

Targeted Drug Delivery Systems Mediated Through Nasal Delivery for Improved Absorption: an Update

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ABSTRACT

Purpose: This review article focuses on providing updated information about targeting the nasal mucosa for drug delivery. The article would serve as a tool for researchers and students to gain insight into the various aspects of nasal drug delivery. **Approach:** The anatomy and physiology of the nasal region have been discussed, followed by a discussion of the factors and barriers affecting the drug absorption, strategies to improve the drug absorption, various excipients employed in nasal formulations, different types of nasal formulations and applications of nasal delivery. **Findings:** The high permeability, high vascularity, very low enzymatic activity, accessible surface area and avoidance of first pass hepatic metabolism are the main factors for which it is being considered as a superior delivery route for many drugs in the recent decades. The effects which are mainly systemic encourage the deployment of this route of administration. This route of drug delivery has been also been exploited for delivering the drugs to the central nervous system bypassing the Blood Brain Barrier (BBB). Different forms of dosage forms such as sprays, powders, gels, solutions are administered through this route. **Conclusion:** Intranasal delivery of drugs is a promising alternative to other routes of administration because, it is rapid and non-invasive and leads to increased bioavailability of poorly bioavailable drugs. The dose of the drug used is minimal compared to other routes hence the systemic side effects are reduced. Compared to parenteral administration it has better compliance and improved patient acceptability. More fundamental research will lead to better understanding of this route and eventually more marketed products.

Key words: Nasal delivery, Peptide delivery, Permeability enhancers, Targeted drug delivery.

INTRODUCTION

The nasal delivery of drugs in the recent decade been considered as a prospective route of administration to achieve higher bioavailability and increased level of drug absorption. The systemic effects achieved of the drugs administered by this route grants an alternative for the drugs given by parenteral delivery which can be sometimes inconvenient or the oral delivery which can decrease bioavailability. This has appealed a great zeal for the development of nasal delivery of drugs. The highly permeable monolayer of the nasal epithelium, the richly vascularised submucosa, and avoidance of hepatic first-pass metabolism has proved to be beneficial for the drug administration via the nasal route. Other important features include accessible surface area

of the nasal cavity and the rich blood flow which promotes rapid absorption.¹ In addition to the above, intranasal drug delivery enables dose reduction, rapid attainment of therapeutic blood levels, quicker onset of pharmacological activity, and fewer side effects.^{2,3} Furthermore, self-medication is easy and convenient. Hence, the rationale behind this article is to provide an expansive review covering the myriad aspects of nasal drug delivery.

ANATOMY AND PHYSIOLOGY OF NASAL CAVITY

The anatomical and physiological aspects of the nasal membrane have been studied with its relation to the drug delivery. The

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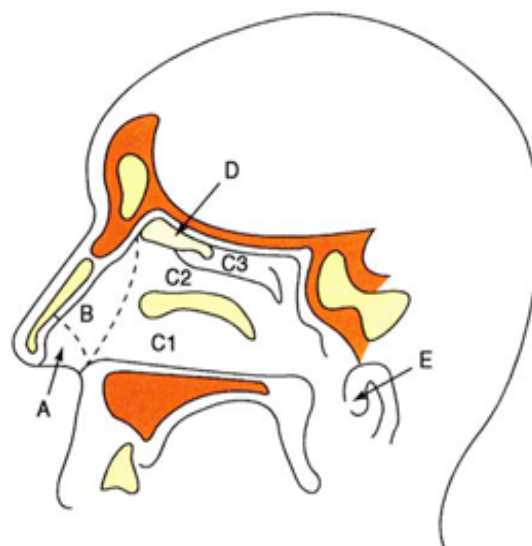
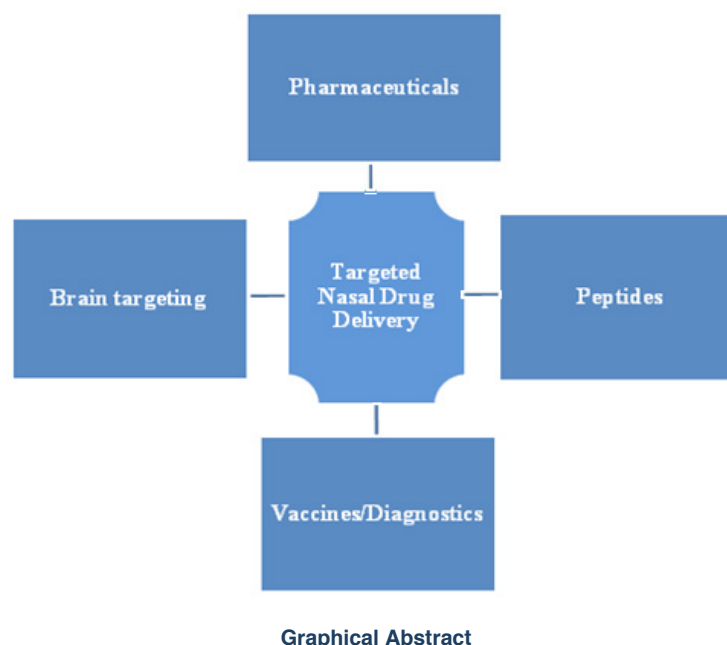


Figure 1: Schematic of a sagittal section of human nasal cavity showing the nasal vestibule (A), atrium (B), respiratory region: inferior turbinate (C1), middle turbinate (C2) and the superior turbinate (C3), the olfactory region (D) and nasopharynx

[Reproduced from: Ugwoke MI, Verbeke N, Kinget R, The biopharmaceutical aspects of nasal mucoadhesive drug delivery, J. Pharm. Pharmacol. 2001;53:3-21]

nasal cavity is divided into two halves by the nasal septum and extends posteriorly to the nasopharynx, while the most anterior part of the nasal cavity, the nasal vestibule, opens to the face through the nostril as depicted in (Fig 1). The atrium is an intermediate region between the vestibule and the respiratory region. The respiratory region, the nasal conchae or turbinates, which occupy the major part of the nasal cavity, possess lateral walls dividing it into three sections: superior, middle and inferior nasal turbinates. These folds provide the nasal cavity with a high surface area compared to its small volume.⁴⁻¹¹ Each cavity has a volume of approximately 7.5 mL and has a surface area around 75 cm². The three

distinct functional regions of the nose are the vestibular, respiratory, and olfactory.¹²⁻¹⁴

Among these, the most important is the respiratory region for systemic drug delivery.^{15,16} The respiratory epithelium comprises of basal, mucus-containing goblet, ciliated columnar and nonciliated columnar cell types as depicted in (Fig 2).^{16,17} The cilia move in a wave-like fashion to transport particles to the pharynx area for ingestion.^{16,18} Additionally, the cells in this region are covered by nearly 300 microvilli, providing a large surface area for absorption.¹⁶ Below the epithelium is the lamina propria. Here, blood vessels, nerves, serous glands, and mucus secreting glands are located.¹⁷ The

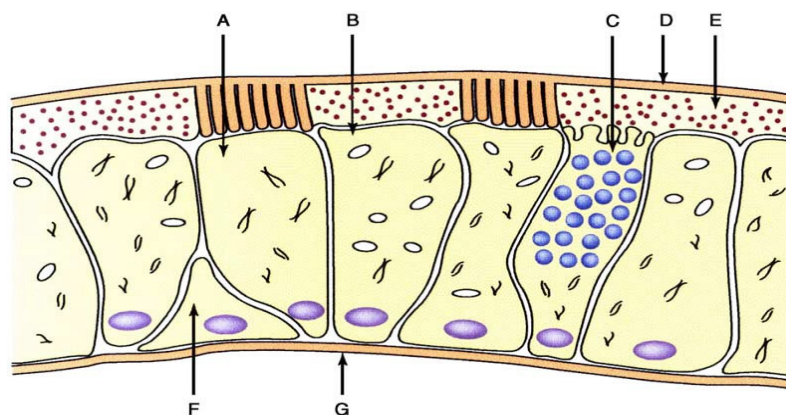


Figure 2: Cell types of the nasal epithelium showing ciliated cell (A), non-ciliated cell (B), goblet cells (C), gel mucus layer (D), sol layer (E), basal cell (F) and basement membrane (G)

[Reproduced from: Ugwoke MI, Verbeke N, Kinget R, The biopharmaceutical aspects of nasal mucoadhesive drug delivery, J. Pharm. Pharmacol. 2001;53:3-21]

Table 1: Structural features and relevance of different nasal anatomical regions²⁶

Region	Structural features	Permeability
Nasal vestibule	Nasal hairs (vibrissae) Epithelial cells are stratified, squamous and keratinized	Least permeable because of the presence of keratinized cells
Atrium	Transepithelial region. Stratified squamous cells present anteriorly; pseudo stratified cells with microvilli present posteriorly	Less permeable (small surface area and stratified cells are present anteriorly)
Respiratory region (inferior turbinate middle turbinate superior turbinate)	Narrowest region of nasal cavity. Pseudo stratified ciliated columnar cells with microvilli (300/cell), large surface area. Receives maximum nasal secretions due to presence of seromucus glands, nasolacrimal duct and goblet cells	Most permeable region (large surface area & rich vasculature)
Olfactory region	Richly supplied with blood for heating and humidification of inspired air, presence of paranasal sinuses. Specialized ciliated olfactory nerve cell for smell perception. Receives ophthalmic and maxillary divisions of trigeminal nerve	Direct access to cerebrospinal fluid
Nasopharynx	Direct access to cerebrospinal fluid. Upper part - ciliated cells; lower part -squamous epithelium	Receives nasal cavity drainage

lamina propria also encompasses a dense network of capillaries, through which drug absorption takes place.

The nasal passage epithelium is covered by a mucous layer that is renewed every 10 to 15 min.¹⁸ The pH of the mucosal secretions ranges from 5.5 to 6.5 in adults and 5.0 and 6.7 in children.¹⁹ The mucus entraps particles, which are then cleared from the nasal cavity by the cilia. The mucus moves through the nose at an approximate rate of 5 to 6 mm/min resulting in particle clearance within the nose every 20 min.¹³ Several enzymes have been identified in the nasal cavity.^{20,21} Discovery of cytochrome P450 enzyme isoforms have been reported and they comprise of cytochrome P1A (CYP1A), cytochrome P2A (CYP2A) and cytochrome P2E (CYP2E).²² Additional enzymes discovered in the human nose consist of carboxylesterases and glutathione-S-transferases.²³⁻²⁵ (Table 1) describes the structural

features of different nasal anatomical regions and their relevance in drug permeability.^{26,27}

Advantages of Nasal Drug Delivery Systems:²⁸

Nasal drug delivery offers a viable alternative for the administration of many pharmaceutical agents. Major advantages offered by the nasal route include:

- Rapid absorption, higher bioavailability, therefore lower dose requirement
- Avoidance of hepatic first-pass metabolism
- Avoidance of metabolism by the gastrointestinal tract
- Avoidance of irritation of the gastrointestinal membrane
- Faster onset of therapeutic action
- Reduced risk of overdose
- Non-invasive, therefore, reduced risk of infection
- Convenient, accessible and self-administration

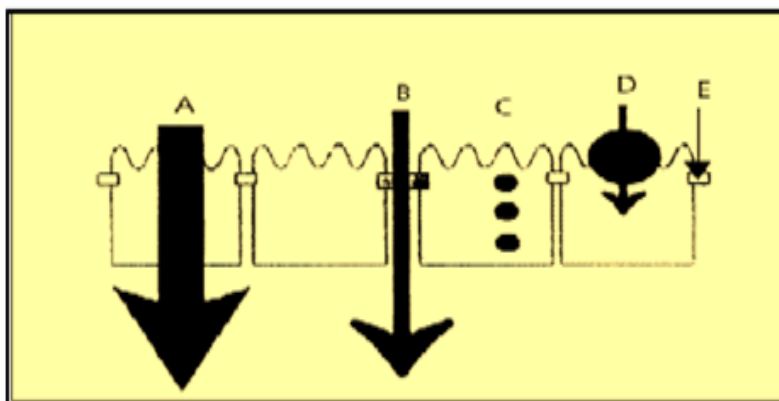


Figure 3: Potential drug transport mechanisms across the nasal epithelium: Transcellular passive diffusion (A), paracellular passive diffusion (B), carrier-mediated transport (C), absorption through transcytosis (D) and efflux transport (E)

[Reproduced from: Illum L. In: Mathiowitz E, Chickering DE, Lehr CM Ed, Bioadhesive formulations for nasal peptide delivery: Fundamentals, Novel Approaches and Development. Marcel Dekker. New York 1999; 507-539.]

possible

- Superior patient compliance
- Reduced risk of infectious disease
- Some unsuitable drug candidates for oral route can be successfully given via nasal route
- Alternative route to parenteral especially for administration of proteins and peptides
- Direct transport of drugs into systemic circulation and CNS is possible
- Convenient route for patients on long term therapy

Limitations of Nasal Drug Delivery Systems:

- High molecular weight compounds cannot be delivered through this route (mass cut off ~ 1 kDa)²⁷
- Normal defense mechanisms like mucociliary clearance and ciliary beating affects the permeability of drug
- Delivery volume in nasal cavity is restricted to 25–200 μ L
- Enzymatic barrier to permeability of drug
- Adversely affected by pathological conditions
- Large inter-species variability is observed in this route
- Smaller absorption surface compared with GIT
- Irritation of nasal mucosa by drugs like Budesonide, Azelastine
- Limited understanding of mechanisms and less developed models at this stage
- Possibility of nasal irritation hence inconvenient compared with oral route

Mechanism of Drug Absorption from the Nasal Cavity:

Initially, the absorption of drug from the nasal cavity is channeled through the mucus.²⁹ Particles which are small and uncharged effortlessly pass through this layer. Large or charged particles may find it more difficult to traverse. Mucin, the chief protein of the mucus, has the potential

to attach to solutes, hindering diffusion. Furthermore, environmental changes (i.e. pH, temperature, etc.) may contribute to the structural changes of the mucus layer.²⁹

After a drug courses through the mucus, there are a number of mechanisms for absorption through the mucosa²⁹ (Fig 3), the primary being the following:

Paracellular route:

It includes aqueous path of transport, which is also called as the Paracellular route. This is slow and passive route. Poor bioavailability was observed for drugs with a molecular weight greater than 1000 Da,²⁷ because there exists an inverse relationship between molecular weight and absorption.

Transcellular route:

The second mechanism of transport is the transcellular process in the course of a lipoidal route and is responsible for the transport of lipophilic drugs that illustrate a rate dependency on their lipophilicity. Drugs also traverse cell membranes by an active transport route via carrier mediated way or transport through the opening of tight junctions.

For example, Chitosan, a natural biopolymer opens tight junctions between epithelial cells to facilitate drug transport i.e. paracellular transport.³⁰

Barriers to Nasal Absorption:

Low bioavailability:

Polar drugs possess bioavailability which is generally low, i.e., not above 1% for peptides such as calcitonin and insulin and 10% for low molecular weight drugs.³¹ Low membrane permeability is the most imperative factor limiting the nasal absorption of polar drugs and in particular large molecular weight polar drugs such as peptides and proteins.

Drugs traverse the epithelial cell membrane either by the transcellular route, by receptor mediated or vesicular transport mechanisms, or by the paracellular route. Polar drugs with molecular weights below 1000 Da will by and large cross the membrane by means of the transcellular route.³² Larger peptides and proteins have been shown to be able to pass the nasal membrane using an endocytic transport process but only in small amounts.³³

Mucociliary clearance:

Mucociliary clearance results in the speedy removal of the drug from the site of deposition mostly of the peptide drugs. The prompt clearance of the administered formulation from the nasal cavity due to the mucociliary clearance mechanism is an added factor of consequence for low membrane transport. This is principally the case when the drug is not absorbed rapidly enough across the nasal mucosa. It has been shown that for both liquid and powder formulations, which are not bioadhesive, the half-life for clearance is of the order of 15-30 min.^{34,35} The use of bioadhesive excipients in the formulations is an approach to overcome the rapid mucociliary clearance. Mucociliary clearance can also be reduced by depositing the formulation in the anterior, less ciliated part of the nasal cavity thus leading to improved absorption.^{36,37}

Enzymatic Degradation:

Numerous compounds are acknowledged to be metabolized by the nasal P450-dependent monooxygenase system, e.g. nasal decongestant, essences, anesthetics, alcohols, nicotine, and cocaine.³⁸⁻⁴² Together with the P450 monooxygenase system, quite a few other enzymes exist in the nasal secretions, e.g. lactate dehydrogenase,⁴³ oxidoreductases,⁴⁴ hydrolases, acid phosphatase and esterases. Additionally to cytochrome P450 enzymes, some oxidative Phase 1 enzymes and conjugative Phase 2 enzymatic activity are also present in the nasal epithelium. The Phase 1 enzymes incorporate flavin-monooxygenases and aldehyde dehydrogenases, epoxide hydrolases, carboxylesterases and carbonic anhydrases. The conjugative Phase 2 enzymes comprise of glucuronyl and sulphate transferases, and glutathione transferase. A further contributing, but often less considered aspect to the low bioavailability of peptides and proteins across the nasal mucosa is the likelihood of an enzymatic degradation of the molecule in the lumen of the nasal cavity or at some point in passage through the epithelial barrier. These sites both contain exopeptidases such as mono and diaminopeptidases that can slice peptides at their N and C termini and endopeptidases such as serine and cysteine, which can cleave internal peptide bonds.⁴⁵ Utilizing enzyme inhibitors and/or saturation of enzymes may be techniques to surmount this barrier.⁴⁶

Summarizing, the nasal cavity offers unique advantages as an administration site for drug delivery. However, challenges like low permeability for polar and high molecular weight drugs, rapid clearance of the delivery system from the cavity and probable enzymatic degradation of the drug in the nasal cavity should be offset. These challenges can be surmounted by diverse approaches, such as use of absorption enhancers and bioadhesive systems.

Factors Influencing Nasal Drug Absorption:

Biological Factors:

- Structural features
- Biochemical changes

Physiological factors:

- Blood supply and neuronal regulation
- Nasal secretions
- Mucociliary clearance and ciliary beat frequency
- Pathological conditions
- Environmental conditions
- Membrane permeability

Physicochemical Properties of Drugs:

- Molecular weight
- Size
- Solubility
- Lipophilicity
- pKa and Partition coefficient
- Chemical form of the drug
- Polymorphism
- Chemical state
- Physical state

Physicochemical Properties of Formulation:

- Physical form of formulation
- pH
- Osmolarity
- Volume of solution applied and drug concentration
- Viscosity

Biological Factors:

Structural features:

The configuration and the type of cells, density and number of cells present in that area affect the permeability.⁴⁷ Absorption enhancers used in combination with drugs augment the permeation of compounds.⁴⁸

Biochemical changes:

The occurrence of a large quantity of enzymes, which include oxidative and conjugative enzymes, peptidases and proteases are accountable for the degradation of drugs in the nasal mucosa and effect in formation of

a pseudo-first pass effect. Owing to P450 dependent monooxygenase system, nasal decongestants, alcohols, nicotine and cocaine are metabolised. Presystemic degradation and ensuing poorer permeation of various peptide drugs, such as calcitonin, insulin, Luteinizing Hormone-Releasing Hormone (LHRH) and desmopressin is due to protease and peptidase. To prevail over these, several approaches have been used such as the use of protease and peptidase inhibitors like bacitracin, amastatin, boroleucine and puromycin.⁴⁹

Physiological factors:

Blood supply and neuronal regulation:

Nasal mucosa is an extremely permeable region. Parasympathetic stimulation effects in high blood supply resulting in congestion and sympathetic stimulation leading to low blood supply resulting in relaxation, regulate the rise and fall in the amounts of drug permeated, in each case respectively.⁵⁰ Parasympathetic stimulation leads to the augmented permeability of a compound.

Nasal secretions:

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

Viscosity of nasal secretion:

The viscous surface layer will hamper the ciliary beating if the sol layer of mucus is excessively thin, while the mucociliary clearance gets impaired if sol layer is too thick, because attachment with cilia is lost. Permeation of the drug is influenced due to injury of mucociliary clearance by varying the time of contact of drug and mucosa.

Solubility of drug in nasal secretions:

Solubilization is necessary for permeation of the drug. A drug is required to have the apt physicochemical characteristics for dissolution in nasal secretions.

Diurnal variation:

Nasal secretions are also influenced by circadian rhythm. Permeation of drug is changed at night due to secretions and the clearance rates are reduced. Chronokinetics dictate the pattern and rate of permeation.

pH of nasal cavity:

The pH varies between 5.5 to 6.5 in adults and 5.0 and 6.7 in infants. Permeation of drug is greater if the nasal pH is lower than the 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, the pH of formula-

tion should be between 4.5 to 6.5 for better absorption, and should also have good buffering capacity.⁵¹

Mucociliary clearance (MCC) and ciliary beating:

When a substance is administered intranasally, 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 into GIT by draining into nasopharynx. Drug permeation is enhanced by increasing contact time between drug and mucus membrane whereas, increased MCC decreases drug permeation.

Pathological conditions:

Mucous cilia dysfunctioning such as hypo or hyper secretion and 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:

It has been estimated that a modest reduction in the rate of MCC occurs at the temperature of 24°C, 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 the key factor. The large molecular weight drugs and water soluble drugs like peptides and proteins have low membrane permeability hence absorbed through endocytic transport in less amounts.⁵²

Physicochemical properties of drug

Molecular weight and size:

Drug permeation is determined by molecular weight, molecular size, hydrophilicity and lipophilicity of the compound. Bioavailability can be directly predicted from knowledge of MW. In general, the bioavailability of large molecules, >1000 Da, ranges from 0.5% to 5%. Physicochemical properties of the drug do not significantly affect permeation of drug <300Da, which will mostly permeate through aqueous channels of the membrane.

Solubility:

Drug solubility is also one of the key factors in influencing absorption of drug through biological membranes. As nasal secretions are runny in nature, a drug should have suitable aqueous solubility for better dissolution. Lipophilic drugs have less solubility in the aqueous secretions. Water soluble drugs are absorbed by

passive diffusion and lipophilic drugs via active transport relative to their solubility.⁵³

Lipophilicity:

The permeation of the compound usually increases through nasal mucosa with a rise in lipophilicity. It appears that nasal mucosa is largely lipophilic in composition and the lipid component plays an important role in the barrier role of these membranes although they have some hydrophilic characteristics. Systemic bioavailability of many drugs is diminished due to surplus hydrophilicity; in such cases, prodrug approach is favorable.

pKa and partition co-efficient:

As stated by the pH partition theory, unionized species are absorbed better compared to the ionized species and the same is followed in case of nasal absorption. There is a constant relationship between pKa and nasal absorption of such drugs. With an increase in lipophilicity or the partition coefficient of the drugs its concentration in biological tissues increases. The key factor governing nasal absorption is partition coefficient.⁵⁴

Polymorphism:

Polymorphism is known to affect dissolution of drugs and their absorption through biological membranes. Polymorphism is an important constraint in the nasal drug product development when the drug is administered in particulate form. This factor should be cautiously considered in the dosage form development for the nasal delivery.²⁸

Chemical state of drug:

Chemically modifying a drug molecule by adding a bio-cleavable lipophilic moiety is an option for improving absorption of the drugs which do not possess the preferred absorption properties. Absorption of the drug is determined by the chemical form of the drug in which it is presented to nasal mucosa. The prodrug approach has its own constraints which need to be taken care of in the drug product development process. The toxicity of the prodrug itself warrants an exhaustive evaluation.²⁸

Physical state of drug:

Particle size and morphology of drug are the two core properties for particulate nasal drug products. These parameters should be controlled to acquire proper drug dissolution properties. Fine particles below 5 microns should be avoided because these may get inhaled into the lungs. Generally, particles in the range of 5–10 μ are deposited in the nostrils.²⁸

Physicochemical properties of formulation:

Physical form of formulation:

Physical form of the formulation is especially significant in nasal drug absorption. Liquid formulations are less effective than powder form in delivering insulin in rabbits. Less efficient systemic nasal drug delivery is observed with more viscous formulation. Viscous formulations may help in minimizing nasal drip.

pH:

Extent of drug ionization is determined by pH-partition hypothesis; hence it is related to the formulation pH. Nasal formulation should be adjusted to the appropriate pH to prevent irritation, to gain efficient absorption and to prevent growth of pathogenic bacteria. Ideal formulation pH should be adjusted between 4.5 and 6.5. The nasal surface pH 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 considerably influences the nasal mucosa. Generally, an isotonic formulation is favored.⁵⁵

Volume of solution applied and drug concentration:

There is no constant relationship between volume of administration and extent of absorption. Clement investigated the effect of three nasal spray concentrations of cetirizine on the clinical efficacy administered three times a day for 2 weeks. The results showed the median PD_{Max1} were 16.7%, 30.8%, 42.9%, and 26.7% for the placebo, 0.06%, 0.125%, and 0.25% groups, respectively. For the global evaluation by the investigator, the best results were seen in the 0.125% group ($P=0.03$). At a greater concentration of 0.25%, the efficacy seemed to be reduced.⁵⁴

Viscosity:

Contact time between the drug and the nasal mucosa is increased by higher viscosity of formulation thereby increasing the time for permeation.⁵⁴

STRATEGIES TO IMPROVE NASAL ABSORPTION

The strategies used to improve the bioavailability of the drug in the nasal mucosa includes

1. To increase the nasal residence time.
2. To modify the drug structure to change the physico-chemical properties.
3. To enhance nasal absorption.

Any one or combination of above approaches are used for the enhancing the absorption and bioavailability of

the formulations.⁵⁶ Several methods have been used to facilitate the nasal absorption of drugs includes:

Permeation enhancers:

Permeation enhancers are chiefly used for the enhancement of absorption of the active medicament. Generally, the absorption enhancers act via one of the following mechanisms:

- Open the tight junctions
- Inhibit enzyme activity
- Diminish mucus viscosity or elasticity
- Lessen mucociliary clearance
- Solubilize or stabilize the drug.

The mechanism of action of absorption enhancer is to effect an increase in the rate at which the drug passes through the nasal mucosa. Several enhancers operate by altering the structure of epithelial cells in some manner, but it is required that they cause this without inflicting injury or permanent alteration to the structure of nasal mucosa. An ideal penetration enhancer should be:

1. Non-irritant and nontoxic.
2. Cause an effective increase in the absorption of the drug.
3. Not cause permanent damage or alteration to the tissues.
4. Effective in small amounts.
5. Compatible with other excipients.
6. Temporary and reversible.
7. Active when absorption is required.

Myriad penetration enhancers have been evaluated for organic drugs including surfactants, bile salts, chelators, fatty acid salts, phospholipids, glycyrrhetic acid derivatives, cyclodextrins and glycols.⁵⁷

Classification of chemical penetration enhancer includes:⁵⁸

Surfactants: Polyoxyethylene-9-lauryl ether (Laureth-9), Saponins

Glycols: n-glycofurols and n-ethylene glycols

Chelators: Salicylates, Ethylenediaminetetraacetic acid (EDTA)

Cyclodextrins: α , β , and γ - cyclodextrins and their derivatives

Fatty acid salts: Oleic acid, Caprylate (C8), Caprate (C10), Laurate (C12)

Phospholipids: Lysophosphatidylcholine (lyso-PC), Di-decanoyl-PC

Bile salts: Trihydroxy salts (glycol and taurocholate), Fusidic acid derivatives (STDHF)

Glycyrrhetic acid derivatives: Carbenozolone, Glycyrrhizinate

Nasal enzyme inhibitors:

Enzyme inhibitors are used to inhibit or to stop nasal metabolism of drugs. Mainly for the formulation of proteins and peptide molecule development, enzyme inhibitors like peptidases and proteases are used.⁵⁹ The absorption enhancers like salts and fusidic acid derivatives also show enzyme inhibition activity resulting in increase in the absorption and bioavailability of the drug.⁶⁰ The other enzyme inhibitors commonly used for the enzymatic activity are trypsin, aprotinin, borovaline, amastatin, bestatin and boroleucine inhibitors.

Prodrug approach:

Prodrug is usually referred to as promoiety. This approach is meant to block the undesired effect of some functional groups with other functional groups. Prodrug approach is chiefly meant for optimizing favorable physicochemical properties such as solubility, taste, odor, stability, etc. This approach is principally used for improving the nasal bioavailability in particular of the proteins and peptides to enhance their membrane permeability along with increased enzymatic stability.⁶¹ The prodrug upon crossing the enzymatic and membrane barrier undergoes enzymatic transformation to discharge the active medicament.

Particulate drug delivery:

Particle design plays an increasingly important role in absorption enhancement. Microspheres, nanoparticles and liposomes are the systems which can be used as carriers to encapsulate an active drug. The properties of these can be varied to maximize therapeutic efficacy. On the whole, this can result in increased absorption efficacy and stability and reduced toxicity of the active ingredient. Systems can be designed to be mucoadhesive to increase the retention time and facilitate sustained release.

Microspheres mainly increase the absorption and bioavailability by adhering to the nasal mucosa and increase the nasal residence time of drug.⁶² The microspheres prepared by using polymers like dextran, chitosan, and biodegradable starch microspheres effectively enhanced the bioavailability of various drugs. Liposomes are amphiphilic in nature, are well characterized for favorable permeation of drugs through the biological membranes, so the water soluble drugs have been delivered to nasal cavity. Cationic liposomes are having good permeation capacity than negatively charged anionic liposomes.⁶³

Structural modification:

Modification of drug structure without altering pharmacological activity is one of the productive ways to improve the nasal absorption. The chemical modification of drug molecule has been commonly used to

modify the physicochemical properties of a drug such as molecular size, molecular weight, pKa and solubility.⁶⁴

Excipients Used in Nasal Formulations:

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

Bioadhesive polymers:

Compounds that are able to interact with biological material through interfacial forces and being retained on such material for prolonged periods of time are called as bioadhesive polymers. They are also called as mucoadhesive, if biological material is a 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).⁴⁷

Buffers:

Nasal formulations are generally administered in small volumes ranging from 25 to 200 μ L with 100 μ L being the most regular dose volume. Hence, nasal secretions may alter the pH of the administered dose which can affect the concentration of unionized drug available for absorption. Therefore, an ample formulation buffer capacity may be required to maintain the pH in situ.⁴⁷

Penetration enhancers:

Chemical penetration enhancers are extensively used in the nasal drug delivery to increase the permeation of drug molecules.

Solubilizers:

Nasal drug delivery in solution form faces the challenge of aqueous solubility of drug. Conventional solvents or co-solvents such as glycols, small quantities of alcohol, transcitol (diethylene glycol monoethyl ether), medium chain glycerides and Labrasol (saturated polyglycolized C8-C10 glyceride) can be utilized to augment the solubility of drugs. Other compounds can be used like, surfactants or cyclodextrins such as HP- β -Cyclodextrin that serve as a biocompatible solubilizer and stabilizer in combination with lipophilic absorption enhancers. In these circumstances, their impact on nasal irritancy should be considered.⁴⁷

Preservatives:

Nasal formulations are aqueous based, hence it is imperative to use preservatives. Parabens, phenyl ethyl

alcohol, benzalkonium chloride, EDTA and benzoyl alcohol are some of the frequently used preservatives in nasal formulations.⁴⁷

Antioxidants:

A small quantity of antioxidants may be necessary 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.⁴⁷

Humectants:

As a consequence of allergic and chronic diseases, there can be crusts and drying of mucous membrane. Certain preservatives/antioxidants are also likely to cause nasal irritation particularly when used in higher quantities. Ample intranasal moisture is crucial for preventing dehydration. Consequently, 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.⁶⁵

Surfactants:

Inclusion of surfactant into nasal dosage forms can amend the permeability of nasal membranes, which may assist the nasal absorption of drug.

Nasal Drug Delivery Systems:

The choice of dosage form depends upon the active pharmaceutical ingredient (API) being employed, proposed indication, patient population and finally, marketing preferences. Four basic formulations are usually considered-solution, suspension, emulsion and dry powder systems.

Liquid nasal formulations:

The most commonly used dosage forms for nasal administration of drugs are liquid preparations. They are mainly based on aqueous state formulations. Their humidifying effect is opportune and useful, since many allergic and chronic diseases are frequently associated with crusts and drying of mucous membranes.⁵⁷ Microbiological stability, irritation and allergic rhinitis are the major drawbacks associated with the water-based dosage forms because the required preservatives diminishes mucociliary function⁶⁶ and the reduced chemical stability of the dissolved drug substance and the short residence time of the formulation in the nasal cavity are major drawbacks of liquid formulations.^{67,68} The numer-

ous variety of dosage forms available in liquid form are described below.

Compressed air nebulizers:

Nebulizer is used to administer medication in the form of a mist which is inhaled into the lungs. Compressed air nebulizers have been thus named since the container is filled with compressed air. The fundamental technique universal for all nebulizers is to use oxygen, compressed air or ultrasonic power, as a source to fragment medical solutions/suspensions into minute aerosol droplets, for direct inhalation from the mouthpiece of the device.⁶⁹ The medication is in the form of a liquid solution, which is frequently laden into the device upon use. Corticosteroids and bronchodilators such as salbutamol are regularly used, and sometimes in combination with ipratropium. The explanation that these medications are inhaled instead of ingested is, in order to target their effect to the respiratory tract, which accelerates the onset of action of the medicine and diminishes the side effects, compared to other alternative intake routes. This device is inappropriate for the systemic delivery of drug by patient himself.

Instillation and rhinyle catheter:

Catheters are employed to direct the drops to a particular region of nasal cavity. The formulation is placed in the tube and one end of the tube is positioned in the nose, and the solution is delivered into the nasal cavity by blowing through the other end by mouth^{70,71} Dosing of catheters is determined by the filling prior to administration and this is primarily used for experimental studies only.

Squeezed bottle:

Squeezed nasal bottles are largely used as delivery device for decongestants. They incorporate a smooth plastic bottle with a plain jet outlet. While pressing the plastic bottle the air inside the container is pushed out of the small nozzle, thereby atomizing a certain volume. By releasing the pressure air is redrawn within the bottle. This procedure frequently results in contamination of the liquid by microorganisms and nasal secretion may get sucked inside. Dose accuracy and deposition of liquids delivered by means of squeezed nasal bottles are majorly dependent on the manner of administration. The differences among vigorously and gently pressed application influence the dose as well as the droplet size of the formulation. Thus the dose is difficult to control. Consequently squeezed bottles with vasoconstrictors are not advised to be used by children.⁷²

Metered-dose pump sprays:

The majority of the pharmaceutical nasal preparations on the market containing solutions, emulsions or sus-

pensions are conveyed by metered-dose pump sprays. Nasal sprays, or nasal mists, are used for the nasal delivery of a drug or drugs, either locally or systemically to assuage cold or allergy symptoms such as nasal congestion. While delivery methods may be different, the majority of nasal sprays function by introducing a fine mist into the nostril by actuation of a hand-operated pump mechanism. The three major types available for local effect are: antihistamines, corticosteroids, and topical decongestants. Metered-dose pump sprays consist of the container, the pump with the valve and the actuator. The dose accuracy of metered-dose pump sprays is dependent on the surface tension and viscosity of the formulation. Higher viscosity solutions are delivered with the help of special pumps equipped with valve combinations.

Powder dosage forms:

Dry powders are less commonly used in nasal drug delivery. Major benefits of this dosage form are the lack of preservatives and the superior stability of the formulation. In contrast to solutions, the administration of powders could effect in an extended contact with the nasal mucosa. The types of powder dosage forms are described below:

Insufflators:

Insufflators are the devices to convey the drug substance for inhalation. Insufflator can be constructed by means of a straw or tube which houses the drug substance and sometimes it contains the syringe also. The particle size attained by using these systems is often greater compared to the particle size of the powder particles due to inadequate deaggregation of the particles and results in a high coefficient of variation for initial deposition areas. Many insufflator systems work with pre-dosed powder doses in capsules.⁷⁰

Dry powder inhalers:

Dry powder inhalers (DPIs) are devices through which a dry powder formulation of an active drug is delivered for local or systemic effect via the pulmonary route. Dry powder inhalers are bolus drug delivery devices that contain solid drug, suspended or dissolved in a non-polar volatile propellant or in dry powder inhaler that is fluidized when the patient inhales.⁷³ These are regularly used to treat respiratory diseases such as asthma, bronchitis, emphysema and Chronic Obstructive Pulmonary Disease (COPD) and have also been used in the treatment of diabetes mellitus. The medication is commonly housed either in a capsule for manual loading or a proprietary form from inside the inhaler. Once loaded or actuated, the operator puts the mouthpiece of the inhaler into the mouth and takes a deep inhalation,

holding the breath for 5-10 s. An array of such devices is available in the market. The dose that can be delivered is characteristically less than a few tenths of milligrams in a single breath since larger powder doses may lead to provocation of cough.⁷⁴

Pressurized Metered Dose Inhalers (MDIs):

A Metered-Dose Inhaler (MDI) is a device that delivers a precise amount of medication to the lungs, in the form of a short burst of aerosolized medicament that is inhaled by the patient. It is the most frequently used delivery system for treating asthma, COPD and other respiratory diseases. The medication in a metered dose inhaler is generally a bronchodilator, corticosteroid or a combination of both for the treatment of asthma and COPD. Other medications less commonly used but also administered by MDI are mast cell stabilizers, such as (cromoglycate or nedocromil). The benefits of MDIs are their portability and small size, availability over a wide dosage range per actuation, dose consistency, dose accuracy, protection of the contents and that they are ready to use.⁷⁵

To use the inhaler the patient depresses the top of the canister, with the thumb supporting the lower portion of the actuator. The propellant offers the force to create the aerosol cloud and is also the medium in which the active component must be suspended or dissolved. Propellants in MDIs typically make up more than 99% of the delivered dose. Actuation of the device discharges a single metered dose of the formulation which contains the medication either dissolved or suspended in the propellant. Disintegration of the volatile propellant into droplets, ensued by rapid evaporation of these droplets consequentially generates an aerosol consisting of micrometer-sized medication particles that are then inhaled.⁷⁴

Nasal Gels:

Nasal gels have elevated viscosity which may be thickened solutions or suspensions. Until the recent advancement of precise dosing devices, there was not much attention devoted to this system. The advantages of a nasal gel consist of the diminution of post-nasal drip due to high viscosity, lessening of taste impact due to reduced swallowing, decrease of anterior leakage of the formulation, reduction of irritation by using soothing/emollient excipients and targeted delivery to the mucosa for superior absorption.⁷⁶

The deposition of the gel in the nasal cavity depends on the manner of administration, because its viscosity leads to poor spreadability. Devoid of special application techniques it only occupies a narrow distribution area in the nasal cavity, where it is placed directly. Recently,

the first nasal gel containing Vitamin B12 for systemic medication has entered the market.

Novel drug formulations:

Many factors, such as, stability, membrane penetration and retention time have led to the development of 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.

Liposomes:

Liposomes are phospholipid vesicles comprising lipid bilayers enclosing one or more aqueous compartments wherein drugs and other substances can be incorporated. Liposomal drug delivery systems present a range of advantages such as the encapsulation of small and large molecules with a wide range of hydrophilicity and pKa values. In effect, they have been found to boost nasal absorption of peptides such as insulin and calcitonin by increasing their membrane penetration. This has been attributed to 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 varying from 1-1000 nm. They comprise 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.

Applications:⁵⁷

Delivery of non-peptide pharmaceuticals:

Low molecular weight (below 1000 Da) small non-peptide lipophilic drugs are adequately absorbed through the nasal mucosa even in the absence of a permeation enhancer. Nasal membrane containing epithelium is

richly vascularized and it contains large surface area it is readily accessible for drug absorption because of the presence of nasal turbinates.

Drugs with extensive pre-systemic metabolism, such as progesterone, estradiol, propranolol, nitroglycerin, sodium chromoglycate can be rapidly absorbed through the nasal mucosa with a systemic bioavailability of approximately 100%. These drugs can attain extensive circulation within few minutes after dosing, as the venous blood passes from the nose directly into the systemic circulation. Indeed, several drugs that are administered intranasally are often absorbed more rapidly and more efficiently than those from oral administration translating into a quick uptake

Some of non-peptide drugs being studied for nasal delivery and have shown good bioavailability by this route includes:

- 1) Adrenal corticosteroids
- 2) Sex hormones: 17 β -estradiol, progesterone, norethindrone, and testosterone.
- 3) Vitamins: vitamin B12
- 4) Cardiovascular drugs: hydralazine, Angiotensin II antagonist, nitroglycerine, isosorbidedinitrate, propranolol, and clofilium tosylate.
- 5) Autonomic nervous system:
 - a. Sympathomimetics: Ephedrine, epinephrine, phenylephrine,
 - b. Xylometazoline, dopamine and dobutamine.
 - c. Parasympathomimetics: nicotine, metacholine
 - d. Parasympatholytics: scopolamine, atropine, ipratropium
 - e. Prostaglandins
- 6) Central nervous systems stimulants: cocaine, lidocaine
- 7) Narcotics and antagonists: buprenorphine, naloxone
- 8) Histamine and antihistamines: disodium cromoglycate, meclizine
- 9) Anti-migraine drugs: diergotamine, ergotamine tartrate
- 10) Penicillin, cephalosporins, gentamycin.
- 11) Antivirals: Phenyl-p-guanidine benzoate, enviroxime.
- 12) Inorganic compounds: Inorganic salts, colloidal gold, colloidal carbon, colloidal silver.

Delivery of Peptide-Based Pharmaceuticals:

Peptides and proteins have in general, low oral bioavailability because of their physicochemical instability and vulnerability to hepato-gastrointestinal first-pass elimina-

tion. Examples are insulin, calcitonin, pituitary hormones etc. These peptides and proteins are hydrophilic polar molecules of comparatively higher molecular weight, are poorly absorbed across biological membranes with bioavailability values obtained in the region of 1–2% when administered as simple solutions. To surmount this problem, absorption enhancers like surfactants, glycosides, cyclodextrins and glycols have been used to augment the bioavailability. Nasal route is proving to be the prominent route for such biotechnological products.

Delivery of Drugs to Brain through Nasal Cavity:

This delivery system is valuable in conditions like Parkinson's disease, Alzheimer's disease or pain because it calls for swift and/or specific targeting of drugs to the brain. The development of nasal delivery system to brain will raise the fraction of drug that reaches the CNS after nasal delivery. The olfactory region located at the upper remote parts of the nasal passages offers the prospective for certain compounds to evade the blood-brain barrier and penetrate into the brain. Studies indicate that neurotropic factors such as, Nerve Growth Factor (NGF), insulin-like growth factor I (IGF-I), basic fibroblast growth factor (bFGF) and activity-dependent neurotrophic factor (ADNF) have been intranasally delivered to the CNS demonstrated an increase in the bioavailability of drugs in the brain. Studies in humans, with proteins such as arginine vasopressin (AVP), cholecystokinin (CCK) analog, melocyte stimulating hormone (MSH)/ adrenocorticotrophic hormone (ACTH) and insulin have revealed that they are delivered directly to the brain from the nasal cavity.

Delivery of Vaccines through Nasal Route:

Mucosal sites provide the primary defense against the exogenous microorganisms entering into the body by filtering the pathogens from the inhaled air by impaction and mucociliary clearance. Nasal-associated lymphoid tissue (NALT) works as an effective site of immune system. It is called Waldeyer's Ring in human beings and nasal secretions mainly contain immunoglobulins (IgA, IgG, IgM, IgE), protective proteins such as complement as well as neutrophils and lymphocytes in the mucosa.⁷⁷⁻⁷⁹ Main reasons for exploiting the nasal route for vaccine delivery are:

- 1) The nasal mucosa is the first site of contacts with inhaled pathogens
 - 2) The nasal passages are rich in lymphoid tissue
 - 3) Creation of both mucosal and systemic immune responses
 - 4) Low cost, patient friendly, non-injectable and safe
- Nasal delivery of vaccines has been reported to not only produce systemic immune response, but also local

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 Pharmaceuticals
Buserelin (Profact nasal)	Buserelin	Solution (spray)	Marketed	Aventis Pharma
Nafarelin (Synarel)	Endometriosis	Solution (spray)	Marketed	Pharmacia
Oxytocin (Syntocinon)	Lactation induction	Solution (spray)	Marketed	Novartis Pharma
Protirelin (Antepan 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 Smith Kline
Dihydroergotamine (Migranal Nasal Spray)	Migraine	Solution (spray)	Marketed	Novartis Pharma
Estradiol (Aerodiol) replacement	Hormone Solution (spray)	Solution (spray)	Marketed	Servier Laboratories

immune response in the nasal lining, providing additional barrier of protection.⁷⁷ Delivering the vaccine to the nasal cavity itself stimulates the production of local secretory IgA antibodies as well as IgG, providing an additional first line of defense, which helps to get rid of the pathogen before it becomes established.⁷⁹

Recently, the diseases like anthrax and influenza have been treated by using the nasal vaccines prepared by using the recombinant *Bacillus anthracis* protective antigen (PA) and chitosan respectively.^{80,81} Measles, pertussis, meningitis and influenza causing pathogens enter into the body primarily through the nasal mucosal surfaces and hence are good candidates for nasal vaccines. Nasally administered vaccines, especially if based on attenuated live cells or adjuvanted by means of an immune stimulator or a delivery system, can induce both mucosal and systemic (i.e. humoral and cell-mediated) immune responses.

Delivery of diagnostic drugs:

Nasal drug delivery system also plays an especially vital role in the delivery of diagnostic agents for the diagnosis of various diseases and disorders in the body. Because the intranasal route is better for systemic release of medicament into blood circulation, one can expect speedy results with less toxicity. Phenolsulfonphthalein is a diagnostic agent used to diagnose the kidney function of the patients. Pancreatic disorders of the diabetic patients were diagnosed by using the 'Secretin'.

And the secretory function of gastric acid was determined by Pentagastrin, diagnostic agent. (Table 2).⁴⁷ and (Table 3).⁴⁷ indicate the nasal drug products available in the market.

FDA Guidance Specific to Nasal Drug Delivery:

The FDA guidelines offer suggestions to applicants who are developing product quality studies to measure bioavailability (BA) and/or establish bioequivalence (BE) in support of new drug applications (NDAs) or abbreviated new drug applications (ANDAs) for locally acting drugs in nasal aerosols (metered-dose inhalers (MDIs) and nasal sprays (metered-dose spray pumps). The guidance tackles the issue of BA and BE studies of prescription corticosteroids, antihistamines, anticholinergic drug products, and the over-the-counter (OTC) mast-cell stabilizer cromolyn sodium.

FDA guidelines specific to NDAs:

In case of NDAs, the FDA recommends that *in vitro* BA studies be presented in NDAs for solution and suspension products, with additional *in vivo* BA studies for suspension products. The data would serve as a standard to characterize the *in vitro* performance, and for suspensions, the *in vivo* performance of the product. In case the formulation and/or method of manufacture of the pivotal clinical trial product changes in terms of physicochemical characteristics of the drug substance, the excipients, or the device characteristics, BE data using *in vitro* tests (for solution and suspension products) and

Table 4: Research on the nasal delivery of insulin

Type of nasal formulation	Results
Insulin-loaded hyperbranched polyglycerol grafted cyclodextrin (HPG-g-CD) nanoparticles	Significantly decreased the blood glucose concentrations in rats. ⁸⁴
Insulin + 0.5% sucrose cocoate	Insulin absorption was enhanced with consequent hypoglycemic effects in rats. ⁸⁵
Insulin/chitosan (CS) microspheres containing 400 mg CS + 70 mg ascorbyl palmitate (as cross-linker)	An increase in absolute bioavailability of 44% and 67% decrease in blood glucose (compared to intravenous insulin) in rats. ⁸⁶
Insulin + aminated gelatin microspheres (AGMS)	AGMS increased nasal insulin absorption significantly when given in dry powder form. ⁸⁷
Insulin/nano- complexes (NC) made with amine-modified poly(vinyl alcohol)- graft-poly(L-lactide)	Significant decrease in rat blood glucose. ⁸⁸

in vivo tests (for suspension products) may be helpful in certain conditions to guarantee that the to-be-marketed product (T) is comparable to very similar clinical trial batches and/or to batches utilized for stability testing (R).

FDA guidelines specific to ANDAs:

Product equivalency is the key in case of ANDAs, hence, as per FDA instructions more than ± 5 percent variation between the test and reference product formulations is not permitted. Also it is prescribed that the inactive ingredients in the test product formulation be Qualitatively (Q1) the same and Quantitatively (Q2) essentially the same as the inactive ingredients in the formulation of the reference listed drug. The container and closure recommendations of FDA should also be complied.⁸²

NASAL DELIVERY FOR THE TREATMENT OF OSTEOPOROSIS AND DIABETES

Calcitonin nasal spray has been approved for the osteoporosis in women who are at least 5 years past menopause. It is marketed as Fortical® and Miacalcin® by Upsher-Smith Laboratories and Novartis respectively.⁸³

The nasal delivery of insulin is being investigated in many research endeavours. (Table 4) highlights some of the research investigations on nasal delivery of insulin for treatment of diabetes.

Various Types of Devices for Nasal Delivery:

Liquid dosage forms:

Dropper bottles, Mechanical spray pumps, Gas-driven atomizers, nasal cannula, electrically powered nebulizers.

Semi- solid dosage forms:

Collapsible metal/plastic tubes.

Solid (Powder) dosage forms:

Mechanical powder sprayers, Breath actuated inhalers, Insufflators.⁸⁹

Outcomes of Clinical Trials on Nasal Delivery of Insulin and Calcitonin

- A randomized, double-blind, placebo-controlled trial was conducted to assess the effects of intranasal insulin administration on cognition, function, cerebral glucose metabolism, and cerebrospinal fluid biomarkers in adults with amnesic mild cognitive impairment (aMCI) or Alzheimer Disease (AD). The results demonstrated that the administration of intranasal insulin stabilized or enhanced cognition, function, and cerebral glucose metabolism for adults with aMCI or AD. The safety profiles and compliance were excellent for this short-term study.⁹⁰
- It was investigated whether intranasal insulin administration in adults with AD or aMCI would cause variations in dose-response curves between subjects with and without the apolipoprotein (APOE) $\epsilon 4$ allele ($\epsilon 4+$ or $\epsilon 4-$), a genetic risk factor for late-onset AD. The results indicated that groups with different genetic risks for AD may show differential dose-response curves following intranasal insulin administration.⁹¹
- In a population-based nested case-control study, the association between calcitonin nasal spray use in osteoporosis patients in Taiwan and their subsequent risk of cancer was evaluated. The results of this study implied that calcitonin nasal spray use may enhance the risk of liver cancer in female osteoporosis patients but decrease the risk of breast cancer.⁹²

CONCLUSION

Intranasal delivery of drugs is a promising alternative to other routes of administration, the main reason being its swift and non-invasive nature. It also leads to increased bioavailability of poorly bioavailable drugs. The dose of the drug used is minimal compared to other routes hence the systemic side effects are reduced. In contrast to parenteral administration of drugs, it has superior compliance and an improved patient acceptability. The drugs can be directly delivered to the CNS, bypassing the Blood-Brain Barrier (BBB). There is a lot of ground for optimism with respect to benefits derivable from more fundamental research and applications leading to a deeper understanding of the subject and eventually more marketed products. Greater emphasis has to be invested in the treatment of conditions like diabetes and osteoporosis where the medications are continued till a life time and also in the delivery of drugs to the CNS.

CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest.

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ABBREVIATIONS

BBB: Blood Brain Barrier

CYP1A: Cytochrome P1A
 CYP2A: Cytochrome P2A
 CYP2E: Cytochrome P2E
 LHRH: Luteinizing Hormone-Releasing Hormone
 COPD: Chronic Obstructive Pulmonary Disease
 MCC: Mucociliary clearance
 EDTA: Ethylenediaminetetraacetic Acid
 Lyso-PC: Lysophosphatidylcholine
 API: Active Pharmaceutical Ingredient
 DPIs: Dry Powder Inhalers
 MDI: Metered-Dose Inhaler
 PA: Protective Antigen
 NGF: Nerve Growth Factor
 IGF-I: Insulin-like Growth Factor I
 bFGF: basic Fibroblast Growth Factor
 ADNF: Activity-Dependent Neurotrophic Factor
 AVP: Arginine vasopressin
 CCK: Cholecystokinin analog
 MSH: Melanocyte Stimulating Hormone
 ACTH: Adrenocorticotrophic Hormone
 NALT: Nasal-Associated Lymphoid Tissue
 BA/BE: Bioavailability/Bioequivalence
 NDAs: New Drug Applications
 ANDAs: Abbreviated New Drug Applications
 OTC: Over-the-Counter
 HPG-g-CD: Hyperbranched Polyglycerol Grafted Cyclodextrin
 CS: Chitosan
 AGMS: Aminated Gelatin Microspheres
 NC: Nano- Complexes
 aMCI: amnesic Mild Cognitive Impairment
 AD: Alzheimer Disease

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