



Review on nasal drug delivery system

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ABSTRACT

The intranasal route has become one of the most explored areas in the field of pharmaceutical research for the delivery of small polar molecules, vaccines, hormones, peptides and proteins. This route has been targeted for the systemic delivery of drugs due to its high membrane permeability, high vasculature, low enzymatic environment and avoidance of hepatic first pass metabolism. The large surface area of the nasal mucosa facilitates rapid onset of therapeutic effect, potential for direct delivery of drug to the central nervous system (CNS), and non-invasiveness. Intranasal route is essentially painless and is easily administered by the patient or physicians all of which may maximize patient convenience, comfort and compliance. This article aims to give an insight into the nasal cavity, its advantages and limitations, consideration of factors affecting nasal absorption, strategies to improve drug absorption, pharmaceutical dosage forms and delivery systems and some of its applications.

Keywords: Mucociliary Clearance, first pass metabolism, proteins, peptides



INTRODUCTION

Oral and parenteral route is the most desirable route of drug administration whenever systemic effect is desired. Therefore it is not surprising that, from the earliest stages of drug discovery and development, prediction of human oral bioavailability of new drug candidates is been targeted^[1,2]. The drug administered by oral route enters systemic circulation via its passage through the gastrointestinal tract (GIT). However for some drugs the gastrointestinal tract presents a hostile environment due to its wide range of pH condition, presence of enzymes and variation in its composition depending upon the presence or absence of food. Those drugs which are extensively metabolized by the liver or undergo acid hydrolysis may show poor bioavailability when administered via this route. Parenteral route of drug administration offers the advantage of direct access to the systemic circulation and produces maximum plasma level, but this route is associated with pain, discomfort and can only be administered by medical personnel. Also certain health risks are associated with this route such as allergies, psychological distress, hypertrophy or atrophy of the subcutaneous fat at the injection site on chronic

administration^[3-5]. To overcome the problems associated with the oral and parenteral route, alternative route of drug administration such as transdermal, rectal, buccal and nasal are being investigated. All these routes bypass hepatic first-pass metabolism and offers alternative routes for systemic delivery of drugs. The present article will emphasize more on nasal drug delivery system, barriers of nasal drug delivery system, strategies to improve absorption, its advantages and disadvantages over other routes, and application of nasal drug delivery system^[3,6]. Nasal drug delivery system which has been practiced for thousands of years, has given a new lease of life. It has also been one of the recognized forms of treatment in the Ayurvedic system of Indian medicines called the "NASAYA KARMA". To achieve faster and higher level of drug absorption, the nasal mucosa has been targeted due to its larger surface area, avoidance of first-pass metabolism, high blood flow, neutral pH, porous endothelial membrane, lack of pancreatic and gastric enzymatic activity, ready accessibility and suitable for self-medication. Hence many drugs have shown to achieve better systemic bioavailability through nasal route than by oral route. Also the nasal route serves to directly deliver the central nervous system- active

compounds by circumventing the obstacles for blood-brain barrier. Nasal drug delivery system can be used for both topical and systemic action. Drugs ranging from small chemicals to large macromolecules including proteins/peptides, vaccines and hormones can be delivered through the nasal cavity. During the past few decades nasal route has received increasing attention from pharmaceutical scientist and clinicians. Few nasal delivery systems used in experimental studies that are currently in the market include nasal sprays, nasal pumps, gels, microemulsions, suspensions, powders and thermoreversible mucoadhesive gels. Nasal delivery system is currently being used in the treatment for migraine, osteoporosis, smoking cessation, nocturnal enuresis and vitamin-B₁₂ deficiency. Other examples of therapeutic areas under development or with potential for nasal delivery include cancer therapy, epilepsy, anti-emetics, rheumatoid arthritis and insulin-dependent diabetes [1, 3, 7].

Advantages of nasal drug delivery system [1, 8, 9]

- Absorption of drug is rapid, through highly vascularised and large mucosal surface area leading to fast onset of action.
- No degradation of drug occurs as observed in gastrointestinal tract.
- No hepatic first pass metabolism as observed in oral route.
- Drugs that are difficult to deliver via oral route can be successfully given by nasal route.
- Small drug molecules show good bioavailability by nasal route.
- Bioavailability of large molecules can be improved by the use of absorption enhancers and other techniques.
- It is an alternative to parenteral route especially for the delivery of proteins and peptides.
- The route helps in dose reduction and thus reduces the side effects.
- Convenient route for the patient on long term therapy especially when compared to parenteral route.
- Direct transport of the drug to systemic circulation and CNS is possible, as it bypasses the hepatic and blood brain barrier (BBB).
- Drug possessing poor GIT stability can be given by this route.
- Easy to administer and self-administration is possible.
- Improved patient compliance.
- Formulation of nasal drug delivery system is simple.

Limitations of nasal drug delivery system [1, 9, 10]

- Relatively inconvenient to patient due to the possibility of nasal irritation when compared to oral delivery system.
- Delivery volume above 200 µl is not possible through this route.
- Nasal cavity provides smaller absorption surface area when compared to GIT.
- Mucociliary clearance and ciliary beatings which are normal defence mechanism may affect the permeability of the drug.
- Systemic toxicity due to the use of absorption enhancers is not yet clearly established.
- Some drugs such as budesonide, azilactine causes irritation of nasal mucosa.
- Surfactants added in high concentration as absorption enhancers may disrupt and even dissolve the membrane.
- Drugs may be delivered to other parts of the respiratory tract like lungs due to improper technique of administration leading to loss of the dosage form.
- Nasal route is highly affected by pathological conditions such as cough and cold.
- Large interpatient variability is observed in this route.
- Low bioavailability of some drug may occur due to enzymatic degradation and metabolism at mucosal surface.

Characteristics of an ideal drug candidate for nasal delivery [5, 11]

An ideal drug candidate should possess the following attributes:-

- It should have appropriate nasal absorption properties.
- Particle size of the drug should be between 5-10 µm. Particles below 5 µm are inhaled directly into the lungs and particles above 10 µm are deposited in the nasal cavity.
- Molecular weight of the drug should be below 1000 Da.
- Cyclic-shaped drug molecules have higher absorption compared to linear molecules.
- The drug should not irritate the nasal mucosa and should not have any offensive odor or aroma.
- Dose of the drug should not be more than 25 mg per dose.
- It should possess suitable stability characteristics and should not produce any toxic nasal metabolites.
- There should be suitable clinical rationale for nasal dosage form.

- It should have adequate aqueous solubility.

Anatomy and physiology of nasal cavity

The primary function of nasal cavity in human and other animal species is breathing and olfaction. However, it also affords an important protective activity once it filters, heats and humidifies the inhaled air before reaching the lowest airways. The nasal cavity is lined with mucus layer and cilia, the primary function of which is trapping the inhaled particles and pathogens. Other essential functions of nasal structures include resonance of produced sound, mucociliary clearance, immunological activities, and metabolism of endogenous substances. The nasal septum divides the nasal cavity into two halves, the posterior of which extends to the nasopharynx and the anterior to the nasal vestibule, which opens to the face through the nostril (as shown in figure 1). The nasal cavity consists of four areas distinguished on the basis of their anatomical and histological characteristic as nasal vestibule, atrium, respiratory region and olfactory region. The human nasal cavity has a total volume of 15-20 mL and a total surface area of approximately 150 cm². The large surface area of the nasal cavity is due to the folded structure of the lateral walls.^[3,12,13]

1. Nasal vestibule: It is the most anterior part of the nasal cavity, just inside the nostrils. It covers an area of 0.6 cm². Nasal vestibule is characterized by the presence of nasal hairs, also called vibrissae, that functions to filter the inhaled particles. Histologically, this portion of nasal cavity is made up of stratified squamous and keratinized epithelium with sebaceous glands. The function of nasal vestibule is to afford high resistance against toxic environmental substances; hence absorption of substances including drugs becomes very difficult in this region.

2. Atrium: The intermediate area between the nasal vestibule and respiratory region is the atrium. The anterior part of this region is made up of stratified squamous epithelium and the posterior part by pseudostratified columnar cells presenting microvilli.

3. Respiratory region: It is the largest part of the nasal cavity and it is divided into three parts superior turbinate, middle turbinate and inferior turbinate. The primary function of respiratory region is temperature regulation and humidification of the inhaled air. Between them there are spaces, called meatus, which are passageways where airflow is created to assure a close contact of the inhaled air with the respiratory mucosal surface. The inferior and middle meatus receive

nasolacrimal ducts and paranasal sinuses which are air-filled pockets located inside the bones of the face and around the nasal cavity. For delivery of drugs to systemic circulation, the respiratory mucosa is considered to be the most important section, which is constituted by the epithelium basement membrane and lamina propria. The nasal respiratory epithelium consists of pseudostratified columnar epithelial cells, goblet cells, basal cells and mucous and serous glands. The apical surfaces of many of the epithelial cells are covered with microvilli and fine projections called cilia. The presence of microvilli enhances the respiratory surface area whereas cilia functions to transport the mucus towards the nasopharynx. Under physiological conditions, nasal epithelium is covered with a thin mucus layer produced by secretory glands and goblet cells. The viscosity of the mucus is governed by mucin, a glycoprotein secreted by these cells. The thickness of the nasal mucus layer is 5 µm which is organized into two distinct layers, external, viscous and dense, and an internal, fluid and serous. The mucus is composed of 95% water, 2.5-3% mucin and 2% electrolytes, proteins, lipids, enzymes, antibodies, sloughed epithelial cells and bacterial products. Nasal mucus is indispensable for several physiological functions, which include humidification and warming of inhaled air, physical and enzymatic protection of nasal epithelium against several foreign compounds including drugs and adhesive characteristic of the mucus to attract inhaled particles or pathogens, which are then removed by nasal mucociliary clearance. The basal cells are progenitor of other cell-types and lie on the thickened layer of collagen called basement membrane. The lamina propria is beneath of it and is richly supplied with blood vessels including very permeable fenestrated capillaries, nerve, glands and immune cells. The immune cells are responsible for the production of immunoglobulin A antibodies that provides protection against bacteria and viruses.

4. Olfactory region: The roof of the nasal cavity is the olfactory region and it extends a short way down the septum and lateral wall. Its neuroepithelium is the only part of the CNS that is directly exposed to the external environment. Like respiratory region, olfactory region also contains pseudostratified but specialized olfactory receptor cells important for smell perceptions. This region also contains serous glands, which are producers of secretions acting as a solvent for odorous substances.^[1,4,14,15]

Mechanism of nasal absorption

The first step in the absorption of the drug from nasal cavity is the passage through the mucus. Large and charged molecules may find it difficult

to cross, whereas small and uncharged molecules will readily pass. Two main transport mechanisms involved in the transport of the drug molecule from the nasal mucosa include paracellular transport i.e. transport via movement between the cells and transcellular transport (as shown in figure 2) i.e. simple diffusion across the membrane.^[16]

1. Paracellular route: It is an aqueous route of transport, between adjacent epithelial cells. It is slow route of transport. The paracellular permeability of the nasal epithelium is same as that of the intestine. There is an inverse log-log correlation between intranasal absorption and the molecular weight of the water soluble compounds. Paracellular route showed poor bioavailability for compound with molecular weight greater than 1000 daltons.^[5,17]

2. Transcellular transport: Transcellular route involves transport of the drug through the lipid route (across the membrane). It is responsible for the transport of lipophilic drugs that show a rate dependency on their lipophilicity. The mechanism may occur by active transport route via carrier mediated means or transport through tight junctions.^[5,17]

Factors affecting nasal drug absorption^[8,18]

The systemic bioavailability of the drug through the nasal route is affected by several factors for e.g. physicochemical properties of the drug, the anatomical and physiological properties of the nasal cavity, type and characteristic of selected nasal drugs delivery system and pathophysiological conditions.

1) Physicochemical properties of drug

- Molecular size and molecular weight
- Lipophilic- hydrophilic balance
- Enzymatic degradation in the nasal cavity
- Polymorphism
- Solubility and dissolution rate

2) Nasal mucosal related factors

- Blood supply and membrane permeability
- Mucociliary clearance and ciliary beatings
- Pathological conditions
- Nasal secretions

3) Formulation related factors

- Physical form
- pH
- osmolarity
- viscosity
- volume of solution applied and drug concentration

1) Physicochemical properties of drug

Molecular size and molecular weight: Absorption through the nasal route is highly influenced by the molecular size and molecular weight of the drug. There exists a direct relationship between the molecular weight and permeability for lipophilic compound, whereas hydrophilic compounds depict an inverse relationship. It has been reported in the past, that absorption through nasal route decreases significantly for compound with molecular weight greater than 1000 Da. Particle size of the drug also affects the absorption process. Drug with particle size above 10 μm tend to deposit in the nasal cavity, whereas too fine particles, below 5 μm gets inhaled directly into the lungs.^[8,19]

Lipophilic-hydrophilic balance: Even though nasal mucosa has some hydrophilic character, it is basically lipophilic in nature and it appears that, the lipophilic domain plays an important role in the barrier function for the hydrophilic drugs. The pharmacokinetic profile of some of the lipophilic drug was found to be identical to intravenous injection with bioavailability approaching 100%.^[8,20]

Enzymatic degradation in the nasal cavity: Some drugs such as proteins and peptides show low bioavailability, due to their tendency to degrade in the lumen of nasal cavity. The presence of broad range of enzymes in the nasal epithelial cells such as carboxyl esterase, aldehyde dehydrogenases, epoxide hydrolases, glutathione S-transferases and cytochrome P-450 isoenzymes play an important role in the enzymatic degradation of drugs. Thus this metabolising enzymes may affect the pharmacokinetic and pharmacodynamic profile of the drug.^[9]

Polymorphism: Since polymorphism is known to play an important role in the solubility and dissolution rate of the drug, it is a critical parameter in the nasal drug development especially when it is administered in particulate form. Thus selection of suitable polymorphic form is important in the dosage form development for the nasal delivery.^[20]

Solubility and dissolution rate: For absorption of drug, dissolution is a pre-requisite condition, since only the molecularly dispersed form of drug crosses the bio-membrane. Therefore the drug must first dissolve in the watery fluid of the nasal cavity. Thus, the drug must have sufficient aqueous solubility to allow enough contact with the nasal mucosa. However apart from drug solubility, the nature of pharmaceutical preparation also influence the absorption profile since it has to guarantee the delivery of drug at therapeutically relevant doses. The small size of the nasal cavity allows a low volume of drug solution for intranasal drug administration, thus drug with poor aqueous solubility or which requires higher doses may constitute a problem.^[1,20]

2) Nasal mucosal related factors

Blood supply and membrane permeability:

Nasal mucosa is highly permeable site; however large molecular weight drugs and water soluble drugs like proteins and peptides have low permeability. It has both sympathetic and parasympathetic interventions. Parasympathetic stimulation results in high blood supply promoting congestion, whereas sympathetic stimulation results in low blood supply promoting relaxation. Thus, they indirectly affect the drug permeation, where increased permeability of a compound is due to parasympathetic stimulation.

Mucociliary clearance (MCC) and ciliary

beatings: Mucociliary clearance and ciliary beatings is the normal defense mechanism of the nasal cavity, which functions to transport the adhered and dissolved substances to the nasopharynx that is eventually discharged into the gastrointestinal tract. Clearance of this mucus and the adsorbed/dissolved substances into the GIT is called the mucociliary clearance. Whenever a substance is nasally administered, it is cleared from the nasal cavity in ~21 min by MCC. Reduced MCC helps in increasing the contact time of the drug with nasal mucosa which aids in increased permeability whereas, increased MCC decreases drug permeation.

Pathological conditions: Disease condition such as common cold, rhinitis, atrophic rhinitis, nasal polyposis affects the function of mucociliary clearance by increasing or decreasing the nasal secretions irritating the nasal mucosa etc thereby, affecting the contact time of the drug with nasal mucosa.

Nasal secretions: The anterior serous and the seromucus glands are responsible for the production of nasal secretions. On an average 1.5-21 ml of mucus is produced daily. The permeability of the drug through the nasal mucosa is affected by the following factors:

- a) **Viscosity of the nasal secretions:** Viscosity of the nasal secretion affects the ciliary beating and MCC. The viscous surface layer will inhibit the ciliary beating if the sol layer of the mucus is too thin and mucociliary clearance is impaired if sol layer is too thick, because contact with cilia is lost. Thus permeation is affected due to impairment of mucociliary clearance by altering the time of contact of drug and mucosa.
- b) **Diurnal variation:** The circadian rhythm also affects the nasal secretions. At night the MCC rates are reduced, thus the permeation of drug is altered. Chronokinetics dictates the pattern and rate of permeation in such cases.
- c) **pH of nasal secretion:** The pH in adult varies from 5.5-6.5 and in infants from 5.0-7.0.

Drug permeation is greater if the nasal pH is lower than the pKa of the drug because under such condition drug remains in mostly unionized form. Ideally the pH of the formulation should be between 4.5 to 6.5 for better absorption and also it should have good buffering capacity^[8,14,20].

3) Formulation related factors

Physical form: The simplest and most convenient form of nasal delivery system is the nasal drops. But the problem associated with this dosage form is its failure to quantify the exact amount of drug delivered, resulting in overdose. Moreover rapid drainage can occur when using this dosage form. Solution and suspension sprays are preferred over powder sprays because the latter usually results in nasal mucosal irritation. Recently, gel based devices have been developed for a more accurate drug delivery. They enhance the drug residence time by fixing the drug formulation in nasal mucosa, reducing the postnasal drip and anterior leakage associated with other nasal liquid dosage form. Other specialized systems developed during the last few years to improve the nasal drug delivery include microspheres, liposomes, and films.^[21]

pH: The pH of the drug formulation should be selected taking into consideration the stability of the drug and delivery of greatest quantity of unionized species at the absorption site, as only the unionized part gets easily absorbed. However, the pH of the formulation should be similar to that of nasal mucosa (5.0-6.5) in order to deliver drug without mucosal irritation. Damages were observed in the past, both intracellularly and at membrane level when the pH of the formulation was kept below 3 and above 10.^[20]

Osmolarity: An isotonic formulation is generally preferred since; formulation's tonicity affects the nasal mucosa. Ohwaki *et.al* (1985) studied the effect of formulation osmolarity on the nasal absorption of secretin in rats. They found that, all cells of nasal mucosa were affected by the concentration of sodium chloride in the formulation. And absorption was found to be maximum at 0.462 M sodium chloride concentration.^[8, 21]

Viscosity: Contact time between the drug and the mucosa is increased by higher viscosity of the formulation, thereby increasing the potential for absorption. At the same time, high viscosity interferes the MCC and ciliary beating, thus increasing the permeability of the drugs.^[14]

Volume of solution applied and drug concentration: Drug concentration, dose and volume of administration are the three interrelated parameters that impact the performance of the nasal delivery. Nasal absorption of L-tyrosine was shown

to increase with drug concentration in nasal perfusion experiments.^[20]

Strategies to improve nasal absorption^[1, 7, 19]

Absorption of drug by nasal route is affected by various barriers in the nasal cavity (as shown in figure 3). Various strategies used to improve bioavailability of drug in the nasal mucosa includes

- 1) To improve nasal residence time
- 2) To enhance nasal absorption
- 3) To change the physicochemical properties of the drug by modifying its structure

To improve the absorption and bioavailability of the formulation, any one or combination of above approaches is used.

Methods employed to facilitate the nasal absorption of the drug includes:

1) Nasal enzyme inhibitors: As discussed earlier, nasal mucosa and nasal mucus layer contains variety of enzyme which acts as a barrier for nasal delivery of drugs. Various kinds of enzyme inhibitors are used to minimize metabolism of drug in the nasal cavity, including the use of proteases and peptidases inhibitors. For example, bestatine and comostate amylase are used as aminopeptidases inhibitors and leupeptine and aprotinin as trypsin inhibitors for preventing degradation of calcitonin. Bacitracin, amastatin, boroleucine, and puromycin have been used to prevent enzymatic degradation of drugs like leucine, enkephaline and human growth hormone. Certain absorption enhancers like fusidic acid derivatives and bile salts also shows enzyme inhibiting properties. It has been studied that disodium ethylene diaminetetracetate, an absorption enhancer, reduces degradation of beta sheet breaker peptide used for the treatment of Alzheimer's disease.^[23]

2) Permeation enhancers: Permeation enhancers are mainly used to aid in the process of absorption of drug. The mechanism of action of the absorption enhancers is not clearly known. However, they tend to increase the absorption by following mechanism:

- Inhibit enzyme activity
- Decreases MCC
- Reduces elasticity and viscosity of the mucus
- Open tight junctions
- Solubilize or stabilize the drug

The role of absorption enhancers is to increase the rate of the drug passage through the nasal mucosa. Permeation enhancer, in some way, increases the absorption of the drug by altering the structure of the epithelial cells, but they should accomplish this without causing any damage or permanent change to the nasal mucosa.

The general requirement of an ideal permeation enhancer is:

- Its addition should lead to an effective increase in the absorption drug.
- It should not cause any damage or permanent alteration to the tissue.
- It should be effective in very low concentration.
- It should be non toxic and non irritant.
- It should be compatible with other excipients.

A wide range of absorption enhancers are evaluated for organic drugs include surfactants, bile salts, chelators, fatty acid salts, phospholipids, glycyrrhetic acid derivatives, cyclodextrins and glycols.

Classification of permeation enhancer includes:

- a) Surfactants: Polyoxyethylene-9-lauryl ether, saponin.
- b) Bile salts: trihydroxy salts (glycol and taurocholate), fusidic acid derivatives
- c) Chelators: salicylates, ethylenediamine tetracetic acid (EDTA)
- d) Fatty acid salts: oleic acid, caprylate, caprate, laurate
- e) Phospholipids: lysophosphatidylcholine, didecanoylphosphatidylcholine
- f) Glycyrrhetic acid derivatives: carbenozolone, glycyrrhizinate
- g) Cyclodextrins: α , β , and γ - cyclodextrins and their derivatives
- h) Glycols: n-glycofurols and n-ethylene glycols^[1,11]

3) Prodrug approach: The term 'prodrug' was coined by Albert in 1951. Prodrugs are itself inactive compounds that undergoes *in vivo* biotransformation to give the active moiety. They may be used to overcome one of the following disadvantages of the drug, bad taste, poor solubility, insufficient stability, improve patient compliance, incomplete absorption across biological barriers, high first pass metabolism, toxic metabolite etc. Intranasal drugs are commonly administered as solutions or powders that need to undergo dissolution first, before absorption. This tends to be a problem for lipophilic drugs that can easily cross the biomembrane, once they dissolve. By using prodrug approach, a hydrophilic moiety can be attached to this lipophilic drug, resulting in a molecule with improved solubility and good permeability. For e.g. L-Dopa is poorly soluble in water, by combining with various esters their solubility can be improved and can be given by nasal route. In contrast, a very hydrophilic drug may undergo dissolution in the nasal fluid but they may not be able to cross the biomembrane. If they are administered as prodrugs with higher lipophilic character, the penetration through the membrane may increase. Prodrug approach can also be used

to improve the enzymatic stability of the drug. For e.g. L-aspartate β -esters prodrug of acyclovir was more permeable and less labile to enzymatic hydrolysis than its parent drug. An alternative approach to improve water solubility is the use of co-solvents. Most commonly used co-solvents for intranasal delivery include glycerol, ethanol, propyleneglycol and polyethylene glycol. The advantage of using co-solvent is their non-irritant, non-toxic and pharmaceutical acceptable properties.^[1,24]

4) Structural modification: Modification of chemical structure of drug is another way of improving nasal absorption. The chemical modification of drug molecule has been commonly used to modify the physiochemical properties of a drug such as molecular size, molecular weight, pKa and solubility are favorable to improve the nasal absorption of drug. For example chemical modification of salmon calcitonin to ecatonin (C-N bond replaced by S-S bond) showed better bioavailability than salmon calcitonin.^[10]

5) Mucoadhesive drug delivery system: The most important factor in the nasal delivery of drug is the mucociliary clearance that reduces the time for drug absorption. Thus by prolonging the contact time between the drug and the nasal mucosa, improved drug absorption can be achieved. For this reason mucoadhesive drug delivery system was developed. Mucoadhesion implies the attachment of the drug delivery system to the mucus, involving an interaction between mucin and a synthetic and a natural polymer called mucoadhesive. The sequential events that occur during mucoadhesion include the following three steps.

- First absorption of water by the mucoadhesive system resulting in wetting and swelling.
- The polymer intimately penetrates the mucus and gets localized in the nasal cavity.
- Enhancing the drug concentration gradient across the epithelium

Most commonly used mucoadhesive system for intranasal delivery includes chitosan, alginate, cellulose and its derivatives, carbacol etc. Some of the polymers may have additional characteristic that also helps in drug absorption. For e.g. chitosan causes widening of epithelial tight junction that increases absorption, carbacol 934P and polycarbophil inhibit trypsin proteolytic enzyme thus increases stability of peptide drug.^[25,26]

6) Particulate drug delivery: Microspheres, liposomes and nanoparticles are all particulate systems which can be used as carrier to encapsulate active drug. Apart from absorption it also provides

good stability, reduced toxicity and increased efficacy of the delivery system. The system can also be formulated as mucoadhesive to increase the retention time and facilitate sustained release. Microspheres adhere to the nasal mucosa thereby, increasing the residence time that aid in increase absorption and better bioavailability. Liposomes are amphiphilic in nature and have good permeation properties that can be used to deliver water soluble drugs.^[3,25,27]

Various nasal dosage forms^[1,3,28]

The type of dosage form depends upon the drug being used, proposed indication, patient population and marketing preferences. Four basic formulations must be considered, i.e. solution, suspension, emulsion and dry powder systems.

1) Liquid dosage form: These are the most widely used dosage forms for nasal delivery of drugs. They are mostly aqueous based system. They have humidifying properties which prevents from allergic and chronic conditions connected with crust and drying of mucus membrane. However, microbiological stability, irritation and allergic rhinitis are the major drawbacks associated with the water based dosage forms because the required preservatives impairs the mucociliary clearance and reduces the chemical stability of the dissolved drug substance. The short residence time of this system is yet another drawback of liquid. Several liquid dosage forms available in the market are discussed below.

Instillation and rhinyle catheter: Catheters are used to deliver the drops to a specified region of the nasal cavity. Delivery is achieved by placing the tube containing formulation in the nose and blowing the tube from the other end by mouth. Dosing of catheter is determined by filling the tube prior to administration.

Compressed air nebulizers: Nebulizer is a device used to administer drug in the form of mist inhaled into the lungs. Since compressed air is filled in the device, so it is called as compressed air nebulizer. The common technical principal of nebulizer is to use either oxygen or compressed air or ultrasonic power, as a means to break up medical solutions or suspensions into small aerosol droplets, for direct inhalation from the mouthpiece of the device (as shown in figure 4). The medicament can only be loaded in liquid form into the nebulizer. Drugs commonly given by this dosage form includes corticosteroids and bronchodilators such as salbutamol, sometimes in combination with ipratropium. The reason these formulations are inhaled instead of ingestion, is in order to target their effect to the respiratory tract, which helps in fast onset of action with reduced side effects.^[5,7,29]

Squeezed bottle: They are mainly used as delivery device for decongestant. They are the simple device, consisting of a smooth plastic bottle with a simple jet outlet. The medicament is delivered by pressing the plastic bottle, due to which air inside the bottle is pushed out through the small nozzle, thereby atomizing a certain volume. By releasing the pressure again air is drawn inside the bottle. This may result in contamination of the left formulation due to microorganism and nasal secretions sucked inside. By using this device, dose of the drug is hard to control, since amount delivered depends on the amount of pressure with which it is pressed and level of the liquid contained in the device. Therefore squeezed bottles with vasoconstrictors are not recommended to be used by children.^[1,5,30]

Metered-dose pump sprays: Metered-dose pump (as shown in figure 5) is used for the delivery of most of the marketed nasal preparations containing solutions, suspensions or emulsions. Nasal sprays or nasal mists are used for the nasal delivery of the drug or drugs, locally to generally alleviate cold or allergy symptoms such as nasal congestion. Although the delivery methods may vary, most nasal sprays operate by instilling a fine mist into the nostril by action of a hand operated pump mechanism. The three main types available for local effects are: antihistamines, corticosteroids, and topical decongestants. The main parts of a metered-dose pump include the container, pump with the valve and the actuator. The accuracy of metered-dose pump depends upon the viscosity and surface tension of the formulation. For solutions with higher viscosity, special pumps and valve combinations are used.^[8,31]

2) Powder dosage form

Dry powders are not frequently used in nasal drug delivery. The major advantage of using this system is the improved stability, increased residence time and the lack of preservatives. The types of powder dosage forms are described below:

Insufflators: They are the devices used to deliver the drug substances for inhalation. They can be made by using straw or tube which contains the drug substance and sometimes it may contain syringe also. The achieved particle size of these systems is often increased compared to the particle size of the powder particles due to insufficient deaggregation of the particles and results in high coefficient of variation for initial deposition areas. Many insufflators work with pre-dosed powder doses in capsules.

Dry powder inhaler: They are devices through which a dry powder formulation containing active drug is delivered for local or systemic action via the pulmonary route. Dry powder inhalers are

bolus delivery devices that contain solid drug, suspended or dissolved in a non polar volatile propellant or in a dry powder inhaler that is fluidized when the patient inhales. Mostly they are used to treat respiratory diseases such as asthma, bronchitis, emphysema and COPD. Now a days, they have also been used in the treatment of diabetes mellitus. The medication is held in capsule for manual loading or proprietary form from inside the inhaler. Once loaded, the patient put the mouthpiece of the inhaler into the mouth and takes a deep breath for 5-10 seconds, thus the drug is delivered. By using this device only a few tens of milligram doses can be delivered, since larger doses may lead to provocation of coughing.^[3,5,32]

3) Pressurized MDI's

This device is used to deliver specific amount of drugs to lungs in the form of a short burst of aerosolized medicine that is inhaled by the patient. It is mostly used in treating diseases such as asthma, chronic pulmonary disease (COPD) and other diseases. The medication is mostly a bronchodilator, corticosteroid or combination of both for the treatment of asthma and COPD. Other medications used by metered-dose inhaler include mast cell stabilizers such as cromoglicate, nedochromil etc. The advantages of this device is their small size, portability, availability over a wide dosage range per actuation, dose consistency, dose accuracy, protection of the contents and they are ready for use. The device works by pressing the top of the canister with thumb supporting the lower portion of the actuator. The propellant, in which the active substance is dissolved or suspended, provides the force to generate the aerosol cloud. Propellants in MDI's typically make up more than 99% of the delivered dose. Actuation of the device results in release of the single metered dose of the formulation containing medicament dissolved or suspended in the propellant. Breakup of the volatile propellant into droplets, followed by the rapid evaporation of these droplets, results in the generation of an aerosol consisting of micrometer-sized medication particles that are then inhaled.^[7,18]

4) Nasal gels

Nasal gels are highly viscous solutions or suspensions containing the medicament. Until the recent development of precise dosing devices, there was not much interest in this system. The advantage of this system is the increased residence time, reduction in post-nasal drip due to high viscosity, reduction of taste impact due to reduced swallowing, reduction of anterior leakage of the formulation, reduction of irritation due to soothing and emollient effect of the excipient and target delivery to mucosa for better absorption.

However, due to their high viscosity they have poor spreading abilities, so the efficacy of this system depends upon ability of the device to deposit the formulation in the nasal cavity.^[4,32,33]

Applications of nasal drug delivery system

1) Local delivery^[1,5,34]

For topical nasal disorders some of the drugs are administered through the nasal route. Most common examples are antihistamines, corticosteroids for rhinosinusitis and nasal decongestant for common cold. In fact only low doses are effective through this route with less systemic side effects.

2) Systemic delivery^[5,26,35]

Intranasal route is a good alternative for systemic delivery of drugs compared to oral and parenteral route. This route is relatively fast with reduced side effects and extended drug absorption, and it has been supported by many studies planned to compare intranasal drug delivery against oral and parenteral administration. Examples of drug administered by this route for systemic effect include analgesics (morphine), cardiovascular drugs such as propranolol and carvedilol, hormones such as levonorgestrel, progesterone and insulin, anti-inflammatory agents as indomethacin and ketorolac and anti-viral drugs such acyclovir. Drugs such as zolmitriptan and sumatriptan are also available in the market for the treatment of migraine and headache.

3) Delivery of drugs to CNS via nasal route^[16,24]

For some diseases like Parkinson's, Alzheimer's or pain requires rapid and specific targeting of drugs to brain. The development of nasal delivery system will increase the fraction of drug that reaches the brain after nasal delivery. The delivery of drug to brain from nasal route occurs via olfactory region circumventing BBB. Studies in humans, with proteins such as AVP, CCK analog, MSH/ACTH and insulin have revealed that they are delivered directly to the brain from the nasal route.

4) Delivery of vaccines through nasal route^[5,36,37]

The delivery of vaccines through this route has been extensively evaluated, since the nasal mucosa is the first site of contact with inhaled antigens, especially after respiratory infections. They are also promising alternative to parenteral route since they are able to enhance the systemic level of specific

immunoglobulin G and nasal secretory immunoglobulin A. Examples of the human efficacy of the intranasal vaccines include those against influenza A and B virus, proteosoma-influenza adenovirus-vectored influenza, group B meningococcal native, attenuated respiratory syncytial virus and parainfluenza 3 virus.

5) Delivery of diagnostic drugs^[8]

Nasal route is also exploited for the delivery of diagnostic agents for the diagnosis of various diseases and disorders in the body. Since, the intranasal route directly delivers the drugs to the systemic circulation, so can get quick results with less toxicity. Drugs delivered by this route include phenolsulfonphthalien, a diagnostic agent used to diagnose kidney function of the patient. Other diagnostic agents administered by this route include secretin for pancreatic disorder of the diabetic patient and pentagastrin for the diagnosis of the secretory function of the gastric acid.

CONCLUSION

Nasal route is a promising route for systemic delivery of drugs with poor bioavailability and it has advantages in terms of improved patient compliance, patient acceptability, reduced side effects and ease of delivery compared to oral and parenteral route. The nasal delivery system has proved beneficial in conditions like Parkinson's disease, Alzheimer's disease and pain associated with brain tumor. It is also a suitable route to produce immune response against various diseases like anthrax, influenza etc, by delivering vaccines through the nasal mucosa. In near future, we hope that intranasal products most probably comprise for crisis treatments, such as erectile dysfunction, sleep induction, acute pain (migraine), panic attacks, nausea, heart attacks and Parkinson's disease and novel nasal products for treatment of long-term illnesses, such as diabetes, growth deficiency, osteoporosis, fertility treatment and endometriosis, will also be marketed. The successful application of these attributes requires careful design of characteristics of both the drug formulation and delivery device, and a clear understanding of the ways in which they impact on each other.

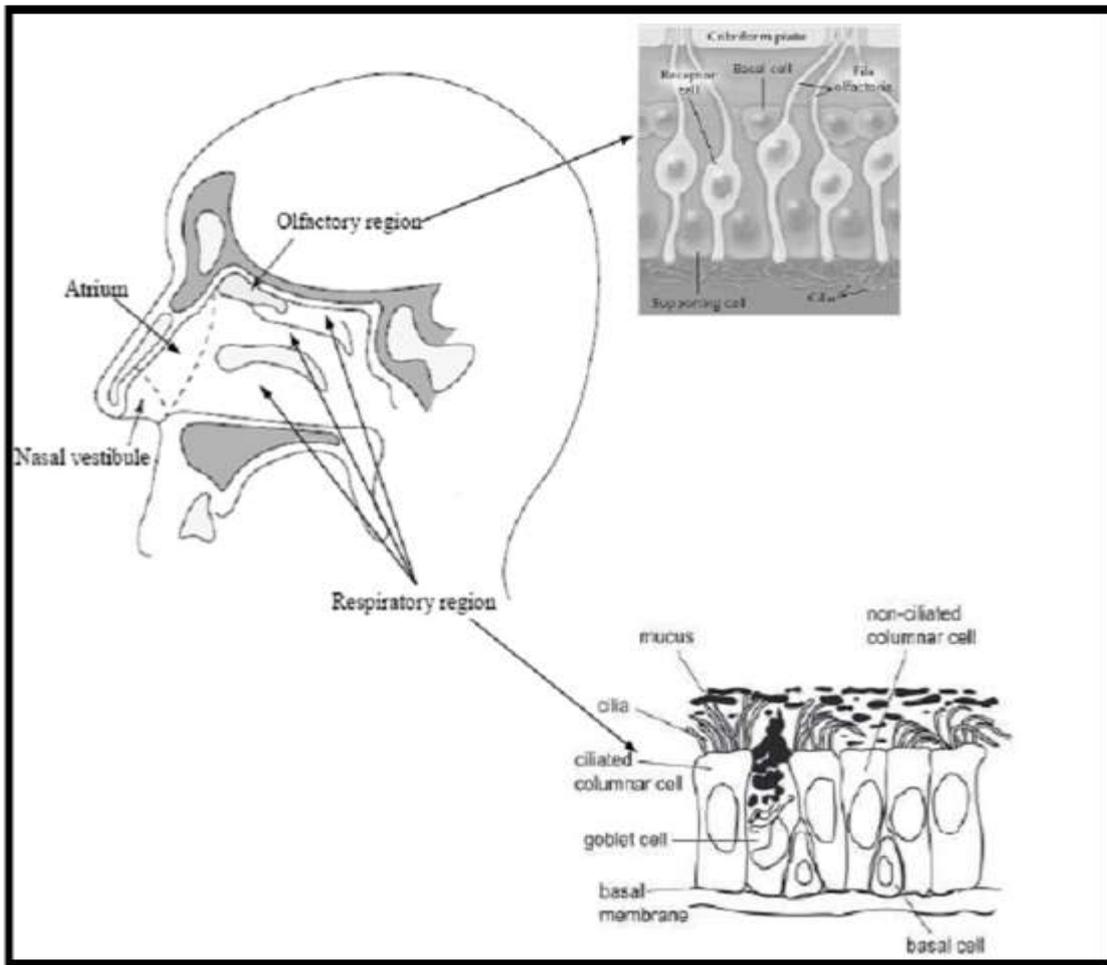


Figure 1. Anatomy and histology of human nasal cavity^[1]

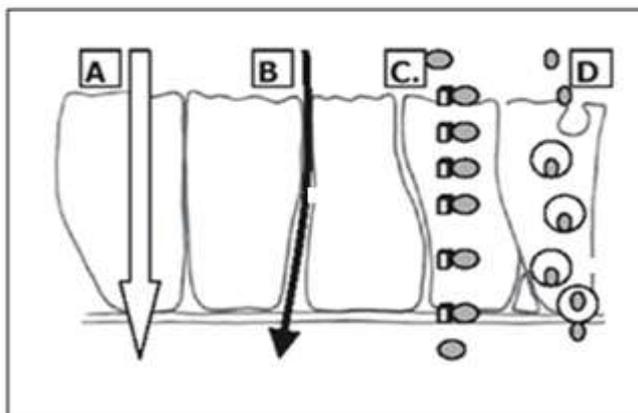


Figure 2. Routes of absorption

(A. Passive intracellular transport, B. Paracellular/ tight junction transport, C. Carrier mediated transcellular transport, D. Transcellular transcytosis)

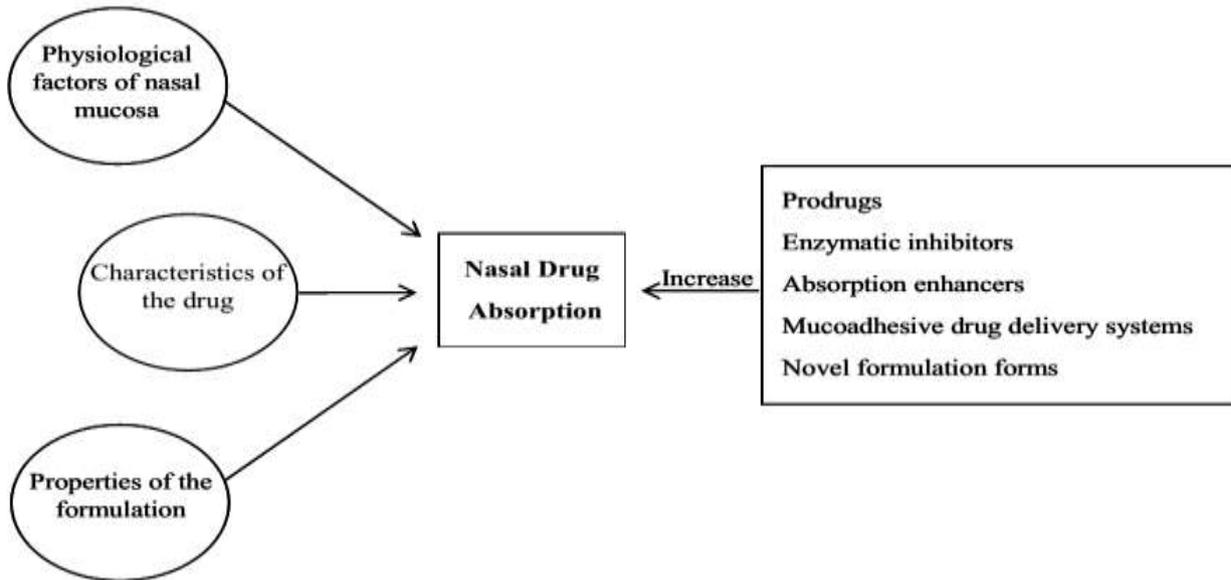


Figure 3. Factors affecting nasal drug absorption and strategies to overcome it^[1]

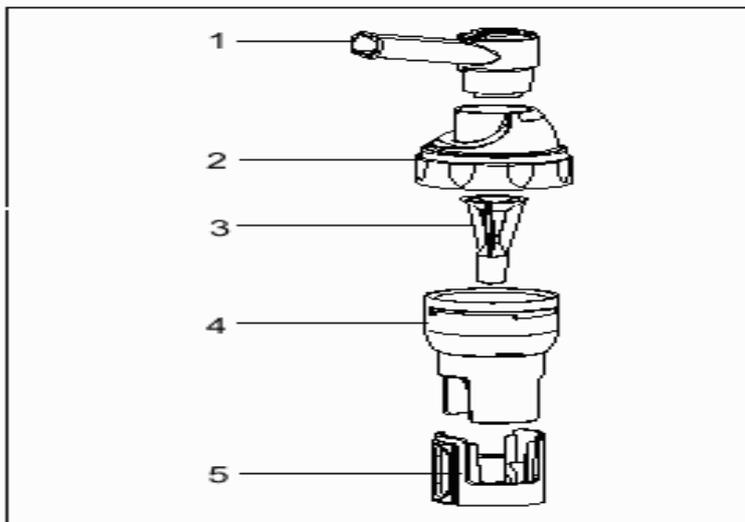


Figure 4. Parts of a nebulizer
(1.Mouth piece, 2.Cap 3.Baffle 4.Medicine cup 5.Interrupter adapter)

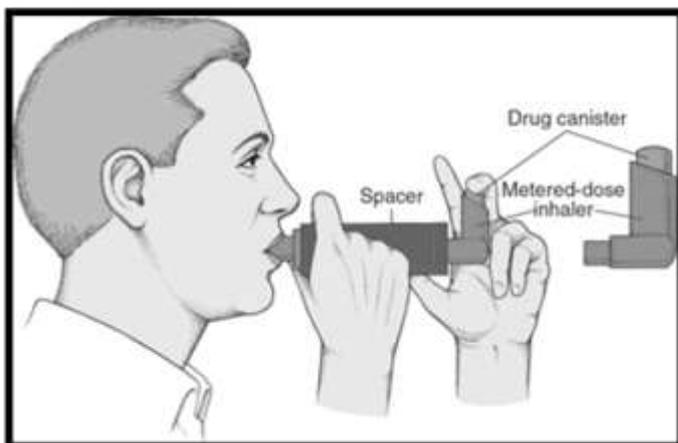


Figure 5. Metered-dose pump

Table No.1 Overview of main types of liquid and powder delivery devices^[38]

LIQUID DEVICES							
	Product stage	Example substance(s)	Example use/indication(s)	Dosing	Mechanism	Actuation	
Vapor							
Vapor inhaler	Marketed	Methol	Rhinitis, Common cold	Multidose	Vaporisation	Nasal inhalation	
Drops							
Rhynyle catheter (Ferring)	Marketed product(s)	Desmopressin	Diabetes incipidus	Single dose	Mechanical	Breath powered	
Multi-dose droppers (multiple)	Marketed product(s)	Decongestants	Rhinitis, Common cold	Multi-dose	Mechanical	Hand actuated	
Unit-dose pipettes (multiple)	Marketed product(s)	Topical steroids	Nasal polyps	Single dose	Mechanical	Hand actuated	
Mechanical spray pumps							
Squeeze bottle (multiple)	Marketed product(s)	Decongestants	Rhinitis, Common cold	Multi-dose	Mechanical	Hand actuated	
Multi-dose Metered-dose spray pumps (multiple)							
	Marketed product(s)	Topicals steroids	Allergic & Perinreal rhinitis	Multi-dose	Mechanical	Hand actuated	
	Marketed product(s)	Desmopressin	Primary nocturnal enuresis	Multi-dose	Mechanical	Hand actuated	
	Marketed product(s)	Calcitonin	Osteoporosis	Multi-dose	Mechanical	Hand actuated	
	Marketed product(s)	Ketrorolac	Pain	Multi-dose	Mechanical	Hand actuated	
	Marketed product(s)	Oxytocin	Induction of lactation & labor	Multi-dose	Mechanical	Hand actuated	
Single/duo-dose spray pumps (multiple)							
	Marketed product(s)	Triptans	Migraine & Cluster headache	Single dose	Mechanical	Hand actuated	
	Marketed device	Device	Vaccine, CRS	Single dose	Mechanical	Hand actuated	
	Marketed device	Vaccine	Influenza vaccine	Single dose	Mechanical	Hand actuated	
	Marketed device	Vaccines	Undisclosed	Single/duo-dose	Mechanical	Hand actuated	
Bi-dir Multi-dose spray pump (OptiNose)	Product in Phase 3	Fluticasone propionate	CRS with Nasal polyps	Multi-dose	Mechanical	Breath powered	
Gas driven spray systems/atomizers							
Slow spray HFA pMDI's (Teva/3M)	Marketed product(s)	Topicals steroids	Allergic rhinitis	Multi-dose	Gas propellant	Hand actuated	
Nitrogen gass driven (Impel)	Preclinical	Not known	Not known	Multi-dose	Gas driven	Gas driven	
Electrically powered Nebulizers/Atomizers							
Pulsation membrane nebulizer (Pari)	Marketed device	Topical steroids	Sinusitis and nasal polyps	Multi-dose	Electical	Electical	
Vibrating mech nebulizer (Aerogen)	Marketed device	Topical drugs	Sinusitis and nasal polyps	Multi-dose	Electical	Electical	
Hand-held mechanical nebuliser (Kurve)	Marketed device	Insulin (Phase 2 trials)	Alzheimer's, Sinusitis	Multi-dose	Electical	Electical	
POWDER DEVICES							
	Product stage	Substances	Indication(s)	Dosing	Mechanism	Actuation	
Mechanical powder sprayers							
Powder spray device (capsule based) (SNBL)	Phase 2	Zlomitriptan	Migraine	Singel dose	Mechanical	Hand actuated	
Powder sprays (Aptar/Vallois)	Device	Not known	Not known	Single dose	Mechanical	Hand actuated	
Powder spray device (BD)	Marketed device	Not known	Not known	Single dose	Mechanical	Hand actuated	
Powder spray device (Bespak)	Marketed device	Not known	Not known	Single dose	Mechanical	Hand actuated	
Breath actuated inhalers							
Multi-dosepowderinhaler(AZ)	Rhinocort Turbohaler	Budesonide	Allergic rhinitis, Nasal polyps	Multi-dose	Mechanical	Nasal inhalation	
Single/duo dose capsule inhaler (Nippon-Shinyaku)	Twin-lizer	Dexamethasone cipeclate	Allergic rhinitis	Single/duo dose	Mechanical	Nasal inhalation	
Nasal inhler (Aptar/Pfeiffer)	Device	Ampomorphine (discont.)	Parkinson's	Single/duo	Mechanical	Nasal inhalation	
Insufflators							
Insufflator - (Trimel)	Preclinical	Undisclosed	Allergic rhinitis,	Single dose	Mechanical	Exhalation driven	
Breath powered Bi-directional deliverv (OntiNose)	Phase 3 trials	Sumatriptan powder	Mieraine	Single dose	Mechanical	Breath powered	

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