.

• Solubility of drug in nasal secretions For permeation of drug solublisation is necessary. A drug needs to have appropriate physicochemical characteristics for dissolution in nasal secretions.

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• Diurnal variation Nasal secretions are also affected by circadian rhythm. Permeation of drug is altered at night due to secretions and clearance rates are reduced. Chronokinetics dictate the pattern and rate of permeation in such cases.

• pH of nasal cavity variation in pH is observed between 5.5–6.5 in adults and 5.0–7.0 in infants. Permeation of drug is greater if the nasal pH is lower than pKa of drug because under such conditions the penetrant molecules exist as unionized species. Increase or decrease in the permeation of drug is observed because ionization is affected by change in pH of mucus, depending on the nature of the drug. pH of formulation should be between 4.5 to 6.5 for better absorption and should also have good buffering capacity[18].

Mucociliary clearance (MCC) and ciliary beating Whenever a substance is nasally administered, it is cleared from the nasal cavity in ~21 min by MCC because mucociliary clearance is the normal defense mechanism of the nasal cavity which clears substances adhering to nasal mucosa and cleared in GIT by draining into nasopharynx. Drug permeation is enhanced by increasing contact time between drug and mucus membrane because reduced MMC; whereas, increased MCC decreases drug permeation.

Pathological conditions: Mucociliary disfunctioning, hypo or hypersecretions, irritation of the nasal mucosa occurs due to diseases such as the common cold, rhinitis, atrophic rhinitis and nasal polyposis, and drug permeation is affected by this.

Environmental conditions: Moderate reduction in the rate of MCC occurs at the temperature of 24oC, it has been predicted that a linear increase in ciliary beat frequency occurs with increase in temperature.

Membrane permeability: Absorption of the drug through the nasal route is affected by membrane permeability which is most important factor. The large molecular weight drugs and water soluble drugs like peptides and proteins have low membrane permeability hence absorbed through endocytic transport in fewer amounts [19].

III Physicochemical properties of drug:

Molecular weight and size: Drug permeation is determined by molecular weight, molecular size, hydrophilicity and lipophilicity of the compound. For compounds 1 kDa, bioavailability can be directly predicted from knowledge of MW. In general, the bioavailability of these large molecules ranges from 0.5% to 5%. Physicochemical properties of the drug don't significantly affect permeation of drug LT 300 Da, which will mostly permeate through aqueous channels of the membrane. By contrast, for compounds with MW 300 Da rate of permeation is highly sensitive.

Solubility: Major factor in determining absorption of drug through biological membranes is drug solubility. As nasal secretions are more watery in nature, a drug should have appropriate aqueous solubility for increased dissolution. Lipophilic drugs have less solubility in the aqueous secretions. Water soluble drugs are absorbed by passive diffusion and lipophilic drugs via active transport depending on their solubility. [20]

Lipophilicity: The permeation of the compound normally increases through nasal mucosa with increase in lipophilicity. It appears that nasal mucosa is primarily lipophilic in nature and the lipid domain plays an important role in the barrier function of these membranes although they have some hydrophilic characteristics. Systemic bioavailability of many drugs is decreased due to excess hydrophilicity in such cases prodrug approach is beneficial.

pKa and partition coefficient: As per the pH partition theory, unionized species are absorbed better compared with ionized species and the same fact is true in the case of nasal absorption. There is constant relationship between pKa and nasal absorption of these drugs. With an increase in lipophilicity or the partition coefficient of the drugs its concentration in biological tissues increases. The absorption rate of aminopyrine increased with the increase in pH and was found to fit well to the theoretical profile Major factor governing nasal absorption is partition coefficient[21].

Polymorphism: Polymorphism is the important parameter in the nasal drug product development which is administered in particulate form. Polymorphism is known to affect dissolution of drugs and their absorption through biological membranes is affected by polymorphism. This factor should be carefully considered in the dosage form development for the nasal delivery. [12]

Chemical state of drug:

Absorption of the drug is determined by the chemical form of the drug in which it is presented to nasal mucosa. Chemically alter a drug molecule by adding a bio-cleavable lipophilic moiety is the alternative for improving absorption of the drug which is not having desired absorption properties. The prodrug approach provides many additional challenges which need to be overcome in the drug product developmental process. The toxicity of the prodrug itself needs to be fully evaluated [16].

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Physical state of drug: Particle size and morphology of drug are two main important properties for particulate nasal drug products. These both parameters should be controlled to obtain suitable drug dissolution properties in the nostrils. Too fine particles below 5 microns should be avoided because it may get inhaled in lungs. Generally, particles in the 5–10 micron range are deposited in the nostrils. [16].

VI Physicochemical properties of formulation:
Physical form of formulation:
Physical form of the formulation is very important in nasal drug absorption. Liquid formulations are less effective than powder form in delivering insulin in rabbits. Less efficient systemic nasal drug delivery observed with more viscous formulation. Scientist found that somewhat more sustained effects of desmopressin are observed with addition of viscous agent but total bioavailability is not enhanced. Viscous formulations may help in minimizing nasal drip.
pH: extent of drug ionization IS determined by pH partition hypothesis hence it is related to formulation pH. Nasal formulation should be adjusted to appropriate pH to avoid irritation, to obtain efficient absorption and to prevent growth of pathogenic bacteria. Ideal formulation pH should be adjusted between 4.5 and 6.5. pH of the nasal surface is 7.39 and the pH of nasal secretions is 5.5–6.5 in adults and 5.0–6.7 in infants and children
Osmolarity: Formulation tonicity substantially affect the nasal mucosa generally, an isotonic formulation is preferred. Some scientist studied the effects of formulation osmolarity, on the nasal absorption of secretin in rats. They found that all cells of the nasal mucosa were affected by the concentration of sodium chloride in the formulation and-the absorption reached a maximum at a 0.462 M sodium chloride concentration. At this concentration shrinkage of epithelial cells was observed. Hence tonicity is also having impact on drug absorption. [22]
Volume of solution applied and drug concentration: There is no constant relationship between volume of administration and extent of absorption. Clement studied the effect of three nasal spray concentrations of cetrizine on the clinical efficacy. The results showed that 16.7%, 30.8%, 42.9%, and 26.7% of days the patients experienced appeared to improve with the drug concentration up to only 0.125%. At the higher concentration, 0.250%, the efficacy declined. [23]
Viscosity: contact time between the drug and the nasal mucosa is increased by higher viscosity of formulation thereby increasing the time for permeation.
Strategies to improve nasal absorption [24]
There are many barriers present in nasal cavity which interfere with absorption of various drugs. There are some methods which have been successfully used for the improvement of nasal drug absorption.
• Nasal enzymes inhibitors: Various kinds of enzyme inhibitors are utilized to minimize metabolism of drug in nasal cavity which minimize activity of enzymes present in nasal cavity includes protease and peptidase, used as inhibitors for the formulation of peptide and protein molecule.
• Structural modification: Modification of drug structure can be done without changing the pharmacological activity for improvement of nasal absorption.
• Permeation enhancer: Permeation enhancers are of different categories and have been investigated to improve the nasal absorption like surfactants, fatty acids, phospholipids, cyclodextrins, bile salts, etc.
• Particulate drug delivery: Carriers are used for the encapsulation of drug which prevent exposure of a drug to nasal environment and improve the retention capacity in nasal cavity. Some examples of carriers may include microspheres, liposomes, nanoparticles and niosomes.
• Prodrug approach: Inactive chemical moiety is called prodrug which becomes active at the target site. Prodrugs are mainly used to improve taste, odor, solubility and stability.
• Bio adhesive polymer: To improve the nasal residence and absorption of the drug bio adhesive polymers are used. They improve the retention time of the drug inside the nasal cavity is increased by making an adhesive force between formulation and nasal mucosa, which leads to minimization of mucociliary clearance of formulation.
• In situ gel: These are the formulations which get converted into gel upon instillation into nasal cavity by the influence of stimuli includes temperature, pH and ionic concentration. Consistency of the gel is thick which makes the formulation difficult to drain by the influence of ciliate movement.

EXCIPIENTS USED IN NASAL FORMULATIONS [14]

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There are various types of excipients used in nasal formulations. Commonly used and frequently added excipients are as follows:

Bio adhesive polymers Compound that is capable of interacting with biological material through interfacial forces and being retained on such material for prolonged periods of time is called as bioadhesive polymer. They are also called as mucoadhesive if biological material is mucus membrane,on molecular level, process of mucoadhesion can be explained on the basis of attractive molecular interactions involving forces such as Van Der Waals, electrostatic interactions, hydrogen bonding, and hydrophobic interactions. The bioadhesive force of a polymer material is dependent on the nature of the polymer, the surrounding medium (pH), swelling and physiological factors (mucin turnover, disease state).

Table 1: Bioadhesive polymers used in nasal drug delivery

Polymer	Characteristics
Cellulose derivatives Soluble: hydroxypropyl methylcellulose, hydroxypropyl cellulose(HPC),methyl cellulose(MC), carboxymethyl cellulose(CMC) Insoluble: ethylcellulose, microcrystalline cellulose(MCC)	-Prolong the residence time of drug in nasal cavity -Sustain the release of drug due to high viscosity -Act as absorption enhancer - Effectively increase intranasal bioavailability
Polyacrylates -Carbomers -Polycarbophils	-Excellent mucoadhesive and gel forming capability -Capable of attaching to mucosal surfaces hence ensure intimate contact between the formulation and membrane surface
Starch -Maize starch -Degradable starch microspheres (DSM)	
-Effectively improve absorption of both small hydrophobic and hydrophilic macromolecular drugs -Mostly used in mucoadhesive microparticulate nasal delivery system	

Gelling agent According to a study by Pennington et al. increasing solution viscosity may provide a means of prolonging the therapeutic effect of nasal preparations. Suzuki et al. showed that a drug carrier such as hydroxypropyl cellulose was effective for improving the absorption of low molecular weight drugs but not for high molecular weight peptides.From a safety (nasal irritancy) point of view use of a combination of carriers is often recommended.[19]

Penetration enhancer Chemical penetration enhancers are widely used in the nasal drug delivery. Classification of chemical penetration enhancer includes, following 1) Solvents2) Alkyl methyl sulphoxides 3) Pyrrolidones 4) 1- Dodecyl azacycloheptan-2-one 5) Surfactants.

Buffers Nasal formulations are generally administered in small volumes ranging from 25 to 200 µL with 100 µL being the most common dose volume. Hence, nasal secretions may alter the pH of the administrated dose which can affect the concentration of un-ionized drug available for absorption. Therefore, an adequate formulation buffer capacity may be required to maintain the pH in-situ.

Solubilizers Aqueous solubility of drug is always a limitation for nasal drug delivery in solution. Conventional solvents or co-solvents such as glycols, small quantities of alcohol, Transcutol

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(diethylene glycol monoethyl ether), medium chain glycerides and Labrasol (saturated polyglycolyzed C8- C10 glyceride) can be used to enhance the solubility of drugs. Other compounds can be used like, the use of surfactants or cyclodextrins such as HP–ß-Cyclodextrin that serve as a biocompatible solubilizer and stabilizer in combination with lipophilic absorption enhancers. In these cases, their impact on nasal irritancy should be considered.

Preservatives Most nasal formulations are aqueous based so needs preservatives to prevent microbial growth. Parabens, phenyl ethyl alcohol, benzalkonium chloride, EDTA and benzoyl alcohol are some of the commonly used preservatives in nasal formulations.

Antioxidants A small quantity of antioxidants may be required to prevent drug oxidation. Commonly used antioxidants are sodium bisulfite, butylated hydroxytoluene, sodium metabisulfite and tocopherol. Usually, antioxidants do not affect drug absorption or cause nasal irritation. Chemical/physical interaction of antioxidants and preservatives with drugs, excipients, manufacturing equipment and packaging components should be considered as part of the formulation development program.

Humectants Because of allergic and chronic diseases there can be crusts and drying of mucous membrane. Certain preservatives/ antioxidants are also likely to cause nasal irritation especially when used in higher quantities. Adequate intranasal moisture is essential for preventing dehydration. Therefore, humectants can be added especially in gel-based nasal products. Humectants avoid nasal irritation and do not affect drug absorption. Common examples include glycerin, sorbitol and mannitol.

Surfactants Surfactant incorporation into nasal dosage forms can modify the permeability of nasal membranes, which may facilitate the nasal absorption of drug.

FORMULATIONS BASED ON NASAL DELIVERY SYSTEM [19, 25]

Liquid dosage forms

• Nasal drops Nasal drops are one of the most simple and convenient delivery systems among all formulations. The main disadvantage of this system is the lack of dose precision.

• Nasal sprays Both solution and suspension formulations can be formulated into nasal sprays. Due to the availability of metered dose pumps and actuators, a nasal spray can deliver an exact dose anywhere from 25 -200 µL.

• Nasal emulsions, micro emulsions Intranasal emulsions have not been studied as extensively as other liquid nasal delivery systems. Nasal emulsions offer the advantages for local application mainly due to the viscosity.

Semi-solid dosage forms Semi-solid systems, for example gels, ointments and liquid systems containing polymers that gel at particular pH changes are usually employed for designing the nasal drug delivery systems.

• Nasal gels Nasal gels are thickened solutions or suspensions, of high-viscosity. The advantages of a nasal gel include the reduction of post-nasal dripping due to its high viscosity, reduction of the taste impact due to reduced swallowing, reduction of anterior leakage of the formulation. Solid dosage forms Solid dosage forms are also becoming popular for intranasal drug delivery, although these formulations are more suitable for pulmonary drug delivery and similar applications, since it can cover the vasculature within the epithelium of nasal mucosa.

• Nasal powders Powder dosage forms may be developed if solution and suspension dosage forms cannot be developed, mainly due to lack of drug stability. The advantages of a nasal powder dosage form are the absence of preservative and superior stability of the drug in the formulation. However, the suitability of the powder formulation is dependent on the solubility, particle size, aerodynamic properties and nasal irritancy of the active drug and/or excipients.

Novel drug formulations Several claims have been made in favour of developing nasal formulations containing liposomes, microspheres and nanoparticles for intranasal drug delivery. These systems can include, besides the drug, enzymatic inhibitors, nasal absorption enhancers or/and mucoadhesive polymers in order to improve the stability, membrane penetration and retention time in nasal cavity.

• Liposomes Liposomes are phospholipids vesicles composed by lipid bilayers enclosing one or more aqueous compartments and wherein drugs and other substances can be included. Liposomal drug delivery systems present various advantages such as the effective encapsulation of small and large molecules with a wide range of hydrophilicity and pKavalues . In fact, they have been found to enhance nasal absorption of peptides such as insulin and calcitonin by increasing their membrane penetration. This has been attributed to

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the increasing nasal retention of peptides. Protection of the entrapped peptides from enzymatic degradation and mucosal membrane disruption.

• Microspheres Microsphere technology has been widely applied in designing formulations for nasal drug delivery. Microspheres are usually based on mucoadhesive polymers (chitosan, alginate), which present advantages for intranasal drug delivery. Furthermore, microspheres may also protect the drug from enzymatic metabolism and sustain drug release, prolonging its effect.

• Nanoparticles Nanoparticles are solid colloidal particles with diameters raging from 1-1000 nm. They consist of macromolecular materials and can be therapeutically used as adjuvant in vaccines or as drug carriers, in which the active substance is dissolved, entrapped, encapsulated, adsorbed or chemically attached. Nanoparticles may offer several advantages due to their small size, but only the smallest nanoparticles penetrate the mucosal membrane by paracellular route and in a limited quantity because the tight junctions are in the order of 3.9-8.4 Å.

EVALUATION OF NASAL DRUG FORMULATIONS [19, 26]

In vitro nasal permeation studies Various approaches used to determine the drug diffusion through nasal mucosa from the formulation. There are two different methods to study diffusion profile of drugs,

(A) In vitro diffusion studies

The nasal diffusion cell is fabricated in glass. The water-jacketed recipient chamber having total 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 donor chamber is 10 cm long with internal diameter of 1.13 cm, and a donor tube chamber has total capacity of 60 ml and a flanged top of about 3mm; the lid has 3 openings, each for sampling, thermometer. The nasal mucosa of sheep was separated from sub layer bony tissues and stoned in distilled water containing few drops at gentamycin injection. After the complete removal of blood from mucosal surface, it is attached to donor chamber tube. The donor chamber tube is placed such a way that it just touches the diffusion medium in recipient chamber. Samples (0.5 ml) from recipient chamber are with draw at predetermined intervals, and transferred to amber colored ampoules. The samples withdrawn are suitably replaced. The samples are estimated for drug content by suitable analytical technique. The temperature is maintained at 37oC throughout the experiment.

(B) In Vivo Nasal Absorption studies

Animal models for nasal absorption studies the animal models employed for nasal absorption studies can be of two types, viz., whole animal or in vivo model and an isolated organ perfusion or ex vivo model. These models are discussed in detail below:

Rat model the surgical preparation of rat for in vivo nasal absorption study is carried out as follows: The rat is anaesthetized by intraperitoneal injection of sodium pentobarbital. An incision is made in the neck and the trachea is cannulated with a polyethylene tube. Another tube is inserted through the esophagus towards the posterior region of the nasal cavity. The passage of the nasopalatine tract is sealed so that the drug solution is not drained from the nasal cavity through the mouth. The drug solution is delivered to the nasal cavity through the nostril or through the cannulation tubing. Femoral vein is used to collect the blood samples. As all the probable outlets of drainage are blocked, the drug can be only absorbed and transported into the systemic circulation by penetration and/or diffusion through nasal mucosa.

Rabbit model the rabbit offers several advantages as an animal model for nasal absorption studies: 1. It permits pharmacokinetic studies as with large animals (like monkey) 2. It is relatively cheap, readily available and easily maintained in laboratory settings 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 pharmacokinetic profile of a drug. Rabbits (approx. 3 kg) are either anaesthetized or maintained in the conscious state depending on the purpose of study. In the anaesthetized model, intramuscular injection of a combination of ketamine and xylazine is given to anesthetized rabbit. The rabbit's head is held in an upright position and nasal spray of drug solution is administered into each nostril. The body temperature of the rabbit is maintained at 37°C during experiment with the help of a heating pad. The blood samples are collected by an indwelling catheter in the marginal ear vein or artery.

Ex vivo Nasal Perfusion Models Surgical preparation is the same as that is for in vivo rat model. During the perfusion studies, to minimize the loss of drug solution a funnel is placed between

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the nose and reservoir. 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. Rabbit can also be used as the animal model for ex vivo nasal perfusion studies. The rabbit is anaesthetized with parenteral uretliane-acepromazine. A midline 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. To avoid drainage of drug solution from the nasal cavity the nasopalatine tract (that connects nasal cavity to the mouth) is closed with an adhesive. The drug in isotonic buffer solution is recirculated using a peristaltic pump.

In-vivo bioavailability studies In-vivo bioavailability study is conducted on healthy male rabbits. Study consists of three groups each containing six rabbits and fasted for 24 h. One group treated with conventional preparation, second group kept as control (i.e. not received any test substances) and third group of test formulation. Water is given ad libitum during fasting and throughout the experiment. For the collection of blood samples the marginal ear vein of the rabbits used and sample of about 2 ml collected in heparinized centrifuge tubes at 0.5, 1, 2, 3, 4, 5, 6, 7 and 8 h after the drug administration. The blood samples are centrifuged at 3000 × g for 15 min to obtain the plasma and stored at -20°C until analysis. The extraction of drug from plasma can be carried out as reported previously and then analyze using the HPLC system.

PHARMACOKINETIC ANALYSIS

Pharmacokinetic parameters are derived from the plasma concentration vs. time plot. The area under the curve (AUC), the peak plasma concentration (Cmax) and the time to attain peak concentration (Tmax) can be obtained from these plots. The elimination rate constant (Kel) is determined from the semilogarithmic plot of plasma concentration vs. time. Elimination half-life (t1/2) can be calculated using the formula; t1/2 = 0.693/Kel.

Marketed Preparation [2, 27]

Table 2: Nasal drug products (proteins and peptides) for systemic drug delivery in the market

Drug Substance (Product name)	Indication	Dosage form	Status	Manufacturer
Salmon calcitonin (Karil 200 I.E.)	Osteoporosis	Solution (spray)	Marketed	Novartis Pharma
Desmopressin (MinirinNasenspray)	Antidiuretic hormone	Solution (spray)	Marketed	Ferring Arzneimitted
Buserelin (Profact nasal)	Buserelin	Solution (spray)	Marketed	Aventis Pharma
Nafarelin (Synarela)	Endometriosis	Solution (spray)	Marketed	Pharmacia
Oxytocin (Syntocinon)	Lactation induction	Solution (spray)	Marketed	Novartis Pharma
Protirelin (antepan* nasal) (Relefact* TRH nasal)	Thyroid diagnostics	Solution (spray)	Marketed	Aventis Pharma

Table 3: Nasal Drug Products (Non Peptide) For Systemic Drug Delivery in the Market

Drug Substance (Product name)	Indication	Dosage form	Status	Manufacturer
Zolmitriptan (AscoTop* Nasal)	Migraine	Solution (spray)	Marketed	Astra Zeneca
Sumatriptan Imigran* Nasal	Migraine	Solution (spray)	Marketed	Glaxo SmithKline
Dihyfroergotamin (Migranal* Nasal	Migraine	Solution (spray)	Marketed	Novartis Pharma

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Spray)				
Estradiol (Aerodiol*)	Hormone replacement	Solution (spray)	Marketed	Servier

APPROPRIATE DRUG CANDIDATE FOR NASAL DELIVERY [4]

1. Appropriate aqueous solubility to provide the desired dose in a 25-150µL volume of formulation administered per nostril.
2. Appropriate nasal absorption properties.
3. No nasal irritation from the drug should be there.
4. A suitable clinical rational for nasal dosage forms e.g. Rapid onset of action.
5. Low dose generally 25mg per dose.
6. No toxic metabolites.
7. No offensive odors associated with the drug. Low permeability while posterior portion of the nose where the drug permeability is generally higher, provides shorter residence time.
2. Nasal Blood Flow: Nasal mucosal membrane is very rich in vascular and plays a vital role in the thermal regulation and humidification of the inhaled air therefore the drug absorption will depend upon the vasoconstriction and vasodilation of the blood vessels. [4]
3. Effect of Enzymatic Activity: Several enzymatic that are present in the nasal mucosa might affect the stability of drugs. For example, proteins and peptides are subjected to degradation by proteases and amino peptidase at the mucosal membrane. The level of amino peptidase present is much lower than that in the gastrointestinal tract. Peptides may also form complexes with immunoglobulin in the nasal cavity leading to an increase in the molecular weight and a reduction of permeability.
4. Effect of Mucociliary Clearance: The absorption of drug is influenced by the residence (contact) time between the drug and the epithelial tissue. The mucociliary clearance is inversely related to the residence time and therefore inversely proportional to the absorption of drugs administered.
5. Effect of Physical Condition: Intranasal pathologies may affect the nasal mucociliary transport process and/or capacity for nasal absorption. There are times when the mucosa is crushing, bleeding, or dry. One may be suffering from rhinorhea, sinitis, or nasal infection. In people suffering from severe nasal allergies, an excessive nasal secretion can wash away the formulation before the drug has a chance of getting absorbed through the mucosa or before acting locally.[4]

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6. No toxic metabolites.
7. No offensive odors associated with the drug.
8. Suitable stability characteristics

CONCLUSION

Nasal drug delivery is a novel platform and it is a promising alternative to injectable route of administration. There is possibility in the near future that more drugs will come in the market in the form of nasal formulation intended for systemic treatment. Development of a drug with a drug delivery system is influenced by several factors. For the treatment of long illnesses such as diabetes, osteoporosis, fertility treatment novel nasal products are also expected to be marketed. Bioavailability of nasal drug products is one of the major challenges in the nasal product development. In contrast, a huge amount of money is investigated by pharmaceutical companies in the development of nasal products, because of growing demand of nasal drug products in global pharmaceutical market. So for the avoidance of side effect and improve effectiveness of nasal products we should pay attention to basic research in nasal drug delivery.

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